

WEBVTT

NOTE duration:"01:02:43"

NOTE recognizability:0.878

NOTE language:en-us

NOTE Confidence: 0.826111342173913

00:00:00.000 --> 00:00:01.449 Grand Rounds It's a pleasure to see

NOTE Confidence: 0.826111342173913

00:00:01.449 --> 00:00:03.543 so many of you here in the colon and

NOTE Confidence: 0.826111342173913

00:00:03.543 --> 00:00:05.040 welcome to everyone joining us on Zoom.

NOTE Confidence: 0.826111342173913

00:00:05.040 --> 00:00:08.136 Also, we'll start today like we start

NOTE Confidence: 0.826111342173913

00:00:08.136 --> 00:00:09.925 every week with just some reminders

NOTE Confidence: 0.826111342173913

00:00:09.925 --> 00:00:11.715 about upcoming Grand Round sessions.

NOTE Confidence: 0.826111342173913

00:00:11.720 --> 00:00:13.820 So next week we'll hear from

NOTE Confidence: 0.826111342173913

00:00:13.820 --> 00:00:15.800 Carrie Epstein and Brianna Browser.

NOTE Confidence: 0.826111342173913

00:00:15.800 --> 00:00:17.996 He'll talk about their trauma focused

NOTE Confidence: 0.826111342173913

00:00:17.996 --> 00:00:19.881 treatment And so exceptionally this

NOTE Confidence: 0.826111342173913

00:00:19.881 --> 00:00:21.676 presentation will be fully virtual.

NOTE Confidence: 0.826111342173913

00:00:21.680 --> 00:00:24.515 So please do join us via Zoom next week.

NOTE Confidence: 0.826111342173913

00:00:24.520 --> 00:00:26.440 And then the following week on February 6th,

NOTE Confidence: 0.826111342173913

00:00:26.440 --> 00:00:28.358 we'll be back here in the cone  
NOTE Confidence: 0.826111342173913

00:00:28.358 --> 00:00:29.600 for compassionate care rounds.  
NOTE Confidence: 0.826111342173913

00:00:29.600 --> 00:00:31.154 And so do join us for that.  
NOTE Confidence: 0.826111342173913

00:00:31.160 --> 00:00:32.588 And then for any of you joining  
NOTE Confidence: 0.826111342173913

00:00:32.588 --> 00:00:34.363 us today and because of the  
NOTE Confidence: 0.826111342173913

00:00:34.363 --> 00:00:35.476 developmental neuroscience focus,  
NOTE Confidence: 0.826111342173913

00:00:35.480 --> 00:00:36.680 I'll make a plug for our  
NOTE Confidence: 0.826111342173913

00:00:36.680 --> 00:00:38.079 speaker on the 13th of February.  
NOTE Confidence: 0.826111342173913

00:00:38.080 --> 00:00:39.370 Doctor Stacy Bilbo,  
NOTE Confidence: 0.826111342173913

00:00:39.370 --> 00:00:41.520 who's joining us from Duke.  
NOTE Confidence: 0.826111342173913

00:00:41.520 --> 00:00:42.437 And as many of you all know,  
NOTE Confidence: 0.826111342173913

00:00:42.440 --> 00:00:44.408 Stacy has done some really elegant  
NOTE Confidence: 0.826111342173913

00:00:44.408 --> 00:00:46.096 work trying to understand the  
NOTE Confidence: 0.826111342173913

00:00:46.096 --> 00:00:47.706 impact of prenatal stress there  
NOTE Confidence: 0.826111342173913

00:00:47.706 --> 00:00:49.782 is on brain development with a  
NOTE Confidence: 0.826111342173913

00:00:49.782 --> 00:00:51.238 particular emphasis on microglia.

NOTE Confidence: 0.826111342173913  
00:00:51.240 --> 00:00:52.760 Now back to today's speaker.  
NOTE Confidence: 0.826111342173913  
00:00:52.760 --> 00:00:54.260 It's a pleasure and a  
NOTE Confidence: 0.826111342173913  
00:00:54.260 --> 00:00:55.160 privilege introduced Dr.  
NOTE Confidence: 0.826111342173913  
00:00:55.160 --> 00:00:57.494 Kristen Brennan to the Charles City  
NOTE Confidence: 0.826111342173913  
00:00:57.494 --> 00:00:59.560 Center community for grand rounds.  
NOTE Confidence: 0.826111342173913  
00:00:59.560 --> 00:01:02.092 Now as you'll hear and appreciate  
NOTE Confidence: 0.826111342173913  
00:01:02.092 --> 00:01:03.358 from Kristen's presentation,  
NOTE Confidence: 0.826111342173913  
00:01:03.360 --> 00:01:05.271 she really has blazed a trail in  
NOTE Confidence: 0.826111342173913  
00:01:05.271 --> 00:01:08.038 the use of stem cells to understand  
NOTE Confidence: 0.826111342173913  
00:01:08.038 --> 00:01:09.914 complex and psychiatric disorders.  
NOTE Confidence: 0.826111342173913  
00:01:09.920 --> 00:01:11.440 Publishing a landmark paper  
NOTE Confidence: 0.826111342173913  
00:01:11.440 --> 00:01:12.960 in Nature in 2011,  
NOTE Confidence: 0.826111342173913  
00:01:12.960 --> 00:01:14.724 holding a postdoc with Rusty Gage  
NOTE Confidence: 0.826111342173913  
00:01:14.724 --> 00:01:16.668 and then in her own independent  
NOTE Confidence: 0.826111342173913  
00:01:16.668 --> 00:01:19.146 research group in Mount Sinai in the  
NOTE Confidence: 0.826111342173913

00:01:19.146 --> 00:01:21.384 Pamela Sklar Division of Psychiatric  
NOTE Confidence: 0.826111342173913

00:01:21.384 --> 00:01:23.520 Genetics and now here at Yale.  
NOTE Confidence: 0.826111342173913

00:01:23.520 --> 00:01:24.314 Since 20,  
NOTE Confidence: 0.826111342173913

00:01:24.314 --> 00:01:26.299 21 has really pushed method  
NOTE Confidence: 0.826111342173913

00:01:26.299 --> 00:01:28.145 development and the integration  
NOTE Confidence: 0.826111342173913

00:01:28.145 --> 00:01:30.461 of computational neuroscience with  
NOTE Confidence: 0.826111342173913

00:01:30.461 --> 00:01:33.356 stem cell technologies to understand  
NOTE Confidence: 0.826111342173913

00:01:33.426 --> 00:01:36.312 and the basis the biological basis  
NOTE Confidence: 0.826111342173913

00:01:36.312 --> 00:01:38.236 for complex psychiatric disorders.  
NOTE Confidence: 0.826111342173913

00:01:38.240 --> 00:01:39.654 And and if you speak to Kristen  
NOTE Confidence: 0.826111342173913

00:01:39.654 --> 00:01:41.040 the other thing you'll appreciate  
NOTE Confidence: 0.826111342173913

00:01:41.040 --> 00:01:42.710 from your conversation is that  
NOTE Confidence: 0.826111342173913

00:01:42.710 --> 00:01:44.803 she places a strong emphasis on  
NOTE Confidence: 0.826111342173913

00:01:44.803 --> 00:01:46.613 mentorship and training the next  
NOTE Confidence: 0.826111342173913

00:01:46.613 --> 00:01:48.409 generation of scientists and she  
NOTE Confidence: 0.826111342173913

00:01:48.409 --> 00:01:50.390 Co directed he was the founding Co

NOTE Confidence: 0.826111342173913  
00:01:50.390 --> 00:01:52.348 director of the YSM and Science  
NOTE Confidence: 0.826111342173913  
00:01:52.348 --> 00:01:54.083 Fellows program which really tries  
NOTE Confidence: 0.826111342173913  
00:01:54.083 --> 00:01:56.160 to provide a structured mentorship  
NOTE Confidence: 0.826111342173913  
00:01:56.160 --> 00:01:58.650 program and a pathway to independent  
NOTE Confidence: 0.826111342173913  
00:01:58.712 --> 00:02:01.272 faculty positions for those from  
NOTE Confidence: 0.826111342173913  
00:02:01.272 --> 00:02:03.320 communities that are traditionally  
NOTE Confidence: 0.826111342173913  
00:02:03.320 --> 00:02:05.172 underrepresented in biomedical sciences.  
NOTE Confidence: 0.826111342173913  
00:02:05.172 --> 00:02:07.836 And so without any further ado,  
NOTE Confidence: 0.826111342173913  
00:02:07.840 --> 00:02:09.195 please join in welcoming Kristen  
NOTE Confidence: 0.826111342173913  
00:02:09.195 --> 00:02:10.920 Brennan to the Child Study Center.  
NOTE Confidence: 0.734978836  
00:02:15.240 --> 00:02:16.680 Thanks, Karen. I'm, oh,  
NOTE Confidence: 0.734978836  
00:02:16.680 --> 00:02:18.840 I got to keep admitting people.  
NOTE Confidence: 0.734978836  
00:02:18.840 --> 00:02:23.076 OK. I'm really excited to be here.  
NOTE Confidence: 0.734978836  
00:02:23.080 --> 00:02:24.438 To those of you in the room  
NOTE Confidence: 0.734978836  
00:02:24.438 --> 00:02:25.759 and also those of you on Zoom.  
NOTE Confidence: 0.934594421904762

00:02:28.840 --> 00:02:30.856 And I'm going to talk today about  
NOTE Confidence: 0.934594421904762

00:02:30.856 --> 00:02:32.425 something that's probably as far from  
NOTE Confidence: 0.934594421904762

00:02:32.425 --> 00:02:34.160 most of your clinical work as can be,  
NOTE Confidence: 0.934594421904762

00:02:34.160 --> 00:02:36.540 but it's using stem cells to explore  
NOTE Confidence: 0.934594421904762

00:02:36.540 --> 00:02:38.879 the genetics of of brain disorders.  
NOTE Confidence: 0.934594421904762

00:02:38.880 --> 00:02:41.400 And I'm hoping that over  
NOTE Confidence: 0.934594421904762

00:02:41.400 --> 00:02:44.040 the the course of the talk,  
NOTE Confidence: 0.934594421904762

00:02:44.040 --> 00:02:45.540 you'll begin to appreciate maybe  
NOTE Confidence: 0.934594421904762

00:02:45.540 --> 00:02:47.482 how little we've done to change  
NOTE Confidence: 0.934594421904762

00:02:47.482 --> 00:02:49.038 your clinical treatment today.  
NOTE Confidence: 0.934594421904762

00:02:49.040 --> 00:02:51.788 But the potential all these models  
NOTE Confidence: 0.934594421904762

00:02:51.788 --> 00:02:54.879 to hopefully one day change the way  
NOTE Confidence: 0.934594421904762

00:02:54.880 --> 00:02:56.320 that your clinical work is proceeding,  
NOTE Confidence: 0.934594421904762

00:02:56.320 --> 00:02:58.196 is somebody else admitting all these people.  
NOTE Confidence: 0.934594421904762

00:02:58.200 --> 00:03:00.396 Awesome. Then I'm going to stop.  
NOTE Confidence: 0.934594421904762

00:03:00.400 --> 00:03:02.158 OK, you're on. It sounds good.

NOTE Confidence: 0.934594421904762

00:03:02.160 --> 00:03:03.438 I'm going to hide that then.

NOTE Confidence: 0.88030240375

00:03:06.440 --> 00:03:09.080 OK. So and I think to this room,

NOTE Confidence: 0.88030240375

00:03:09.080 --> 00:03:11.276 this introduction is obviously overly basic,

NOTE Confidence: 0.88030240375

00:03:11.280 --> 00:03:13.160 but I do think it's,

NOTE Confidence: 0.88030240375

00:03:13.160 --> 00:03:15.240 it's fundamental to, you know,

NOTE Confidence: 0.88030240375

00:03:15.240 --> 00:03:16.704 stop for a moment and talk

NOTE Confidence: 0.88030240375

00:03:16.704 --> 00:03:18.208 about the fact that psychiatric

NOTE Confidence: 0.88030240375

00:03:18.208 --> 00:03:20.080 disorders are incredibly common.

NOTE Confidence: 0.88030240375

00:03:20.080 --> 00:03:21.934 They, in fact they affect about

NOTE Confidence: 0.88030240375

00:03:21.934 --> 00:03:23.949 one in five people across the

NOTE Confidence: 0.88030240375

00:03:23.949 --> 00:03:25.719 country and around the world.

NOTE Confidence: 0.88030240375

00:03:25.720 --> 00:03:29.271 They're, they're they're severe.

NOTE Confidence: 0.88030240375

00:03:29.271 --> 00:03:31.856 The disability adjusted impact of

NOTE Confidence: 0.88030240375

00:03:31.856 --> 00:03:33.627 psychiatric disorders actually

NOTE Confidence: 0.88030240375

00:03:33.627 --> 00:03:35.640 exceeds neurodegenerative disease,

NOTE Confidence: 0.88030240375

00:03:35.640 --> 00:03:37.968 which I think a lot of people intuitively

NOTE Confidence: 0.88030240375

00:03:37.968 --> 00:03:40.115 always think about as a bigger problem.

NOTE Confidence: 0.88030240375

00:03:40.120 --> 00:03:41.564 In fact, psychiatric disorders

NOTE Confidence: 0.88030240375

00:03:41.564 --> 00:03:43.730 come right behind cancer in terms

NOTE Confidence: 0.88030240375

00:03:43.794 --> 00:03:45.318 of of worldwide disability.

NOTE Confidence: 0.88030240375

00:03:45.320 --> 00:03:46.088 They're diverse.

NOTE Confidence: 0.88030240375

00:03:46.088 --> 00:03:48.392 The types of disorders that fall

NOTE Confidence: 0.88030240375

00:03:48.392 --> 00:03:50.600 under this umbrella, I think,

NOTE Confidence: 0.88030240375

00:03:50.600 --> 00:03:53.000 range from autism and psychosis and

NOTE Confidence: 0.88030240375

00:03:53.000 --> 00:03:55.496 bipolar to eating disorders, anxiety,

NOTE Confidence: 0.88030240375

00:03:55.496 --> 00:03:57.000 depression and substance abuse.

NOTE Confidence: 0.88030240375

00:03:57.000 --> 00:03:58.716 So some of them more rare,

NOTE Confidence: 0.88030240375

00:03:58.720 --> 00:03:59.760 some of them more common,

NOTE Confidence: 0.88030240375

00:03:59.760 --> 00:04:02.600 but very different clinical presentations.

NOTE Confidence: 0.88030240375

00:04:02.600 --> 00:04:04.500 And the two introductory facts

NOTE Confidence: 0.88030240375

00:04:04.500 --> 00:04:06.847 that I think really ground my

NOTE Confidence: 0.88030240375

00:04:06.847 --> 00:04:09.079 discussion today are these next two.

NOTE Confidence: 0.88030240375

00:04:09.080 --> 00:04:12.032 The first one being the average delay of

NOTE Confidence: 0.88030240375

00:04:12.032 --> 00:04:14.799 time between symptom onset and treatment,

NOTE Confidence: 0.88030240375

00:04:14.800 --> 00:04:16.732 which ranges from 8 to 10 years

NOTE Confidence: 0.88030240375

00:04:16.732 --> 00:04:17.560 in this country.

NOTE Confidence: 0.88030240375

00:04:17.560 --> 00:04:19.560 Now this is far too long for patients

NOTE Confidence: 0.88030240375

00:04:19.560 --> 00:04:21.029 to be experiencing debilitating

NOTE Confidence: 0.88030240375

00:04:21.029 --> 00:04:23.299 symptoms impacting the quality of

NOTE Confidence: 0.88030240375

00:04:23.299 --> 00:04:25.800 their life without even having a

NOTE Confidence: 0.88030240375

00:04:25.800 --> 00:04:28.880 diagnosis to explain what is going on.

NOTE Confidence: 0.88030240375

00:04:28.880 --> 00:04:30.651 And the second fact that I think

NOTE Confidence: 0.88030240375

00:04:30.651 --> 00:04:32.964 is atrocious is that 60% of adults

NOTE Confidence: 0.88030240375

00:04:32.964 --> 00:04:35.104 with psychiatric disorders did not

NOTE Confidence: 0.88030240375

00:04:35.104 --> 00:04:36.977 receive treatment last year, right.

NOTE Confidence: 0.88030240375

00:04:36.977 --> 00:04:38.759 We have got to do better.

NOTE Confidence: 0.88030240375

00:04:38.760 --> 00:04:39.978 We have got to diagnose better  
NOTE Confidence: 0.88030240375

00:04:39.978 --> 00:04:41.399 and we've got to treat better.  
NOTE Confidence: 0.88030240375

00:04:41.400 --> 00:04:43.260 And that includes finding new treatments  
NOTE Confidence: 0.88030240375

00:04:43.260 --> 00:04:45.068 that don't have the side effects  
NOTE Confidence: 0.88030240375

00:04:45.068 --> 00:04:46.680 of all of our existing approaches.  
NOTE Confidence: 0.88030240375

00:04:46.680 --> 00:04:49.560 Now, the next thing I want to point out,  
NOTE Confidence: 0.88030240375

00:04:49.560 --> 00:04:50.340 of course,  
NOTE Confidence: 0.88030240375

00:04:50.340 --> 00:04:52.680 is that psychiatric disorders are heritable.  
NOTE Confidence: 0.88030240375

00:04:52.680 --> 00:04:54.570 We know this because there are  
NOTE Confidence: 0.88030240375

00:04:54.570 --> 00:04:56.130 families that have, you know,  
NOTE Confidence: 0.88030240375

00:04:56.130 --> 00:04:57.655 a greater percentage of affected  
NOTE Confidence: 0.88030240375

00:04:57.655 --> 00:04:59.040 individuals than other families.  
NOTE Confidence: 0.88030240375

00:04:59.040 --> 00:05:01.825 Now, this alone is not definitive, right,  
NOTE Confidence: 0.88030240375

00:05:01.825 --> 00:05:05.640 because we share DNA with our families.  
NOTE Confidence: 0.88030240375

00:05:05.640 --> 00:05:07.305 But I want to remind you that we also  
NOTE Confidence: 0.88030240375

00:05:07.305 --> 00:05:09.164 share environments with our families, right?

NOTE Confidence: 0.88030240375  
00:05:09.164 --> 00:05:11.720 So if you come from a family of affluence,  
NOTE Confidence: 0.88030240375  
00:05:11.720 --> 00:05:13.670 you're like more likely to have  
NOTE Confidence: 0.88030240375  
00:05:13.670 --> 00:05:14.852 healthier food, better environments.  
NOTE Confidence: 0.88030240375  
00:05:14.852 --> 00:05:16.714 And if you come from a family,  
NOTE Confidence: 0.88030240375  
00:05:16.720 --> 00:05:18.756 from a disadvantaged population,  
NOTE Confidence: 0.88030240375  
00:05:18.756 --> 00:05:21.301 you might live in environments  
NOTE Confidence: 0.88030240375  
00:05:21.301 --> 00:05:23.760 that have increased exposures.  
NOTE Confidence: 0.88030240375  
00:05:23.760 --> 00:05:24.650 OK, OK.  
NOTE Confidence: 0.88030240375  
00:05:24.650 --> 00:05:27.320 I trust you or you know,  
NOTE Confidence: 0.88030240375  
00:05:27.320 --> 00:05:30.160 you know, decreased, you know,  
NOTE Confidence: 0.88030240375  
00:05:30.160 --> 00:05:31.393 quality of foods,  
NOTE Confidence: 0.88030240375  
00:05:31.393 --> 00:05:33.037 decreased exposures through work.  
NOTE Confidence: 0.88030240375  
00:05:33.040 --> 00:05:36.183 And so it's very hard but critical  
NOTE Confidence: 0.88030240375  
00:05:36.183 --> 00:05:38.239 to differentiate these genetic  
NOTE Confidence: 0.88030240375  
00:05:38.239 --> 00:05:40.759 and these environmental effects,  
NOTE Confidence: 0.88030240375

00:05:40.760 --> 00:05:42.724 impacts that conflate and  
NOTE Confidence: 0.88030240375

00:05:42.724 --> 00:05:44.197 confound each other.  
NOTE Confidence: 0.88030240375

00:05:44.200 --> 00:05:45.400 What I can tell you,  
NOTE Confidence: 0.88030240375

00:05:45.400 --> 00:05:46.920 and I'll start with  
NOTE Confidence: 0.88030240375

00:05:46.920 --> 00:05:48.440 schizophrenia as an example,  
NOTE Confidence: 0.88030240375

00:05:48.440 --> 00:05:51.368 is that we know we can estimate from  
NOTE Confidence: 0.88030240375

00:05:51.368 --> 00:05:53.396 genetic studies that the heritability  
NOTE Confidence: 0.88030240375

00:05:53.396 --> 00:05:56.119 of schizophrenia is as high as 80%.  
NOTE Confidence: 0.88030240375

00:05:56.119 --> 00:05:57.793 Now that doesn't mean we can  
NOTE Confidence: 0.88030240375

00:05:57.793 --> 00:05:59.679 explain all of the heritability.  
NOTE Confidence: 0.88030240375

00:05:59.680 --> 00:06:01.608 It just says that we you know think  
NOTE Confidence: 0.88030240375

00:06:01.608 --> 00:06:03.553 from the the best and the largest  
NOTE Confidence: 0.88030240375

00:06:03.553 --> 00:06:05.613 twin studies that 80% of the cause  
NOTE Confidence: 0.88030240375

00:06:05.613 --> 00:06:08.240 is in the DNA that we're born with.  
NOTE Confidence: 0.88030240375

00:06:08.240 --> 00:06:10.916 Now we can explain about 20,  
NOTE Confidence: 0.825779975

00:06:10.920 --> 00:06:13.104 like 30% of that heritability through

NOTE Confidence: 0.825779975  
00:06:13.104 --> 00:06:14.560 genome wide association studies.  
NOTE Confidence: 0.825779975  
00:06:14.560 --> 00:06:15.825 We were looking at common  
NOTE Confidence: 0.825779975  
00:06:15.825 --> 00:06:16.837 variants and underlying it.  
NOTE Confidence: 0.825779975  
00:06:16.840 --> 00:06:18.725 To expand this across the  
NOTE Confidence: 0.825779975  
00:06:18.725 --> 00:06:20.233 spectrum of psychiatric disorders,  
NOTE Confidence: 0.825779975  
00:06:20.240 --> 00:06:21.556 you can see that there are some  
NOTE Confidence: 0.825779975  
00:06:21.556 --> 00:06:22.800 disorders that are highly heritable,  
NOTE Confidence: 0.825779975  
00:06:22.800 --> 00:06:23.776 like schizophrenia,  
NOTE Confidence: 0.825779975  
00:06:23.776 --> 00:06:25.657 Autism spectrum disorder, ADHD,  
NOTE Confidence: 0.825779975  
00:06:25.657 --> 00:06:28.880 and bipolar are all over 75% heritable.  
NOTE Confidence: 0.825779975  
00:06:28.880 --> 00:06:30.680 But reciprocally there are some  
NOTE Confidence: 0.825779975  
00:06:30.680 --> 00:06:32.599 that are extremely not heritable.  
NOTE Confidence: 0.825779975  
00:06:32.600 --> 00:06:34.517 And at the bottom end of this plot we  
NOTE Confidence: 0.825779975  
00:06:34.517 --> 00:06:36.558 have major depressive disorder and PTSD.  
NOTE Confidence: 0.825779975  
00:06:36.560 --> 00:06:38.678 This should surprise nobody that these,  
NOTE Confidence: 0.825779975

00:06:38.680 --> 00:06:39.034 you know,  
NOTE Confidence: 0.825779975

00:06:39.034 --> 00:06:40.273 disorders that are in fact you know,  
NOTE Confidence: 0.825779975

00:06:40.280 --> 00:06:42.782 often defined by an environmental exposure  
NOTE Confidence: 0.825779975

00:06:42.782 --> 00:06:45.519 like PTSD are indeed less heritable.  
NOTE Confidence: 0.825779975

00:06:45.520 --> 00:06:47.680 But whether at the top or the bottom,  
NOTE Confidence: 0.825779975

00:06:47.680 --> 00:06:50.440 our ability to explain that decreasing  
NOTE Confidence: 0.825779975

00:06:50.440 --> 00:06:52.280 heritability is is constant.  
NOTE Confidence: 0.825779975

00:06:52.280 --> 00:06:54.149 We can explain about 1/4 to at  
NOTE Confidence: 0.825779975

00:06:54.149 --> 00:06:55.895 most 1/3 of genetic heritability  
NOTE Confidence: 0.825779975

00:06:55.895 --> 00:06:58.080 for any of these disorders,  
NOTE Confidence: 0.825779975

00:06:58.080 --> 00:06:59.872 going back to schizophrenia.  
NOTE Confidence: 0.825779975

00:06:59.872 --> 00:07:02.112 To explain how complex this  
NOTE Confidence: 0.825779975

00:07:02.112 --> 00:07:03.800 known heritability is,  
NOTE Confidence: 0.825779975

00:07:03.800 --> 00:07:06.218 this plot is plotting the frequency  
NOTE Confidence: 0.825779975

00:07:06.218 --> 00:07:09.097 in the population on the Y axis  
NOTE Confidence: 0.825779975

00:07:09.097 --> 00:07:11.077 and the impact towards diagnosis,

NOTE Confidence: 0.825779975

00:07:11.080 --> 00:07:13.558 the effect size on the X axis.

NOTE Confidence: 0.825779975

00:07:13.560 --> 00:07:15.200 And so to start with,

NOTE Confidence: 0.825779975

00:07:15.200 --> 00:07:16.640 we've got these green dots.

NOTE Confidence: 0.825779975

00:07:16.640 --> 00:07:17.928 These are the oldest,

NOTE Confidence: 0.825779975

00:07:17.928 --> 00:07:19.216 longest known genetic variants

NOTE Confidence: 0.825779975

00:07:19.216 --> 00:07:20.640 linked to schizophrenia.

NOTE Confidence: 0.825779975

00:07:20.640 --> 00:07:22.860 Their copy number variations that are

NOTE Confidence: 0.825779975

00:07:22.860 --> 00:07:25.519 either large deletions or large duplications.

NOTE Confidence: 0.825779975

00:07:25.520 --> 00:07:27.140 They were first identified almost 15

NOTE Confidence: 0.825779975

00:07:27.140 --> 00:07:29.518 years ago now and they're highly penetrant.

NOTE Confidence: 0.825779975

00:07:29.520 --> 00:07:30.780 If for example,

NOTE Confidence: 0.825779975

00:07:30.780 --> 00:07:33.372 you're born with 22 Q 11.2 deletions,

NOTE Confidence: 0.825779975

00:07:33.372 --> 00:07:35.037 you are extremely unlikely to

NOTE Confidence: 0.825779975

00:07:35.037 --> 00:07:36.880 be a neurotypical control,

NOTE Confidence: 0.825779975

00:07:36.880 --> 00:07:38.160 but they're pleiotropic.

NOTE Confidence: 0.825779975

00:07:38.160 --> 00:07:41.111 So you know you you could end up  
NOTE Confidence: 0.825779975

00:07:41.111 --> 00:07:43.516 diagnosed with schizophrenia or autism  
NOTE Confidence: 0.825779975

00:07:43.516 --> 00:07:44.959 or neurodevelopmental disorders.  
NOTE Confidence: 0.825779975

00:07:44.960 --> 00:07:46.400 So that's the green dots,  
NOTE Confidence: 0.825779975

00:07:46.400 --> 00:07:47.456 highly penetrant,  
NOTE Confidence: 0.825779975

00:07:47.456 --> 00:07:51.152 but not specific to any specific disorder.  
NOTE Confidence: 0.825779975

00:07:51.160 --> 00:07:52.918 The red dots are were identified  
NOTE Confidence: 0.825779975

00:07:52.918 --> 00:07:53.797 much more recently,  
NOTE Confidence: 0.825779975

00:07:53.800 --> 00:07:55.120 in fact in the last year or two.  
NOTE Confidence: 0.825779975

00:07:55.120 --> 00:07:56.899 These are protein,  
NOTE Confidence: 0.825779975

00:07:56.899 --> 00:07:58.678 protein truncating variations.  
NOTE Confidence: 0.825779975

00:07:58.680 --> 00:07:59.936 They're much more rare,  
NOTE Confidence: 0.825779975

00:07:59.936 --> 00:08:00.878 they're about tenfold,  
NOTE Confidence: 0.825779975

00:08:00.880 --> 00:08:02.160 less common in the population,  
NOTE Confidence: 0.825779975

00:08:02.160 --> 00:08:03.760 but they're just as penetrant.  
NOTE Confidence: 0.825779975

00:08:03.760 --> 00:08:04.558 So in total,

NOTE Confidence: 0.825779975

00:08:04.558 --> 00:08:06.799 all of the known green and red dots

NOTE Confidence: 0.825779975

00:08:06.799 --> 00:08:08.872 explain less than 5% of schizophrenia.

NOTE Confidence: 0.825779975

00:08:08.872 --> 00:08:12.200 So they're very penetrant when you have them,

NOTE Confidence: 0.825779975

00:08:12.200 --> 00:08:14.545 but most of your cases don't carry

NOTE Confidence: 0.825779975

00:08:14.545 --> 00:08:16.440 these dilutions or duplications.

NOTE Confidence: 0.825779975

00:08:16.440 --> 00:08:17.086 In fact,

NOTE Confidence: 0.825779975

00:08:17.086 --> 00:08:19.347 most of the known genetic risks for

NOTE Confidence: 0.825779975

00:08:19.347 --> 00:08:20.957 schizophrenia is in these blue dots.

NOTE Confidence: 0.825779975

00:08:20.960 --> 00:08:22.468 They're extremely common variants.

NOTE Confidence: 0.825779975

00:08:22.468 --> 00:08:25.167 Each of us as controls were born

NOTE Confidence: 0.825779975

00:08:25.167 --> 00:08:27.429 with over a dozen common risk

NOTE Confidence: 0.825779975

00:08:27.429 --> 00:08:28.560 variants for schizophrenia.

NOTE Confidence: 0.825779975

00:08:28.560 --> 00:08:29.802 Your cases, though,

NOTE Confidence: 0.825779975

00:08:29.802 --> 00:08:32.286 will have over 60 common variants

NOTE Confidence: 0.825779975

00:08:32.286 --> 00:08:34.000 associated with schizophrenia,

NOTE Confidence: 0.825779975

00:08:34.000 --> 00:08:35.398 so all of us have them.  
NOTE Confidence: 0.825779975

00:08:35.400 --> 00:08:37.696 But each common variant confers less than  
NOTE Confidence: 0.825779975

00:08:37.696 --> 00:08:39.940 a 1% increase risk for schizophrenia.  
NOTE Confidence: 0.825779975

00:08:39.940 --> 00:08:42.310 So very small effect sizes that  
NOTE Confidence: 0.825779975

00:08:42.378 --> 00:08:44.478 seem meaningful only in aggregate.  
NOTE Confidence: 0.825779975

00:08:44.480 --> 00:08:46.076 On the right is the most recent.  
NOTE Confidence: 0.825779975

00:08:46.080 --> 00:08:47.355 You know why the association  
NOTE Confidence: 0.825779975

00:08:47.355 --> 00:08:48.120 study for schizophrenia.  
NOTE Confidence: 0.825779975

00:08:48.120 --> 00:08:52.197 So this is our G wash plot for schizophrenia.  
NOTE Confidence: 0.825779975

00:08:52.200 --> 00:08:52.480 Briefly,  
NOTE Confidence: 0.825779975

00:08:52.480 --> 00:08:54.440 the Y axis is the P value,  
NOTE Confidence: 0.825779975

00:08:54.440 --> 00:08:56.558 the significance of any given loci.  
NOTE Confidence: 0.825779975

00:08:56.560 --> 00:08:58.600 And that line you see at 10 to the -8,  
NOTE Confidence: 0.825779975

00:08:58.600 --> 00:09:00.008 that's genome wide significance.  
NOTE Confidence: 0.825779975

00:09:00.008 --> 00:09:02.511 So every line that goes over every  
NOTE Confidence: 0.825779975

00:09:02.511 --> 00:09:04.515 vertical line that goes over that

NOTE Confidence: 0.825779975

00:09:04.515 --> 00:09:06.091 horizontal line is significantly

NOTE Confidence: 0.825779975

00:09:06.091 --> 00:09:08.636 associated with risk for schizophrenia.

NOTE Confidence: 0.87906658

00:09:08.640 --> 00:09:10.534 But they're not actually lines, they're dots.

NOTE Confidence: 0.87906658

00:09:10.534 --> 00:09:12.736 And each dot in those vertical

NOTE Confidence: 0.87906658

00:09:12.736 --> 00:09:15.276 lines is one single DNA base pair,

NOTE Confidence: 0.87906658

00:09:15.280 --> 00:09:17.368 one single nucleotide polymorphism.

NOTE Confidence: 0.87906658

00:09:17.368 --> 00:09:19.978 And so it's actually incredibly

NOTE Confidence: 0.87906658

00:09:19.978 --> 00:09:22.470 challenging at some of these loci to

NOTE Confidence: 0.87906658

00:09:22.470 --> 00:09:24.599 know which DNA variants are actually

NOTE Confidence: 0.87906658

00:09:24.600 --> 00:09:25.984 attributable to schizophrenia risk.

NOTE Confidence: 0.87906658

00:09:25.984 --> 00:09:28.060 And so the first major question

NOTE Confidence: 0.87906658

00:09:28.112 --> 00:09:29.630 that we have outlying is how

NOTE Confidence: 0.87906658

00:09:29.630 --> 00:09:31.160 do we translate risk variants.

NOTE Confidence: 0.87906658

00:09:31.160 --> 00:09:33.386 So again, here you might have thousands

NOTE Confidence: 0.87906658

00:09:33.386 --> 00:09:35.199 of risk variants at chromosome.

NOTE Confidence: 0.87906658

00:09:35.200 --> 00:09:37.000 I think that's chromosome 6,  
NOTE Confidence: 0.87906658

00:09:37.000 --> 00:09:38.981 the MHC cluster, and maybe only one  
NOTE Confidence: 0.87906658

00:09:38.981 --> 00:09:41.320 of them is like the schizophrenia,  
NOTE Confidence: 0.87906658

00:09:41.320 --> 00:09:44.120 whereas like this loci is much more clear,  
NOTE Confidence: 0.87906658

00:09:44.120 --> 00:09:44.372 right?  
NOTE Confidence: 0.87906658

00:09:44.372 --> 00:09:45.884 There's only six or seven of  
NOTE Confidence: 0.87906658

00:09:45.884 --> 00:09:46.920 these snips linked here,  
NOTE Confidence: 0.87906658

00:09:46.920 --> 00:09:47.880 so we might have a better.  
NOTE Confidence: 0.87906658

00:09:47.880 --> 00:09:50.080 I guess that this top one is it.  
NOTE Confidence: 0.87906658

00:09:50.080 --> 00:09:52.462 But top is most significant doesn't  
NOTE Confidence: 0.87906658

00:09:52.462 --> 00:09:54.469 actually mean it's causal because  
NOTE Confidence: 0.87906658

00:09:54.469 --> 00:09:56.919 we don't scramble our DNA well when  
NOTE Confidence: 0.87906658

00:09:56.920 --> 00:09:59.038 when eggs and sperm come together.  
NOTE Confidence: 0.87906658

00:09:59.040 --> 00:10:00.568 So major question #1,  
NOTE Confidence: 0.87906658

00:10:00.568 --> 00:10:03.399 how to translate risk variants to their  
NOTE Confidence: 0.87906658

00:10:03.399 --> 00:10:06.195 target genes and their cellular function?

NOTE Confidence: 0.87906658

00:10:06.200 --> 00:10:08.377 Question #2 How do all of these

NOTE Confidence: 0.87906658

00:10:08.377 --> 00:10:09.960 hundreds of risk variants,

NOTE Confidence: 0.87906658

00:10:09.960 --> 00:10:11.735 And again, there's 250 risk

NOTE Confidence: 0.87906658

00:10:11.735 --> 00:10:13.155 variants here for schizophrenia.

NOTE Confidence: 0.87906658

00:10:13.160 --> 00:10:13.932 For depression,

NOTE Confidence: 0.87906658

00:10:13.932 --> 00:10:16.449 we already have over 350 risk variants.

NOTE Confidence: 0.87906658

00:10:16.449 --> 00:10:18.387 How do all of these risk

NOTE Confidence: 0.87906658

00:10:18.387 --> 00:10:19.840 variants interact and sum?

NOTE Confidence: 0.87906658

00:10:19.840 --> 00:10:21.304 And in fact,

NOTE Confidence: 0.87906658

00:10:21.304 --> 00:10:23.256 do these interactions explain

NOTE Confidence: 0.87906658

00:10:23.256 --> 00:10:24.720 that unknown misinheritability?

NOTE Confidence: 0.87906658

00:10:24.720 --> 00:10:26.676 And I think the really interesting

NOTE Confidence: 0.87906658

00:10:26.676 --> 00:10:28.999 question then is how do these

NOTE Confidence: 0.87906658

00:10:28.999 --> 00:10:30.919 interactions and summings underlie

NOTE Confidence: 0.87906658

00:10:30.919 --> 00:10:32.839 variable penetrance and expressivity?

NOTE Confidence: 0.87906658

00:10:32.840 --> 00:10:34.820 Why can two individuals have  
NOTE Confidence: 0.87906658

00:10:34.820 --> 00:10:36.800 the exact same genetic risk,  
NOTE Confidence: 0.87906658

00:10:36.800 --> 00:10:38.051 but really different,  
NOTE Confidence: 0.87906658

00:10:38.051 --> 00:10:38.468 different,  
NOTE Confidence: 0.87906658

00:10:38.468 --> 00:10:39.719 different clinical presentations,  
NOTE Confidence: 0.87906658

00:10:39.720 --> 00:10:42.115 either not having any symptoms  
NOTE Confidence: 0.87906658

00:10:42.115 --> 00:10:44.031 altogether or changing severity  
NOTE Confidence: 0.87906658

00:10:44.031 --> 00:10:46.640 despite sharing the same genetic risk?  
NOTE Confidence: 0.87906658

00:10:46.640 --> 00:10:48.736 And so my talk today is really about  
NOTE Confidence: 0.87906658

00:10:48.736 --> 00:10:51.059 how do we use genetics and stem  
NOTE Confidence: 0.87906658

00:10:51.059 --> 00:10:52.794 cells to answer these questions.  
NOTE Confidence: 0.87906658

00:10:52.800 --> 00:10:55.092 The first goal that we have  
NOTE Confidence: 0.87906658

00:10:55.092 --> 00:10:56.238 is improving diagnosis.  
NOTE Confidence: 0.87906658

00:10:56.240 --> 00:10:59.826 If we could predict who was had  
NOTE Confidence: 0.87906658

00:10:59.826 --> 00:11:01.558 schizophrenia from their DNA,  
NOTE Confidence: 0.87906658

00:11:01.560 --> 00:11:03.090 right, we would add an extra

NOTE Confidence: 0.87906658

00:11:03.090 --> 00:11:04.360 measurement for all of you,

NOTE Confidence: 0.87906658

00:11:04.360 --> 00:11:04.665 right?

NOTE Confidence: 0.87906658

00:11:04.665 --> 00:11:06.800 Like I think all of you would

NOTE Confidence: 0.87906658

00:11:06.800 --> 00:11:08.223 appreciate blood based biomarkers

NOTE Confidence: 0.87906658

00:11:08.223 --> 00:11:10.467 or DNA genotype that tells you

NOTE Confidence: 0.87906658

00:11:10.467 --> 00:11:12.088 definitively that somebody has

NOTE Confidence: 0.87906658

00:11:12.088 --> 00:11:14.103 schizophrenia versus bipolar or that

NOTE Confidence: 0.87906658

00:11:14.103 --> 00:11:16.296 somebody's high risk or low risk, right?

NOTE Confidence: 0.87906658

00:11:16.296 --> 00:11:17.516 Like this would be informative.

NOTE Confidence: 0.87906658

00:11:17.520 --> 00:11:19.920 You have them in cancer,

NOTE Confidence: 0.87906658

00:11:19.920 --> 00:11:22.398 we have them in many human diseases.

NOTE Confidence: 0.87906658

00:11:22.400 --> 00:11:25.358 We don't have them in psychiatry.

NOTE Confidence: 0.87906658

00:11:25.360 --> 00:11:26.352 And second of all,

NOTE Confidence: 0.87906658

00:11:26.352 --> 00:11:29.000 I'd like to use all this genetic information

NOTE Confidence: 0.87906658

00:11:29.000 --> 00:11:31.440 to improve prevention or treatment.

NOTE Confidence: 0.87906658

00:11:31.440 --> 00:11:32.000 Now again,  
NOTE Confidence: 0.87906658

00:11:32.000 --> 00:11:33.960 if we are so good by use,  
NOTE Confidence: 0.87906658

00:11:33.960 --> 00:11:37.050 at one day at using DNA  
NOTE Confidence: 0.87906658

00:11:37.050 --> 00:11:38.595 to identify diagnosis,  
NOTE Confidence: 0.87906658

00:11:38.600 --> 00:11:40.556 our DNA stable across our lifetime.  
NOTE Confidence: 0.87906658

00:11:40.560 --> 00:11:42.048 So that means instead of waiting  
NOTE Confidence: 0.87906658

00:11:42.048 --> 00:11:43.521 till your patients show up in  
NOTE Confidence: 0.87906658

00:11:43.521 --> 00:11:44.596 the clinic with first onset,  
NOTE Confidence: 0.87906658

00:11:44.600 --> 00:11:45.728 we could actually,  
NOTE Confidence: 0.87906658

00:11:45.728 --> 00:11:46.480 you know,  
NOTE Confidence: 0.87906658

00:11:46.480 --> 00:11:48.504 accurately predict who might  
NOTE Confidence: 0.87906658

00:11:48.504 --> 00:11:51.034 have these disorders at birth.  
NOTE Confidence: 0.87906658

00:11:51.040 --> 00:11:53.320 And if you can define who is high  
NOTE Confidence: 0.87906658

00:11:53.320 --> 00:11:55.316 risk and who is not at birth,  
NOTE Confidence: 0.87906658

00:11:55.320 --> 00:11:57.595 if you've changed the window  
NOTE Confidence: 0.87906658

00:11:57.595 --> 00:11:58.960 for therapeutic intervention.

NOTE Confidence: 0.87906658

00:11:58.960 --> 00:12:00.604 I think it's really intuitive to

NOTE Confidence: 0.87906658

00:12:00.604 --> 00:12:02.314 everybody that if we are going

NOTE Confidence: 0.87906658

00:12:02.314 --> 00:12:03.714 to have Alzheimer's one day,

NOTE Confidence: 0.87906658

00:12:03.720 --> 00:12:05.056 I know for myself,

NOTE Confidence: 0.87906658

00:12:05.056 --> 00:12:07.567 I would much rather treat my Alzheimer's

NOTE Confidence: 0.87906658

00:12:07.567 --> 00:12:10.556 when I'm 50 prior to neuronal death,

NOTE Confidence: 0.885227824166667

00:12:10.560 --> 00:12:13.066 then when I'm 80, after half of

NOTE Confidence: 0.885227824166667

00:12:13.066 --> 00:12:14.919 my cortical neurons have died.

NOTE Confidence: 0.885227824166667

00:12:14.920 --> 00:12:16.803 But it should also be intuitive that

NOTE Confidence: 0.885227824166667

00:12:16.803 --> 00:12:18.793 the type of treatment might change

NOTE Confidence: 0.885227824166667

00:12:18.793 --> 00:12:21.037 as we expand that therapeutic window.

NOTE Confidence: 0.885227824166667

00:12:21.040 --> 00:12:23.947 At age 80, any drug is just focused on

NOTE Confidence: 0.885227824166667

00:12:23.947 --> 00:12:26.239 keeping my remaining neurons alive.

NOTE Confidence: 0.885227824166667

00:12:26.240 --> 00:12:29.187 But at age 50, we might actually

NOTE Confidence: 0.885227824166667

00:12:29.187 --> 00:12:30.909 target microglia activation and

NOTE Confidence: 0.885227824166667

00:12:30.909 --> 00:12:33.195 try to prevent neurons from dying,  
NOTE Confidence: 0.885227824166667

00:12:33.200 --> 00:12:34.496 try to prevent inflammation.  
NOTE Confidence: 0.885227824166667

00:12:34.496 --> 00:12:37.443 And so if you can expand the therapeutic  
NOTE Confidence: 0.885227824166667

00:12:37.443 --> 00:12:39.319 window by improving diagnosis,  
NOTE Confidence: 0.885227824166667

00:12:39.320 --> 00:12:41.315 you also change the cell types and  
NOTE Confidence: 0.885227824166667

00:12:41.315 --> 00:12:43.328 the pathways that you might have  
NOTE Confidence: 0.885227824166667

00:12:43.328 --> 00:12:44.800 as possible therapeutic targets.  
NOTE Confidence: 0.885227824166667

00:12:44.800 --> 00:12:46.291 And So what I'm really talking about  
NOTE Confidence: 0.885227824166667

00:12:46.291 --> 00:12:47.959 is the idea of precision medicine.  
NOTE Confidence: 0.885227824166667

00:12:47.960 --> 00:12:49.983 How can we take knowledge of all  
NOTE Confidence: 0.885227824166667

00:12:49.983 --> 00:12:51.644 the genetic risk variants carried  
NOTE Confidence: 0.885227824166667

00:12:51.644 --> 00:12:54.206 by any individual as well as the  
NOTE Confidence: 0.885227824166667

00:12:54.206 --> 00:12:55.604 interactions between those variants  
NOTE Confidence: 0.885227824166667

00:12:55.604 --> 00:12:58.513 and use that to best predict the drug  
NOTE Confidence: 0.885227824166667

00:12:58.513 --> 00:13:01.678 that will improve their symptoms?  
NOTE Confidence: 0.885227824166667

00:13:01.680 --> 00:13:03.624 I want to really quickly ground

NOTE Confidence: 0.885227824166667  
00:13:03.624 --> 00:13:05.938 my talk about stem cells in what  
NOTE Confidence: 0.885227824166667  
00:13:05.938 --> 00:13:07.840 we know about the human brain.  
NOTE Confidence: 0.885227824166667  
00:13:07.840 --> 00:13:10.990 And so I'm going to summarize 50  
NOTE Confidence: 0.885227824166667  
00:13:10.990 --> 00:13:13.525 years of human research in in  
NOTE Confidence: 0.885227824166667  
00:13:13.525 --> 00:13:15.193 one overly simple slide.  
NOTE Confidence: 0.885227824166667  
00:13:15.200 --> 00:13:16.803 But the first thing that I want  
NOTE Confidence: 0.885227824166667  
00:13:16.803 --> 00:13:19.026 you all to know is that the brains  
NOTE Confidence: 0.885227824166667  
00:13:19.026 --> 00:13:20.678 of patients with schizophrenia,  
NOTE Confidence: 0.885227824166667  
00:13:20.680 --> 00:13:21.568 on average,  
NOTE Confidence: 0.885227824166667  
00:13:21.568 --> 00:13:23.788 are smaller than the brains  
NOTE Confidence: 0.885227824166667  
00:13:23.788 --> 00:13:25.120 of neurotypical controls.  
NOTE Confidence: 0.885227824166667  
00:13:25.120 --> 00:13:28.132 We knew this decades ago from  
NOTE Confidence: 0.885227824166667  
00:13:28.132 --> 00:13:29.993 autopsy studies where literally  
NOTE Confidence: 0.885227824166667  
00:13:29.993 --> 00:13:31.758 the brains were just weighed.  
NOTE Confidence: 0.885227824166667  
00:13:31.760 --> 00:13:33.392 And we know this more recently  
NOTE Confidence: 0.885227824166667

00:13:33.392 --> 00:13:34.480 from brain imaging studies.  
NOTE Confidence: 0.885227824166667

00:13:34.480 --> 00:13:36.118 So these are images from Judy  
NOTE Confidence: 0.885227824166667

00:13:36.120 --> 00:13:37.960 Rappaport's group at the NIH  
NOTE Confidence: 0.885227824166667

00:13:37.960 --> 00:13:39.878 almost gosh over 20 years ago now.  
NOTE Confidence: 0.885227824166667

00:13:39.880 --> 00:13:41.896 But the areas in red are brain  
NOTE Confidence: 0.885227824166667

00:13:41.896 --> 00:13:43.320 regions that are smaller,  
NOTE Confidence: 0.885227824166667

00:13:43.320 --> 00:13:45.498 but the brain regions are not  
NOTE Confidence: 0.885227824166667

00:13:45.498 --> 00:13:47.400 smaller because neurons are dying.  
NOTE Confidence: 0.885227824166667

00:13:47.400 --> 00:13:49.332 They seem to be smaller because  
NOTE Confidence: 0.885227824166667

00:13:49.332 --> 00:13:51.120 the neurons themselves are smaller.  
NOTE Confidence: 0.885227824166667

00:13:51.120 --> 00:13:52.878 So this again is postmortem imaging,  
NOTE Confidence: 0.885227824166667

00:13:52.880 --> 00:13:53.688 neuronal reconstruction,  
NOTE Confidence: 0.885227824166667

00:13:53.688 --> 00:13:55.708 showing that cortical neurons are  
NOTE Confidence: 0.885227824166667

00:13:55.708 --> 00:13:57.959 smaller in patients with schizophrenia,  
NOTE Confidence: 0.885227824166667

00:13:57.960 --> 00:13:59.717 and in fact they have fewer synapses.  
NOTE Confidence: 0.885227824166667

00:13:59.720 --> 00:14:02.005 There's fewer connections between neurons

NOTE Confidence: 0.885227824166667  
00:14:02.005 --> 00:14:05.160 in these brain regions that are smaller.  
NOTE Confidence: 0.885227824166667  
00:14:05.160 --> 00:14:06.444 And so this is the first  
NOTE Confidence: 0.885227824166667  
00:14:06.444 --> 00:14:07.760 truth that I want to hold,  
NOTE Confidence: 0.885227824166667  
00:14:07.760 --> 00:14:09.340 that neurons from patients with  
NOTE Confidence: 0.885227824166667  
00:14:09.340 --> 00:14:10.920 schizophrenia seem to be less  
NOTE Confidence: 0.885227824166667  
00:14:10.976 --> 00:14:12.476 well connected to each other.  
NOTE Confidence: 0.885227824166667  
00:14:12.480 --> 00:14:14.757 But there's so much that we still don't know.  
NOTE Confidence: 0.885227824166667  
00:14:14.760 --> 00:14:16.432 We don't know if these neurons are the  
NOTE Confidence: 0.885227824166667  
00:14:16.432 --> 00:14:18.118 cell type of origin for schizophrenia.  
NOTE Confidence: 0.885227824166667  
00:14:18.120 --> 00:14:19.938 Is this where the disorder starts  
NOTE Confidence: 0.885227824166667  
00:14:19.938 --> 00:14:21.520 or does something happen Right,  
NOTE Confidence: 0.885227824166667  
00:14:21.520 --> 00:14:23.080 Because this is end stage disease.  
NOTE Confidence: 0.885227824166667  
00:14:23.080 --> 00:14:24.676 These are patients who are decades  
NOTE Confidence: 0.885227824166667  
00:14:24.676 --> 00:14:25.474 and decades old,  
NOTE Confidence: 0.885227824166667  
00:14:25.480 --> 00:14:28.315 who probably have had decades of treatment.  
NOTE Confidence: 0.885227824166667

00:14:28.320 --> 00:14:29.920 Where did this start?  
NOTE Confidence: 0.885227824166667

00:14:29.920 --> 00:14:32.320 In their adolescence or in childhood?  
NOTE Confidence: 0.885227824166667

00:14:32.320 --> 00:14:34.805 Which cell type and when and and  
NOTE Confidence: 0.885227824166667

00:14:34.805 --> 00:14:36.980 these are the questions that  
NOTE Confidence: 0.885227824166667

00:14:36.980 --> 00:14:39.040 I'm really interested in.  
NOTE Confidence: 0.885227824166667

00:14:39.040 --> 00:14:40.699 You know it it's it's kind of  
NOTE Confidence: 0.885227824166667

00:14:40.699 --> 00:14:41.774 preposterous that we actually  
NOTE Confidence: 0.885227824166667

00:14:41.774 --> 00:14:43.319 don't know this already right?  
NOTE Confidence: 0.885227824166667

00:14:43.320 --> 00:14:46.029 That we don't know what cell type  
NOTE Confidence: 0.885227824166667

00:14:46.029 --> 00:14:48.558 goes wrong 1st and why and how.  
NOTE Confidence: 0.885227824166667

00:14:48.560 --> 00:14:50.303 And the reason that we don't know  
NOTE Confidence: 0.885227824166667

00:14:50.303 --> 00:14:51.981 this in truth is that there's  
NOTE Confidence: 0.885227824166667

00:14:51.981 --> 00:14:53.727 just not enough live human brain  
NOTE Confidence: 0.885227824166667

00:14:53.727 --> 00:14:55.460 tissue for studies of schizophrenia  
NOTE Confidence: 0.885227824166667

00:14:55.460 --> 00:14:56.840 and for drug discovery.  
NOTE Confidence: 0.885227824166667

00:14:56.840 --> 00:14:57.604 You know,

NOTE Confidence: 0.885227824166667  
00:14:57.604 --> 00:15:00.278 and and in truth across human disease,  
NOTE Confidence: 0.885227824166667  
00:15:00.280 --> 00:15:02.320 with the exception of cancer,  
NOTE Confidence: 0.927506948  
00:15:02.320 --> 00:15:03.520 where patients are, you know,  
NOTE Confidence: 0.927506948  
00:15:03.520 --> 00:15:05.100 begging and paying their doctors  
NOTE Confidence: 0.927506948  
00:15:05.100 --> 00:15:07.232 to cut the material out, this is a,  
NOTE Confidence: 0.927506948  
00:15:07.232 --> 00:15:09.376 you know, a common phenomenon.  
NOTE Confidence: 0.927506948  
00:15:09.376 --> 00:15:12.336 There are mouse models of  
NOTE Confidence: 0.927506948  
00:15:12.336 --> 00:15:13.520 psychiatric disorders.  
NOTE Confidence: 0.927506948  
00:15:13.520 --> 00:15:16.142 But I like to joke that I was  
NOTE Confidence: 0.927506948  
00:15:16.142 --> 00:15:17.997 not trained as a neuroscientist.  
NOTE Confidence: 0.927506948  
00:15:18.000 --> 00:15:18.855 And Despite that,  
NOTE Confidence: 0.927506948  
00:15:18.855 --> 00:15:20.565 I can tell the difference between  
NOTE Confidence: 0.927506948  
00:15:20.565 --> 00:15:22.520 a mouse brain and a human brain,  
NOTE Confidence: 0.927506948  
00:15:22.520 --> 00:15:24.470 and I still can tell that  
NOTE Confidence: 0.927506948  
00:15:24.470 --> 00:15:26.399 difference when we control for size.  
NOTE Confidence: 0.927506948

00:15:26.400 --> 00:15:28.090 So there are some fundamental  
NOTE Confidence: 0.927506948

00:15:28.090 --> 00:15:29.442 differences here that might  
NOTE Confidence: 0.927506948

00:15:29.442 --> 00:15:31.278 not be captured in this model.  
NOTE Confidence: 0.927506948

00:15:31.280 --> 00:15:32.775 Now what are the differences  
NOTE Confidence: 0.927506948

00:15:32.775 --> 00:15:34.640 that I'm most worried about not  
NOTE Confidence: 0.927506948

00:15:34.640 --> 00:15:36.200 being captured in mouse models?  
NOTE Confidence: 0.927506948

00:15:36.200 --> 00:15:37.052 So again,  
NOTE Confidence: 0.927506948

00:15:37.052 --> 00:15:39.180 mouse models are fantastic at  
NOTE Confidence: 0.927506948

00:15:39.180 --> 00:15:41.280 revealing the interactions between genes,  
NOTE Confidence: 0.927506948

00:15:41.280 --> 00:15:42.309 circuits and behaviors.  
NOTE Confidence: 0.927506948

00:15:42.309 --> 00:15:44.710 But there's no such thing as a  
NOTE Confidence: 0.927506948

00:15:44.774 --> 00:15:47.392 perfect model and and so where  
NOTE Confidence: 0.927506948

00:15:47.392 --> 00:15:49.632 mouse models actually fall apart  
NOTE Confidence: 0.927506948

00:15:49.640 --> 00:15:51.230 is looking at non coding common  
NOTE Confidence: 0.927506948

00:15:51.230 --> 00:15:52.920 variants and these are the exact  
NOTE Confidence: 0.927506948

00:15:52.920 --> 00:15:54.943 variants I told you are the greatest

NOTE Confidence: 0.927506948

00:15:54.943 --> 00:15:55.872 contributor. Psychiatric risk.

NOTE Confidence: 0.927506948

00:15:55.872 --> 00:15:57.452 Now why'd the mouse models

NOTE Confidence: 0.927506948

00:15:57.452 --> 00:15:58.400 probably capture this?

NOTE Confidence: 0.927506948

00:15:58.400 --> 00:16:00.170 Well these are actually the variants

NOTE Confidence: 0.927506948

00:16:00.170 --> 00:16:01.695 that are not conserved between

NOTE Confidence: 0.927506948

00:16:01.695 --> 00:16:03.592 humans and mice and so it's very

NOTE Confidence: 0.927506948

00:16:03.592 --> 00:16:06.100 hard to look at the impact of a risk

NOTE Confidence: 0.927506948

00:16:06.100 --> 00:16:08.200 variant that doesn't even exist in mice.

NOTE Confidence: 0.927506948

00:16:08.200 --> 00:16:09.136 Second of all,

NOTE Confidence: 0.927506948

00:16:09.136 --> 00:16:11.872 mouse models are not great at looking at

NOTE Confidence: 0.927506948

00:16:11.872 --> 00:16:13.840 complex interactions between variants.

NOTE Confidence: 0.927506948

00:16:13.840 --> 00:16:14.608 I don't know many.

NOTE Confidence: 0.927506948

00:16:14.608 --> 00:16:16.105 How many of you had the pleasure

NOTE Confidence: 0.927506948

00:16:16.105 --> 00:16:17.555 of working with mouse models?

NOTE Confidence: 0.927506948

00:16:17.560 --> 00:16:19.132 But putting even 2 trans genes

NOTE Confidence: 0.927506948

00:16:19.132 --> 00:16:20.689 together always took me a lot  
NOTE Confidence: 0.927506948

00:16:20.689 --> 00:16:22.057 more than the 8 offspring it  
NOTE Confidence: 0.927506948

00:16:22.057 --> 00:16:23.440 was supposed to to get a match.  
NOTE Confidence: 0.927506948

00:16:23.440 --> 00:16:25.198 And we're talking about looking at  
NOTE Confidence: 0.927506948

00:16:25.198 --> 00:16:27.238 the interactions of dozens of risk variants.  
NOTE Confidence: 0.927506948

00:16:27.240 --> 00:16:29.270 And I don't think there's a grad  
NOTE Confidence: 0.927506948

00:16:29.270 --> 00:16:30.683 student out there willing to  
NOTE Confidence: 0.927506948

00:16:30.683 --> 00:16:33.005 look at crosses of 12 or 20 or 50  
NOTE Confidence: 0.927506948

00:16:33.005 --> 00:16:35.129 strains trying to get to complex  
NOTE Confidence: 0.927506948

00:16:35.129 --> 00:16:37.270 interactions so difficult to engineer  
NOTE Confidence: 0.927506948

00:16:37.270 --> 00:16:40.480 and even more difficult to breed.  
NOTE Confidence: 0.927506948

00:16:40.480 --> 00:16:42.588 And the final thing is, you know,  
NOTE Confidence: 0.927506948

00:16:42.588 --> 00:16:44.460 I don't know how we would ever look  
NOTE Confidence: 0.927506948

00:16:44.519 --> 00:16:46.234 at Priya Trophy in a mouse model.  
NOTE Confidence: 0.927506948

00:16:46.240 --> 00:16:47.815 What is the difference between  
NOTE Confidence: 0.927506948

00:16:47.815 --> 00:16:49.760 schizophrenia and autism in a mouse,

NOTE Confidence: 0.927506948

00:16:49.760 --> 00:16:50.274 right?

NOTE Confidence: 0.927506948

00:16:50.274 --> 00:16:53.358 What is the difference between moderate,

NOTE Confidence: 0.927506948

00:16:53.360 --> 00:16:56.076 severe and mild autism in a mouse?

NOTE Confidence: 0.927506948

00:16:56.080 --> 00:16:58.880 How do we really get AT variable

NOTE Confidence: 0.927506948

00:16:58.880 --> 00:17:01.278 penetrance and expressivity in rodent models?

NOTE Confidence: 0.927506948

00:17:01.280 --> 00:17:02.876 And so these are the types of

NOTE Confidence: 0.927506948

00:17:02.876 --> 00:17:04.341 questions that I most want to

NOTE Confidence: 0.927506948

00:17:04.341 --> 00:17:05.793 ask with our cell based models.

NOTE Confidence: 0.927506948

00:17:05.800 --> 00:17:08.065 What are the complex interactions

NOTE Confidence: 0.927506948

00:17:08.065 --> 00:17:10.330 between common variants to impact

NOTE Confidence: 0.927506948

00:17:10.399 --> 00:17:12.359 cellular phenotypes in vitro?

NOTE Confidence: 0.927506948

00:17:12.360 --> 00:17:14.446 And so when we talk about modeling

NOTE Confidence: 0.927506948

00:17:14.446 --> 00:17:16.268 brain disease and psychiatric disorders

NOTE Confidence: 0.927506948

00:17:16.268 --> 00:17:18.438 with stem cell derived neurons,

NOTE Confidence: 0.927506948

00:17:18.440 --> 00:17:19.808 what I'm really talking about is

NOTE Confidence: 0.927506948

00:17:19.808 --> 00:17:21.394 the fact that since 2006 with  
NOTE Confidence: 0.927506948

00:17:21.394 --> 00:17:23.079 the discovery by Shinya Yamanaka,  
NOTE Confidence: 0.927506948

00:17:23.080 --> 00:17:24.958 we could reprogram skin cells or  
NOTE Confidence: 0.927506948

00:17:24.958 --> 00:17:26.895 blood cells from anybody on the  
NOTE Confidence: 0.927506948

00:17:26.895 --> 00:17:29.072 planet and to induce pluripotent stem cells.  
NOTE Confidence: 0.927506948

00:17:29.080 --> 00:17:31.800 And these IPS cells as I'll call them,  
NOTE Confidence: 0.927506948

00:17:31.800 --> 00:17:33.354 have the capacity to make every  
NOTE Confidence: 0.927506948

00:17:33.354 --> 00:17:34.720 cell type in the body.  
NOTE Confidence: 0.927506948

00:17:34.720 --> 00:17:36.208 And then in 2011,  
NOTE Confidence: 0.927506948

00:17:36.208 --> 00:17:38.440 with the discovery of CRISPR engineering,  
NOTE Confidence: 0.927506948

00:17:38.440 --> 00:17:41.716 I can now at scale and relatively  
NOTE Confidence: 0.927506948

00:17:41.716 --> 00:17:44.563 easily introduce or remove genetic  
NOTE Confidence: 0.927506948

00:17:44.563 --> 00:17:46.398 variants linked to disease.  
NOTE Confidence: 0.927506948

00:17:46.398 --> 00:17:49.100 And so I can add risk variants  
NOTE Confidence: 0.913071744615385

00:17:49.180 --> 00:17:52.092 to control cells. I can take away  
NOTE Confidence: 0.913071744615385

00:17:52.092 --> 00:17:53.588 risk variants from patient cells,

NOTE Confidence: 0.913071744615385  
00:17:53.588 --> 00:17:55.517 and then I can make them into all  
NOTE Confidence: 0.913071744615385  
00:17:55.517 --> 00:17:57.113 the major cell types of the brain.  
NOTE Confidence: 0.913071744615385  
00:17:57.120 --> 00:18:00.172 And I can ask across people and  
NOTE Confidence: 0.913071744615385  
00:18:00.172 --> 00:18:01.480 across genetic manipulations,  
NOTE Confidence: 0.913071744615385  
00:18:01.480 --> 00:18:03.720 what is the impact?  
NOTE Confidence: 0.913071744615385  
00:18:03.720 --> 00:18:05.005 Now before I start telling  
NOTE Confidence: 0.913071744615385  
00:18:05.005 --> 00:18:06.033 you about these comparisons,  
NOTE Confidence: 0.913071744615385  
00:18:06.040 --> 00:18:07.654 I think it's important to pause  
NOTE Confidence: 0.913071744615385  
00:18:07.654 --> 00:18:09.714 and ask how good are the cells  
NOTE Confidence: 0.913071744615385  
00:18:09.714 --> 00:18:11.254 that we're making relative to  
NOTE Confidence: 0.913071744615385  
00:18:11.254 --> 00:18:12.998 those found in the human brain.  
NOTE Confidence: 0.913071744615385  
00:18:13.000 --> 00:18:14.368 So we've done this analysis over  
NOTE Confidence: 0.913071744615385  
00:18:14.368 --> 00:18:16.318 and over time and again and we keep  
NOTE Confidence: 0.913071744615385  
00:18:16.318 --> 00:18:17.558 getting about the same results.  
NOTE Confidence: 0.913071744615385  
00:18:17.560 --> 00:18:20.048 So this is a version of the analysis  
NOTE Confidence: 0.913071744615385

00:18:20.048 --> 00:18:22.106 that we did back in 2017 based  
NOTE Confidence: 0.913071744615385

00:18:22.106 --> 00:18:24.157 on all the available RNA seq that  
NOTE Confidence: 0.913071744615385

00:18:24.157 --> 00:18:26.222 we could find from the postmortem  
NOTE Confidence: 0.913071744615385

00:18:26.222 --> 00:18:28.440 brain and from stem cell models.  
NOTE Confidence: 0.913071744615385

00:18:28.440 --> 00:18:30.558 So I'm coloring here in blue  
NOTE Confidence: 0.913071744615385

00:18:30.560 --> 00:18:33.400 about 800 postmortem brain RNA  
NOTE Confidence: 0.913071744615385

00:18:33.400 --> 00:18:36.693 seek samples that came from Gtex,  
NOTE Confidence: 0.913071744615385

00:18:36.693 --> 00:18:38.958 from the Allen Brainspan Atlas,  
NOTE Confidence: 0.913071744615385

00:18:38.960 --> 00:18:40.760 and from the Common Mind Consortium.  
NOTE Confidence: 0.913071744615385

00:18:40.760 --> 00:18:42.278 They all tend to cluster together  
NOTE Confidence: 0.913071744615385

00:18:42.278 --> 00:18:43.580 in the same, you know,  
NOTE Confidence: 0.913071744615385

00:18:43.580 --> 00:18:45.986 left hand part of the plot you can see  
NOTE Confidence: 0.913071744615385

00:18:45.986 --> 00:18:48.240 over here in red these are blood cells.  
NOTE Confidence: 0.913071744615385

00:18:48.240 --> 00:18:50.000 Over here are skin cells.  
NOTE Confidence: 0.913071744615385

00:18:50.000 --> 00:18:51.650 Over here are those induced  
NOTE Confidence: 0.913071744615385

00:18:51.650 --> 00:18:52.640 pluripotent stem cells.

NOTE Confidence: 0.913071744615385  
00:18:52.640 --> 00:18:54.632 And then I took all the neural progenitor  
NOTE Confidence: 0.913071744615385  
00:18:54.632 --> 00:18:56.839 cells and neurons that my lab had ever made,  
NOTE Confidence: 0.913071744615385  
00:18:56.840 --> 00:18:58.838 as well as two other labs,  
NOTE Confidence: 0.913071744615385  
00:18:58.840 --> 00:19:01.318 Tracy Young Pierce's lab at Harvard and  
NOTE Confidence: 0.913071744615385  
00:19:01.318 --> 00:19:03.720 Hong Joon Song's lab at John Hopkins.  
NOTE Confidence: 0.913071744615385  
00:19:03.720 --> 00:19:05.428 And all of our stem cell derived  
NOTE Confidence: 0.913071744615385  
00:19:05.428 --> 00:19:07.159 neurons and NPCS clustered together.  
NOTE Confidence: 0.913071744615385  
00:19:07.160 --> 00:19:08.822 The NPCS are in green and  
NOTE Confidence: 0.913071744615385  
00:19:08.822 --> 00:19:10.440 the neurons are in orange.  
NOTE Confidence: 0.913071744615385  
00:19:10.440 --> 00:19:11.920 And what I think you can see is  
NOTE Confidence: 0.913071744615385  
00:19:11.920 --> 00:19:13.137 that these cells don't pile up  
NOTE Confidence: 0.913071744615385  
00:19:13.137 --> 00:19:14.640 right on top of the brain cells,  
NOTE Confidence: 0.913071744615385  
00:19:14.640 --> 00:19:15.688 but they do overlap.  
NOTE Confidence: 0.913071744615385  
00:19:15.688 --> 00:19:17.260 And the cells that are overlapping  
NOTE Confidence: 0.913071744615385  
00:19:17.316 --> 00:19:18.078 are our neurons.  
NOTE Confidence: 0.913071744615385

00:19:18.080 --> 00:19:20.432 And what they're overlapping with are the  
NOTE Confidence: 0.913071744615385

00:19:20.432 --> 00:19:22.598 fetal brain samples here in darker blue.  
NOTE Confidence: 0.913071744615385

00:19:22.600 --> 00:19:24.182 And So what we learn from these  
NOTE Confidence: 0.913071744615385

00:19:24.182 --> 00:19:26.108 analysis is that the cells that we make  
NOTE Confidence: 0.913071744615385

00:19:26.108 --> 00:19:27.640 from stem cells are actually fetal.  
NOTE Confidence: 0.913071744615385

00:19:27.640 --> 00:19:28.699 Like they're immature.  
NOTE Confidence: 0.913071744615385

00:19:28.699 --> 00:19:29.758 This makes sense.  
NOTE Confidence: 0.913071744615385

00:19:29.760 --> 00:19:31.176 We cultured them in the dish  
NOTE Confidence: 0.913071744615385

00:19:31.176 --> 00:19:32.120 for about 3 months,  
NOTE Confidence: 0.913071744615385

00:19:32.120 --> 00:19:34.717 and they look like late 1st trimester,  
NOTE Confidence: 0.913071744615385

00:19:34.720 --> 00:19:35.928 early 2nd trimester cells.  
NOTE Confidence: 0.913071744615385

00:19:35.928 --> 00:19:39.080 It's not that my lab is uniquely bad at this.  
NOTE Confidence: 0.913071744615385

00:19:39.080 --> 00:19:41.000 Every neural stem cell lab has done this.  
NOTE Confidence: 0.913071744615385

00:19:41.000 --> 00:19:42.995 The only way to make cells that  
NOTE Confidence: 0.913071744615385

00:19:42.995 --> 00:19:44.892 look like birth neurons is to  
NOTE Confidence: 0.913071744615385

00:19:44.892 --> 00:19:46.836 culture organoids for over a year.

NOTE Confidence: 0.913071744615385  
00:19:46.840 --> 00:19:48.140 It's not just the neurobiologists  
NOTE Confidence: 0.913071744615385  
00:19:48.140 --> 00:19:49.440 who are terrible at this.  
NOTE Confidence: 0.913071744615385  
00:19:49.440 --> 00:19:51.442 You see the same thing whether you're  
NOTE Confidence: 0.913071744615385  
00:19:51.442 --> 00:19:53.078 making vascular cells or heart cells.  
NOTE Confidence: 0.913071744615385  
00:19:53.080 --> 00:19:55.320 We reset age and we make stem cells,  
NOTE Confidence: 0.913071744615385  
00:19:55.320 --> 00:19:58.830 and age gets reset back at the same rate  
NOTE Confidence: 0.913071744615385  
00:19:58.830 --> 00:20:01.999 that we set it as developing humans.  
NOTE Confidence: 0.913071744615385  
00:20:02.000 --> 00:20:02.746 Turns out,  
NOTE Confidence: 0.913071744615385  
00:20:02.746 --> 00:20:04.800 Mother Nature's been making people for,  
NOTE Confidence: 0.913071744615385  
00:20:04.800 --> 00:20:05.360 you know,  
NOTE Confidence: 0.913071744615385  
00:20:05.360 --> 00:20:06.760 hundreds of thousands of years,  
NOTE Confidence: 0.913071744615385  
00:20:06.760 --> 00:20:09.316 and she does it as fast as she can  
NOTE Confidence: 0.913071744615385  
00:20:09.320 --> 00:20:11.560 and we're not any faster at it.  
NOTE Confidence: 0.913071744615385  
00:20:11.560 --> 00:20:13.272 And so I don't like to say we  
NOTE Confidence: 0.913071744615385  
00:20:13.272 --> 00:20:14.718 have disease in addition models.  
NOTE Confidence: 0.913071744615385

00:20:14.720 --> 00:20:16.768 I really prefer to say that we have  
NOTE Confidence: 0.913071744615385

00:20:16.768 --> 00:20:18.237 disease risk in a dish models.  
NOTE Confidence: 0.913071744615385

00:20:18.240 --> 00:20:20.520 We're modeling predisposition to disease,  
NOTE Confidence: 0.913071744615385

00:20:20.520 --> 00:20:21.524 not the disease state.  
NOTE Confidence: 0.913071744615385

00:20:21.524 --> 00:20:23.030 But I actually think that's a  
NOTE Confidence: 0.889826263181818

00:20:23.079 --> 00:20:25.242 really informative place to study and it's  
NOTE Confidence: 0.889826263181818

00:20:25.242 --> 00:20:27.280 really different from postmortem approaches.  
NOTE Confidence: 0.889826263181818

00:20:27.280 --> 00:20:29.240 So going back in time,  
NOTE Confidence: 0.889826263181818

00:20:29.240 --> 00:20:32.354 what can I tell you about stem cell neurons?  
NOTE Confidence: 0.889826263181818

00:20:32.360 --> 00:20:34.976 So here I'm showing you representative  
NOTE Confidence: 0.889826263181818

00:20:34.976 --> 00:20:36.720 images from stem cells,  
NOTE Confidence: 0.889826263181818

00:20:36.720 --> 00:20:38.061 neural progenitor cells,  
NOTE Confidence: 0.889826263181818

00:20:38.061 --> 00:20:40.296 and neurons derived from neurotypical  
NOTE Confidence: 0.889826263181818

00:20:40.296 --> 00:20:42.759 controls in cases with schizophrenia.  
NOTE Confidence: 0.889826263181818

00:20:42.760 --> 00:20:43.920 This is really old data,  
NOTE Confidence: 0.889826263181818

00:20:43.920 --> 00:20:45.800 but I like to show this to make one point,

NOTE Confidence: 0.889826263181818  
00:20:45.800 --> 00:20:48.117 which is at this level of magnification,  
NOTE Confidence: 0.889826263181818  
00:20:48.120 --> 00:20:49.832 you shouldn't be able to see any differences  
NOTE Confidence: 0.889826263181818  
00:20:49.832 --> 00:20:51.158 between neurons from cases and controls.  
NOTE Confidence: 0.889826263181818  
00:20:51.160 --> 00:20:51.812 I can't.  
NOTE Confidence: 0.889826263181818  
00:20:51.812 --> 00:20:53.116 And that's really important.  
NOTE Confidence: 0.889826263181818  
00:20:53.120 --> 00:20:54.878 Patients walk and talk and breathe,  
NOTE Confidence: 0.889826263181818  
00:20:54.880 --> 00:20:55.680 just like you and I.  
NOTE Confidence: 0.889826263181818  
00:20:55.680 --> 00:20:57.520 If I was up here telling you we  
NOTE Confidence: 0.889826263181818  
00:20:57.520 --> 00:20:59.159 couldn't make neurons from patients,  
NOTE Confidence: 0.889826263181818  
00:20:59.160 --> 00:21:00.808 that should be concerning.  
NOTE Confidence: 0.889826263181818  
00:21:00.808 --> 00:21:02.456 The differences that we  
NOTE Confidence: 0.889826263181818  
00:21:02.456 --> 00:21:04.639 see are incredibly subtle.  
NOTE Confidence: 0.889826263181818  
00:21:04.640 --> 00:21:06.656 One of the differences that the  
NOTE Confidence: 0.889826263181818  
00:21:06.656 --> 00:21:08.000 neurons had fewer branches.  
NOTE Confidence: 0.889826263181818  
00:21:08.000 --> 00:21:09.446 This should remind you of the  
NOTE Confidence: 0.889826263181818

00:21:09.446 --> 00:21:11.006 difference that I had previously told  
NOTE Confidence: 0.889826263181818

00:21:11.006 --> 00:21:12.917 you about from the post mortem work.  
NOTE Confidence: 0.889826263181818

00:21:12.920 --> 00:21:15.300 And the neurons have not just fewer  
NOTE Confidence: 0.889826263181818

00:21:15.300 --> 00:21:16.720 connections between each other,  
NOTE Confidence: 0.889826263181818

00:21:16.720 --> 00:21:18.068 but fewer functional connections  
NOTE Confidence: 0.889826263181818

00:21:18.068 --> 00:21:19.079 between each other,  
NOTE Confidence: 0.889826263181818

00:21:19.080 --> 00:21:21.080 so there's less synaptic activity.  
NOTE Confidence: 0.889826263181818

00:21:21.080 --> 00:21:23.576 And neurons derive from cases versus  
NOTE Confidence: 0.889826263181818

00:21:23.576 --> 00:21:25.240 neurons derive from controls.  
NOTE Confidence: 0.889826263181818

00:21:25.240 --> 00:21:27.994 So this is great, but we don't know why,  
NOTE Confidence: 0.889826263181818

00:21:28.000 --> 00:21:28.379 right?  
NOTE Confidence: 0.889826263181818

00:21:28.379 --> 00:21:30.653 So do the molecular causes underlying  
NOTE Confidence: 0.889826263181818

00:21:30.653 --> 00:21:32.962 these in vitro phenotypes represent  
NOTE Confidence: 0.889826263181818

00:21:32.962 --> 00:21:35.717 genetic risk factors for schizophrenia?  
NOTE Confidence: 0.889826263181818

00:21:35.720 --> 00:21:36.779 Or you know,  
NOTE Confidence: 0.889826263181818

00:21:36.779 --> 00:21:37.838 put another way,

NOTE Confidence: 0.889826263181818  
00:21:37.840 --> 00:21:40.312 can we decipher the genetic risk factors of  
NOTE Confidence: 0.889826263181818  
00:21:40.312 --> 00:21:42.117 schizophrenia using these stem cell models,  
NOTE Confidence: 0.889826263181818  
00:21:42.120 --> 00:21:42.426 right.  
NOTE Confidence: 0.889826263181818  
00:21:42.426 --> 00:21:43.956 Are these neurons acting differently  
NOTE Confidence: 0.889826263181818  
00:21:43.956 --> 00:21:46.291 in vitro for the very same reasons  
NOTE Confidence: 0.889826263181818  
00:21:46.291 --> 00:21:48.051 that patients with schizophrenia act  
NOTE Confidence: 0.889826263181818  
00:21:48.051 --> 00:21:49.811 differently in real life? Right.  
NOTE Confidence: 0.889826263181818  
00:21:49.811 --> 00:21:52.757 Does this model capture genetic risk?  
NOTE Confidence: 0.889826263181818  
00:21:52.760 --> 00:21:55.168 And so that's where you know our our  
NOTE Confidence: 0.889826263181818  
00:21:55.168 --> 00:21:57.276 lab pivoted about 10 years ago now.  
NOTE Confidence: 0.889826263181818  
00:21:57.280 --> 00:21:59.160 So this is work done by a former postdoc lab,  
NOTE Confidence: 0.889826263181818  
00:21:59.160 --> 00:22:01.491 Nadine Shroud where she worked with the  
NOTE Confidence: 0.889826263181818  
00:22:01.491 --> 00:22:03.977 the Gwas that existed in circa 2015,  
NOTE Confidence: 0.889826263181818  
00:22:03.977 --> 00:22:05.228 the PGC 2.  
NOTE Confidence: 0.889826263181818  
00:22:05.228 --> 00:22:07.611 There was about 145 genome wide  
NOTE Confidence: 0.889826263181818

00:22:07.611 --> 00:22:09.873 significant risk loci at this period  
NOTE Confidence: 0.889826263181818

00:22:09.880 --> 00:22:12.368 and she wanted to test one of these  
NOTE Confidence: 0.889826263181818

00:22:12.368 --> 00:22:14.330 common variants to see if we could  
NOTE Confidence: 0.889826263181818

00:22:14.330 --> 00:22:16.160 see a difference in the neurons.  
NOTE Confidence: 0.889826263181818

00:22:16.160 --> 00:22:17.124 Now at the time,  
NOTE Confidence: 0.889826263181818

00:22:17.124 --> 00:22:18.570 nobody had ever tried to manipulate  
NOTE Confidence: 0.889826263181818

00:22:18.619 --> 00:22:19.869 these common variants and I'll  
NOTE Confidence: 0.889826263181818

00:22:19.869 --> 00:22:21.434 remind you that each of them  
NOTE Confidence: 0.889826263181818

00:22:21.434 --> 00:22:23.046 confers like 1% increased risk.  
NOTE Confidence: 0.889826263181818

00:22:23.046 --> 00:22:26.120 So could we see an impact in vitro?  
NOTE Confidence: 0.889826263181818

00:22:26.120 --> 00:22:28.120 Everybody told us that we couldn't do it.  
NOTE Confidence: 0.889826263181818

00:22:28.120 --> 00:22:30.024 And so I'll forever call Nadine the  
NOTE Confidence: 0.889826263181818

00:22:30.024 --> 00:22:32.084 bravest postdoc in the lab because she  
NOTE Confidence: 0.889826263181818

00:22:32.084 --> 00:22:33.866 didn't care what everybody else thought  
NOTE Confidence: 0.889826263181818

00:22:33.924 --> 00:22:35.639 and she just went ahead and tried.  
NOTE Confidence: 0.889826263181818

00:22:35.640 --> 00:22:37.452 Now this going ahead and tried

NOTE Confidence: 0.889826263181818  
00:22:37.452 --> 00:22:39.120 it took her two years.  
NOTE Confidence: 0.889826263181818  
00:22:39.120 --> 00:22:39.528 And so,  
NOTE Confidence: 0.889826263181818  
00:22:39.528 --> 00:22:41.599 because we knew it was going to be so hard,  
NOTE Confidence: 0.889826263181818  
00:22:41.600 --> 00:22:43.780 we really want to pick the  
NOTE Confidence: 0.889826263181818  
00:22:43.780 --> 00:22:45.880 best variant in this plot.  
NOTE Confidence: 0.889826263181818  
00:22:45.880 --> 00:22:48.994 Now for those of you who are not geneticists,  
NOTE Confidence: 0.889826263181818  
00:22:49.000 --> 00:22:50.976 I was really tempted to go after this  
NOTE Confidence: 0.889826263181818  
00:22:50.976 --> 00:22:52.919 dot here just because it's so tall.  
NOTE Confidence: 0.889826263181818  
00:22:52.920 --> 00:22:54.873 And I was really fortunate to work  
NOTE Confidence: 0.889826263181818  
00:22:54.873 --> 00:22:56.037 with some brilliant geneticists  
NOTE Confidence: 0.889826263181818  
00:22:56.037 --> 00:22:58.229 who told me to stay clear of this  
NOTE Confidence: 0.889826263181818  
00:22:58.229 --> 00:23:00.155 because the tallest plot does not  
NOTE Confidence: 0.889826263181818  
00:23:00.155 --> 00:23:01.755 necessarily mean the best candidate.  
NOTE Confidence: 0.889826263181818  
00:23:01.760 --> 00:23:03.398 We were looking for the plot  
NOTE Confidence: 0.889826263181818  
00:23:03.398 --> 00:23:04.490 where we knew the  
NOTE Confidence: 0.911123221333333

00:23:04.557 --> 00:23:06.517 single snip was most significant.  
NOTE Confidence: 0.911123221333333

00:23:06.520 --> 00:23:08.312 So you're really looking for a plot  
NOTE Confidence: 0.911123221333333

00:23:08.312 --> 00:23:09.727 where you've got better separation  
NOTE Confidence: 0.911123221333333

00:23:09.727 --> 00:23:11.799 between the top snip and the others.  
NOTE Confidence: 0.911123221333333

00:23:11.800 --> 00:23:15.220 And So what we did is we asked 2  
NOTE Confidence: 0.911123221333333

00:23:15.220 --> 00:23:16.986 questions and we asked of all the  
NOTE Confidence: 0.911123221333333

00:23:16.986 --> 00:23:18.679 SNPs that were genome Y significant,  
NOTE Confidence: 0.911123221333333

00:23:18.680 --> 00:23:20.955 which ones were most likely to regulate  
NOTE Confidence: 0.911123221333333

00:23:20.955 --> 00:23:23.120 expression of a nearby target gene.  
NOTE Confidence: 0.911123221333333

00:23:23.120 --> 00:23:25.286 And so here we're intersecting that  
NOTE Confidence: 0.911123221333333

00:23:25.286 --> 00:23:27.619 G wash the genetic study from over  
NOTE Confidence: 0.911123221333333

00:23:27.619 --> 00:23:29.924 here on the Y axis with a brain  
NOTE Confidence: 0.911123221333333

00:23:29.924 --> 00:23:32.476 postmortem RNA C study on the X axis.  
NOTE Confidence: 0.911123221333333

00:23:32.480 --> 00:23:37.720 And of those 145 genome Y significant loci,  
NOTE Confidence: 0.911123221333333

00:23:37.720 --> 00:23:41.080 only one time did we see a plot this clean,  
NOTE Confidence: 0.911123221333333

00:23:41.080 --> 00:23:43.220 which is to say only one time was there a

NOTE Confidence: 0.911123221333333  
00:23:43.272 --> 00:23:45.360 single dot in the top right hand corner.  
NOTE Confidence: 0.911123221333333  
00:23:45.360 --> 00:23:47.728 So this single dot is a putative causal  
NOTE Confidence: 0.911123221333333  
00:23:47.728 --> 00:23:49.657 snip for schizophrenia because that  
NOTE Confidence: 0.911123221333333  
00:23:49.657 --> 00:23:52.632 single DNA variant is the most significant  
NOTE Confidence: 0.911123221333333  
00:23:52.700 --> 00:23:54.920 at that loci for schizophrenia risk.  
NOTE Confidence: 0.911123221333333  
00:23:54.920 --> 00:23:57.419 But it's also the most significant DNA  
NOTE Confidence: 0.911123221333333  
00:23:57.419 --> 00:23:59.574 variant for regulating expression of a  
NOTE Confidence: 0.911123221333333  
00:23:59.574 --> 00:24:02.040 nearby target gene, in this case fear.  
NOTE Confidence: 0.911123221333333  
00:24:02.040 --> 00:24:05.280 In the second best example.  
NOTE Confidence: 0.911123221333333  
00:24:05.280 --> 00:24:05.560 Oops.  
NOTE Confidence: 0.911123221333333  
00:24:05.560 --> 00:24:08.228 Oh, and the and the SNP is called RS47-O2.  
NOTE Confidence: 0.911123221333333  
00:24:08.228 --> 00:24:10.796 The second best example happened at  
NOTE Confidence: 0.911123221333333  
00:24:10.796 --> 00:24:12.759 this gene of SNAP 91.  
NOTE Confidence: 0.911123221333333  
00:24:12.760 --> 00:24:14.664 And what you can see here is that  
NOTE Confidence: 0.911123221333333  
00:24:14.664 --> 00:24:16.781 in this case we had about 20 or 30  
NOTE Confidence: 0.911123221333333

00:24:16.781 --> 00:24:18.798 snips in the top right hand corner,  
NOTE Confidence: 0.911123221333333

00:24:18.800 --> 00:24:20.272 all implicated in schizophrenia  
NOTE Confidence: 0.911123221333333

00:24:20.272 --> 00:24:22.112 and regulation of SNAP 91.  
NOTE Confidence: 0.911123221333333

00:24:22.120 --> 00:24:23.597 We don't know which one to edit.  
NOTE Confidence: 0.911123221333333

00:24:23.600 --> 00:24:25.968 Is there one causal SNIP in that cluster  
NOTE Confidence: 0.911123221333333

00:24:25.968 --> 00:24:28.838 or are all 20 or 30 of those causing risk?  
NOTE Confidence: 0.911123221333333

00:24:28.840 --> 00:24:30.982 And so we're going to use different  
NOTE Confidence: 0.911123221333333

00:24:30.982 --> 00:24:33.160 CRISPR edits for these two case examples,  
NOTE Confidence: 0.911123221333333

00:24:33.160 --> 00:24:34.648 our top two ones.  
NOTE Confidence: 0.911123221333333

00:24:34.648 --> 00:24:37.496 So coming back to the Spheron Rs 4/7/02,  
NOTE Confidence: 0.911123221333333

00:24:37.496 --> 00:24:39.344 it took Nadine about two years  
NOTE Confidence: 0.911123221333333

00:24:39.344 --> 00:24:40.920 to achieve a perfect edit.  
NOTE Confidence: 0.911123221333333

00:24:40.920 --> 00:24:42.579 But in a control donor line she  
NOTE Confidence: 0.911123221333333

00:24:42.579 --> 00:24:44.251 was able to take the non risk  
NOTE Confidence: 0.911123221333333

00:24:44.251 --> 00:24:46.160 variant A A and turn it into AGG.  
NOTE Confidence: 0.911123221333333

00:24:46.160 --> 00:24:48.482 And when she did so the first thing that

NOTE Confidence: 0.911123221333333  
00:24:48.482 --> 00:24:50.521 she saw was that fear and expression  
NOTE Confidence: 0.911123221333333  
00:24:50.521 --> 00:24:53.076 was in fact down in those GG risk cells,  
NOTE Confidence: 0.911123221333333  
00:24:53.080 --> 00:24:55.520 exactly like we had predicted.  
NOTE Confidence: 0.911123221333333  
00:24:55.520 --> 00:24:56.759 In the two years that it took  
NOTE Confidence: 0.911123221333333  
00:24:56.759 --> 00:24:57.560 her to the edit,  
NOTE Confidence: 0.911123221333333  
00:24:57.560 --> 00:24:59.037 it was learned that this SNP which  
NOTE Confidence: 0.911123221333333  
00:24:59.037 --> 00:25:00.762 is in the three prime UTR of the  
NOTE Confidence: 0.911123221333333  
00:25:00.762 --> 00:25:02.149 of the fear and gene regulating  
NOTE Confidence: 0.911123221333333  
00:25:02.149 --> 00:25:03.967 its RNA stability is actually in  
NOTE Confidence: 0.911123221333333  
00:25:03.967 --> 00:25:05.104 a microarny binding site,  
NOTE Confidence: 0.911123221333333  
00:25:05.104 --> 00:25:06.448 which is probably why this SNIP  
NOTE Confidence: 0.911123221333333  
00:25:06.448 --> 00:25:07.720 came out so significant.  
NOTE Confidence: 0.911123221333333  
00:25:07.720 --> 00:25:09.631 And if we inhibit that micro RNA  
NOTE Confidence: 0.911123221333333  
00:25:09.631 --> 00:25:11.039 we'd actually eliminate the effect.  
NOTE Confidence: 0.911123221333333  
00:25:11.040 --> 00:25:13.408 So now we have a context dependent risk  
NOTE Confidence: 0.911123221333333

00:25:13.408 --> 00:25:15.511 variant that only confers risk if this  
NOTE Confidence: 0.911123221333333

00:25:15.511 --> 00:25:17.880 micro RNA is expressed in that cell type.  
NOTE Confidence: 0.911123221333333

00:25:17.880 --> 00:25:19.658 The name was also able to show  
NOTE Confidence: 0.911123221333333

00:25:19.658 --> 00:25:21.384 that neurons with the GG genotype  
NOTE Confidence: 0.911123221333333

00:25:21.384 --> 00:25:22.894 have fewer branches than neurons  
NOTE Confidence: 0.911123221333333

00:25:22.894 --> 00:25:24.558 with the wild type genotype,  
NOTE Confidence: 0.911123221333333

00:25:24.560 --> 00:25:26.690 and that these neurons have reduced  
NOTE Confidence: 0.911123221333333

00:25:26.690 --> 00:25:28.110 activity relative to neurons  
NOTE Confidence: 0.911123221333333

00:25:28.166 --> 00:25:29.716 with the wild type genotype.  
NOTE Confidence: 0.911123221333333

00:25:29.720 --> 00:25:31.463 Until she's really been able to show  
NOTE Confidence: 0.911123221333333

00:25:31.463 --> 00:25:33.339 that we can see differences when  
NOTE Confidence: 0.911123221333333

00:25:33.339 --> 00:25:35.432 we have added just a single common  
NOTE Confidence: 0.911123221333333

00:25:35.432 --> 00:25:37.757 snip on a on a control background.  
NOTE Confidence: 0.911123221333333

00:25:37.760 --> 00:25:39.314 But I'll remind you this was the  
NOTE Confidence: 0.911123221333333

00:25:39.314 --> 00:25:39.758 best example,  
NOTE Confidence: 0.973799862

00:25:39.760 --> 00:25:41.968 and I don't know whether the second or

NOTE Confidence: 0.973799862

00:25:41.968 --> 00:25:44.200 third or 250th example would be this clear,

NOTE Confidence: 0.973799862

00:25:44.200 --> 00:25:45.928 but we have a tool where we can

NOTE Confidence: 0.973799862

00:25:45.928 --> 00:25:47.240 test these common variants.

NOTE Confidence: 0.973799862

00:25:47.240 --> 00:25:49.940 So we finished this work in 2019 and

NOTE Confidence: 0.973799862

00:25:49.940 --> 00:25:53.760 then something happened in 2020, right?

NOTE Confidence: 0.973799862

00:25:53.760 --> 00:25:55.542 We shut the lab down when

NOTE Confidence: 0.973799862

00:25:55.542 --> 00:25:56.433 the pandemic started,

NOTE Confidence: 0.973799862

00:25:56.440 --> 00:25:59.112 and we kept hearing reports on the news

NOTE Confidence: 0.973799862

00:25:59.112 --> 00:26:01.545 about how the major difference between

NOTE Confidence: 0.973799862

00:26:01.545 --> 00:26:04.522 the original SARS virus and Cyrus Kobe

NOTE Confidence: 0.973799862

00:26:04.522 --> 00:26:07.098 two was the introduction of a furin

NOTE Confidence: 0.973799862

00:26:07.098 --> 00:26:09.600 cleavage site in in Cyrus Kobe 2.

NOTE Confidence: 0.973799862

00:26:09.600 --> 00:26:10.044 And you know,

NOTE Confidence: 0.973799862

00:26:10.044 --> 00:26:11.320 we kind of laughed about it on Slack.

NOTE Confidence: 0.973799862

00:26:11.320 --> 00:26:13.084 Like, what are the odds our favorite

NOTE Confidence: 0.973799862

00:26:13.084 --> 00:26:14.512 schizophrenia gene is, like,  
NOTE Confidence: 0.973799862

00:26:14.512 --> 00:26:17.200 responsible for this pandemic?  
NOTE Confidence: 0.973799862

00:26:17.200 --> 00:26:18.863 And then we started thinking like, well,  
NOTE Confidence: 0.973799862

00:26:18.863 --> 00:26:21.544 we actually could test if furin was  
NOTE Confidence: 0.973799862

00:26:21.544 --> 00:26:24.092 important for this virus and if it was,  
NOTE Confidence: 0.973799862

00:26:24.092 --> 00:26:25.845 maybe that would be helpful, right?  
NOTE Confidence: 0.973799862

00:26:25.845 --> 00:26:27.300 Like, it's April,  
NOTE Confidence: 0.973799862

00:26:27.300 --> 00:26:28.755 May of 2020,  
NOTE Confidence: 0.973799862

00:26:28.760 --> 00:26:29.975 and what Christina really decided  
NOTE Confidence: 0.973799862

00:26:29.975 --> 00:26:32.198 was that she was sick of being in her  
NOTE Confidence: 0.973799862

00:26:32.198 --> 00:26:33.739 really small apartment in Manhattan and  
NOTE Confidence: 0.973799862

00:26:33.739 --> 00:26:36.000 that she wanted to come back to work.  
NOTE Confidence: 0.973799862

00:26:36.000 --> 00:26:37.820 And so because we had these tools  
NOTE Confidence: 0.973799862

00:26:37.820 --> 00:26:39.662 and because we actually had a  
NOTE Confidence: 0.973799862

00:26:39.662 --> 00:26:40.994 a really great collaborator,  
NOTE Confidence: 0.973799862

00:26:41.000 --> 00:26:41.904 we'd worked with already,

NOTE Confidence: 0.973799862  
00:26:41.904 --> 00:26:43.034 Ben Tanover at Mount Sinai,  
NOTE Confidence: 0.973799862  
00:26:43.040 --> 00:26:44.810 who was actually a virologist  
NOTE Confidence: 0.973799862  
00:26:44.810 --> 00:26:47.280 in putting SARS COV 2 on cells,  
NOTE Confidence: 0.973799862  
00:26:47.280 --> 00:26:49.422 we asked well,  
NOTE Confidence: 0.973799862  
00:26:49.422 --> 00:26:53.026 does Fiorin regulate expression of the  
NOTE Confidence: 0.973799862  
00:26:53.026 --> 00:26:55.637 receptor for SARS COV 2IN lung cells?  
NOTE Confidence: 0.973799862  
00:26:55.640 --> 00:26:58.232 And so remotely by zoom in  
NOTE Confidence: 0.973799862  
00:26:58.232 --> 00:27:00.320 collaboration with Daryl Cotton's lab,  
NOTE Confidence: 0.973799862  
00:27:00.320 --> 00:27:02.399 Christina learned how to make lung cells.  
NOTE Confidence: 0.973799862  
00:27:02.400 --> 00:27:04.728 She was able to show that these GG  
NOTE Confidence: 0.973799862  
00:27:04.728 --> 00:27:06.927 lung cells expressed less furin than  
NOTE Confidence: 0.973799862  
00:27:06.927 --> 00:27:09.548 their A A counterparts and that they  
NOTE Confidence: 0.973799862  
00:27:09.548 --> 00:27:10.972 were massively less susceptible  
NOTE Confidence: 0.973799862  
00:27:10.972 --> 00:27:13.184 to SARS COV TWO infection than  
NOTE Confidence: 0.973799862  
00:27:13.184 --> 00:27:14.240 their A A counterparts.  
NOTE Confidence: 0.973799862

00:27:14.240 --> 00:27:14.718 In fact,  
NOTE Confidence: 0.973799862

00:27:14.718 --> 00:27:17.066 so much so you can see it by imaging  
NOTE Confidence: 0.973799862

00:27:17.066 --> 00:27:19.244 that these GG lung cells are  
NOTE Confidence: 0.973799862

00:27:19.244 --> 00:27:21.240 less susceptible to SARS COV Two.  
NOTE Confidence: 0.973799862

00:27:21.240 --> 00:27:23.452 Now it turned out the biggest predictor  
NOTE Confidence: 0.973799862

00:27:23.452 --> 00:27:26.359 of who got severe COVID was not genotype,  
NOTE Confidence: 0.973799862

00:27:26.360 --> 00:27:27.400 it was antibody repertoire.  
NOTE Confidence: 0.973799862

00:27:27.400 --> 00:27:29.920 And so this was not a direction that we  
NOTE Confidence: 0.973799862

00:27:29.920 --> 00:27:32.034 actually continue to pursue in the lab,  
NOTE Confidence: 0.973799862

00:27:32.040 --> 00:27:34.407 but it was our first Test case of gene  
NOTE Confidence: 0.973799862

00:27:34.407 --> 00:27:36.569 by environment interaction, right?  
NOTE Confidence: 0.973799862

00:27:36.569 --> 00:27:38.303 There's nothing wrong with GG lung  
NOTE Confidence: 0.973799862

00:27:38.303 --> 00:27:40.400 cells until you throw a bunch of stars,  
NOTE Confidence: 0.973799862

00:27:40.400 --> 00:27:42.080 COVID 2 in the dish and then they all die,  
NOTE Confidence: 0.973799862

00:27:42.080 --> 00:27:42.337 right?  
NOTE Confidence: 0.973799862

00:27:42.337 --> 00:27:44.136 So you have a genotype and you

NOTE Confidence: 0.973799862

00:27:44.136 --> 00:27:45.771 have an environmental insult and

NOTE Confidence: 0.973799862

00:27:45.771 --> 00:27:47.895 together you see a phenotype that

NOTE Confidence: 0.973799862

00:27:47.895 --> 00:27:49.278 you didn't see alone.

NOTE Confidence: 0.973799862

00:27:49.280 --> 00:27:51.260 And that's really changed the direction

NOTE Confidence: 0.973799862

00:27:51.260 --> 00:27:53.558 of work in the lab ever since.

NOTE Confidence: 0.973799862

00:27:53.560 --> 00:27:54.845 The question that I'm really

NOTE Confidence: 0.973799862

00:27:54.845 --> 00:27:55.873 interested in asking is,

NOTE Confidence: 0.973799862

00:27:55.880 --> 00:27:58.720 can we modify the impact of genetic risk,

NOTE Confidence: 0.973799862

00:27:58.720 --> 00:27:59.115 right?

NOTE Confidence: 0.973799862

00:27:59.115 --> 00:28:01.880 Are we are genetic fate or are

NOTE Confidence: 0.973799862

00:28:01.880 --> 00:28:04.198 there pop multiple outcomes with

NOTE Confidence: 0.973799862

00:28:04.198 --> 00:28:07.551 the genetic risk we are born with?

NOTE Confidence: 0.973799862

00:28:07.560 --> 00:28:09.604 I think in college we were all

NOTE Confidence: 0.973799862

00:28:09.604 --> 00:28:10.480 taught about genotype,

NOTE Confidence: 0.973799862

00:28:10.480 --> 00:28:11.488 phenotype relationships,

NOTE Confidence: 0.973799862

00:28:11.488 --> 00:28:15.520 but these are not necessarily one to one.  
NOTE Confidence: 0.973799862

00:28:15.520 --> 00:28:17.000 I think it's really intuitive,  
NOTE Confidence: 0.973799862

00:28:17.000 --> 00:28:18.608 especially to you psychiatrists,  
NOTE Confidence: 0.973799862

00:28:18.608 --> 00:28:20.618 that there are environments that  
NOTE Confidence: 0.973799862

00:28:20.618 --> 00:28:22.359 can make phenotypes worse.  
NOTE Confidence: 0.973799862

00:28:22.360 --> 00:28:24.614 You can be born with really high  
NOTE Confidence: 0.973799862

00:28:24.614 --> 00:28:26.320 risk for opioid addiction,  
NOTE Confidence: 0.973799862

00:28:26.320 --> 00:28:30.120 but if you never get your hands on any drugs,  
NOTE Confidence: 0.895418828

00:28:30.120 --> 00:28:32.485 you won't have this phenotype, right?  
NOTE Confidence: 0.895418828

00:28:32.485 --> 00:28:34.420 Abusive childhoods make  
NOTE Confidence: 0.895418828

00:28:34.420 --> 00:28:37.000 psychiatric disorders more severe.  
NOTE Confidence: 0.895418828

00:28:37.000 --> 00:28:39.196 They can make them onset earlier.  
NOTE Confidence: 0.895418828

00:28:39.200 --> 00:28:41.920 Likewise, there are good  
NOTE Confidence: 0.895418828

00:28:41.920 --> 00:28:44.640 environments that can minimize  
NOTE Confidence: 0.895418828

00:28:44.640 --> 00:28:46.548 phenotypic outcomes of genetic risk.  
NOTE Confidence: 0.895418828

00:28:46.548 --> 00:28:49.127 And So what I really want to do

NOTE Confidence: 0.895418828

00:28:49.127 --> 00:28:51.149 is begin to understand what these

NOTE Confidence: 0.895418828

00:28:51.149 --> 00:28:53.163 environments are and if we can

NOTE Confidence: 0.895418828

00:28:53.163 --> 00:28:54.758 understand the mechanisms by which

NOTE Confidence: 0.895418828

00:28:54.758 --> 00:28:56.013 they protect against disease.

NOTE Confidence: 0.895418828

00:28:56.013 --> 00:28:58.604 And and so I'm going to use the

NOTE Confidence: 0.895418828

00:28:58.604 --> 00:29:00.016 word environment throughout the

NOTE Confidence: 0.895418828

00:29:00.016 --> 00:29:02.320 rest of the talk pretty loosely.

NOTE Confidence: 0.895418828

00:29:02.320 --> 00:29:04.270 I'm going to say that the

NOTE Confidence: 0.895418828

00:29:04.270 --> 00:29:05.570 environment includes the other

NOTE Confidence: 0.895418828

00:29:05.634 --> 00:29:07.319 DNA around a genetic variant.

NOTE Confidence: 0.895418828

00:29:07.320 --> 00:29:09.288 So what's the impact of other

NOTE Confidence: 0.895418828

00:29:09.288 --> 00:29:10.600 risk variants on resilience?

NOTE Confidence: 0.895418828

00:29:10.600 --> 00:29:11.572 Cell type, right?

NOTE Confidence: 0.895418828

00:29:11.572 --> 00:29:13.516 How do different variants have different

NOTE Confidence: 0.895418828

00:29:13.516 --> 00:29:15.120 effects and different cell types?

NOTE Confidence: 0.895418828

00:29:15.120 --> 00:29:16.233 And finally, context,  
NOTE Confidence: 0.895418828

00:29:16.233 --> 00:29:18.830 which might be putting drugs on a  
NOTE Confidence: 0.895418828

00:29:18.903 --> 00:29:21.199 cell or stress hormones on a cell.  
NOTE Confidence: 0.895418828

00:29:21.200 --> 00:29:22.212 And so with that,  
NOTE Confidence: 0.895418828

00:29:22.212 --> 00:29:24.297 I'm going to dive first into an example  
NOTE Confidence: 0.895418828

00:29:24.297 --> 00:29:26.321 of a rare variant where we think we  
NOTE Confidence: 0.895418828

00:29:26.382 --> 00:29:28.428 can modify genetic outcomes and then  
NOTE Confidence: 0.895418828

00:29:28.428 --> 00:29:30.796 into some common variants and how we  
NOTE Confidence: 0.895418828

00:29:30.796 --> 00:29:33.120 think we can modify genetic outcomes there.  
NOTE Confidence: 0.895418828

00:29:33.120 --> 00:29:34.944 So these are some of the rare variants  
NOTE Confidence: 0.895418828

00:29:34.944 --> 00:29:36.639 linked to schizophrenia and autism.  
NOTE Confidence: 0.895418828

00:29:36.640 --> 00:29:38.570 You'll know that there's actually  
NOTE Confidence: 0.895418828

00:29:38.570 --> 00:29:41.000 more rare variants linked to autism,  
NOTE Confidence: 0.895418828

00:29:41.000 --> 00:29:42.115 but there's one here that's  
NOTE Confidence: 0.895418828

00:29:42.115 --> 00:29:43.560 in common on both of these,  
NOTE Confidence: 0.895418828

00:29:43.560 --> 00:29:45.720 and that's a deletion that

NOTE Confidence: 0.895418828

00:29:45.720 --> 00:29:47.824 on chromosome 2 two P 13.3,

NOTE Confidence: 0.895418828

00:29:47.824 --> 00:29:49.484 and it encompasses a single

NOTE Confidence: 0.895418828

00:29:49.484 --> 00:29:50.480 gene nurexanal one.

NOTE Confidence: 0.895418828

00:29:50.480 --> 00:29:51.330 In fact,

NOTE Confidence: 0.895418828

00:29:51.330 --> 00:29:53.880 it's the only copy number variant

NOTE Confidence: 0.895418828

00:29:53.880 --> 00:29:55.610 for schizophrenia or autism that

NOTE Confidence: 0.895418828

00:29:55.610 --> 00:29:56.994 encompasses a single gene.

NOTE Confidence: 0.895418828

00:29:57.000 --> 00:29:58.440 But it's really interesting

NOTE Confidence: 0.895418828

00:29:58.440 --> 00:29:59.880 for a few reasons.

NOTE Confidence: 0.895418828

00:29:59.880 --> 00:30:00.861 A it's pleiotropic,

NOTE Confidence: 0.895418828

00:30:00.861 --> 00:30:03.150 so this deletion can confer risk not

NOTE Confidence: 0.895418828

00:30:03.212 --> 00:30:05.197 just for autism and schizophrenia,

NOTE Confidence: 0.895418828

00:30:05.200 --> 00:30:06.955 but also OCD,

NOTE Confidence: 0.895418828

00:30:06.955 --> 00:30:09.880 epilepsy and several other diagnosis.

NOTE Confidence: 0.895418828

00:30:09.880 --> 00:30:13.520 2 is variably penetrant so some people

NOTE Confidence: 0.895418828

00:30:13.520 --> 00:30:17.405 have minimal impact and and some you know

NOTE Confidence: 0.895418828

00:30:17.405 --> 00:30:21.320 are are are nonverbal and have psychosis.

NOTE Confidence: 0.895418828

00:30:21.320 --> 00:30:23.959 2 nerexin one is the most highly

NOTE Confidence: 0.895418828

00:30:23.959 --> 00:30:25.480 alternatively spliced gene in

NOTE Confidence: 0.895418828

00:30:25.480 --> 00:30:26.440 the human genome.

NOTE Confidence: 0.895418828

00:30:26.440 --> 00:30:27.240 There are,

NOTE Confidence: 0.895418828

00:30:27.240 --> 00:30:28.440 from mouse studies,

NOTE Confidence: 0.895418828

00:30:28.440 --> 00:30:30.410 hundreds of distinct nerexin 1

NOTE Confidence: 0.895418828

00:30:30.410 --> 00:30:32.380 isoforms and nerexin one's a

NOTE Confidence: 0.895418828

00:30:32.449 --> 00:30:34.318 critical synaptic organizer,

NOTE Confidence: 0.895418828

00:30:34.320 --> 00:30:36.075 with the hypothesis being that

NOTE Confidence: 0.895418828

00:30:36.075 --> 00:30:38.237 each nerexin isoform will have a

NOTE Confidence: 0.895418828

00:30:38.237 --> 00:30:39.617 different post synaptic binding

NOTE Confidence: 0.895418828

00:30:39.617 --> 00:30:41.342 partner and might confer a

NOTE Confidence: 0.895418828

00:30:41.406 --> 00:30:43.476 different type of synaptic function.

NOTE Confidence: 0.895418828

00:30:43.480 --> 00:30:44.985 This is evidence from mouse

NOTE Confidence: 0.895418828

00:30:44.985 --> 00:30:46.926 showing us that we see hundreds

NOTE Confidence: 0.895418828

00:30:46.926 --> 00:30:49.134 of Nurexa 1 splice isoforms with

NOTE Confidence: 0.895418828

00:30:49.134 --> 00:30:51.000 more splice isoform complexity in

NOTE Confidence: 0.895418828

00:30:51.000 --> 00:30:53.100 brain regions like the cortex that

NOTE Confidence: 0.895418828

00:30:53.100 --> 00:30:56.160 have more cellular complexity.

NOTE Confidence: 0.895418828

00:30:56.160 --> 00:30:56.541 Likewise,

NOTE Confidence: 0.895418828

00:30:56.541 --> 00:30:58.827 nurexa 1 isoforms are sufficient to

NOTE Confidence: 0.895418828

00:30:58.827 --> 00:31:01.240 distinguish types of neurons in the brain.

NOTE Confidence: 0.895418828

00:31:01.240 --> 00:31:02.588 Again, this is mouse.

NOTE Confidence: 0.895418828

00:31:02.588 --> 00:31:05.437 So when we started this project back in 2015,

NOTE Confidence: 0.895418828

00:31:05.437 --> 00:31:07.022 we knew there were hundreds

NOTE Confidence: 0.895418828

00:31:07.022 --> 00:31:08.640 of splice isoforms in mice,

NOTE Confidence: 0.895418828

00:31:08.640 --> 00:31:10.565 but we didn't know if this was

NOTE Confidence: 0.895418828

00:31:10.565 --> 00:31:11.840 also true in human.

NOTE Confidence: 0.895418828

00:31:11.840 --> 00:31:13.184 And so this was work led by a

NOTE Confidence: 0.895418828

00:31:13.184 --> 00:31:14.358 former PhD student in the lab,  
NOTE Confidence: 0.895418828

00:31:14.360 --> 00:31:15.096 Aaron Flaherty,  
NOTE Confidence: 0.895418828

00:31:15.096 --> 00:31:16.568 in really close collaboration  
NOTE Confidence: 0.895418828

00:31:16.568 --> 00:31:18.360 with my collaborator Gong Fang,  
NOTE Confidence: 0.895418828

00:31:18.360 --> 00:31:20.277 and a postdoc, a former postdoc in his team,  
NOTE Confidence: 0.895418828

00:31:20.280 --> 00:31:20.884 Shu Zhu.  
NOTE Confidence: 0.895418828

00:31:20.884 --> 00:31:22.394 So our first question was,  
NOTE Confidence: 0.895418828

00:31:22.400 --> 00:31:24.470 is Narexin one highly determinedly  
NOTE Confidence: 0.895418828

00:31:24.470 --> 00:31:27.160 spliced in the human brain as well?  
NOTE Confidence: 0.895418828

00:31:27.160 --> 00:31:28.051 And so here,  
NOTE Confidence: 0.895418828

00:31:28.051 --> 00:31:29.833 and this was the best way  
NOTE Confidence: 0.895418828

00:31:29.840 --> 00:31:30.885 anybody actually in the field  
NOTE Confidence: 0.895418828

00:31:30.885 --> 00:31:31.930 is able to figure out  
NOTE Confidence: 0.783742715294118

00:31:31.971 --> 00:31:33.196 how to show this type of data.  
NOTE Confidence: 0.783742715294118

00:31:33.200 --> 00:31:35.396 So this is the Narexin 1 locus at the  
NOTE Confidence: 0.783742715294118

00:31:35.396 --> 00:31:37.720 top each Exon dot vertical Barb.

NOTE Confidence: 0.783742715294118  
00:31:37.720 --> 00:31:39.260 And what we're showing you here in  
NOTE Confidence: 0.783742715294118  
00:31:39.260 --> 00:31:41.139 the very top row is the most abundant  
NOTE Confidence: 0.783742715294118  
00:31:41.139 --> 00:31:42.640 Neurexa 1 isoform that we found.  
NOTE Confidence: 0.783742715294118  
00:31:42.640 --> 00:31:44.080 At the bottom, the least abundant.  
NOTE Confidence: 0.783742715294118  
00:31:44.080 --> 00:31:45.980 This is long range sequencing, so we're  
NOTE Confidence: 0.783742715294118  
00:31:45.980 --> 00:31:47.600 reading each isoform start to finish.  
NOTE Confidence: 0.783742715294118  
00:31:47.600 --> 00:31:49.640 If an exon's included, it's colored,  
NOTE Confidence: 0.783742715294118  
00:31:49.640 --> 00:31:50.720 if it's skipped, it's white.  
NOTE Confidence: 0.783742715294118  
00:31:50.720 --> 00:31:52.478 So in this most abundant isoform,  
NOTE Confidence: 0.783742715294118  
00:31:52.480 --> 00:31:53.998 exons one and two are included,  
NOTE Confidence: 0.783742715294118  
00:31:54.000 --> 00:31:55.324 exons 3 is skipped,  
NOTE Confidence: 0.783742715294118  
00:31:55.324 --> 00:31:57.799 4-5 and six are included and so on.  
NOTE Confidence: 0.783742715294118  
00:31:57.800 --> 00:32:00.650 Now we've colored them either orange  
NOTE Confidence: 0.783742715294118  
00:32:00.650 --> 00:32:02.955 or green and that's based on whether  
NOTE Confidence: 0.783742715294118  
00:32:02.955 --> 00:32:05.004 the samples came from a human brain  
NOTE Confidence: 0.783742715294118

00:32:05.004 --> 00:32:06.918 tissue or stem cell derived neurons.  
NOTE Confidence: 0.783742715294118

00:32:06.920 --> 00:32:08.915 If an isoform was detected in both  
NOTE Confidence: 0.783742715294118

00:32:08.915 --> 00:32:10.798 the human brain and stem cell Dr.  
NOTE Confidence: 0.783742715294118

00:32:10.800 --> 00:32:11.001 neurons,  
NOTE Confidence: 0.783742715294118

00:32:11.001 --> 00:32:12.810 so we colored it orange and if it was  
NOTE Confidence: 0.783742715294118

00:32:12.857 --> 00:32:14.519 only detected in the postmortem brain,  
NOTE Confidence: 0.783742715294118

00:32:14.520 --> 00:32:15.624 we colored it green.  
NOTE Confidence: 0.783742715294118

00:32:15.624 --> 00:32:17.840 And what I think you can see here  
NOTE Confidence: 0.783742715294118

00:32:17.840 --> 00:32:19.796 is that the most abundant isoforms  
NOTE Confidence: 0.783742715294118

00:32:19.796 --> 00:32:21.440 were actually shared in both.  
NOTE Confidence: 0.783742715294118

00:32:21.440 --> 00:32:23.040 And so we think that we not only  
NOTE Confidence: 0.783742715294118

00:32:23.040 --> 00:32:25.032 but we know that we can see hundreds  
NOTE Confidence: 0.783742715294118

00:32:25.032 --> 00:32:26.660 of splice isoforms in the human  
NOTE Confidence: 0.783742715294118

00:32:26.660 --> 00:32:28.292 brain and that to the sequencing  
NOTE Confidence: 0.783742715294118

00:32:28.292 --> 00:32:29.494 depth that I could afford,  
NOTE Confidence: 0.783742715294118

00:32:29.494 --> 00:32:31.020 that was also true in stem cell

NOTE Confidence: 0.783742715294118  
00:32:31.074 --> 00:32:32.802 derived neurons that the most abundant  
NOTE Confidence: 0.783742715294118  
00:32:32.802 --> 00:32:34.240 isoforms are present in both.  
NOTE Confidence: 0.783742715294118  
00:32:34.240 --> 00:32:36.080 And so we thought we could model the  
NOTE Confidence: 0.783742715294118  
00:32:36.080 --> 00:32:37.838 impact of deletions in nerexin one,  
NOTE Confidence: 0.783742715294118  
00:32:37.840 --> 00:32:40.312 asking how it might change the  
NOTE Confidence: 0.783742715294118  
00:32:40.312 --> 00:32:41.960 nerexin 1 isoform repertoire.  
NOTE Confidence: 0.783742715294118  
00:32:41.960 --> 00:32:43.496 The last really critical thing that  
NOTE Confidence: 0.783742715294118  
00:32:43.496 --> 00:32:45.759 you need to know is that these nerexin  
NOTE Confidence: 0.783742715294118  
00:32:45.759 --> 00:32:47.239 1 phenotypes are human specific,  
NOTE Confidence: 0.783742715294118  
00:32:47.240 --> 00:32:49.478 so the people who carry them  
NOTE Confidence: 0.783742715294118  
00:32:49.478 --> 00:32:50.597 are heterozygous deletions,  
NOTE Confidence: 0.783742715294118  
00:32:50.600 --> 00:32:52.575 but there's actually no phenotype  
NOTE Confidence: 0.783742715294118  
00:32:52.575 --> 00:32:53.760 in heterozygous mice.  
NOTE Confidence: 0.783742715294118  
00:32:53.760 --> 00:32:55.181 You have to have a full knockout  
NOTE Confidence: 0.783742715294118  
00:32:55.181 --> 00:32:56.917 of nerexin one to see behavioral  
NOTE Confidence: 0.783742715294118

00:32:56.917 --> 00:32:57.997 or electrophysiological effects.  
NOTE Confidence: 0.783742715294118

00:32:58.000 --> 00:32:59.704 This was a really clever experiment  
NOTE Confidence: 0.783742715294118

00:32:59.704 --> 00:33:01.912 done by Thomas Sudoff a few years ago  
NOTE Confidence: 0.783742715294118

00:33:01.912 --> 00:33:03.880 where he took skin cells from mice,  
NOTE Confidence: 0.783742715294118

00:33:03.880 --> 00:33:05.480 reprogrammed those to stem cells,  
NOTE Confidence: 0.783742715294118

00:33:05.480 --> 00:33:06.788 made those into neurons,  
NOTE Confidence: 0.783742715294118

00:33:06.788 --> 00:33:08.423 and they did electrophysiology and  
NOTE Confidence: 0.783742715294118

00:33:08.423 --> 00:33:10.352 showed that there was no effect of  
NOTE Confidence: 0.783742715294118

00:33:10.352 --> 00:33:11.880 a heterozygous *nerxin 1* deletion.  
NOTE Confidence: 0.783742715294118

00:33:11.880 --> 00:33:14.680 But when he introduced the exact same  
NOTE Confidence: 0.783742715294118

00:33:14.680 --> 00:33:16.678 mutation into humans stem cells and  
NOTE Confidence: 0.783742715294118

00:33:16.678 --> 00:33:18.800 made them into neurons the exact same way,  
NOTE Confidence: 0.783742715294118

00:33:18.800 --> 00:33:20.088 there was a phenotype.  
NOTE Confidence: 0.783742715294118

00:33:20.088 --> 00:33:22.444 And so these are complex spliced genes  
NOTE Confidence: 0.783742715294118

00:33:22.444 --> 00:33:24.957 that only show phenotypes in human neurons,  
NOTE Confidence: 0.783742715294118

00:33:24.960 --> 00:33:25.700 not mice.

NOTE Confidence: 0.783742715294118

00:33:25.700 --> 00:33:27.920 And we have no idea why.

NOTE Confidence: 0.783742715294118

00:33:27.920 --> 00:33:29.726 But it's a really good example of

NOTE Confidence: 0.783742715294118

00:33:29.726 --> 00:33:32.148 a gene that has to be studied in a

NOTE Confidence: 0.783742715294118

00:33:32.148 --> 00:33:34.320 human context. So here's our human context.

NOTE Confidence: 0.783742715294118

00:33:34.320 --> 00:33:35.856 These are rare carriers and in

NOTE Confidence: 0.783742715294118

00:33:35.856 --> 00:33:36.880 collaboration with 2D rapport,

NOTE Confidence: 0.783742715294118

00:33:36.880 --> 00:33:39.869 we actually got skin samples from 4

NOTE Confidence: 0.783742715294118

00:33:39.869 --> 00:33:41.960 nerexin 1 heterozygous deletions.

NOTE Confidence: 0.783742715294118

00:33:41.960 --> 00:33:43.213 The last thing you have to know

NOTE Confidence: 0.783742715294118

00:33:43.213 --> 00:33:44.535 about nerexin 1 deletions in people

NOTE Confidence: 0.783742715294118

00:33:44.535 --> 00:33:45.519 is they're non recurrent.

NOTE Confidence: 0.783742715294118

00:33:45.520 --> 00:33:47.080 They incur in different parts of

NOTE Confidence: 0.783742715294118

00:33:47.080 --> 00:33:48.640 the gene in every instance.

NOTE Confidence: 0.783742715294118

00:33:48.640 --> 00:33:51.342 There's no hotspot and so we have

NOTE Confidence: 0.783742715294118

00:33:51.342 --> 00:33:53.400 a 5 prime deletion.

NOTE Confidence: 0.783742715294118

00:33:53.400 --> 00:33:56.190 This is a mom and her son who share a  
NOTE Confidence: 0.783742715294118

00:33:56.267 --> 00:33:59.355 deletion in the promoter and 1st 2 exons,  
NOTE Confidence: 0.783742715294118

00:33:59.360 --> 00:34:01.796 both of them are diagnosed with psychosis.  
NOTE Confidence: 0.798684798888889

00:34:01.800 --> 00:34:03.980 And this is a pair of models that got like  
NOTE Confidence: 0.798684798888889

00:34:04.032 --> 00:34:06.160 twins who share a deletion in the second,  
NOTE Confidence: 0.798684798888889

00:34:06.160 --> 00:34:09.193 third and 4th from last exon of this gene.  
NOTE Confidence: 0.798684798888889

00:34:09.200 --> 00:34:11.896 And so we've got stem cells from these  
NOTE Confidence: 0.798684798888889

00:34:11.896 --> 00:34:14.320 four carriers and from 4 match controls.  
NOTE Confidence: 0.798684798888889

00:34:14.320 --> 00:34:16.093 The first thing that I can show you is  
NOTE Confidence: 0.798684798888889

00:34:16.093 --> 00:34:17.799 that from both the five prime patients  
NOTE Confidence: 0.798684798888889

00:34:17.799 --> 00:34:19.866 who I'm coloring in blue and the three  
NOTE Confidence: 0.798684798888889

00:34:19.866 --> 00:34:21.432 prime patients colored colored in red,  
NOTE Confidence: 0.798684798888889

00:34:21.440 --> 00:34:23.798 but we see reduced neural branching.  
NOTE Confidence: 0.798684798888889

00:34:23.800 --> 00:34:25.438 We also see reduced neural activity,  
NOTE Confidence: 0.798684798888889

00:34:25.440 --> 00:34:26.580 again consistent with some  
NOTE Confidence: 0.798684798888889

00:34:26.580 --> 00:34:27.720 of the earlier studies.

NOTE Confidence: 0.798684798888889  
00:34:27.720 --> 00:34:28.560 But the question is why?  
NOTE Confidence: 0.798684798888889  
00:34:28.560 --> 00:34:30.480 What's the mechanism for this?  
NOTE Confidence: 0.798684798888889  
00:34:30.480 --> 00:34:32.958 To what extent do these phenotypes  
NOTE Confidence: 0.798684798888889  
00:34:32.958 --> 00:34:35.416 reflect perturbations in few or many  
NOTE Confidence: 0.798684798888889  
00:34:35.416 --> 00:34:36.517 Neurexin 1 isoforms?  
NOTE Confidence: 0.798684798888889  
00:34:36.520 --> 00:34:37.504 Put another way,  
NOTE Confidence: 0.798684798888889  
00:34:37.504 --> 00:34:39.800 are these neurons from the cases firing  
NOTE Confidence: 0.798684798888889  
00:34:39.865 --> 00:34:41.770 less because one really critical  
NOTE Confidence: 0.798684798888889  
00:34:41.770 --> 00:34:43.675 neurxin 1 isoform has decreased?  
NOTE Confidence: 0.798684798888889  
00:34:43.680 --> 00:34:45.264 And the heterozygous deletions,  
NOTE Confidence: 0.798684798888889  
00:34:45.264 --> 00:34:48.089 are they firing less because all 100  
NOTE Confidence: 0.798684798888889  
00:34:48.089 --> 00:34:49.999 nerexin 1 isoforms are decreased?  
NOTE Confidence: 0.798684798888889  
00:34:50.000 --> 00:34:52.256 Or are they firing less for  
NOTE Confidence: 0.798684798888889  
00:34:52.256 --> 00:34:53.760 some other reason altogether?  
NOTE Confidence: 0.798684798888889  
00:34:53.760 --> 00:34:56.016 And so we went back and we did  
NOTE Confidence: 0.798684798888889

00:34:56.016 --> 00:34:58.100 sequencing of the nerexin 1 isoforms

NOTE Confidence: 0.798684798888889

00:34:58.100 --> 00:34:59.915 from the cases and controls.

NOTE Confidence: 0.798684798888889

00:34:59.920 --> 00:35:01.460 The first thing that I want to

NOTE Confidence: 0.798684798888889

00:35:01.460 --> 00:35:03.289 show you is that about half of

NOTE Confidence: 0.798684798888889

00:35:03.289 --> 00:35:04.957 the isoforms were decreased in the

NOTE Confidence: 0.798684798888889

00:35:05.012 --> 00:35:06.637 cases relative to the controls.

NOTE Confidence: 0.798684798888889

00:35:06.640 --> 00:35:08.280 Another third weren't even detected,

NOTE Confidence: 0.798684798888889

00:35:08.280 --> 00:35:09.450 which again I think is a

NOTE Confidence: 0.798684798888889

00:35:09.450 --> 00:35:10.035 sequencing depth thing.

NOTE Confidence: 0.798684798888889

00:35:10.040 --> 00:35:11.645 So we've got massive dysregulation

NOTE Confidence: 0.798684798888889

00:35:11.645 --> 00:35:14.057 of all of the wild type Neurexin

NOTE Confidence: 0.798684798888889

00:35:14.057 --> 00:35:15.917 1 isoforms in these patients.

NOTE Confidence: 0.798684798888889

00:35:15.920 --> 00:35:17.884 But then something unexpected

NOTE Confidence: 0.798684798888889

00:35:17.884 --> 00:35:19.357 occurred as well.

NOTE Confidence: 0.798684798888889

00:35:19.360 --> 00:35:22.618 We've got 31 unique mutant isoforms

NOTE Confidence: 0.798684798888889

00:35:22.618 --> 00:35:25.461 caused by splicing around this

NOTE Confidence: 0.798684798888889  
00:35:25.461 --> 00:35:27.720 deletion that we never saw in  
NOTE Confidence: 0.798684798888889  
00:35:27.720 --> 00:35:29.400 control neurons or in neurons  
NOTE Confidence: 0.798684798888889  
00:35:29.474 --> 00:35:31.359 from or in postmortem brain.  
NOTE Confidence: 0.798684798888889  
00:35:31.360 --> 00:35:32.552 And so you know,  
NOTE Confidence: 0.798684798888889  
00:35:32.552 --> 00:35:34.797 now the question is are the phenotypes  
NOTE Confidence: 0.798684798888889  
00:35:34.797 --> 00:35:37.408 from loss of these like 75 plus  
NOTE Confidence: 0.798684798888889  
00:35:37.408 --> 00:35:39.472 isoforms or the phenotypes from one  
NOTE Confidence: 0.798684798888889  
00:35:39.472 --> 00:35:41.920 or more of these mutant isoforms.  
NOTE Confidence: 0.798684798888889  
00:35:41.920 --> 00:35:43.720 And so we began to do exactly that.  
NOTE Confidence: 0.798684798888889  
00:35:43.720 --> 00:35:44.953 We tested this,  
NOTE Confidence: 0.798684798888889  
00:35:44.953 --> 00:35:47.830 we could take control neurons which are  
NOTE Confidence: 0.798684798888889  
00:35:47.908 --> 00:35:50.662 here in in oh in Gray and we can over  
NOTE Confidence: 0.798684798888889  
00:35:50.662 --> 00:35:52.271 express 4 different mutant isoforms  
NOTE Confidence: 0.798684798888889  
00:35:52.271 --> 00:35:54.805 and all of them were sufficient to  
NOTE Confidence: 0.798684798888889  
00:35:54.805 --> 00:35:56.720 decrease activity in control neurons.  
NOTE Confidence: 0.798684798888889

00:35:56.720 --> 00:35:58.960 So control neurons can be  
NOTE Confidence: 0.798684798888889

00:35:58.960 --> 00:36:00.752 impaired by mutant isoforms.  
NOTE Confidence: 0.798684798888889

00:36:00.760 --> 00:36:02.160 In these five prime cases,  
NOTE Confidence: 0.798684798888889

00:36:02.160 --> 00:36:04.956 the ones that don't have mutinisoforms,  
NOTE Confidence: 0.798684798888889

00:36:04.960 --> 00:36:07.529 we can make them better by over  
NOTE Confidence: 0.798684798888889

00:36:07.529 --> 00:36:10.000 expressing just one wild type isoform.  
NOTE Confidence: 0.798684798888889

00:36:10.000 --> 00:36:11.920 But in these three prime cases,  
NOTE Confidence: 0.798684798888889

00:36:11.920 --> 00:36:13.468 the ones expressing mutinisoforms,  
NOTE Confidence: 0.798684798888889

00:36:13.468 --> 00:36:16.196 we cannot make them better by over  
NOTE Confidence: 0.798684798888889

00:36:16.196 --> 00:36:17.572 expressing wild type isoforms  
NOTE Confidence: 0.798684798888889

00:36:17.572 --> 00:36:20.147 and we can't make them any worse  
NOTE Confidence: 0.798684798888889

00:36:20.147 --> 00:36:21.719 by adding more mutinisoforms.  
NOTE Confidence: 0.798684798888889

00:36:21.720 --> 00:36:23.220 So we actually think there's  
NOTE Confidence: 0.798684798888889

00:36:23.220 --> 00:36:24.720 two things going on here.  
NOTE Confidence: 0.798684798888889

00:36:24.720 --> 00:36:25.956 In all cases,  
NOTE Confidence: 0.798684798888889

00:36:25.956 --> 00:36:29.320 phenotypes reflect a loss of nerexin 1 dose,

NOTE Confidence: 0.798684798888889  
00:36:29.320 --> 00:36:30.916 but in a subset of cases,  
NOTE Confidence: 0.798684798888889  
00:36:30.920 --> 00:36:32.760 there's an additive effect caused  
NOTE Confidence: 0.798684798888889  
00:36:32.760 --> 00:36:34.600 by a mutant isoform activity.  
NOTE Confidence: 0.798684798888889  
00:36:34.600 --> 00:36:35.720 Now how big a subset?  
NOTE Confidence: 0.798684798888889  
00:36:35.720 --> 00:36:36.141 Right,  
NOTE Confidence: 0.798684798888889  
00:36:36.141 --> 00:36:39.509 We were able to get 4 samples and  
NOTE Confidence: 0.798684798888889  
00:36:39.509 --> 00:36:41.484 half of them had mutant isoforms.  
NOTE Confidence: 0.798684798888889  
00:36:41.484 --> 00:36:43.360 That doesn't mean half of all cases.  
NOTE Confidence: 0.798684798888889  
00:36:43.360 --> 00:36:45.040 And so we went back into the genic  
NOTE Confidence: 0.798684798888889  
00:36:45.040 --> 00:36:46.536 data sets to ask how often do  
NOTE Confidence: 0.798684798888889  
00:36:46.536 --> 00:36:47.940 we think there might be patients  
NOTE Confidence: 0.798684798888889  
00:36:47.940 --> 00:36:49.240 who have mutant isoforms?  
NOTE Confidence: 0.9258216375  
00:36:49.240 --> 00:36:51.544 And we think our best guess is about  
NOTE Confidence: 0.9258216375  
00:36:51.544 --> 00:36:54.356 one in five that 20% of Narexan 1  
NOTE Confidence: 0.9258216375  
00:36:54.356 --> 00:36:56.301 deletions might actually be producing  
NOTE Confidence: 0.9258216375

00:36:56.301 --> 00:36:58.797 mutant isoforms that can be translated.  
NOTE Confidence: 0.9258216375

00:36:58.800 --> 00:37:00.726 So a lot more work to be done to  
NOTE Confidence: 0.9258216375

00:37:00.726 --> 00:37:02.560 see how generalizable this is.  
NOTE Confidence: 0.9258216375

00:37:02.560 --> 00:37:05.200 But I think we weren't so lucky as to find  
NOTE Confidence: 0.9258216375

00:37:05.272 --> 00:37:07.918 the only example in in all of of humanity.  
NOTE Confidence: 0.9258216375

00:37:07.920 --> 00:37:10.992 And so this is where Aaron graduated and  
NOTE Confidence: 0.9258216375

00:37:10.992 --> 00:37:13.319 Michael Fernando picked up the project.  
NOTE Confidence: 0.9258216375

00:37:13.320 --> 00:37:14.220 Michael's really interested  
NOTE Confidence: 0.9258216375

00:37:14.220 --> 00:37:15.120 in precision medicine,  
NOTE Confidence: 0.9258216375

00:37:15.120 --> 00:37:17.199 so he really wanted to understand if  
NOTE Confidence: 0.9258216375

00:37:17.199 --> 00:37:19.759 we could do anything to help patients.  
NOTE Confidence: 0.9258216375

00:37:19.760 --> 00:37:21.512 We understand he's done a lot of work  
NOTE Confidence: 0.9258216375

00:37:21.512 --> 00:37:23.440 that I'm not going to talk about today,  
NOTE Confidence: 0.9258216375

00:37:23.440 --> 00:37:25.168 that there are different effects of  
NOTE Confidence: 0.9258216375

00:37:25.168 --> 00:37:26.810 nurexin 1 deletions in glutamatergic  
NOTE Confidence: 0.9258216375

00:37:26.810 --> 00:37:28.558 neurons and Gabaergic neurons.

NOTE Confidence: 0.9258216375

00:37:28.560 --> 00:37:30.204 We understand very well that these

NOTE Confidence: 0.9258216375

00:37:30.204 --> 00:37:32.039 wild type isoforms and these mutant

NOTE Confidence: 0.9258216375

00:37:32.039 --> 00:37:33.754 isoforms are having different effects,

NOTE Confidence: 0.9258216375

00:37:33.760 --> 00:37:35.440 the level of the synapse.

NOTE Confidence: 0.9258216375

00:37:35.440 --> 00:37:37.264 But he wanted to know in the case

NOTE Confidence: 0.9258216375

00:37:37.264 --> 00:37:39.105 of the patients that only have

NOTE Confidence: 0.9258216375

00:37:39.105 --> 00:37:40.755 a loss of function mutation,

NOTE Confidence: 0.9258216375

00:37:40.760 --> 00:37:43.399 can we rescue it by turning up

NOTE Confidence: 0.9258216375

00:37:43.399 --> 00:37:46.038 expression from the one healthy allele.

NOTE Confidence: 0.9258216375

00:37:46.040 --> 00:37:48.392 And so he looked for examples of

NOTE Confidence: 0.9258216375

00:37:48.392 --> 00:37:50.718 drugs that might increase expression.

NOTE Confidence: 0.9258216375

00:37:50.720 --> 00:37:54.892 And it turns out that the by chip seek,

NOTE Confidence: 0.9258216375

00:37:54.892 --> 00:37:56.664 the estradiol receptor binds

NOTE Confidence: 0.9258216375

00:37:56.664 --> 00:37:58.439 just upstream of nurexin.

NOTE Confidence: 0.9258216375

00:37:58.440 --> 00:38:00.222 And there's been a couple examples

NOTE Confidence: 0.9258216375

00:38:00.222 --> 00:38:01.937 in the literature of estradiol  
NOTE Confidence: 0.9258216375

00:38:01.937 --> 00:38:03.797 increasing expression of nurexin.  
NOTE Confidence: 0.9258216375

00:38:03.800 --> 00:38:05.634 So he tested it in our cells.  
NOTE Confidence: 0.9258216375

00:38:05.640 --> 00:38:08.598 And so if you add estradiol  
NOTE Confidence: 0.9258216375

00:38:08.598 --> 00:38:10.077 to glutamatergic neurons,  
NOTE Confidence: 0.9258216375

00:38:10.080 --> 00:38:11.809 the first thing that you see is  
NOTE Confidence: 0.9258216375

00:38:11.809 --> 00:38:13.665 that yes indeed we can express  
NOTE Confidence: 0.9258216375

00:38:13.665 --> 00:38:15.077 increase nurexin one expression.  
NOTE Confidence: 0.9258216375

00:38:15.080 --> 00:38:16.624 And second of all,  
NOTE Confidence: 0.9258216375

00:38:16.624 --> 00:38:18.817 you can actually rescue activity all  
NOTE Confidence: 0.9258216375

00:38:18.817 --> 00:38:20.616 of the neurons from that five prime  
NOTE Confidence: 0.9258216375

00:38:20.616 --> 00:38:22.410 case just by providing beta estradiol  
NOTE Confidence: 0.9258216375

00:38:22.410 --> 00:38:24.240 and he could quantify it here.  
NOTE Confidence: 0.9258216375

00:38:24.240 --> 00:38:26.641 So it's a significant and robust rescue  
NOTE Confidence: 0.9258216375

00:38:26.641 --> 00:38:28.880 of synaptic activity by adding estradiol,  
NOTE Confidence: 0.9258216375

00:38:28.880 --> 00:38:31.638 that sex hormone to five prime neurons.

NOTE Confidence: 0.9258216375

00:38:31.640 --> 00:38:33.638 But that doesn't tell us a lot about those

NOTE Confidence: 0.9258216375

00:38:33.638 --> 00:38:35.477 three prime cases with the mutinisoform.

NOTE Confidence: 0.9258216375

00:38:35.480 --> 00:38:37.346 And so here he's testing antisense

NOTE Confidence: 0.9258216375

00:38:37.346 --> 00:38:38.897 oligos which have already been

NOTE Confidence: 0.9258216375

00:38:38.897 --> 00:38:40.929 applied as you know as end of 1

NOTE Confidence: 0.9258216375

00:38:40.929 --> 00:38:41.869 therapeutics for neurodegeneration

NOTE Confidence: 0.9258216375

00:38:41.869 --> 00:38:44.081 and asked can we design Asos that

NOTE Confidence: 0.9258216375

00:38:44.081 --> 00:38:45.628 might knock down mutant isoforms.

NOTE Confidence: 0.9258216375

00:38:45.628 --> 00:38:47.775 He's been able to design one he

NOTE Confidence: 0.9258216375

00:38:47.775 --> 00:38:49.275 can show it has knocked down.

NOTE Confidence: 0.9258216375

00:38:49.280 --> 00:38:50.744 But we don't have any data

NOTE Confidence: 0.9258216375

00:38:50.744 --> 00:38:51.720 on functional rescue yet.

NOTE Confidence: 0.9258216375

00:38:51.720 --> 00:38:53.672 But this is kind of what we envision

NOTE Confidence: 0.9258216375

00:38:53.672 --> 00:38:55.336 here moving forward is the type

NOTE Confidence: 0.9258216375

00:38:55.336 --> 00:38:56.736 of precision medicine that might

NOTE Confidence: 0.9258216375

00:38:56.736 --> 00:38:58.493 be possible once we understand the  
NOTE Confidence: 0.9258216375

00:38:58.493 --> 00:39:01.560 mechanisms at play for a patient.  
NOTE Confidence: 0.9258216375

00:39:01.560 --> 00:39:03.568 And so I hope that with what I  
NOTE Confidence: 0.9258216375

00:39:03.568 --> 00:39:05.120 showed you about estradiol,  
NOTE Confidence: 0.9258216375

00:39:05.120 --> 00:39:08.096 I've shown you one example of an environment  
NOTE Confidence: 0.9258216375

00:39:08.096 --> 00:39:10.597 that might make phenotypes less bad.  
NOTE Confidence: 0.9258216375

00:39:10.600 --> 00:39:12.088 And I think this is actually  
NOTE Confidence: 0.9258216375

00:39:12.088 --> 00:39:13.667 consistent with what we know about  
NOTE Confidence: 0.9258216375

00:39:13.667 --> 00:39:15.269 sex bias in brain disorders, right?  
NOTE Confidence: 0.9258216375

00:39:15.269 --> 00:39:17.690 So we know that males are at a higher  
NOTE Confidence: 0.9258216375

00:39:17.757 --> 00:39:19.837 risk for autism and schizophrenia,  
NOTE Confidence: 0.9258216375

00:39:19.840 --> 00:39:22.240 whereas females are at a higher  
NOTE Confidence: 0.9258216375

00:39:22.240 --> 00:39:24.192 risk for Alzheimer's disease,  
NOTE Confidence: 0.9258216375

00:39:24.192 --> 00:39:25.920 depression and anxiety.  
NOTE Confidence: 0.9258216375

00:39:25.920 --> 00:39:27.873 And so maybe sex hormones are one  
NOTE Confidence: 0.9258216375

00:39:27.873 --> 00:39:30.000 clue about how we can modulate risk,

NOTE Confidence: 0.9258216375

00:39:30.000 --> 00:39:32.324 and why two people with the same

NOTE Confidence: 0.9258216375

00:39:32.324 --> 00:39:33.320 risk factors might

NOTE Confidence: 0.966651100769231

00:39:33.394 --> 00:39:34.960 have different outcomes.

NOTE Confidence: 0.966651100769231

00:39:34.960 --> 00:39:37.968 We had changed gears now and pivot to

NOTE Confidence: 0.966651100769231

00:39:37.968 --> 00:39:39.960 environments that are less helpful.

NOTE Confidence: 0.966651100769231

00:39:39.960 --> 00:39:42.272 One thing that we know is that stress

NOTE Confidence: 0.966651100769231

00:39:42.272 --> 00:39:44.358 increases risk for psychiatric disorders.

NOTE Confidence: 0.966651100769231

00:39:44.360 --> 00:39:47.160 But that stress alone is not causal.

NOTE Confidence: 0.966651100769231

00:39:47.160 --> 00:39:50.100 About half of the US population will

NOTE Confidence: 0.966651100769231

00:39:50.100 --> 00:39:52.865 experience a trauma event sufficient of

NOTE Confidence: 0.966651100769231

00:39:52.865 --> 00:39:55.715 magnitude to be associated with PTSD.

NOTE Confidence: 0.966651100769231

00:39:55.720 --> 00:39:59.128 But half of us don't have PTSD, right?

NOTE Confidence: 0.966651100769231

00:39:59.128 --> 00:40:02.800 And so who are these people who develop PTSD?

NOTE Confidence: 0.966651100769231

00:40:02.800 --> 00:40:04.320 And do we are there?

NOTE Confidence: 0.966651100769231

00:40:04.320 --> 00:40:07.398 Ways of predicting or preventing that

NOTE Confidence: 0.966651100769231

00:40:07.398 --> 00:40:10.200 relationship between trauma and exposure.

NOTE Confidence: 0.966651100769231

00:40:10.200 --> 00:40:12.363 So one thing that we know is

NOTE Confidence: 0.966651100769231

00:40:12.363 --> 00:40:13.860 that our environment influences

NOTE Confidence: 0.966651100769231

00:40:13.860 --> 00:40:15.876 our susceptibility to trauma.

NOTE Confidence: 0.966651100769231

00:40:15.880 --> 00:40:18.005 People with unstable housing and

NOTE Confidence: 0.966651100769231

00:40:18.005 --> 00:40:20.576 less social support are more likely

NOTE Confidence: 0.966651100769231

00:40:20.576 --> 00:40:23.194 to have PTSD when exposed to trauma.

NOTE Confidence: 0.966651100769231

00:40:23.200 --> 00:40:24.840 But what about their DNA?

NOTE Confidence: 0.966651100769231

00:40:24.840 --> 00:40:27.836 Does their DNA also predict the likelihood

NOTE Confidence: 0.966651100769231

00:40:27.836 --> 00:40:30.600 of PTSD when exposed to stress?

NOTE Confidence: 0.966651100769231

00:40:30.600 --> 00:40:31.888 So the question being,

NOTE Confidence: 0.966651100769231

00:40:31.888 --> 00:40:33.498 do our genetics determine how

NOTE Confidence: 0.966651100769231

00:40:33.498 --> 00:40:35.520 we respond to traumatic stress?

NOTE Confidence: 0.966651100769231

00:40:35.520 --> 00:40:37.000 How do we model that in a dish?

NOTE Confidence: 0.966651100769231

00:40:37.000 --> 00:40:37.348 Well,

NOTE Confidence: 0.966651100769231

00:40:37.348 --> 00:40:40.000 we thought about it a lot and we

NOTE Confidence: 0.966651100769231

00:40:40.000 --> 00:40:41.400 decided to go after cortisol,

NOTE Confidence: 0.966651100769231

00:40:41.400 --> 00:40:43.392 which is an essential part of the HPA

NOTE Confidence: 0.966651100769231

00:40:43.392 --> 00:40:45.195 axis and something that we can just

NOTE Confidence: 0.966651100769231

00:40:45.195 --> 00:40:47.218 add to our cells in a dish, right?

NOTE Confidence: 0.966651100769231

00:40:47.218 --> 00:40:48.908 We can't put an environmental

NOTE Confidence: 0.966651100769231

00:40:48.908 --> 00:40:51.119 trauma on cells in an incubator,

NOTE Confidence: 0.966651100769231

00:40:51.120 --> 00:40:52.480 but we can apply cortisol.

NOTE Confidence: 0.966651100769231

00:40:52.480 --> 00:40:53.584 And what's nice about this is

NOTE Confidence: 0.966651100769231

00:40:53.584 --> 00:40:54.720 if we can control the dose,

NOTE Confidence: 0.966651100769231

00:40:54.720 --> 00:40:56.760 I mean, control the duration.

NOTE Confidence: 0.966651100769231

00:40:56.760 --> 00:40:57.840 And so this is exactly what we did.

NOTE Confidence: 0.966651100769231

00:40:57.840 --> 00:40:59.436 We're putting hydrocortisone and

NOTE Confidence: 0.966651100769231

00:40:59.436 --> 00:41:01.032 synthetic cortisol on neurons

NOTE Confidence: 0.966651100769231

00:41:01.032 --> 00:41:02.560 and monitoring the response.

NOTE Confidence: 0.966651100769231

00:41:02.560 --> 00:41:05.367 And we can do this to neurons

NOTE Confidence: 0.966651100769231

00:41:05.367 --> 00:41:08.278 derived from PTSD cases and controls.  
NOTE Confidence: 0.966651100769231

00:41:08.280 --> 00:41:09.762 We can ask how they're different  
NOTE Confidence: 0.966651100769231

00:41:09.762 --> 00:41:11.040 and how they're the same.  
NOTE Confidence: 0.966651100769231

00:41:11.040 --> 00:41:12.720 So here's the first analysis.  
NOTE Confidence: 0.966651100769231

00:41:12.720 --> 00:41:15.160 We're looking at transcatomic response  
NOTE Confidence: 0.966651100769231

00:41:15.160 --> 00:41:19.055 to Low dose H Corp and high dose H  
NOTE Confidence: 0.966651100769231

00:41:19.055 --> 00:41:21.880 Corp from neurons from 39 donors.  
NOTE Confidence: 0.966651100769231

00:41:21.880 --> 00:41:23.064 I think the first one that you can  
NOTE Confidence: 0.966651100769231

00:41:23.064 --> 00:41:24.597 see is that the more you stress neurons,  
NOTE Confidence: 0.966651100769231

00:41:24.600 --> 00:41:26.040 the more they change gene expression.  
NOTE Confidence: 0.966651100769231

00:41:26.040 --> 00:41:28.680 There's more blue in the high dose case.  
NOTE Confidence: 0.966651100769231

00:41:28.680 --> 00:41:30.324 What types of genes change expression  
NOTE Confidence: 0.966651100769231

00:41:30.324 --> 00:41:32.190 as you stress neurons where they're  
NOTE Confidence: 0.966651100769231

00:41:32.190 --> 00:41:33.995 actually related to neurdevelopment and  
NOTE Confidence: 0.966651100769231

00:41:33.995 --> 00:41:36.320 immune response. So this all makes sense.  
NOTE Confidence: 0.966651100769231

00:41:36.320 --> 00:41:37.940 Now there's 39 donors actually

NOTE Confidence: 0.966651100769231  
00:41:37.940 --> 00:41:39.882 came from a cohort recruited by  
NOTE Confidence: 0.966651100769231  
00:41:39.882 --> 00:41:41.436 Rachel Yehuda to the Bronx VA.  
NOTE Confidence: 0.966651100769231  
00:41:41.440 --> 00:41:44.079 They were all about combat exposed veterans,  
NOTE Confidence: 0.966651100769231  
00:41:44.080 --> 00:41:46.416 half of whom nineteen of whom had PTSD  
NOTE Confidence: 0.966651100769231  
00:41:46.416 --> 00:41:49.112 and twenty of whom after really careful  
NOTE Confidence: 0.966651100769231  
00:41:49.112 --> 00:41:50.752 clinical characterization did not  
NOTE Confidence: 0.966651100769231  
00:41:50.760 --> 00:41:52.760 and suddenly broke down that same data set.  
NOTE Confidence: 0.966651100769231  
00:41:52.760 --> 00:41:54.674 Now by diagnosis we actually kind  
NOTE Confidence: 0.966651100769231  
00:41:54.674 --> 00:41:56.710 of see the opposite result, right?  
NOTE Confidence: 0.966651100769231  
00:41:56.710 --> 00:41:57.520 There's more pink,  
NOTE Confidence: 0.966651100769231  
00:41:57.520 --> 00:41:59.140 there's more color at the low  
NOTE Confidence: 0.966651100769231  
00:41:59.193 --> 00:42:00.519 dose than at the high dose.  
NOTE Confidence: 0.966651100769231  
00:42:00.520 --> 00:42:02.480 What we think this data is telling  
NOTE Confidence: 0.966651100769231  
00:42:02.480 --> 00:42:04.877 us is that PTSD cases are hyper  
NOTE Confidence: 0.966651100769231  
00:42:04.877 --> 00:42:06.284 responsive to stress, right.  
NOTE Confidence: 0.966651100769231

00:42:06.284 --> 00:42:08.556 So everybody changed at a high dose stress,  
NOTE Confidence: 0.966651100769231

00:42:08.560 --> 00:42:10.400 but PTSD cases changed gene  
NOTE Confidence: 0.966651100769231

00:42:10.400 --> 00:42:12.715 expression at low dose stress before  
NOTE Confidence: 0.966651100769231

00:42:12.715 --> 00:42:14.319 the control neurons due.  
NOTE Confidence: 0.966651100769231

00:42:14.320 --> 00:42:16.462 In fact their their their hyper  
NOTE Confidence: 0.966651100769231

00:42:16.462 --> 00:42:18.406 response to stress was sufficient  
NOTE Confidence: 0.966651100769231

00:42:18.406 --> 00:42:21.064 to separate neurons that came from  
NOTE Confidence: 0.966651100769231

00:42:21.064 --> 00:42:23.213 cases versus controls and the types  
NOTE Confidence: 0.966651100769231

00:42:23.213 --> 00:42:25.110 of genes that change in neurons from  
NOTE Confidence: 0.920982550909091

00:42:25.169 --> 00:42:27.738 PTSD. Cases with stress that didn't change  
NOTE Confidence: 0.920982550909091

00:42:27.738 --> 00:42:30.058 in neurons from controls with stress  
NOTE Confidence: 0.920982550909091

00:42:30.058 --> 00:42:32.592 were enriched for known PTSD risk genes,  
NOTE Confidence: 0.920982550909091

00:42:32.600 --> 00:42:35.320 both the genetic risk variants like the PTSD  
NOTE Confidence: 0.920982550909091

00:42:35.320 --> 00:42:37.540 but also genes that were differentially  
NOTE Confidence: 0.920982550909091

00:42:37.540 --> 00:42:39.720 expressed in PTSD brains postmortem.  
NOTE Confidence: 0.920982550909091

00:42:39.720 --> 00:42:41.208 But that being said,

NOTE Confidence: 0.920982550909091  
00:42:41.208 --> 00:42:43.960 it's not specific to PTSD risk genes.  
NOTE Confidence: 0.920982550909091  
00:42:43.960 --> 00:42:46.340 We also have a ton of developmental  
NOTE Confidence: 0.920982550909091  
00:42:46.340 --> 00:42:47.926 disorder risk genes, schizophrenia,  
NOTE Confidence: 0.920982550909091  
00:42:47.926 --> 00:42:50.756 epilepsy and autism risk genes.  
NOTE Confidence: 0.920982550909091  
00:42:50.760 --> 00:42:53.714 And so I actually think that stress  
NOTE Confidence: 0.920982550909091  
00:42:53.714 --> 00:42:54.980 broadly dysregulates psychiatric  
NOTE Confidence: 0.920982550909091  
00:42:55.050 --> 00:42:57.040 risk gene expression in neurons.  
NOTE Confidence: 0.920982550909091  
00:42:57.040 --> 00:42:58.840 Karina, Doug a little bit further  
NOTE Confidence: 0.920982550909091  
00:42:58.840 --> 00:43:00.435 trying to understand why neurons  
NOTE Confidence: 0.920982550909091  
00:43:00.435 --> 00:43:02.155 were hyper responsive to stress.  
NOTE Confidence: 0.920982550909091  
00:43:02.160 --> 00:43:03.875 Here's an example of a transcription factor,  
NOTE Confidence: 0.920982550909091  
00:43:03.880 --> 00:43:06.729 Mick, one where its targets were activated  
NOTE Confidence: 0.920982550909091  
00:43:06.729 --> 00:43:08.879 higher at increased stress doses and  
NOTE Confidence: 0.920982550909091  
00:43:08.879 --> 00:43:11.559 it's at the middle of a hub of genes.  
NOTE Confidence: 0.920982550909091  
00:43:11.560 --> 00:43:13.035 And so now we're asking  
NOTE Confidence: 0.920982550909091

00:43:13.035 --> 00:43:13.920 if stress dysregulates,  
NOTE Confidence: 0.920982550909091

00:43:13.920 --> 00:43:15.939 specifically psychiatric risk  
NOTE Confidence: 0.920982550909091

00:43:15.939 --> 00:43:17.958 loci in neurons.  
NOTE Confidence: 0.920982550909091

00:43:17.960 --> 00:43:20.480 So we talked about EQTL at the beginning.  
NOTE Confidence: 0.920982550909091

00:43:20.480 --> 00:43:21.275 We prioritized furin.  
NOTE Confidence: 0.920982550909091

00:43:21.275 --> 00:43:22.600 This is an example of,  
NOTE Confidence: 0.920982550909091

00:43:22.600 --> 00:43:23.356 you know,  
NOTE Confidence: 0.920982550909091

00:43:23.356 --> 00:43:25.624 one location where two nucleotides differ  
NOTE Confidence: 0.920982550909091

00:43:25.624 --> 00:43:28.480 or one nucleotide differs at 2 copies.  
NOTE Confidence: 0.920982550909091

00:43:28.480 --> 00:43:30.752 And you might see for example an increase  
NOTE Confidence: 0.920982550909091

00:43:30.752 --> 00:43:32.517 in expression and that furin example  
NOTE Confidence: 0.920982550909091

00:43:32.517 --> 00:43:34.798 the GG neurons had less remember and the A,  
NOTE Confidence: 0.920982550909091

00:43:34.800 --> 00:43:35.658 A had more.  
NOTE Confidence: 0.920982550909091

00:43:35.658 --> 00:43:38.808 Now with A, a stress interactive EQTL,  
NOTE Confidence: 0.920982550909091

00:43:38.808 --> 00:43:41.096 you see differential stress  
NOTE Confidence: 0.920982550909091

00:43:41.096 --> 00:43:43.199 relationships depending on genotype.

NOTE Confidence: 0.920982550909091  
00:43:43.200 --> 00:43:44.780 The GG neurons show increased  
NOTE Confidence: 0.920982550909091  
00:43:44.780 --> 00:43:46.520 expression with stress and the A,  
NOTE Confidence: 0.920982550909091  
00:43:46.520 --> 00:43:48.295 A neurons would show decreased  
NOTE Confidence: 0.920982550909091  
00:43:48.295 --> 00:43:49.360 expression with stress.  
NOTE Confidence: 0.920982550909091  
00:43:49.360 --> 00:43:51.340 And so we asked across our  
NOTE Confidence: 0.920982550909091  
00:43:51.340 --> 00:43:53.239 40 donors how often we saw,  
NOTE Confidence: 0.920982550909091  
00:43:53.240 --> 00:43:54.094 you know,  
NOTE Confidence: 0.920982550909091  
00:43:54.094 --> 00:43:55.802 genotype dependent stress relationships  
NOTE Confidence: 0.920982550909091  
00:43:55.802 --> 00:43:57.891 in both glutamatergic neurons and  
NOTE Confidence: 0.920982550909091  
00:43:57.891 --> 00:43:59.167 separately in Gabaergic neurons  
NOTE Confidence: 0.920982550909091  
00:43:59.167 --> 00:44:01.200 to derive from those 39 donors.  
NOTE Confidence: 0.920982550909091  
00:44:01.200 --> 00:44:03.336 And what you can see is that there's  
NOTE Confidence: 0.920982550909091  
00:44:03.336 --> 00:44:05.151 actually an enrichment for psychiatric  
NOTE Confidence: 0.920982550909091  
00:44:05.151 --> 00:44:07.599 risk disorder loci in both populations.  
NOTE Confidence: 0.920982550909091  
00:44:07.600 --> 00:44:08.208 But again,  
NOTE Confidence: 0.920982550909091

00:44:08.208 --> 00:44:09.120 not just psychiatric,  
NOTE Confidence: 0.920982550909091

00:44:09.120 --> 00:44:11.214 We're also getting an enrichment for  
NOTE Confidence: 0.920982550909091

00:44:11.214 --> 00:44:12.920 metabolic and inflammatory risk loci.  
NOTE Confidence: 0.920982550909091

00:44:12.920 --> 00:44:14.875 So we're learning broadly about  
NOTE Confidence: 0.920982550909091

00:44:14.875 --> 00:44:16.830 stress responsiveness and how it  
NOTE Confidence: 0.920982550909091

00:44:16.898 --> 00:44:19.040 underlies a risk for human disease.  
NOTE Confidence: 0.920982550909091

00:44:19.040 --> 00:44:20.920 I think,  
NOTE Confidence: 0.920982550909091

00:44:20.920 --> 00:44:22.711 and I and I think really cool because you  
NOTE Confidence: 0.920982550909091

00:44:22.711 --> 00:44:24.436 could argue that all of this is in vitro.  
NOTE Confidence: 0.920982550909091

00:44:24.440 --> 00:44:25.880 What does this actually tell  
NOTE Confidence: 0.920982550909091

00:44:25.880 --> 00:44:27.320 us about real brain cells?  
NOTE Confidence: 0.920982550909091

00:44:27.320 --> 00:44:29.756 And so in collaboration with Matt Triganti,  
NOTE Confidence: 0.920982550909091

00:44:29.760 --> 00:44:32.838 who has brains from 304 individuals,  
NOTE Confidence: 0.920982550909091

00:44:32.840 --> 00:44:34.200 1/3 of whom were controlled,  
NOTE Confidence: 0.920982550909091

00:44:34.200 --> 00:44:35.658 a third of whom had depression  
NOTE Confidence: 0.920982550909091

00:44:35.658 --> 00:44:37.440 and a third of whom had PTSD,

NOTE Confidence: 0.920982550909091  
00:44:37.440 --> 00:44:40.184 we were able to replicate half of  
NOTE Confidence: 0.920982550909091  
00:44:40.184 --> 00:44:41.784 our stress interactive genotypes  
NOTE Confidence: 0.920982550909091  
00:44:41.784 --> 00:44:43.904 in postmortem brains from people  
NOTE Confidence: 0.920982550909091  
00:44:43.904 --> 00:44:45.895 who had trauma exposures, which,  
NOTE Confidence: 0.920982550909091  
00:44:45.895 --> 00:44:46.485 you know,  
NOTE Confidence: 0.920982550909091  
00:44:46.485 --> 00:44:48.976 I think was a much higher rate of  
NOTE Confidence: 0.920982550909091  
00:44:48.976 --> 00:44:50.756 validation than I had expected.  
NOTE Confidence: 0.920982550909091  
00:44:50.760 --> 00:44:52.758 And so now I've given you an example of  
NOTE Confidence: 0.920982550909091  
00:44:52.758 --> 00:44:54.396 an environment that makes phenotypes  
NOTE Confidence: 0.920982550909091  
00:44:54.396 --> 00:44:56.430 less severe and then stress as  
NOTE Confidence: 0.920982550909091  
00:44:56.487 --> 00:44:58.182 the example of an environment  
NOTE Confidence: 0.920982550909091  
00:44:58.182 --> 00:44:59.877 that makes phenotypes more severe.  
NOTE Confidence: 0.920982550909091  
00:44:59.880 --> 00:45:00.302 Now,  
NOTE Confidence: 0.920982550909091  
00:45:00.302 --> 00:45:02.412 how specific are these relationships  
NOTE Confidence: 0.920982550909091  
00:45:02.412 --> 00:45:03.678 to different stressors?  
NOTE Confidence: 0.920982550909091

00:45:03.680 --> 00:45:05.736 And so now we want to ask if  
NOTE Confidence: 0.920982550909091

00:45:05.736 --> 00:45:07.041 distinct stressors have unique  
NOTE Confidence: 0.920982550909091

00:45:07.041 --> 00:45:08.876 impacts on the regulatory variants.  
NOTE Confidence: 0.807351215714286

00:45:10.960 --> 00:45:12.794 Oops, I think I repeated this slide.  
NOTE Confidence: 0.807351215714286

00:45:12.800 --> 00:45:14.225 OK, so here,  
NOTE Confidence: 0.807351215714286

00:45:14.225 --> 00:45:17.075 how do we pick multiple stressors?  
NOTE Confidence: 0.807351215714286

00:45:17.080 --> 00:45:18.760 Well, we know for example,  
NOTE Confidence: 0.807351215714286

00:45:18.760 --> 00:45:20.716 that during pregnancy, fever,  
NOTE Confidence: 0.807351215714286

00:45:20.716 --> 00:45:23.650 but also trauma and also famine  
NOTE Confidence: 0.807351215714286

00:45:23.739 --> 00:45:26.967 and also infection can all increase  
NOTE Confidence: 0.807351215714286

00:45:26.967 --> 00:45:29.119 risk for psychiatric disorders.  
NOTE Confidence: 0.807351215714286

00:45:29.120 --> 00:45:32.208 Some of these can be mediated by Illinois  
NOTE Confidence: 0.807351215714286

00:45:32.208 --> 00:45:34.560 6 activation in the immune system.  
NOTE Confidence: 0.807351215714286

00:45:34.560 --> 00:45:35.198 And likewise,  
NOTE Confidence: 0.807351215714286

00:45:35.198 --> 00:45:37.112 we know in adolescents that stress  
NOTE Confidence: 0.807351215714286

00:45:37.112 --> 00:45:39.578 and drugs of abuse can also increase

NOTE Confidence: 0.807351215714286  
00:45:39.578 --> 00:45:40.994 risk for psychiatric disorders.  
NOTE Confidence: 0.807351215714286  
00:45:41.000 --> 00:45:43.496 So we're going to add a few different  
NOTE Confidence: 0.807351215714286  
00:45:43.496 --> 00:45:44.919 inflammatory cues to our cells,  
NOTE Confidence: 0.807351215714286  
00:45:44.920 --> 00:45:46.880 and we're going to ask at large scale.  
NOTE Confidence: 0.807351215714286  
00:45:46.880 --> 00:45:49.096 So this is at the thousands of risk  
NOTE Confidence: 0.807351215714286  
00:45:49.096 --> 00:45:50.628 varying simultaneously using an assay  
NOTE Confidence: 0.807351215714286  
00:45:50.628 --> 00:45:52.476 called a massively parallel reporter assay.  
NOTE Confidence: 0.807351215714286  
00:45:52.480 --> 00:45:54.580 Now, the details of how this assay  
NOTE Confidence: 0.807351215714286  
00:45:54.580 --> 00:45:56.040 works aren't really relevant,  
NOTE Confidence: 0.807351215714286  
00:45:56.040 --> 00:45:57.832 but what it will do is it will  
NOTE Confidence: 0.807351215714286  
00:45:57.832 --> 00:45:58.802 call a DNARNA ratio.  
NOTE Confidence: 0.807351215714286  
00:45:58.802 --> 00:46:00.629 So we can ask which risk variants  
NOTE Confidence: 0.807351215714286  
00:46:00.629 --> 00:46:02.442 are changing expression in different  
NOTE Confidence: 0.807351215714286  
00:46:02.442 --> 00:46:04.317 cell types in different contexts.  
NOTE Confidence: 0.807351215714286  
00:46:04.320 --> 00:46:06.049 And so a risk variant that has  
NOTE Confidence: 0.807351215714286

00:46:06.049 --> 00:46:07.555 no effect on regulation will  
NOTE Confidence: 0.807351215714286

00:46:07.555 --> 00:46:09.320 just give the same outcome,  
NOTE Confidence: 0.807351215714286

00:46:09.320 --> 00:46:11.250 the same DNARA ratio for  
NOTE Confidence: 0.807351215714286

00:46:11.250 --> 00:46:12.794 risk and protective variants.  
NOTE Confidence: 0.807351215714286

00:46:12.800 --> 00:46:14.132 But a risk variant that changes  
NOTE Confidence: 0.807351215714286

00:46:14.132 --> 00:46:15.585 expression will all of a different  
NOTE Confidence: 0.807351215714286

00:46:15.585 --> 00:46:16.880 outcome for risk and protective.  
NOTE Confidence: 0.807351215714286

00:46:16.880 --> 00:46:19.796 And we're going to stress the cells in vitro.  
NOTE Confidence: 0.807351215714286

00:46:19.800 --> 00:46:21.660 And so here's an example of  
NOTE Confidence: 0.807351215714286

00:46:21.660 --> 00:46:23.244 risk variants that change their  
NOTE Confidence: 0.807351215714286

00:46:23.244 --> 00:46:25.239 effect in the context of H court,  
NOTE Confidence: 0.807351215714286

00:46:25.240 --> 00:46:26.800 IL 6 and interferon alpha.  
NOTE Confidence: 0.807351215714286

00:46:26.800 --> 00:46:29.320 So A21 stressor H court from earlier and  
NOTE Confidence: 0.807351215714286

00:46:29.320 --> 00:46:31.359 two different inflammatory stressors.  
NOTE Confidence: 0.807351215714286

00:46:31.360 --> 00:46:32.827 I think all that I really want you to  
NOTE Confidence: 0.807351215714286

00:46:32.827 --> 00:46:34.436 take home is that we have a Venn diagram.

NOTE Confidence: 0.807351215714286  
00:46:34.440 --> 00:46:35.600 We don't have a circle.  
NOTE Confidence: 0.807351215714286  
00:46:35.600 --> 00:46:37.952 So it's actually a unique effect  
NOTE Confidence: 0.807351215714286  
00:46:37.952 --> 00:46:40.280 of these three different stressors,  
NOTE Confidence: 0.807351215714286  
00:46:40.280 --> 00:46:42.155 up regulating but also down  
NOTE Confidence: 0.807351215714286  
00:46:42.155 --> 00:46:43.280 regulating risk variants.  
NOTE Confidence: 0.807351215714286  
00:46:43.280 --> 00:46:46.885 And so our our take home here  
NOTE Confidence: 0.807351215714286  
00:46:46.885 --> 00:46:49.330 across disorders is that different  
NOTE Confidence: 0.807351215714286  
00:46:49.330 --> 00:46:51.210 inflammatory stressors have different  
NOTE Confidence: 0.807351215714286  
00:46:51.210 --> 00:46:53.600 effects on cross disorder risk.  
NOTE Confidence: 0.807351215714286  
00:46:53.600 --> 00:46:55.370 So you know,  
NOTE Confidence: 0.807351215714286  
00:46:55.370 --> 00:47:00.066 as as an example here with Interferon Alpha,  
NOTE Confidence: 0.807351215714286  
00:47:00.066 --> 00:47:03.558 we see strong up regulation of  
NOTE Confidence: 0.807351215714286  
00:47:03.558 --> 00:47:06.080 ASD and schizophrenia,  
NOTE Confidence: 0.807351215714286  
00:47:06.080 --> 00:47:10.880 whereas over here with H core,  
NOTE Confidence: 0.807351215714286  
00:47:10.880 --> 00:47:11.320 you know,  
NOTE Confidence: 0.807351215714286

00:47:11.320 --> 00:47:13.400 we get a bit more of the bipolar risk,  
NOTE Confidence: 0.807351215714286

00:47:13.400 --> 00:47:13.752 right.  
NOTE Confidence: 0.807351215714286

00:47:13.752 --> 00:47:16.216 So we get different disorders with different  
NOTE Confidence: 0.807351215714286

00:47:16.216 --> 00:47:18.278 stressors and different risk variants,  
NOTE Confidence: 0.807351215714286

00:47:18.280 --> 00:47:20.380 kind of suggesting that there's a  
NOTE Confidence: 0.807351215714286

00:47:20.380 --> 00:47:22.190 specificity to the environmental insult  
NOTE Confidence: 0.807351215714286

00:47:22.190 --> 00:47:24.333 that might make phenotypes worse, right?  
NOTE Confidence: 0.807351215714286

00:47:24.333 --> 00:47:25.825 Some diseases are more  
NOTE Confidence: 0.807351215714286

00:47:25.825 --> 00:47:27.317 worse in some environments.  
NOTE Confidence: 0.807351215714286

00:47:27.320 --> 00:47:29.175 And so Kieran asked me to really  
NOTE Confidence: 0.807351215714286

00:47:29.175 --> 00:47:30.879 focus on clinical take homes here.  
NOTE Confidence: 0.807351215714286

00:47:30.880 --> 00:47:32.797 I don't get to take credit for this slide,  
NOTE Confidence: 0.807351215714286

00:47:32.800 --> 00:47:35.495 an MDPH in the lab, Karina made it,  
NOTE Confidence: 0.807351215714286

00:47:35.495 --> 00:47:37.120 but I think it's fantastic.  
NOTE Confidence: 0.807351215714286

00:47:37.120 --> 00:47:39.368 And so the first one is of course  
NOTE Confidence: 0.807351215714286

00:47:39.368 --> 00:47:40.792 that individual susceptibility is

NOTE Confidence: 0.807351215714286  
00:47:40.792 --> 00:47:42.808 not a personal weakness, right?  
NOTE Confidence: 0.807351215714286  
00:47:42.808 --> 00:47:44.848 There's a genetic component to  
NOTE Confidence: 0.807351215714286  
00:47:44.848 --> 00:47:46.480 our susceptibility to trauma.  
NOTE Confidence: 0.807351215714286  
00:47:46.480 --> 00:47:47.004 Second,  
NOTE Confidence: 0.807351215714286  
00:47:47.004 --> 00:47:50.672 it I think seems very likely that  
NOTE Confidence: 0.807351215714286  
00:47:50.672 --> 00:47:53.481 heterogeneous outcomes will require  
NOTE Confidence: 0.807351215714286  
00:47:53.481 --> 00:47:55.159 heterogeneous interventions.  
NOTE Confidence: 0.807351215714286  
00:47:55.160 --> 00:47:55.510 Third,  
NOTE Confidence: 0.807351215714286  
00:47:55.510 --> 00:47:57.960 I think it's going to be very  
NOTE Confidence: 0.807351215714286  
00:47:57.960 --> 00:47:59.719 important not just for PTSD,  
NOTE Confidence: 0.807351215714286  
00:47:59.720 --> 00:48:01.946 but maybe for all brain disorders  
NOTE Confidence: 0.807351215714286  
00:48:01.946 --> 00:48:03.430 stretching into Alzheimer's and  
NOTE Confidence: 0.807351215714286  
00:48:03.487 --> 00:48:05.312 Parkinson's that we assess for  
NOTE Confidence: 0.807351215714286  
00:48:05.312 --> 00:48:07.137 potential trauma in every patient  
NOTE Confidence: 0.807351215714286  
00:48:07.197 --> 00:48:09.477 because that's going to inform outcomes.  
NOTE Confidence: 0.807351215714286

00:48:09.480 --> 00:48:10.750 And finally,  
NOTE Confidence: 0.807351215714286

00:48:10.750 --> 00:48:12.655 earlier identification and  
NOTE Confidence: 0.807351215714286

00:48:12.655 --> 00:48:15.830 intervention will expand the net  
NOTE Confidence: 0.769038959230769

00:48:15.923 --> 00:48:18.620 type of therapeutic avenues  
NOTE Confidence: 0.769038959230769

00:48:18.620 --> 00:48:21.680 available to clinicians.  
NOTE Confidence: 0.769038959230769

00:48:21.680 --> 00:48:23.680 I'm checking on time I I also have  
NOTE Confidence: 0.769038959230769

00:48:23.680 --> 00:48:25.317 we've we're also really interested  
NOTE Confidence: 0.769038959230769

00:48:25.317 --> 00:48:27.117 in gene gene interactions now.  
NOTE Confidence: 0.769038959230769

00:48:27.120 --> 00:48:29.019 And so I'll try to just give you the  
NOTE Confidence: 0.769038959230769

00:48:29.019 --> 00:48:30.879 take homes of this part of the talk.  
NOTE Confidence: 0.769038959230769

00:48:30.880 --> 00:48:33.197 We're interested in how risk variants some.  
NOTE Confidence: 0.769038959230769

00:48:33.200 --> 00:48:34.922 So here's an example of two  
NOTE Confidence: 0.769038959230769

00:48:34.922 --> 00:48:36.070 risk genes showing different  
NOTE Confidence: 0.769038959230769

00:48:36.128 --> 00:48:37.720 effects on transchomic effects.  
NOTE Confidence: 0.769038959230769

00:48:37.720 --> 00:48:39.407 But now we're going to look at  
NOTE Confidence: 0.769038959230769

00:48:39.407 --> 00:48:40.800 their effects in combination.

NOTE Confidence: 0.769038959230769  
00:48:40.800 --> 00:48:42.153 So this was led by, again,  
NOTE Confidence: 0.769038959230769  
00:48:42.153 --> 00:48:44.118 Nadine a while back now.  
NOTE Confidence: 0.769038959230769  
00:48:44.120 --> 00:48:45.895 So we've got 4 schizophrenia  
NOTE Confidence: 0.769038959230769  
00:48:45.895 --> 00:48:46.960 common risk genes.  
NOTE Confidence: 0.769038959230769  
00:48:46.960 --> 00:48:49.048 We're perturbing them doing RNA seek  
NOTE Confidence: 0.769038959230769  
00:48:49.048 --> 00:48:51.400 of these risk gene effects alone,  
NOTE Confidence: 0.769038959230769  
00:48:51.400 --> 00:48:53.370 but also in combination she  
NOTE Confidence: 0.769038959230769  
00:48:53.370 --> 00:48:54.946 created from those individual  
NOTE Confidence: 0.769038959230769  
00:48:54.946 --> 00:48:56.399 perturbations an additive model.  
NOTE Confidence: 0.769038959230769  
00:48:56.400 --> 00:48:57.960 If each of these things happened  
NOTE Confidence: 0.769038959230769  
00:48:57.960 --> 00:48:59.000 with these four perturbations,  
NOTE Confidence: 0.769038959230769  
00:48:59.000 --> 00:49:00.416 here's what I think would happen if we  
NOTE Confidence: 0.769038959230769  
00:49:00.416 --> 00:49:01.964 did all of them at once and then in  
NOTE Confidence: 0.769038959230769  
00:49:01.964 --> 00:49:03.308 parallel we did all four at the same  
NOTE Confidence: 0.769038959230769  
00:49:03.308 --> 00:49:05.500 time and we asked how good the model was.  
NOTE Confidence: 0.769038959230769

00:49:05.500 --> 00:49:06.880 And so genome wide,  
NOTE Confidence: 0.769038959230769

00:49:06.880 --> 00:49:07.960 the model is pretty good.  
NOTE Confidence: 0.769038959230769

00:49:07.960 --> 00:49:09.720 About 82% of the time,  
NOTE Confidence: 0.769038959230769

00:49:09.720 --> 00:49:11.640 downstream genes changed exactly as you  
NOTE Confidence: 0.769038959230769

00:49:11.640 --> 00:49:13.759 would predict from an additive model.  
NOTE Confidence: 0.769038959230769

00:49:13.760 --> 00:49:16.346 But those times the model failed  
NOTE Confidence: 0.769038959230769

00:49:16.346 --> 00:49:17.639 were particularly interesting.  
NOTE Confidence: 0.769038959230769

00:49:17.640 --> 00:49:20.028 The 7% of the time that genes  
NOTE Confidence: 0.769038959230769

00:49:20.028 --> 00:49:21.398 were more down than expected,  
NOTE Confidence: 0.769038959230769

00:49:21.400 --> 00:49:22.928 we were enriched for  
NOTE Confidence: 0.769038959230769

00:49:22.928 --> 00:49:24.074 neurotransmitter risk genes,  
NOTE Confidence: 0.769038959230769

00:49:24.080 --> 00:49:25.438 and the 11% of time that genes  
NOTE Confidence: 0.769038959230769

00:49:25.438 --> 00:49:26.720 are more up than expected,  
NOTE Confidence: 0.769038959230769

00:49:26.720 --> 00:49:28.346 we are enriched for the rare  
NOTE Confidence: 0.769038959230769

00:49:28.346 --> 00:49:29.430 and common variants linked  
NOTE Confidence: 0.769038959230769

00:49:29.487 --> 00:49:30.919 to schizophrenia and bipolar.

NOTE Confidence: 0.769038959230769  
00:49:30.920 --> 00:49:32.620 This really suggests there's an  
NOTE Confidence: 0.769038959230769  
00:49:32.620 --> 00:49:34.320 emergent biology that comes from  
NOTE Confidence: 0.769038959230769  
00:49:34.376 --> 00:49:35.800 manipulating genes in combination  
NOTE Confidence: 0.769038959230769  
00:49:35.800 --> 00:49:37.936 that you could never predict from  
NOTE Confidence: 0.769038959230769  
00:49:37.991 --> 00:49:39.476 one at a time perturbations,  
NOTE Confidence: 0.769038959230769  
00:49:39.480 --> 00:49:41.208 and that ultimately we're going to  
NOTE Confidence: 0.769038959230769  
00:49:41.208 --> 00:49:43.547 have to test these risk variants in  
NOTE Confidence: 0.769038959230769  
00:49:43.547 --> 00:49:45.797 combination to understand their full impacts.  
NOTE Confidence: 0.769038959230769  
00:49:45.800 --> 00:49:47.005 The caveat to this particular  
NOTE Confidence: 0.769038959230769  
00:49:47.005 --> 00:49:48.509 study was that we picked these  
NOTE Confidence: 0.769038959230769  
00:49:48.509 --> 00:49:50.287 four risk genes on the strength of  
NOTE Confidence: 0.769038959230769  
00:49:50.287 --> 00:49:51.382 genetic evidence without paying  
NOTE Confidence: 0.769038959230769  
00:49:51.382 --> 00:49:52.837 attention to their biological roles,  
NOTE Confidence: 0.769038959230769  
00:49:52.840 --> 00:49:54.016 and it turns out that three of  
NOTE Confidence: 0.769038959230769  
00:49:54.016 --> 00:49:55.319 the four of them were synaptic.  
NOTE Confidence: 0.769038959230769

00:49:55.320 --> 00:49:57.196 And so we've gone back now and  
NOTE Confidence: 0.769038959230769

00:49:57.196 --> 00:49:58.000 repeated this approach,  
NOTE Confidence: 0.769038959230769

00:49:58.000 --> 00:50:00.024 but on a larger list of genes to  
NOTE Confidence: 0.769038959230769

00:50:00.024 --> 00:50:02.394 ask if what we saw was only because  
NOTE Confidence: 0.769038959230769

00:50:02.394 --> 00:50:04.759 those 3 genes had related function.  
NOTE Confidence: 0.769038959230769

00:50:04.760 --> 00:50:08.000 So going from the PGC 2 to the PGC 3,  
NOTE Confidence: 0.769038959230769

00:50:08.000 --> 00:50:09.680 using the same prioritization approach,  
NOTE Confidence: 0.769038959230769

00:50:09.680 --> 00:50:10.832 instead of having just four genes  
NOTE Confidence: 0.769038959230769

00:50:10.832 --> 00:50:12.740 that she was from, we had 25.  
NOTE Confidence: 0.769038959230769

00:50:12.740 --> 00:50:15.215 And from those 25 prioritized genes,  
NOTE Confidence: 0.769038959230769

00:50:15.215 --> 00:50:17.440 we picked 5 synaptic genes,  
NOTE Confidence: 0.769038959230769

00:50:17.440 --> 00:50:18.475 5 regulatory genes,  
NOTE Confidence: 0.769038959230769

00:50:18.475 --> 00:50:19.855 and five multifunction genes  
NOTE Confidence: 0.769038959230769

00:50:19.855 --> 00:50:21.613 that were neither synaptic nor  
NOTE Confidence: 0.769038959230769

00:50:21.613 --> 00:50:23.617 regulatory and they had no apparent  
NOTE Confidence: 0.769038959230769

00:50:23.617 --> 00:50:24.919 relationship to each other.

NOTE Confidence: 0.769038959230769  
00:50:24.920 --> 00:50:26.520 And so for all three of these examples,  
NOTE Confidence: 0.769038959230769  
00:50:26.520 --> 00:50:27.176 we perturb,  
NOTE Confidence: 0.769038959230769  
00:50:27.176 --> 00:50:29.144 We perturb risk genes alone and  
NOTE Confidence: 0.769038959230769  
00:50:29.144 --> 00:50:30.752 in combination and asked how  
NOTE Confidence: 0.769038959230769  
00:50:30.752 --> 00:50:32.237 good the additive model was.  
NOTE Confidence: 0.769038959230769  
00:50:32.240 --> 00:50:33.440 So in the synaptic model  
NOTE Confidence: 0.769038959230769  
00:50:33.440 --> 00:50:34.640 with the five synaptic genes,  
NOTE Confidence: 0.769038959230769  
00:50:34.640 --> 00:50:36.290 we saw the exact same thing  
NOTE Confidence: 0.769038959230769  
00:50:36.290 --> 00:50:37.115 we'd seen previously,  
NOTE Confidence: 0.769038959230769  
00:50:37.120 --> 00:50:40.158 but 15% of the genome wide effects  
NOTE Confidence: 0.769038959230769  
00:50:40.160 --> 00:50:42.518 did not follow the additive model.  
NOTE Confidence: 0.769038959230769  
00:50:42.520 --> 00:50:43.708 Likewise in the regulatory  
NOTE Confidence: 0.769038959230769  
00:50:43.708 --> 00:50:45.193 genes that we again saw,  
NOTE Confidence: 0.769038959230769  
00:50:45.200 --> 00:50:47.685 about 17 or 18% of genes did  
NOTE Confidence: 0.769038959230769  
00:50:47.685 --> 00:50:50.079 not follow the additive model.  
NOTE Confidence: 0.769038959230769

00:50:50.080 --> 00:50:52.160 But unexpectedly in the  
NOTE Confidence: 0.769038959230769

00:50:52.160 --> 00:50:53.720 multifunction genes that  
NOTE Confidence: 0.91187008

00:50:53.720 --> 00:50:55.020 all the effects came  
NOTE Confidence: 0.91187008

00:50:55.020 --> 00:50:56.320 through the additive model.  
NOTE Confidence: 0.91187008

00:50:56.320 --> 00:50:57.560 So what's going on here?  
NOTE Confidence: 0.91187008

00:50:57.560 --> 00:50:59.910 How does gene function predict  
NOTE Confidence: 0.91187008

00:50:59.910 --> 00:51:01.320 the combinatorial effects?  
NOTE Confidence: 0.91187008

00:51:01.320 --> 00:51:03.795 I don't have the full answer to you here,  
NOTE Confidence: 0.91187008

00:51:03.800 --> 00:51:06.383 but I can say amongst the 17 I guess  
NOTE Confidence: 0.91187008

00:51:06.383 --> 00:51:08.757 percent of non additive changing genes,  
NOTE Confidence: 0.91187008

00:51:08.760 --> 00:51:10.749 we had a huge investment for genes with that  
NOTE Confidence: 0.91187008

00:51:10.749 --> 00:51:12.599 were convergent that had shared effects.  
NOTE Confidence: 0.91187008

00:51:12.600 --> 00:51:14.226 And I'll I'll explain more carefully  
NOTE Confidence: 0.91187008

00:51:14.226 --> 00:51:16.158 what I mean on the next slide.  
NOTE Confidence: 0.91187008

00:51:16.160 --> 00:51:20.120 Likewise in the regulatory perturbation,  
NOTE Confidence: 0.91187008

00:51:20.120 --> 00:51:22.087 those genes with non additive effects were

NOTE Confidence: 0.91187008

00:51:22.087 --> 00:51:24.318 again in which for the convergent targets,

NOTE Confidence: 0.91187008

00:51:24.320 --> 00:51:26.680 but in the multifunction group we had very,

NOTE Confidence: 0.91187008

00:51:26.680 --> 00:51:28.660 very few convergent targets and

NOTE Confidence: 0.91187008

00:51:28.660 --> 00:51:31.073 that might be explaining why we

NOTE Confidence: 0.91187008

00:51:31.073 --> 00:51:33.275 didn't see any non additive effects.

NOTE Confidence: 0.91187008

00:51:33.280 --> 00:51:35.954 So what do I mean by convergent?

NOTE Confidence: 0.91187008

00:51:35.960 --> 00:51:36.780 Well, first of all,

NOTE Confidence: 0.91187008

00:51:36.780 --> 00:51:38.378 I guess I should know that these

NOTE Confidence: 0.91187008

00:51:38.378 --> 00:51:39.993 convergent risk genes are enriched

NOTE Confidence: 0.91187008

00:51:39.993 --> 00:51:41.398 for schizophrenia risk variants

NOTE Confidence: 0.91187008

00:51:41.398 --> 00:51:43.293 and they're different across the

NOTE Confidence: 0.91187008

00:51:43.293 --> 00:51:44.920 synaptic and regulatory effects.

NOTE Confidence: 0.91187008

00:51:44.920 --> 00:51:46.840 So they're different convergent

NOTE Confidence: 0.91187008

00:51:46.840 --> 00:51:49.000 downstream networks in these

NOTE Confidence: 0.91187008

00:51:49.000 --> 00:51:50.680 different biological functions.

NOTE Confidence: 0.91187008

00:51:50.680 --> 00:51:51.786 And in here I'm going to explain  
NOTE Confidence: 0.91187008

00:51:51.786 --> 00:51:52.840 what I mean by convergence.  
NOTE Confidence: 0.91187008

00:51:52.840 --> 00:51:55.070 So let's say we have 10 risk genes and each  
NOTE Confidence: 0.91187008

00:51:55.126 --> 00:51:57.359 of them have a different individual effect.  
NOTE Confidence: 0.91187008

00:51:57.360 --> 00:51:58.530 The expected additive  
NOTE Confidence: 0.91187008

00:51:58.530 --> 00:52:00.480 model is the full rainbow,  
NOTE Confidence: 0.91187008

00:52:00.480 --> 00:52:03.300 the full add additive value of  
NOTE Confidence: 0.91187008

00:52:03.300 --> 00:52:05.960 each of these individual effects.  
NOTE Confidence: 0.91187008

00:52:05.960 --> 00:52:07.760 But if I manipulate them in  
NOTE Confidence: 0.91187008

00:52:07.760 --> 00:52:08.360 combination experimentally,  
NOTE Confidence: 0.91187008

00:52:08.360 --> 00:52:10.040 what we see is something just  
NOTE Confidence: 0.91187008

00:52:10.040 --> 00:52:11.160 less than the prediction.  
NOTE Confidence: 0.91187008

00:52:11.160 --> 00:52:13.240 Things don't change as expected.  
NOTE Confidence: 0.91187008

00:52:13.240 --> 00:52:15.400 Now convergent effects are those shared  
NOTE Confidence: 0.91187008

00:52:15.400 --> 00:52:18.279 things that are in all of these rainbows.  
NOTE Confidence: 0.91187008

00:52:18.280 --> 00:52:21.468 So what are the genes that show up in each of

NOTE Confidence: 0.91187008

00:52:21.468 --> 00:52:23.878 these individual single gene perturbations?

NOTE Confidence: 0.91187008

00:52:23.880 --> 00:52:25.716 And here I'm coloring them black.

NOTE Confidence: 0.91187008

00:52:25.720 --> 00:52:28.345 So these are downstream genes of all

NOTE Confidence: 0.91187008

00:52:28.345 --> 00:52:31.519 of the of the 10 individual genes.

NOTE Confidence: 0.91187008

00:52:31.520 --> 00:52:33.836 And those downstream genes we think

NOTE Confidence: 0.91187008

00:52:33.836 --> 00:52:36.686 are the ones explaining the the the

NOTE Confidence: 0.91187008

00:52:36.686 --> 00:52:38.334 non additive interactions between

NOTE Confidence: 0.91187008

00:52:38.334 --> 00:52:40.560 risk variants and schizophrenia.

NOTE Confidence: 0.91187008

00:52:40.560 --> 00:52:41.788 With the last minute,

NOTE Confidence: 0.91187008

00:52:41.788 --> 00:52:44.600 I want to talk about drugs and therapies,

NOTE Confidence: 0.91187008

00:52:44.600 --> 00:52:46.500 'cause I think that's where

NOTE Confidence: 0.91187008

00:52:46.500 --> 00:52:48.680 everybody wants to see this go.

NOTE Confidence: 0.91187008

00:52:48.680 --> 00:52:51.056 It's been very hard in neuroscience

NOTE Confidence: 0.91187008

00:52:51.056 --> 00:52:53.135 to discover new drugs, right?

NOTE Confidence: 0.91187008

00:52:53.135 --> 00:52:55.610 We haven't had new indications

NOTE Confidence: 0.91187008

00:52:55.610 --> 00:52:58.160 in schizophrenia for 50 years,  
NOTE Confidence: 0.91187008

00:52:58.160 --> 00:52:59.966 and I like to point out this  
NOTE Confidence: 0.91187008

00:52:59.966 --> 00:53:02.419 figure from a review of Nature Drug  
NOTE Confidence: 0.91187008

00:53:02.419 --> 00:53:04.434 Discovery written for biotech people.  
NOTE Confidence: 0.91187008

00:53:04.440 --> 00:53:06.250 If you're investing in biotech  
NOTE Confidence: 0.91187008

00:53:06.250 --> 00:53:08.560 and you want to make money,  
NOTE Confidence: 0.91187008

00:53:08.560 --> 00:53:11.278 this chart tells you where to put your money,  
NOTE Confidence: 0.91187008

00:53:11.280 --> 00:53:11.688 right?  
NOTE Confidence: 0.91187008

00:53:11.688 --> 00:53:13.320 Companies that have more  
NOTE Confidence: 0.91187008

00:53:13.320 --> 00:53:14.952 publications per R&D dollar,  
NOTE Confidence: 0.91187008

00:53:14.960 --> 00:53:16.196 I'm more likely to make money.  
NOTE Confidence: 0.91187008

00:53:16.200 --> 00:53:18.120 The in fact only negative predictor  
NOTE Confidence: 0.91187008

00:53:18.120 --> 00:53:20.034 of whether a company will make  
NOTE Confidence: 0.91187008

00:53:20.034 --> 00:53:21.720 money is if they're looking  
NOTE Confidence: 0.91187008

00:53:21.720 --> 00:53:23.120 at a neuroscience indication.  
NOTE Confidence: 0.91187008

00:53:23.120 --> 00:53:25.448 And I think this really points to how

NOTE Confidence: 0.91187008

00:53:25.448 --> 00:53:27.743 hard the challenge has been and why

NOTE Confidence: 0.91187008

00:53:27.743 --> 00:53:30.144 it's so important that we keep trying

NOTE Confidence: 0.91187008

00:53:30.144 --> 00:53:32.552 in academics to move the needle here.

NOTE Confidence: 0.91187008

00:53:32.560 --> 00:53:35.731 So how can we use stem cells

NOTE Confidence: 0.91187008

00:53:35.731 --> 00:53:39.479 as a drug screening platform?

NOTE Confidence: 0.91187008

00:53:39.480 --> 00:53:43.320 Is clinical drug responsiveness predictable?

NOTE Confidence: 0.91187008

00:53:43.320 --> 00:53:46.120 So can we show that a drug that we know

NOTE Confidence: 0.91187008

00:53:46.196 --> 00:53:48.638 patients respond to in the clinic,

NOTE Confidence: 0.91187008

00:53:48.640 --> 00:53:50.410 can we show that their neurons

NOTE Confidence: 0.91187008

00:53:50.410 --> 00:53:51.880 respond to that drug too?

NOTE Confidence: 0.91187008

00:53:51.880 --> 00:53:54.238 So if we were to do this experiment properly,

NOTE Confidence: 0.946461733571428

00:53:54.240 --> 00:53:57.024 you would want to have a drug where

NOTE Confidence: 0.946461733571428

00:53:57.024 --> 00:53:59.718 patients show a lifetime stable response.

NOTE Confidence: 0.946461733571428

00:53:59.720 --> 00:54:01.862 Now as psychiatrists, I think you know

NOTE Confidence: 0.946461733571428

00:54:01.862 --> 00:54:04.751 how small a list of drugs we have where

NOTE Confidence: 0.946461733571428

00:54:04.751 --> 00:54:06.640 patients show show clear lifetime,  
NOTE Confidence: 0.946461733571428

00:54:06.640 --> 00:54:07.434 stable responsiveness.  
NOTE Confidence: 0.946461733571428

00:54:07.434 --> 00:54:10.610 Ideally, you would also use a drug where  
NOTE Confidence: 0.946461733571428

00:54:10.673 --> 00:54:12.513 patient responsiveness is predicted  
NOTE Confidence: 0.946461733571428

00:54:12.513 --> 00:54:15.273 by the responsiveness of their family  
NOTE Confidence: 0.946461733571428

00:54:15.336 --> 00:54:17.919 members who might have the same disorder.  
NOTE Confidence: 0.946461733571428

00:54:17.920 --> 00:54:20.104 So we're looking for a heritable  
NOTE Confidence: 0.946461733571428

00:54:20.104 --> 00:54:21.560 lifetime stable drug response.  
NOTE Confidence: 0.946461733571428

00:54:21.560 --> 00:54:22.508 I don't know how many are  
NOTE Confidence: 0.946461733571428

00:54:22.508 --> 00:54:23.320 coming to mind for you,  
NOTE Confidence: 0.946461733571428

00:54:23.320 --> 00:54:25.276 but the best example I've seen  
NOTE Confidence: 0.946461733571428

00:54:25.276 --> 00:54:27.632 of this gold standard example is  
NOTE Confidence: 0.946461733571428

00:54:27.632 --> 00:54:29.600 lithium responsive bipolar disorder.  
NOTE Confidence: 0.946461733571428

00:54:29.600 --> 00:54:31.796 So not true for every patient,  
NOTE Confidence: 0.946461733571428

00:54:31.800 --> 00:54:32.920 but there is, you know,  
NOTE Confidence: 0.946461733571428

00:54:32.920 --> 00:54:35.460 a very heritable and lifetime

NOTE Confidence: 0.946461733571428  
00:54:35.460 --> 00:54:38.000 stable proportion of patients here.  
NOTE Confidence: 0.946461733571428  
00:54:38.000 --> 00:54:40.088 So this was back when I was still  
NOTE Confidence: 0.946461733571428  
00:54:40.088 --> 00:54:42.168 a postdoc with Rusty but work that  
NOTE Confidence: 0.946461733571428  
00:54:42.168 --> 00:54:43.944 was you know really nicely finished  
NOTE Confidence: 0.946461733571428  
00:54:43.944 --> 00:54:46.015 by Jerel Mertens and Jun Yao.  
NOTE Confidence: 0.946461733571428  
00:54:46.015 --> 00:54:48.290 We were able to recruit 6 patients  
NOTE Confidence: 0.946461733571428  
00:54:48.359 --> 00:54:49.880 with bipolar disorder,  
NOTE Confidence: 0.946461733571428  
00:54:49.880 --> 00:54:51.240 three of them lithium responsive,  
NOTE Confidence: 0.946461733571428  
00:54:51.240 --> 00:54:53.184 three of them non lithium responsive  
NOTE Confidence: 0.946461733571428  
00:54:53.184 --> 00:54:54.156 and three controls.  
NOTE Confidence: 0.946461733571428  
00:54:54.160 --> 00:54:56.752 The neurons from the bipolar cases  
NOTE Confidence: 0.946461733571428  
00:54:56.752 --> 00:54:58.480 were universally hyper excitable,  
NOTE Confidence: 0.946461733571428  
00:54:58.480 --> 00:55:00.754 but only those neurons from lithium  
NOTE Confidence: 0.946461733571428  
00:55:00.754 --> 00:55:02.270 responsive cases showed reduced  
NOTE Confidence: 0.946461733571428  
00:55:02.336 --> 00:55:04.316 activity when treated with lithium.  
NOTE Confidence: 0.946461733571428

00:55:04.320 --> 00:55:06.738 The non responsive cases showed no  
NOTE Confidence: 0.946461733571428

00:55:06.738 --> 00:55:09.000 reduced activity in lithium treatment  
NOTE Confidence: 0.946461733571428

00:55:09.000 --> 00:55:10.686 and Rusty then subsequently went and  
NOTE Confidence: 0.946461733571428

00:55:10.686 --> 00:55:12.425 got a second cohort lithium responsive  
NOTE Confidence: 0.946461733571428

00:55:12.425 --> 00:55:14.673 cases and was there able to show that  
NOTE Confidence: 0.946461733571428

00:55:14.727 --> 00:55:16.473 by doing activity recording from just  
NOTE Confidence: 0.946461733571428

00:55:16.473 --> 00:55:18.588 five neurons with or without lithium,  
NOTE Confidence: 0.946461733571428

00:55:18.588 --> 00:55:21.432 he could predict which patients had  
NOTE Confidence: 0.946461733571428

00:55:21.432 --> 00:55:23.603 lithium responsive or non responsive  
NOTE Confidence: 0.946461733571428

00:55:23.603 --> 00:55:25.913 bipolar with an accuracy over 90%.  
NOTE Confidence: 0.946461733571428

00:55:25.920 --> 00:55:28.674 So I think this is the gold standard example,  
NOTE Confidence: 0.946461733571428

00:55:28.680 --> 00:55:30.741 but it's the one that we hold out for  
NOTE Confidence: 0.946461733571428

00:55:30.741 --> 00:55:32.834 that we might be able to to follow up.  
NOTE Confidence: 0.946461733571428

00:55:32.840 --> 00:55:35.016 And so we've gone back to this convergence  
NOTE Confidence: 0.946461733571428

00:55:35.016 --> 00:55:37.664 idea and asked if we can use this to  
NOTE Confidence: 0.946461733571428

00:55:37.664 --> 00:55:39.080 predict drug responsiveness or sorry,

NOTE Confidence: 0.946461733571428  
00:55:39.080 --> 00:55:41.201 if we can use convergence to predict  
NOTE Confidence: 0.946461733571428  
00:55:41.201 --> 00:55:43.153 novel drugs that we could then  
NOTE Confidence: 0.946461733571428  
00:55:43.153 --> 00:55:44.793 test responsiveness to in cells.  
NOTE Confidence: 0.946461733571428  
00:55:44.800 --> 00:55:47.173 And so Kayla's looking at drugs that  
NOTE Confidence: 0.946461733571428  
00:55:47.173 --> 00:55:48.880 reverse our convergent signatures.  
NOTE Confidence: 0.946461733571428  
00:55:48.880 --> 00:55:51.376 I think these are convergent targets  
NOTE Confidence: 0.946461733571428  
00:55:51.376 --> 00:55:53.040 of schizophrenia risk genes.  
NOTE Confidence: 0.946461733571428  
00:55:53.040 --> 00:55:55.472 But one of the top drugs that she  
NOTE Confidence: 0.946461733571428  
00:55:55.472 --> 00:55:57.208 predicted is actually glucocorticoid  
NOTE Confidence: 0.946461733571428  
00:55:57.208 --> 00:55:59.320 receptor stress hormones, right?  
NOTE Confidence: 0.946461733571428  
00:55:59.320 --> 00:56:01.520 So everything kind of keeps  
NOTE Confidence: 0.946461733571428  
00:56:01.520 --> 00:56:03.280 coming back full circle.  
NOTE Confidence: 0.946461733571428  
00:56:03.280 --> 00:56:04.856 This was not the first drug that we  
NOTE Confidence: 0.946461733571428  
00:56:04.856 --> 00:56:06.439 tested on her convergent signatures.  
NOTE Confidence: 0.946461733571428  
00:56:06.440 --> 00:56:08.396 Here we're looking at a toxamir.  
NOTE Confidence: 0.946461733571428

00:56:08.400 --> 00:56:10.040 This data is not being  
NOTE Confidence: 0.946461733571428

00:56:10.040 --> 00:56:11.680 presented the most clear way,  
NOTE Confidence: 0.946461733571428

00:56:11.680 --> 00:56:14.585 but the green is the genome wide  
NOTE Confidence: 0.946461733571428

00:56:14.585 --> 00:56:17.316 effect of our risk variants on gene  
NOTE Confidence: 0.946461733571428

00:56:17.316 --> 00:56:19.628 expression and the yellow dots I  
NOTE Confidence: 0.946461733571428

00:56:19.628 --> 00:56:21.716 think you can see are flattened.  
NOTE Confidence: 0.946461733571428

00:56:21.720 --> 00:56:24.924 So the the genome wide effect of risk is  
NOTE Confidence: 0.946461733571428

00:56:24.924 --> 00:56:27.278 being minimized by treatment with a TOXAMIR.  
NOTE Confidence: 0.946461733571428

00:56:27.280 --> 00:56:29.160 And so this is kind of the way  
NOTE Confidence: 0.946461733571428

00:56:29.160 --> 00:56:31.122 that we're trying to screen for  
NOTE Confidence: 0.946461733571428

00:56:31.122 --> 00:56:32.554 impact on convergent effects.  
NOTE Confidence: 0.946461733571428

00:56:32.560 --> 00:56:34.126 I don't have any more data  
NOTE Confidence: 0.946461733571428

00:56:34.126 --> 00:56:35.920 on drug NIST at this point,  
NOTE Confidence: 0.946461733571428

00:56:35.920 --> 00:56:36.808 but it's kind of the model  
NOTE Confidence: 0.946461733571428

00:56:36.808 --> 00:56:37.400 that we're looking at.  
NOTE Confidence: 0.946461733571428

00:56:37.400 --> 00:56:39.479 Can we identify new not new drugs

NOTE Confidence: 0.946461733571428

00:56:39.479 --> 00:56:41.388 that might perturb not those risk

NOTE Confidence: 0.946461733571428

00:56:41.388 --> 00:56:43.023 genes but their shared downstream

NOTE Confidence: 0.946461733571428

00:56:43.023 --> 00:56:44.842 effects and ultimately will this

NOTE Confidence: 0.946461733571428

00:56:44.842 --> 00:56:45.916 inform patient outcomes.

NOTE Confidence: 0.9194437345

00:56:45.920 --> 00:56:47.792 And so the idea that I want to leave

NOTE Confidence: 0.9194437345

00:56:47.792 --> 00:56:50.083 you with is that genetics alone does

NOTE Confidence: 0.9194437345

00:56:50.083 --> 00:56:51.435 not determine clinical outcomes.

NOTE Confidence: 0.9194437345

00:56:51.440 --> 00:56:52.840 But as I think all of you know,

NOTE Confidence: 0.9194437345

00:56:52.840 --> 00:56:54.788 psychiatric disorders are much

NOTE Confidence: 0.9194437345

00:56:54.788 --> 00:56:57.223 more complex in etiology than

NOTE Confidence: 0.9194437345

00:56:57.223 --> 00:56:59.838 I think anybody anticipated.

NOTE Confidence: 0.9194437345

00:56:59.840 --> 00:57:01.740 With advancing genetic studies,

NOTE Confidence: 0.9194437345

00:57:01.740 --> 00:57:05.283 we have now identified hundreds of risk

NOTE Confidence: 0.9194437345

00:57:05.283 --> 00:57:07.759 variants across psychiatric disorders.

NOTE Confidence: 0.9194437345

00:57:07.760 --> 00:57:10.352 And I think one of the most obvious outcomes

NOTE Confidence: 0.9194437345

00:57:10.352 --> 00:57:13.000 will be that we'll have genetic risk scores.  
NOTE Confidence: 0.9194437345

00:57:13.000 --> 00:57:15.120 Now they're not accurate yet,  
NOTE Confidence: 0.9194437345

00:57:15.120 --> 00:57:17.718 but I think this is coming.  
NOTE Confidence: 0.9194437345

00:57:17.720 --> 00:57:18.632 That being said,  
NOTE Confidence: 0.9194437345

00:57:18.632 --> 00:57:20.760 these genetic risk scores will never be  
NOTE Confidence: 0.9194437345

00:57:20.815 --> 00:57:23.335 perfect if we don't take into account the  
NOTE Confidence: 0.9194437345

00:57:23.335 --> 00:57:25.160 environment that our patients live in.  
NOTE Confidence: 0.9194437345

00:57:25.160 --> 00:57:28.065 So it's important to think about things  
NOTE Confidence: 0.9194437345

00:57:28.065 --> 00:57:30.840 like social supports and housing security,  
NOTE Confidence: 0.9194437345

00:57:30.840 --> 00:57:33.156 but it's also important to think  
NOTE Confidence: 0.9194437345

00:57:33.156 --> 00:57:34.314 about drug exposures,  
NOTE Confidence: 0.9194437345

00:57:34.320 --> 00:57:38.718 nutrition and pollutants in the environment.  
NOTE Confidence: 0.9194437345

00:57:38.720 --> 00:57:40.826 All of these things together are  
NOTE Confidence: 0.9194437345

00:57:40.826 --> 00:57:43.109 going to inform the outcomes in  
NOTE Confidence: 0.9194437345

00:57:43.109 --> 00:57:45.560 our patients and it's going to be  
NOTE Confidence: 0.9194437345

00:57:45.560 --> 00:57:47.200 important to advocate for equity,

NOTE Confidence: 0.9194437345

00:57:47.200 --> 00:57:49.216 right in some of the context

NOTE Confidence: 0.9194437345

00:57:49.216 --> 00:57:50.560 in which people live.

NOTE Confidence: 0.9194437345

00:57:50.560 --> 00:57:51.481 And the final,

NOTE Confidence: 0.9194437345

00:57:51.481 --> 00:57:53.016 more optimistic thought that I

NOTE Confidence: 0.9194437345

00:57:53.016 --> 00:57:54.877 want to leave you with is that

NOTE Confidence: 0.9194437345

00:57:54.877 --> 00:57:56.856 if we can begin to really dissect

NOTE Confidence: 0.9194437345

00:57:56.856 --> 00:57:58.676 the mechanisms of these gene,

NOTE Confidence: 0.9194437345

00:57:58.680 --> 00:58:00.665 gene and gene environment interactions

NOTE Confidence: 0.9194437345

00:58:00.665 --> 00:58:03.640 that I'm hoping it will inform what

NOTE Confidence: 0.9194437345

00:58:03.640 --> 00:58:05.476 I'm calling genetic resilience.

NOTE Confidence: 0.9194437345

00:58:05.480 --> 00:58:07.405 If we understand why when you put

NOTE Confidence: 0.9194437345

00:58:07.405 --> 00:58:09.240 some genes with some environment,

NOTE Confidence: 0.9194437345

00:58:09.240 --> 00:58:11.400 the effects are less than we would expect,

NOTE Confidence: 0.9194437345

00:58:11.400 --> 00:58:13.404 are those pathways that we can

NOTE Confidence: 0.9194437345

00:58:13.404 --> 00:58:15.132 target to decrease the impact

NOTE Confidence: 0.9194437345

00:58:15.132 --> 00:58:17.076 of genetic risk in our cases?  
NOTE Confidence: 0.9194437345

00:58:17.080 --> 00:58:18.712 And this is really what I'm hoping that  
NOTE Confidence: 0.9194437345

00:58:18.712 --> 00:58:20.480 the lab will ultimately be able to do.  
NOTE Confidence: 0.9194437345

00:58:20.480 --> 00:58:22.328 How do we allow everyone to  
NOTE Confidence: 0.9194437345

00:58:22.328 --> 00:58:23.560 achieve their genetic maximum,  
NOTE Confidence: 0.9194437345

00:58:23.560 --> 00:58:25.570 the best possible outcome given the  
NOTE Confidence: 0.9194437345

00:58:25.570 --> 00:58:27.839 genetic risk that they were born with?  
NOTE Confidence: 0.9194437345

00:58:27.840 --> 00:58:31.116 Can we inform clinical treatments by gene,  
NOTE Confidence: 0.9194437345

00:58:31.120 --> 00:58:33.200 gene and gene environment interactions?  
NOTE Confidence: 0.9194437345

00:58:33.200 --> 00:58:34.240 And so with that,  
NOTE Confidence: 0.9194437345

00:58:34.240 --> 00:58:36.479 this is the most important slide in the deck.  
NOTE Confidence: 0.9194437345

00:58:36.480 --> 00:58:38.314 These are all the people who contributed  
NOTE Confidence: 0.9194437345

00:58:38.314 --> 00:58:40.160 to the work that I've shown you.  
NOTE Confidence: 0.9194437345

00:58:40.160 --> 00:58:41.518 A lot of the gene environment stuff  
NOTE Confidence: 0.9194437345

00:58:41.518 --> 00:58:42.958 was by Kayla Townsley and Karina.  
NOTE Confidence: 0.9194437345

00:58:42.960 --> 00:58:47.040 So Michael led the autism studies.

NOTE Confidence: 0.9194437345

00:58:47.040 --> 00:58:48.200 It's been, you know,

NOTE Confidence: 0.9194437345

00:58:48.200 --> 00:58:50.291 a remarkable effort over the last 10

NOTE Confidence: 0.9194437345

00:58:50.291 --> 00:58:52.356 years to really pull this story together.

NOTE Confidence: 0.9194437345

00:58:52.360 --> 00:58:53.044 And with that,

NOTE Confidence: 0.9194437345

00:58:53.044 --> 00:58:55.000 I know I I'm kind of at time,

NOTE Confidence: 0.9194437345

00:58:55.000 --> 00:58:56.554 but I'm happy to take questions too.

NOTE Confidence: 0.21696029

00:59:02.280 --> 00:59:03.918 Well, let's stop

NOTE Confidence: 0.76760735

00:59:04.000 --> 00:59:05.960 playing. Yeah, I believe the

NOTE Confidence: 0.76760735

00:59:05.960 --> 00:59:07.920 audience might should be unmuted.

NOTE Confidence: 0.76760735

00:59:07.920 --> 00:59:10.285 Anyone has question for example

NOTE Confidence: 0.76760735

00:59:10.285 --> 00:59:11.840 and I know we are at times.

NOTE Confidence: 0.76760735

00:59:11.840 --> 00:59:13.070 So if anyone wants to leave

NOTE Confidence: 0.76760735

00:59:13.070 --> 00:59:14.160 and anyone wants to stay,

NOTE Confidence: 0.76760735

00:59:14.160 --> 00:59:15.920 we continue the conversation.

NOTE Confidence: 0.7262500475

00:59:21.840 --> 00:59:22.600 Thanks for the next

NOTE Confidence: 0.435390025

00:59:22.640 --> 00:59:25.678 talk. I'd like to the time frame  
NOTE Confidence: 0.435390025

00:59:25.680 --> 00:59:28.080 was the stress exposure to the  
NOTE Confidence: 0.435390025

00:59:28.080 --> 00:59:29.850 courses or how long was it?  
NOTE Confidence: 0.435390025

00:59:29.850 --> 00:59:34.020 How do you reconcile your findings  
NOTE Confidence: 0.435390025

00:59:34.020 --> 00:59:36.600 with findings that hydrocortisone  
NOTE Confidence: 0.435390025

00:59:36.600 --> 00:59:38.880 might be preventive for PTSD?  
NOTE Confidence: 0.81888974625

00:59:39.280 --> 00:59:40.680 Yeah, the the hydrocortisone  
NOTE Confidence: 0.81888974625

00:59:40.680 --> 00:59:42.080 field is really confusing.  
NOTE Confidence: 0.81888974625

00:59:42.080 --> 00:59:43.600 I'm going to be honest.  
NOTE Confidence: 0.81888974625

00:59:43.600 --> 00:59:45.538 One of the things that we don't  
NOTE Confidence: 0.81888974625

00:59:45.538 --> 00:59:47.228 even really know is whether  
NOTE Confidence: 0.81888974625

00:59:47.228 --> 00:59:48.881 what's important is exposure to  
NOTE Confidence: 0.81888974625

00:59:48.881 --> 00:59:50.596 H court or recovery from H court.  
NOTE Confidence: 0.81888974625

00:59:50.600 --> 00:59:52.715 And given that we only had one time point,  
NOTE Confidence: 0.81888974625

00:59:52.720 --> 00:59:55.005 I can't even resolve that  
NOTE Confidence: 0.81888974625

00:59:55.005 --> 00:59:56.184 simple question, right?

NOTE Confidence: 0.81888974625

00:59:56.184 --> 00:59:58.560 Is it that the patient just wanted faster or

NOTE Confidence: 0.81888974625

00:59:58.620 --> 01:00:00.796 came down slower on our 24 hour treatment?

NOTE Confidence: 0.81888974625

01:00:00.800 --> 01:00:03.752 There's a ton of work to be done there.

NOTE Confidence: 0.81888974625

01:00:03.760 --> 01:00:05.992 We picked a 24 hour treatment

NOTE Confidence: 0.81888974625

01:00:05.992 --> 01:00:07.872 honestly because the field had

NOTE Confidence: 0.81888974625

01:00:07.872 --> 01:00:09.477 been using that in blood.

NOTE Confidence: 0.81888974625

01:00:09.480 --> 01:00:13.314 I think stress can be both acute and chronic.

NOTE Confidence: 0.81888974625

01:00:13.320 --> 01:00:14.724 This is not all of it and even more

NOTE Confidence: 0.81888974625

01:00:14.724 --> 01:00:16.281 so remember that I told you that

NOTE Confidence: 0.81888974625

01:00:16.281 --> 01:00:17.639 neurons that we're making are young,

NOTE Confidence: 0.81888974625

01:00:17.640 --> 01:00:18.561 they're fetal like.

NOTE Confidence: 0.81888974625

01:00:18.561 --> 01:00:20.710 So I'm not even sure we're modeling

NOTE Confidence: 0.81888974625

01:00:20.767 --> 01:00:22.362 the type of environment that

NOTE Confidence: 0.81888974625

01:00:22.362 --> 01:00:24.172 would cause PTSDI think we're more

NOTE Confidence: 0.81888974625

01:00:24.172 --> 01:00:25.930 accurately modeling the type of fetal

NOTE Confidence: 0.81888974625

01:00:25.982 --> 01:00:27.837 environment that might cause outcomes,  
NOTE Confidence: 0.81888974625

01:00:27.840 --> 01:00:28.170 right.  
NOTE Confidence: 0.81888974625

01:00:28.170 --> 01:00:30.150 But then again that's why it's  
NOTE Confidence: 0.81888974625

01:00:30.150 --> 01:00:32.447 so amazing that we were able to  
NOTE Confidence: 0.81888974625

01:00:32.447 --> 01:00:33.996 reproduce our stress dynamic EQTLS  
NOTE Confidence: 0.81888974625

01:00:33.996 --> 01:00:35.850 in a postmortem base that where  
NOTE Confidence: 0.81888974625

01:00:35.909 --> 01:00:37.767 people had adult exposures, right.  
NOTE Confidence: 0.81888974625

01:00:37.767 --> 01:00:39.969 Like I was shocked at the  
NOTE Confidence: 0.81888974625

01:00:39.969 --> 01:00:42.280 percentage and that half of our our,  
NOTE Confidence: 0.81888974625

01:00:42.280 --> 01:00:44.196 our variants replicated here.  
NOTE Confidence: 0.81888974625

01:00:44.196 --> 01:00:47.070 We've got adult human brains with  
NOTE Confidence: 0.81888974625

01:00:47.147 --> 01:00:48.999 adult trauma exposures decades  
NOTE Confidence: 0.81888974625

01:00:48.999 --> 01:00:51.777 ago and fetal like human cells  
NOTE Confidence: 0.81888974625

01:00:51.862 --> 01:00:54.305 with acute exposures a day ago and  
NOTE Confidence: 0.81888974625

01:00:54.305 --> 01:00:56.290 and half of it's replicating.  
NOTE Confidence: 0.81888974625

01:00:56.290 --> 01:00:59.545 And so it might mean that neurons

NOTE Confidence: 0.81888974625

01:00:59.545 --> 01:01:01.786 respond to stress pretty similarly

NOTE Confidence: 0.81888974625

01:01:01.786 --> 01:01:03.758 regardless of their maturation.

NOTE Confidence: 0.81888974625

01:01:03.760 --> 01:01:04.476 That's possible,

NOTE Confidence: 0.81888974625

01:01:04.476 --> 01:01:06.624 but there's a lot of specificity

NOTE Confidence: 0.81888974625

01:01:06.624 --> 01:01:08.680 here that has to get untangled.

NOTE Confidence: 0.6949646

01:01:11.040 --> 01:01:12.120 Thanks for the great talk, Kristen.

NOTE Confidence: 0.963165035714286

01:01:12.120 --> 01:01:14.955 I was wondering with any of the

NOTE Confidence: 0.963165035714286

01:01:14.960 --> 01:01:17.260 patient derived stem cell samples

NOTE Confidence: 0.963165035714286

01:01:17.260 --> 01:01:19.560 schizophrenia that you've worked with,

NOTE Confidence: 0.963165035714286

01:01:19.560 --> 01:01:22.500 has there ever been a correlation between

NOTE Confidence: 0.963165035714286

01:01:22.500 --> 01:01:24.918 what you've observed in these cells,

NOTE Confidence: 0.963165035714286

01:01:24.918 --> 01:01:27.234 any sort of phenotype with symptoms,

NOTE Confidence: 0.963165035714286

01:01:27.240 --> 01:01:29.380 severity, onset of illness or

NOTE Confidence: 0.963165035714286

01:01:29.380 --> 01:01:31.092 any other behaviorally observable

NOTE Confidence: 0.963165035714286

01:01:31.092 --> 01:01:32.399 characteristic of the patient?

NOTE Confidence: 0.71700234

01:01:33.000 --> 01:01:35.560 It's a great question.  
NOTE Confidence: 0.71700234

01:01:35.560 --> 01:01:37.807 I think this kind of thing depends  
NOTE Confidence: 0.71700234

01:01:37.807 --> 01:01:40.118 on the cohort that you get right.  
NOTE Confidence: 0.71700234

01:01:40.120 --> 01:01:42.928 So the patients that a lot of my work  
NOTE Confidence: 0.71700234

01:01:42.928 --> 01:01:45.322 initially represented were with Judy  
NOTE Confidence: 0.71700234

01:01:45.322 --> 01:01:47.832 Rapport on childhood onset schizophrenia,  
NOTE Confidence: 0.71700234

01:01:47.840 --> 01:01:50.198 all of whom are particularly severe.  
NOTE Confidence: 0.71700234

01:01:50.200 --> 01:01:52.880 I thought at the time this was 15 years ago,  
NOTE Confidence: 0.71700234

01:01:52.880 --> 01:01:54.518 this would be a great cohort because  
NOTE Confidence: 0.71700234

01:01:54.518 --> 01:01:55.934 they were the youngest on set  
NOTE Confidence: 0.71700234

01:01:55.934 --> 01:01:57.474 and I knew my cells were young.  
NOTE Confidence: 0.71700234

01:01:57.480 --> 01:01:59.664 But in hindsight it was a terrible choice  
NOTE Confidence: 0.71700234

01:01:59.664 --> 01:02:01.877 because they were all very severely impacted,  
NOTE Confidence: 0.71700234

01:02:01.880 --> 01:02:04.718 but through very different rare variants.  
NOTE Confidence: 0.71700234

01:02:04.720 --> 01:02:07.440 I don't think any of my cohorts we,  
NOTE Confidence: 0.71700234

01:02:07.440 --> 01:02:09.078 I guess what I can say in the PTSD,

NOTE Confidence: 0.71700234

01:02:09.080 --> 01:02:10.540 we checked for correlations,

NOTE Confidence: 0.71700234

01:02:10.540 --> 01:02:12.000 didn't really see it.

NOTE Confidence: 0.71700234

01:02:12.000 --> 01:02:13.536 Honestly, Florabacarina has one

NOTE Confidence: 0.71700234

01:02:13.536 --> 01:02:15.456 of the best demonstrations of

NOTE Confidence: 0.71700234

01:02:15.456 --> 01:02:17.358 this in the context of autism.

NOTE Confidence: 0.71700234

01:02:17.360 --> 01:02:20.920 I think it was looking at language delays,

NOTE Confidence: 0.71700234

01:02:20.920 --> 01:02:22.848 but you really have to have the right

NOTE Confidence: 0.71700234

01:02:22.848 --> 01:02:24.879 cohort to be able to quantify symptoms,

NOTE Confidence: 0.71700234

01:02:24.880 --> 01:02:26.632 severity and have a good enough

NOTE Confidence: 0.71700234

01:02:26.632 --> 01:02:27.800 power to do it.

NOTE Confidence: 0.71700234

01:02:27.800 --> 01:02:30.680 So I haven't been able to, a few others have.

NOTE Confidence: 0.78826378

01:02:34.840 --> 01:02:36.068 Well, that was through the force.

NOTE Confidence: 0.78826378

01:02:36.068 --> 01:02:37.310 Thank you so much for an

NOTE Confidence: 0.78826378

01:02:37.362 --> 01:02:40.040 excellent talk and thank you.