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 nerdogenerative 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 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 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 plea atrophic.

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 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 pliotrophic,

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 Exxon 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 spice 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 nerexin 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 mutan

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 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.