

WEBVTT

NOTE duration:"00:17:15.2620000"

NOTE language:en-us

NOTE Confidence: 0.83446324

00:00:00.000 --> 00:00:01.974 My name is Karen Marshall an I'm

NOTE Confidence: 0.83446324

00:00:01.974 --> 00:00:04.011 a PhD student in the genetics

NOTE Confidence: 0.83446324

00:00:04.011 --> 00:00:05.881 Department and Doctor Bloom malicious

NOTE Confidence: 0.83446324

00:00:05.881 --> 00:00:08.200 lab and it's my privilege to

NOTE Confidence: 0.83446324

00:00:08.200 --> 00:00:10.075 introduce our next speaker doctor,

NOTE Confidence: 0.83446324

00:00:10.080 --> 00:00:11.810 Kristin Byrne and Doctor Brown,

NOTE Confidence: 0.83446324

00:00:11.810 --> 00:00:14.194 and is a new faculty member in the

NOTE Confidence: 0.83446324

00:00:14.194 --> 00:00:15.954 Department of Psychiatry at the

NOTE Confidence: 0.83446324

00:00:15.954 --> 00:00:18.150 Yale School of Medicine and most

NOTE Confidence: 0.83446324

00:00:18.150 --> 00:00:20.025 recently was an associate professor

NOTE Confidence: 0.83446324

00:00:20.025 --> 00:00:22.185 in the Pamela Sklar division of

NOTE Confidence: 0.83446324

00:00:22.190 --> 00:00:23.920 Psychiatric Genomics at Mount Sinai.

NOTE Confidence: 0.83446324

00:00:23.920 --> 00:00:25.695 Her research integrates stem cell

NOTE Confidence: 0.83446324

00:00:25.695 --> 00:00:27.470 based approaches with CRISPR mediated

NOTE Confidence: 0.83446324

00:00:27.524 --> 00:00:28.454 genomic engineering strategies

NOTE Confidence: 0.83446324

00:00:28.454 --> 00:00:30.624 in order to study the impact of

NOTE Confidence: 0.83446324

00:00:30.678 --> 00:00:32.330 patient specific variance across.

NOTE Confidence: 0.83446324

00:00:32.330 --> 00:00:34.874 In between the cell types of the brain,

NOTE Confidence: 0.83446324

00:00:34.880 --> 00:00:37.232 the goal of her research is to uncover

NOTE Confidence: 0.83446324

00:00:37.232 --> 00:00:38.831 the convergence and synergy arising

NOTE Confidence: 0.83446324

00:00:38.831 --> 00:00:41.043 from the complex interplay of the many

NOTE Confidence: 0.83446324

00:00:41.105 --> 00:00:43.175 risk variants linked to brain disease,

NOTE Confidence: 0.83446324

00:00:43.180 --> 00:00:45.724 and her work is funded by the NIH,

NOTE Confidence: 0.83446324

00:00:45.730 --> 00:00:47.638 the New York Stem Cell Foundation,

NOTE Confidence: 0.83446324

00:00:47.640 --> 00:00:48.828 the Brain Research Foundation,

NOTE Confidence: 0.83446324

00:00:48.828 --> 00:00:50.313 and the brain and Behavior

NOTE Confidence: 0.83446324

00:00:50.313 --> 00:00:51.150 Research Foundation.

NOTE Confidence: 0.83446324

00:00:51.150 --> 00:00:52.430 Thank you doctor Brennan.

NOTE Confidence: 0.7978637

00:00:54.300 --> 00:00:56.932 Hey, thank you so much. Anne Anne.

NOTE Confidence: 0.7978637

00:00:56.932 --> 00:00:59.940 Firstly I want to thank Dean Brown uh,
NOTE Confidence: 0.7978637

00:00:59.940 --> 00:01:01.444 an IRA for organizing
NOTE Confidence: 0.7978637

00:01:01.444 --> 00:01:02.948 this really great event.
NOTE Confidence: 0.7978637

00:01:02.950 --> 00:01:05.575 I I really enjoyed myself so much.
NOTE Confidence: 0.7978637

00:01:05.580 --> 00:01:07.770 So to begin the only conflict
NOTE Confidence: 0.7978637

00:01:07.770 --> 00:01:10.452 I have to declare is that my
NOTE Confidence: 0.7978637

00:01:10.452 --> 00:01:12.347 husband works at our Venice.
NOTE Confidence: 0.7978637

00:01:12.350 --> 00:01:14.471 My talk today is about now validating
NOTE Confidence: 0.7978637

00:01:14.471 --> 00:01:16.824 all of the genetic findings that
NOTE Confidence: 0.7978637

00:01:16.824 --> 00:01:19.114 everyone's been talking about today.
NOTE Confidence: 0.7978637

00:01:19.120 --> 00:01:21.633 So using stem cells to explore the
NOTE Confidence: 0.7978637

00:01:21.633 --> 00:01:23.250 genetics underlying brain disease.
NOTE Confidence: 0.85930526

00:01:25.960 --> 00:01:29.050 And a lot of what I'm going to talk about
NOTE Confidence: 0.85930526

00:01:29.128 --> 00:01:32.215 today is in the context of schizophrenia,
NOTE Confidence: 0.85930526

00:01:32.220 --> 00:01:34.464 not because there's anything uniquely suited
NOTE Confidence: 0.85930526

00:01:34.464 --> 00:01:37.369 from of my tools to study this disease,

NOTE Confidence: 0.85930526

00:01:37.370 --> 00:01:40.190 but because it's a highly complex

NOTE Confidence: 0.85930526

00:01:40.190 --> 00:01:42.070 genetic disorder for which

NOTE Confidence: 0.85930526

00:01:42.151 --> 00:01:44.575 there still really are no good.

NOTE Confidence: 0.85930526

00:01:44.580 --> 00:01:45.772 Here's how it is.

NOTE Confidence: 0.85930526

00:01:45.772 --> 00:01:47.900 Extremely common and I'm showing you here.

NOTE Confidence: 0.85930526

00:01:47.900 --> 00:01:49.910 One of the most recent descriptions

NOTE Confidence: 0.85930526

00:01:49.910 --> 00:01:51.833 of the genetics of this disease

NOTE Confidence: 0.85930526

00:01:51.833 --> 00:01:54.278 and what I want you to see is just

NOTE Confidence: 0.85930526

00:01:54.278 --> 00:01:56.357 how there's almost 300 of them is

NOTE Confidence: 0.85930526

00:01:56.357 --> 00:01:57.809 about 250 common variants here,

NOTE Confidence: 0.85930526

00:01:57.809 --> 00:01:59.507 with really small effects of one

NOTE Confidence: 0.85930526

00:01:59.507 --> 00:02:01.190 or two percent increased risk,

NOTE Confidence: 0.85930526

00:02:01.190 --> 00:02:03.290 and then a few dozen rare variants

NOTE Confidence: 0.85930526

00:02:03.290 --> 00:02:05.147 that are either protein truncating

NOTE Confidence: 0.85930526

00:02:05.147 --> 00:02:07.377 variants or copy number variants.

NOTE Confidence: 0.85930526

00:02:07.380 --> 00:02:08.556 And most importantly,
NOTE Confidence: 0.85930526

00:02:08.556 --> 00:02:10.516 genetics here is not diagnostic.
NOTE Confidence: 0.85930526

00:02:10.520 --> 00:02:12.794 There are strong and significant group
NOTE Confidence: 0.85930526

00:02:12.794 --> 00:02:14.850 differences between patients and controls,
NOTE Confidence: 0.85930526

00:02:14.850 --> 00:02:16.992 but we can't yet harness the power
NOTE Confidence: 0.85930526

00:02:16.992 --> 00:02:19.905 of all this genic information to make
NOTE Confidence: 0.85930526

00:02:19.905 --> 00:02:22.310 meaningful insights for their patients.
NOTE Confidence: 0.85930526

00:02:22.310 --> 00:02:25.014 And so the goal then is to derive
NOTE Confidence: 0.85930526

00:02:25.014 --> 00:02:26.737 revised polygenic risk scores
NOTE Confidence: 0.85930526

00:02:26.737 --> 00:02:28.207 that improve diagnostics,
NOTE Confidence: 0.85930526

00:02:28.210 --> 00:02:29.476 predict clinical trajectories,
NOTE Confidence: 0.85930526

00:02:29.476 --> 00:02:32.008 and ultimately allow us to discover
NOTE Confidence: 0.85930526

00:02:32.008 --> 00:02:33.670 novel therapeutic targets.
NOTE Confidence: 0.85930526

00:02:33.670 --> 00:02:34.312 And again,
NOTE Confidence: 0.85930526

00:02:34.312 --> 00:02:36.238 here is the the common variant
NOTE Confidence: 0.85930526

00:02:36.238 --> 00:02:37.730 restructure for schizophrenia.

NOTE Confidence: 0.85930526

00:02:37.730 --> 00:02:40.130 The last time it was published in two

NOTE Confidence: 0.85930526

00:02:40.130 --> 00:02:42.511 2018 is about 145 significant loci

NOTE Confidence: 0.85930526

00:02:42.511 --> 00:02:45.480 here over the genome wide significant line.

NOTE Confidence: 0.85930526

00:02:45.480 --> 00:02:48.144 But the question then here is which of

NOTE Confidence: 0.85930526

00:02:48.144 --> 00:02:50.638 these variants are causal disease variants?

NOTE Confidence: 0.85930526

00:02:50.640 --> 00:02:52.490 There's many sniffs and linkages.

NOTE Confidence: 0.85930526

00:02:52.490 --> 00:02:53.962 Equilibrium at each location.

NOTE Confidence: 0.85930526

00:02:53.962 --> 00:02:55.802 What are their target genes?

NOTE Confidence: 0.85930526

00:02:55.810 --> 00:02:58.054 Were the proximal target genes and

NOTE Confidence: 0.85930526

00:02:58.054 --> 00:03:00.239 there are often more than one.

NOTE Confidence: 0.85930526

00:03:00.240 --> 00:03:02.742 What are the distal target genes

NOTE Confidence: 0.85930526

00:03:02.742 --> 00:03:03.993 that are regulated?

NOTE Confidence: 0.85930526

00:03:04.000 --> 00:03:06.100 Far distances from these risk variants.

NOTE Confidence: 0.85930526

00:03:06.100 --> 00:03:07.850 Are there any context dependent

NOTE Confidence: 0.85930526

00:03:07.850 --> 00:03:09.250 effects and an altogether?

NOTE Confidence: 0.85930526

00:03:09.250 --> 00:03:11.314 Does this answer the question of
NOTE Confidence: 0.85930526

00:03:11.314 --> 00:03:13.100 variable penetrance in this order?
NOTE Confidence: 0.85930526

00:03:13.100 --> 00:03:14.108 And of course,
NOTE Confidence: 0.85930526

00:03:14.108 --> 00:03:17.300 because all of us carry dozens of risk areas.
NOTE Confidence: 0.85930526

00:03:17.300 --> 00:03:19.050 But the patients carry dozens
NOTE Confidence: 0.85930526

00:03:19.050 --> 00:03:20.100 and dozens more.
NOTE Confidence: 0.85930526

00:03:20.100 --> 00:03:21.965 As this really important question
NOTE Confidence: 0.85930526

00:03:21.965 --> 00:03:24.275 of how to experience interact in
NOTE Confidence: 0.85930526

00:03:24.275 --> 00:03:25.815 some because their phenotypic
NOTE Confidence: 0.85930526

00:03:25.815 --> 00:03:27.740 effects only occur in aggregate.
NOTE Confidence: 0.85930526

00:03:27.740 --> 00:03:29.973 Now and so these are the kind
NOTE Confidence: 0.85930526

00:03:29.973 --> 00:03:31.999 of questions my lab is asking.
NOTE Confidence: 0.85930526

00:03:32.000 --> 00:03:33.956 How do risk area risk variant
NOTE Confidence: 0.85930526

00:03:33.956 --> 00:03:35.610 effects vary with polygenic risk.
NOTE Confidence: 0.85930526

00:03:35.610 --> 00:03:37.415 Innocent project led by Christina
NOTE Confidence: 0.85930526

00:03:37.415 --> 00:03:39.548 Brandt across no development led by

NOTE Confidence: 0.85930526

00:03:39.548 --> 00:03:41.186 Liz La Marca between cell types.

NOTE Confidence: 0.85930526

00:03:41.190 --> 00:03:43.170 This is Michael Fernando and Sam

NOTE Confidence: 0.85930526

00:03:43.170 --> 00:03:45.237 Powell across sexes and open project

NOTE Confidence: 0.85930526

00:03:45.237 --> 00:03:47.289 that we haven't really started yet

NOTE Confidence: 0.85930526

00:03:47.289 --> 00:03:49.388 and Karina so and and Kayla towns.

NOTE Confidence: 0.85930526

00:03:49.390 --> 00:03:51.358 They're looking at how they are

NOTE Confidence: 0.85930526

00:03:51.358 --> 00:03:52.670 impacted by the environment,

NOTE Confidence: 0.85930526

00:03:52.670 --> 00:03:54.620 particularly stress.

NOTE Confidence: 0.85930526

00:03:54.620 --> 00:03:55.270 So again,

NOTE Confidence: 0.85930526

00:03:55.270 --> 00:03:57.220 turning back to this gys and

NOTE Confidence: 0.85930526

00:03:57.220 --> 00:03:59.668 asking how do we begin to validate

NOTE Confidence: 0.85930526

00:03:59.668 --> 00:04:01.798 both the variant effects and how

NOTE Confidence: 0.85930526

00:04:01.798 --> 00:04:03.458 their modulated in a dish?

NOTE Confidence: 0.85930526

00:04:03.460 --> 00:04:05.560 And we started here with this

NOTE Confidence: 0.85930526

00:04:05.560 --> 00:04:07.200 particular snip on chromosome 16,

NOTE Confidence: 0.85930526

00:04:07.200 --> 00:04:09.558 and I want to tell you why we picked
NOTE Confidence: 0.85930526

00:04:09.558 --> 00:04:12.201 it because something unique a curd at
NOTE Confidence: 0.85930526

00:04:12.201 --> 00:04:15.019 this location that was seen nowhere else,
NOTE Confidence: 0.85930526

00:04:15.020 --> 00:04:17.474 and there's 145 loci that are
NOTE Confidence: 0.85930526

00:04:17.474 --> 00:04:19.110 above genome wide significance.
NOTE Confidence: 0.85930526

00:04:19.110 --> 00:04:20.157 At this location,
NOTE Confidence: 0.85930526

00:04:20.157 --> 00:04:22.600 the same snip that was most significant
NOTE Confidence: 0.85930526

00:04:22.666 --> 00:04:24.430 for schizophrenia risk in the G
NOTE Confidence: 0.85930526

00:04:24.430 --> 00:04:26.970 was that's the Y axis was also the
NOTE Confidence: 0.85930526

00:04:26.970 --> 00:04:28.920 same snip that was most significant
NOTE Confidence: 0.8053212

00:04:28.920 --> 00:04:30.580 for regulating the expression of
NOTE Confidence: 0.8053212

00:04:30.580 --> 00:04:32.606 the nearby coding gene furin in
NOTE Confidence: 0.8053212

00:04:32.606 --> 00:04:34.146 a brain post mortem collection.
NOTE Confidence: 0.8053212

00:04:34.150 --> 00:04:36.724 And so here what we have is a single
NOTE Confidence: 0.8053212

00:04:36.724 --> 00:04:38.897 putative causal snip linked to disease
NOTE Confidence: 0.8053212

00:04:38.897 --> 00:04:41.669 risk and gene expression of a target gene.

NOTE Confidence: 0.8053212

00:04:41.670 --> 00:04:42.970 The next best examples.

NOTE Confidence: 0.8053212

00:04:42.970 --> 00:04:45.600 I look more like what we see here.

NOTE Confidence: 0.8053212

00:04:45.600 --> 00:04:49.280 It's nap 91 with a cluster of 20 or 30 jeans.

NOTE Confidence: 0.8053212

00:04:49.280 --> 00:04:50.900 That are associated with both disease

NOTE Confidence: 0.8053212

00:04:50.900 --> 00:04:52.540 risk ANAN target gene expression,

NOTE Confidence: 0.8053212

00:04:52.540 --> 00:04:54.395 but we can't really figure out which

NOTE Confidence: 0.8053212

00:04:54.395 --> 00:04:56.851 one or many of these top snips are

NOTE Confidence: 0.8053212

00:04:56.851 --> 00:04:58.451 responsible for the disease effect.

NOTE Confidence: 0.8053212

00:04:58.460 --> 00:05:00.110 It could be that there's one

NOTE Confidence: 0.8053212

00:05:00.110 --> 00:05:01.900 putative causal snip in that cluster

NOTE Confidence: 0.8053212

00:05:01.900 --> 00:05:03.485 that we haven't resolved yet,

NOTE Confidence: 0.8053212

00:05:03.490 --> 00:05:05.457 and it could be that each of

NOTE Confidence: 0.8053212

00:05:05.457 --> 00:05:06.971 these many snypes is confirming

NOTE Confidence: 0.8053212

00:05:06.971 --> 00:05:09.106 part of the risk at that locus,

NOTE Confidence: 0.8053212

00:05:09.110 --> 00:05:12.149 and so this is a project that was led by a

NOTE Confidence: 0.8053212

00:05:12.149 --> 00:05:14.733 former postdoc in the lab and then shroud,
NOTE Confidence: 0.8053212

00:05:14.740 --> 00:05:16.892 and I will head up forever say that
NOTE Confidence: 0.8053212

00:05:16.892 --> 00:05:19.121 she was the bravest postdoc to join
NOTE Confidence: 0.8053212

00:05:19.121 --> 00:05:21.629 the lab because the flip side of that.
NOTE Confidence: 0.8053212

00:05:21.630 --> 00:05:23.786 You know beautiful, clean data for fear.
NOTE Confidence: 0.8053212

00:05:23.790 --> 00:05:25.330 And is this analysis here.
NOTE Confidence: 0.8053212

00:05:25.330 --> 00:05:27.786 This is now the post mortem gene expression.
NOTE Confidence: 0.8053212

00:05:27.790 --> 00:05:29.946 The few and by individual brain sample.
NOTE Confidence: 0.8053212

00:05:29.950 --> 00:05:31.792 So there's about 600 brains in
NOTE Confidence: 0.8053212

00:05:31.792 --> 00:05:32.406 this collection.
NOTE Confidence: 0.8053212

00:05:32.410 --> 00:05:34.240 But what you'll see is these
NOTE Confidence: 0.8053212

00:05:34.240 --> 00:05:35.800 error bars are incredibly huge.
NOTE Confidence: 0.8053212

00:05:35.800 --> 00:05:36.724 There's a very,
NOTE Confidence: 0.8053212

00:05:36.724 --> 00:05:38.880 very significant effect of genotype at Rs.
NOTE Confidence: 0.8053212

00:05:38.880 --> 00:05:41.336 4702, which is in the three prime UTR.
NOTE Confidence: 0.8053212

00:05:41.340 --> 00:05:42.448 The fear in gene.

NOTE Confidence: 0.8053212
00:05:42.448 --> 00:05:44.110 But there's a lot of variation
NOTE Confidence: 0.8053212
00:05:44.173 --> 00:05:45.039 between brains.
NOTE Confidence: 0.8053212
00:05:45.040 --> 00:05:46.575 That's because every brand came
NOTE Confidence: 0.8053212
00:05:46.575 --> 00:05:47.803 from a different person,
NOTE Confidence: 0.8053212
00:05:47.810 --> 00:05:49.350 and these people married at
NOTE Confidence: 0.8053212
00:05:49.350 --> 00:05:50.890 many many genotype genome wide,
NOTE Confidence: 0.8053212
00:05:50.890 --> 00:05:52.760 not just the Rs 4702.
NOTE Confidence: 0.8053212
00:05:52.760 --> 00:05:54.656 Some of these people had schizophrenia
NOTE Confidence: 0.8053212
00:05:54.656 --> 00:05:55.920 or some did not.
NOTE Confidence: 0.8053212
00:05:55.920 --> 00:05:57.180 They had different histories
NOTE Confidence: 0.8053212
00:05:57.180 --> 00:05:58.125 of antipsychotic treatment,
NOTE Confidence: 0.8053212
00:05:58.130 --> 00:05:59.394 drug and alcohol abuse.
NOTE Confidence: 0.8053212
00:05:59.394 --> 00:06:00.658 They were different sexes.
NOTE Confidence: 0.8053212
00:06:00.660 --> 00:06:02.452 They do have different causes in a
NOTE Confidence: 0.8053212
00:06:02.452 --> 00:06:04.060 different ages and different postmortem
NOTE Confidence: 0.8053212

00:06:04.060 --> 00:06:06.030 intervals before they were examined.

NOTE Confidence: 0.8053212

00:06:06.030 --> 00:06:07.710 And so our hypothesis was really

NOTE Confidence: 0.8053212

00:06:07.710 --> 00:06:10.272 that if we did the experiment in the

NOTE Confidence: 0.8053212

00:06:10.272 --> 00:06:12.342 dish in the same genetic background,

NOTE Confidence: 0.8053212

00:06:12.350 --> 00:06:13.702 we controlled everything and

NOTE Confidence: 0.8053212

00:06:13.702 --> 00:06:15.730 generated the neurons in parallel in

NOTE Confidence: 0.8053212

00:06:15.788 --> 00:06:17.268 neighboring wells or hypothesis was

NOTE Confidence: 0.8053212

00:06:17.268 --> 00:06:19.413 that we would see the same effect

NOTE Confidence: 0.8053212

00:06:19.413 --> 00:06:20.923 size but the variation between

NOTE Confidence: 0.8053212

00:06:20.923 --> 00:06:22.572 samples will be dramatically reduced.

NOTE Confidence: 0.8053212

00:06:22.572 --> 00:06:24.056 And so with that,

NOTE Confidence: 0.8053212

00:06:24.060 --> 00:06:25.868 Nadine took out to be set out to

NOTE Confidence: 0.8053212

00:06:25.868 --> 00:06:27.900 begin this editing of a single non

NOTE Confidence: 0.8053212

00:06:27.900 --> 00:06:29.425 coding snippet actually turned out

NOTE Confidence: 0.8053212

00:06:29.479 --> 00:06:31.320 to be much harder than we expected.

NOTE Confidence: 0.8053212

00:06:31.320 --> 00:06:32.952 Took about two years to achieve

NOTE Confidence: 0.8053212

00:06:32.952 --> 00:06:35.351 or what you can see here is that a

NOTE Confidence: 0.8053212

00:06:35.351 --> 00:06:37.240 single snip in the three prime UTR,

NOTE Confidence: 0.8053212

00:06:37.240 --> 00:06:39.550 the Fusion gene again have been

NOTE Confidence: 0.8053212

00:06:39.550 --> 00:06:40.320 edited successfully.

NOTE Confidence: 0.8053212

00:06:40.320 --> 00:06:42.480 And when she generated generated neurons

NOTE Confidence: 0.8053212

00:06:42.480 --> 00:06:44.840 from these isagenix mashta stem cell lines,

NOTE Confidence: 0.8053212

00:06:44.840 --> 00:06:46.008 just as we predicted,

NOTE Confidence: 0.8053212

00:06:46.008 --> 00:06:48.668 the team was able to see a significant

NOTE Confidence: 0.8053212

00:06:48.668 --> 00:06:50.758 decrease in fear and expression.

NOTE Confidence: 0.8053212

00:06:50.760 --> 00:06:51.069 Now,

NOTE Confidence: 0.8053212

00:06:51.069 --> 00:06:53.541 in the two years that it took to

NOTE Confidence: 0.8053212

00:06:53.541 --> 00:06:55.501 engineer these edits is actually

NOTE Confidence: 0.8053212

00:06:55.501 --> 00:06:57.877 discovered that this up three prime

NOTE Confidence: 0.8053212

00:06:57.947 --> 00:07:00.499 snip is in a Micron 8338 binding site.

NOTE Confidence: 0.8053212

00:07:00.500 --> 00:07:02.936 And so when you inhibit near 338,

NOTE Confidence: 0.8053212

00:07:02.940 --> 00:07:05.376 you can eliminate this EQ TL effect.
NOTE Confidence: 0.8053212

00:07:05.380 --> 00:07:05.713 Really,
NOTE Confidence: 0.8053212

00:07:05.713 --> 00:07:07.378 I think suggesting that you
NOTE Confidence: 0.8053212

00:07:07.378 --> 00:07:08.710 could see context specific
NOTE Confidence: 0.79231584

00:07:08.770 --> 00:07:10.624 effects, so here the ability
NOTE Confidence: 0.79231584

00:07:10.624 --> 00:07:12.048 of this noncoding snip.
NOTE Confidence: 0.79231584

00:07:12.050 --> 00:07:14.055 To regulate foreign expressions depended
NOTE Confidence: 0.79231584

00:07:14.055 --> 00:07:16.649 upon mere 338 expression in the cell.
NOTE Confidence: 0.79231584

00:07:16.650 --> 00:07:19.428 Moreover, changing nothing more in this
NOTE Confidence: 0.79231584

00:07:19.428 --> 00:07:22.174 noncoding snip was sufficient to decrease
NOTE Confidence: 0.79231584

00:07:22.174 --> 00:07:25.044 in the right length and alternate activity.
NOTE Confidence: 0.79231584

00:07:25.050 --> 00:07:27.012 Moving forward, this projects and picked
NOTE Confidence: 0.79231584

00:07:27.012 --> 00:07:29.421 up by Christina the last couple of years
NOTE Confidence: 0.79231584

00:07:29.421 --> 00:07:31.540 and over the course of this pandemic.
NOTE Confidence: 0.79231584

00:07:31.540 --> 00:07:33.568 Increasing evidence showed that fear and
NOTE Confidence: 0.79231584

00:07:33.568 --> 00:07:36.169 actually had a role in the entry of SARS,

NOTE Confidence: 0.79231584

00:07:36.170 --> 00:07:38.354 Co V2 the the fear and cleavage

NOTE Confidence: 0.79231584

00:07:38.354 --> 00:07:40.190 site is specific to SARS, Co.

NOTE Confidence: 0.79231584

00:07:40.190 --> 00:07:42.272 V2 not found in SARS, Co V1.

NOTE Confidence: 0.79231584

00:07:42.272 --> 00:07:44.134 It was hypothesize to be part of

NOTE Confidence: 0.79231584

00:07:44.134 --> 00:07:46.576 Wise are Scobie too is so much more

NOTE Confidence: 0.79231584

00:07:46.576 --> 00:07:48.257 infectious since we were sitting

NOTE Confidence: 0.79231584

00:07:48.257 --> 00:07:50.387 on these isagenix stem cell lines.

NOTE Confidence: 0.79231584

00:07:50.390 --> 00:07:51.622 Christina working together with

NOTE Confidence: 0.79231584

00:07:51.622 --> 00:07:52.238 Daisy Hoagland,

NOTE Confidence: 0.79231584

00:07:52.240 --> 00:07:54.067 invent Hanover's lab began to ask could

NOTE Confidence: 0.79231584

00:07:54.067 --> 00:07:56.320 we alter the susceptibility to infection?

NOTE Confidence: 0.79231584

00:07:56.320 --> 00:07:58.567 By changing just a single noncoding snip.

NOTE Confidence: 0.79231584

00:07:58.570 --> 00:08:00.640 So here she's pivoted and we're

NOTE Confidence: 0.79231584

00:08:00.640 --> 00:08:02.364 making lung alveolar cells in

NOTE Confidence: 0.79231584

00:08:02.364 --> 00:08:04.044 the lab and across two donors.

NOTE Confidence: 0.79231584

00:08:04.050 --> 00:08:06.642 She can show that those GG lung alveolar
NOTE Confidence: 0.79231584

00:08:06.642 --> 00:08:08.970 cells express less fear and and also
NOTE Confidence: 0.79231584

00:08:08.970 --> 00:08:11.130 that there are less susceptible to SARS,
NOTE Confidence: 0.79231584

00:08:11.130 --> 00:08:12.249 Co V2 infection.
NOTE Confidence: 0.79231584

00:08:12.249 --> 00:08:14.487 Think the visual here is really
NOTE Confidence: 0.79231584

00:08:14.487 --> 00:08:16.463 striking so you can see a protein
NOTE Confidence: 0.79231584

00:08:16.463 --> 00:08:18.540 in the SARS Co V2 genome here,
NOTE Confidence: 0.79231584

00:08:18.540 --> 00:08:20.884 labeled in red and those AA alveolar cells
NOTE Confidence: 0.79231584

00:08:20.884 --> 00:08:23.688 on the top are much more brightly infected,
NOTE Confidence: 0.79231584

00:08:23.690 --> 00:08:25.652 and those on the bottom we
NOTE Confidence: 0.79231584

00:08:25.652 --> 00:08:26.960 turn back to neurons.
NOTE Confidence: 0.79231584

00:08:26.960 --> 00:08:27.520 And again,
NOTE Confidence: 0.79231584

00:08:27.520 --> 00:08:28.920 as I told you previously,
NOTE Confidence: 0.79231584

00:08:28.920 --> 00:08:30.395 Gigi neurons express last year
NOTE Confidence: 0.79231584

00:08:30.395 --> 00:08:32.170 and but they're also less well
NOTE Confidence: 0.79231584

00:08:32.170 --> 00:08:33.400 infected by SARS Co V2.

NOTE Confidence: 0.79231584

00:08:33.400 --> 00:08:36.199 So I think this was a really fun direction

NOTE Confidence: 0.79231584

00:08:36.199 --> 00:08:38.797 to take the lab over the last year.

NOTE Confidence: 0.79231584

00:08:38.800 --> 00:08:39.829 I'll remind you,

NOTE Confidence: 0.79231584

00:08:39.829 --> 00:08:40.172 though,

NOTE Confidence: 0.79231584

00:08:40.172 --> 00:08:42.230 that many of these common variants

NOTE Confidence: 0.79231584

00:08:42.289 --> 00:08:44.004 don't only exert their effect

NOTE Confidence: 0.79231584

00:08:44.004 --> 00:08:45.719 on the closest neighbor gene.

NOTE Confidence: 0.79231584

00:08:45.720 --> 00:08:47.869 Our DNA is not packed into our

NOTE Confidence: 0.79231584

00:08:47.869 --> 00:08:49.870 nucleus in a straight line.

NOTE Confidence: 0.79231584

00:08:49.870 --> 00:08:50.192 Instead,

NOTE Confidence: 0.79231584

00:08:50.192 --> 00:08:52.124 it folds in a very organized

NOTE Confidence: 0.79231584

00:08:52.124 --> 00:08:53.680 way into the nucleus,

NOTE Confidence: 0.79231584

00:08:53.680 --> 00:08:54.330 in ourselves,

NOTE Confidence: 0.79231584

00:08:54.330 --> 00:08:57.722 and so a former MD PhD student lab for Sale

NOTE Confidence: 0.79231584

00:08:57.722 --> 00:09:00.594 Missouri and asked at the genome wide level,

NOTE Confidence: 0.79231584

00:09:00.600 --> 00:09:02.676 how were their cell type specific
NOTE Confidence: 0.79231584

00:09:02.676 --> 00:09:04.060 differences in chromatin folding,
NOTE Confidence: 0.79231584

00:09:04.060 --> 00:09:07.004 and how did this impact the target potential
NOTE Confidence: 0.79231584

00:09:07.004 --> 00:09:09.550 target genes of schizophrenia risk loci?
NOTE Confidence: 0.79231584

00:09:09.550 --> 00:09:11.030 So here he is,
NOTE Confidence: 0.79231584

00:09:11.030 --> 00:09:12.880 applying Heisey analysis in isagenix
NOTE Confidence: 0.79231584

00:09:12.880 --> 00:09:15.204 stem cell derived astrocytes and
NOTE Confidence: 0.79231584

00:09:15.204 --> 00:09:17.088 regenerate cells and neurons.
NOTE Confidence: 0.79231584

00:09:17.090 --> 00:09:18.775 So each of those schizophrenia
NOTE Confidence: 0.79231584

00:09:18.775 --> 00:09:19.786 risk loci have,
NOTE Confidence: 0.79231584

00:09:19.790 --> 00:09:20.434 you know,
NOTE Confidence: 0.79231584

00:09:20.434 --> 00:09:22.688 a number of target genes that are
NOTE Confidence: 0.79231584

00:09:22.688 --> 00:09:25.177 close by here from those 145 variants,
NOTE Confidence: 0.79231584

00:09:25.180 --> 00:09:27.196 he's calling 224 proximal target genes,
NOTE Confidence: 0.79231584

00:09:27.200 --> 00:09:29.517 but an additional couple 100 target genes
NOTE Confidence: 0.79231584

00:09:29.517 --> 00:09:32.258 that occur in a cell type specific manner,

NOTE Confidence: 0.79231584

00:09:32.260 --> 00:09:34.556 and he was able to validate the

NOTE Confidence: 0.79231584

00:09:34.556 --> 00:09:36.970 impact of each loci at a distance.

NOTE Confidence: 0.79231584

00:09:36.970 --> 00:09:37.981 Here, for example,

NOTE Confidence: 0.79231584

00:09:37.981 --> 00:09:40.003 the product here in Alpha cluster.

NOTE Confidence: 0.79231584

00:09:40.010 --> 00:09:42.264 So here we have for schizophrenia risk

NOTE Confidence: 0.79231584

00:09:42.264 --> 00:09:44.671 NIPS that about 93 kilobases away from

NOTE Confidence: 0.79231584

00:09:44.671 --> 00:09:46.741 this product here in Alpha cluster,

NOTE Confidence: 0.79231584

00:09:46.750 --> 00:09:47.806 he applied crisper.

NOTE Confidence: 0.79231584

00:09:47.806 --> 00:09:50.702 To delete these nips and was able to

NOTE Confidence: 0.79231584

00:09:50.702 --> 00:09:52.856 show in the direction that deleting

NOTE Confidence: 0.79231584

00:09:52.856 --> 00:09:55.176 these risk nips impacted the expression

NOTE Confidence: 0.79231584

00:09:55.176 --> 00:09:57.522 of a very distal target gene.

NOTE Confidence: 0.79231584

00:09:57.530 --> 00:10:00.150 Here, PC DH, EA 10.

NOTE Confidence: 0.783096567272727

00:10:00.150 --> 00:10:02.712 Come. Now, of course, these risk

NOTE Confidence: 0.783096567272727

00:10:02.712 --> 00:10:05.270 variants don't occur in isolation.

NOTE Confidence: 0.783096567272727

00:10:05.270 --> 00:10:07.508 We all inherit them in combination,
NOTE Confidence: 0.783096567272727

00:10:07.510 --> 00:10:10.750 and so the questions that I think are
NOTE Confidence: 0.783096567272727

00:10:10.750 --> 00:10:13.585 most important to ask moving forward is
NOTE Confidence: 0.783096567272727

00:10:13.585 --> 00:10:16.857 how to risk variants some so Mail in in
NOTE Confidence: 0.783096567272727

00:10:16.857 --> 00:10:19.104 my group is looking at the convergence
NOTE Confidence: 0.783096567272727

00:10:19.104 --> 00:10:21.348 of schizophrenia and autism risk genes,
NOTE Confidence: 0.783096567272727

00:10:21.350 --> 00:10:22.994 particularly around synaptic biology,
NOTE Confidence: 0.783096567272727

00:10:22.994 --> 00:10:25.049 and epigenetics patrons been looking
NOTE Confidence: 0.783096567272727

00:10:25.049 --> 00:10:27.197 at networks of genes that change
NOTE Confidence: 0.783096567272727

00:10:27.197 --> 00:10:28.877 together in a coordinated fashion
NOTE Confidence: 0.783096567272727

00:10:28.937 --> 00:10:30.752 focused here on Alzheimer's disease
NOTE Confidence: 0.783096567272727

00:10:30.752 --> 00:10:32.567 and their microglia and neurons.
NOTE Confidence: 0.783096567272727

00:10:32.570 --> 00:10:33.797 Drivers of disease.
NOTE Confidence: 0.783096567272727

00:10:33.797 --> 00:10:35.433 Anne Michaels been looking
NOTE Confidence: 0.783096567272727

00:10:35.433 --> 00:10:36.660 at additive affect.
NOTE Confidence: 0.783096567272727

00:10:36.660 --> 00:10:39.210 So how does schizophrenia risk variance

NOTE Confidence: 0.783096567272727

00:10:39.210 --> 00:10:41.610 add within and across pathways?

NOTE Confidence: 0.783096567272727

00:10:41.610 --> 00:10:43.602 Here's some of the work that

NOTE Confidence: 0.783096567272727

00:10:43.602 --> 00:10:45.729 Adrian has a recently wrapped up.

NOTE Confidence: 0.783096567272727

00:10:45.730 --> 00:10:47.776 This was a collaboration with Mingwei,

NOTE Confidence: 0.783096567272727

00:10:47.780 --> 00:10:49.076 weighing in Bendzans lab.

NOTE Confidence: 0.783096567272727

00:10:49.076 --> 00:10:51.020 It began with a post mortem

NOTE Confidence: 0.783096567272727

00:10:51.087 --> 00:10:52.862 analysis of through all 350

NOTE Confidence: 0.783096567272727

00:10:52.862 --> 00:10:54.637 plus frames for brain regions,

NOTE Confidence: 0.783096567272727

00:10:54.640 --> 00:10:56.758 each looking for jeans that were

NOTE Confidence: 0.783096567272727

00:10:56.758 --> 00:10:58.170 coexpressed together and predicting

NOTE Confidence: 0.783096567272727

00:10:58.229 --> 00:10:59.789 the drivers of those networks.

NOTE Confidence: 0.783096567272727

00:10:59.790 --> 00:11:01.883 And so one network here I'm pointing

NOTE Confidence: 0.783096567272727

00:11:01.883 --> 00:11:04.386 out is M 64 for that predicted

NOTE Confidence: 0.783096567272727

00:11:04.386 --> 00:11:06.306 causal driver Gene was 80P61A.

NOTE Confidence: 0.783096567272727

00:11:06.310 --> 00:11:08.907 Atron knocked it down in EPS derived

NOTE Confidence: 0.783096567272727

00:11:08.907 --> 00:11:11.637 neurons and here you can show see that.
NOTE Confidence: 0.783096567272727

00:11:11.640 --> 00:11:13.550 In these two independent knockdowns,
NOTE Confidence: 0.783096567272727

00:11:13.550 --> 00:11:14.426 one and two,
NOTE Confidence: 0.783096567272727

00:11:14.426 --> 00:11:16.470 there is reduced neural activity and by
NOTE Confidence: 0.783096567272727

00:11:16.535 --> 00:11:18.899 electrophysiology that's actually reduced.
NOTE Confidence: 0.783096567272727

00:11:18.900 --> 00:11:21.015 Excitability of these knock down
NOTE Confidence: 0.783096567272727

00:11:21.015 --> 00:11:23.130 neurons Mingwei predicted a drug
NOTE Confidence: 0.783096567272727

00:11:23.198 --> 00:11:24.823 that was thought to increase
NOTE Confidence: 0.783096567272727

00:11:24.823 --> 00:11:27.299 expression of 80 P 61 eight drugs.
NOTE Confidence: 0.783096567272727

00:11:27.300 --> 00:11:30.020 NCH 51 and he was able to show in a
NOTE Confidence: 0.783096567272727

00:11:30.107 --> 00:11:32.675 dose dependent manner that it did
NOTE Confidence: 0.783096567272727

00:11:32.675 --> 00:11:35.328 just that and finally that treatment
NOTE Confidence: 0.783096567272727

00:11:35.328 --> 00:11:38.324 of neurons with NCH 51 was sufficient
NOTE Confidence: 0.783096567272727

00:11:38.324 --> 00:11:40.670 to ameliorate some of these deficits,
NOTE Confidence: 0.783096567272727

00:11:40.670 --> 00:11:41.904 partially restoring.
NOTE Confidence: 0.783096567272727

00:11:41.904 --> 00:11:44.989 Neural activity in 80P61A knock

NOTE Confidence: 0.783096567272727

00:11:44.989 --> 00:11:46.840 down Ipps neurons.

NOTE Confidence: 0.783096567272727

00:11:46.840 --> 00:11:48.700 Coming back to schizophrenia here

NOTE Confidence: 0.783096567272727

00:11:48.700 --> 00:11:50.973 this is work that was largely

NOTE Confidence: 0.783096567272727

00:11:50.973 --> 00:11:53.388 led by Sacramento when he was a

NOTE Confidence: 0.783096567272727

00:11:53.388 --> 00:11:54.890 PhD student in the lab.

NOTE Confidence: 0.783096567272727

00:11:54.890 --> 00:11:56.810 Here we're going after a handful

NOTE Confidence: 0.783096567272727

00:11:56.810 --> 00:11:58.740 of of common risk variants.

NOTE Confidence: 0.783096567272727

00:11:58.740 --> 00:12:01.190 Associated genes SNAP 91 and T snare.

NOTE Confidence: 0.783096567272727

00:12:01.190 --> 00:12:01.507 Here,

NOTE Confidence: 0.783096567272727

00:12:01.507 --> 00:12:03.409 some RNA seek showing that by

NOTE Confidence: 0.783096567272727

00:12:03.409 --> 00:12:05.040 CRISPR activation or inhibition.

NOTE Confidence: 0.783096567272727

00:12:05.040 --> 00:12:06.790 We can upregulate or down

NOTE Confidence: 0.783096567272727

00:12:06.790 --> 00:12:07.840 regulate those jeans.

NOTE Confidence: 0.783096567272727

00:12:07.840 --> 00:12:09.610 The other jeans that are changing

NOTE Confidence: 0.783096567272727

00:12:09.610 --> 00:12:11.168 with think our downstream network

NOTE Confidence: 0.783096567272727

00:12:11.168 --> 00:12:12.793 effects of these preparations that
NOTE Confidence: 0.783096567272727

00:12:12.793 --> 00:12:14.590 are enriched for brain pathology
NOTE Confidence: 0.783096567272727

00:12:14.590 --> 00:12:16.366 and specifically synaptic function
NOTE Confidence: 0.783096567272727

00:12:16.366 --> 00:12:18.142 genes and hereby electrophysiology.
NOTE Confidence: 0.783096567272727

00:12:18.150 --> 00:12:20.758 So I was able to show that reciprocal
NOTE Confidence: 0.783096567272727

00:12:20.758 --> 00:12:23.794 changes in step 91 expression that are
NOTE Confidence: 0.783096567272727

00:12:23.794 --> 00:12:26.104 reciprocal changes in synaptic activity.
NOTE Confidence: 0.783096567272727

00:12:26.110 --> 00:12:28.762 So increasing SNAP 91 increased excitatory
NOTE Confidence: 0.783096567272727

00:12:28.762 --> 00:12:30.530 postsynaptic currents and decreasing
NOTE Confidence: 0.783096567272727

00:12:30.586 --> 00:12:32.318 it decreased synaptic activity.
NOTE Confidence: 0.783096567272727

00:12:32.320 --> 00:12:32.996 Of course,
NOTE Confidence: 0.783096567272727

00:12:32.996 --> 00:12:34.010 these jeans again,
NOTE Confidence: 0.783096567272727

00:12:34.010 --> 00:12:36.460 we wanted to ask how they impacted
NOTE Confidence: 0.783096567272727

00:12:36.460 --> 00:12:38.191 neurons in combination and so
NOTE Confidence: 0.783096567272727

00:12:38.191 --> 00:12:39.726 here stuck started the project
NOTE Confidence: 0.783096567272727

00:12:39.726 --> 00:12:41.758 and then the Dean finished it.

NOTE Confidence: 0.783096567272727

00:12:41.760 --> 00:12:43.650 This is a RNA seek experiment

NOTE Confidence: 0.783096567272727

00:12:43.650 --> 00:12:45.662 that started with single RNA seek

NOTE Confidence: 0.783096567272727

00:12:45.662 --> 00:12:47.382 for our four top schizophrenia

NOTE Confidence: 0.783096567272727

00:12:47.382 --> 00:12:48.830 common variant risk genes.

NOTE Confidence: 0.783096567272727

00:12:48.830 --> 00:12:50.520 Nap nanny One T snare,

NOTE Confidence: 0.783096567272727

00:12:50.520 --> 00:12:52.752 CLC and three in fear and an Indian

NOTE Confidence: 0.783096567272727

00:12:52.752 --> 00:12:54.900 took those single gene perturbation.

NOTE Confidence: 0.783096567272727

00:12:54.900 --> 00:12:56.248 Arnie seeks and computationally

NOTE Confidence: 0.783096567272727

00:12:56.248 --> 00:12:57.259 added them together,

NOTE Confidence: 0.783096567272727

00:12:57.260 --> 00:12:58.724 yielding an expected additive

NOTE Confidence: 0.783096567272727

00:12:58.724 --> 00:13:00.920 model of what she thought would

NOTE Confidence: 0.783096567272727

00:13:00.987 --> 00:13:02.907 happen if we did comma tutorial.

NOTE Confidence: 0.783096567272727

00:13:02.910 --> 00:13:04.605 Perturbation but in parallel we

NOTE Confidence: 0.783096567272727

00:13:04.605 --> 00:13:06.300 actually did this comma toryal

NOTE Confidence: 0.8056938

00:13:06.355 --> 00:13:08.587 probation and somebody was able to ask how

NOTE Confidence: 0.8056938

00:13:08.587 --> 00:13:10.839 well the model performed and will hold.
NOTE Confidence: 0.8056938

00:13:10.840 --> 00:13:12.736 The mark was actually pretty good.
NOTE Confidence: 0.8056938

00:13:12.740 --> 00:13:15.268 About 82% of the genes changed as expected,
NOTE Confidence: 0.8056938

00:13:15.270 --> 00:13:17.293 but seven of the percent of the
NOTE Confidence: 0.8056938

00:13:17.293 --> 00:13:19.389 jeans were more down than affected.
NOTE Confidence: 0.8056938

00:13:19.390 --> 00:13:21.298 An 11% more up than expected,
NOTE Confidence: 0.8056938

00:13:21.300 --> 00:13:24.410 and so they ended further into the day to ask
NOTE Confidence: 0.8056938

00:13:24.483 --> 00:13:27.318 what types of genes were more down or up.
NOTE Confidence: 0.8056938

00:13:27.320 --> 00:13:28.900 And so there's more down.
NOTE Confidence: 0.8056938

00:13:28.900 --> 00:13:30.655 Genes were actually enriched for
NOTE Confidence: 0.8056938

00:13:30.655 --> 00:13:32.410 all of the major neurotransmitter
NOTE Confidence: 0.8056938

00:13:32.469 --> 00:13:34.119 released pathways in the brain.
NOTE Confidence: 0.8056938

00:13:34.120 --> 00:13:36.264 And the more up genes are enriched for
NOTE Confidence: 0.8056938

00:13:36.264 --> 00:13:38.687 both the rare and the common variants
NOTE Confidence: 0.8056938

00:13:38.687 --> 00:13:40.860 linked to schizophrenia and bipolar risk.
NOTE Confidence: 0.8056938

00:13:40.860 --> 00:13:43.107 And so I think what we're saying.

NOTE Confidence: 0.8056938

00:13:43.110 --> 00:13:45.672 So what we're seeing here is that

NOTE Confidence: 0.8056938

00:13:45.672 --> 00:13:47.872 studying these risk genes one at a

NOTE Confidence: 0.8056938

00:13:47.872 --> 00:13:50.170 time gives us a lot of the story,

NOTE Confidence: 0.8056938

00:13:50.170 --> 00:13:52.096 but not all of the story.

NOTE Confidence: 0.8056938

00:13:52.100 --> 00:13:54.172 And if you want to fully understand

NOTE Confidence: 0.8056938

00:13:54.172 --> 00:13:55.950 the biological impact of manipulating,

NOTE Confidence: 0.8056938

00:13:55.950 --> 00:13:57.350 risk variance is really important

NOTE Confidence: 0.8056938

00:13:57.350 --> 00:13:59.480 that we do it in combination.

NOTE Confidence: 0.8056938

00:13:59.480 --> 00:14:00.443 Along those lines.

NOTE Confidence: 0.8056938

00:14:00.443 --> 00:14:01.727 One last story here,

NOTE Confidence: 0.8056938

00:14:01.730 --> 00:14:03.656 pivoting to some other rare variants

NOTE Confidence: 0.8056938

00:14:03.656 --> 00:14:04.940 linked to schizophrenia risk.

NOTE Confidence: 0.8056938

00:14:04.940 --> 00:14:05.885 So this was.

NOTE Confidence: 0.8056938

00:14:05.885 --> 00:14:08.090 The most recent copy variant analysis of

NOTE Confidence: 0.8056938

00:14:08.157 --> 00:14:10.477 deletions linked to schizophrenia risk.

NOTE Confidence: 0.8056938

00:14:10.480 --> 00:14:13.657 We're focusing here on this one at 2 P.
NOTE Confidence: 0.8056938

00:14:13.660 --> 00:14:15.790 16.3, which encompasses a single gene,
NOTE Confidence: 0.8056938

00:14:15.790 --> 00:14:16.144 neurexin,
NOTE Confidence: 0.8056938

00:14:16.144 --> 00:14:17.560 one that is inherited,
NOTE Confidence: 0.8056938

00:14:17.560 --> 00:14:19.678 non recurrent Lee or with varying
NOTE Confidence: 0.8056938

00:14:19.678 --> 00:14:20.737 boundaries between donors,
NOTE Confidence: 0.8056938

00:14:20.740 --> 00:14:23.841 and that impacts one of the most
NOTE Confidence: 0.8056938

00:14:23.841 --> 00:14:25.170 highly Alternatively spliced
NOTE Confidence: 0.8056938

00:14:25.249 --> 00:14:27.139 genes in the human genome.
NOTE Confidence: 0.8056938

00:14:27.140 --> 00:14:29.058 Here's a look by long range sequencing
NOTE Confidence: 0.8056938

00:14:29.058 --> 00:14:31.219 at the number of neurexin one isoforms
NOTE Confidence: 0.8056938

00:14:31.219 --> 00:14:33.520 seen across different regions of the brain,
NOTE Confidence: 0.8056938

00:14:33.520 --> 00:14:35.410 and in fact these differences in
NOTE Confidence: 0.8056938

00:14:35.410 --> 00:14:37.438 direction one splice rapid horrors are
NOTE Confidence: 0.8056938

00:14:37.438 --> 00:14:38.866 sufficient to distinguish different
NOTE Confidence: 0.8056938

00:14:38.866 --> 00:14:40.890 types of neurons in the brain.

NOTE Confidence: 0.8056938

00:14:40.890 --> 00:14:43.106 So this study was Alco led by Aaron

NOTE Confidence: 0.8056938

00:14:43.106 --> 00:14:44.624 Player Tia former PhD student

NOTE Confidence: 0.8056938

00:14:44.624 --> 00:14:46.129 in my lab and Shoujo,

NOTE Confidence: 0.8056938

00:14:46.130 --> 00:14:47.585 a former postdoc in my

NOTE Confidence: 0.8056938

00:14:47.585 --> 00:14:48.415 collaborator ***** Lab.

NOTE Confidence: 0.8056938

00:14:48.415 --> 00:14:50.130 So here we have a cohort of

NOTE Confidence: 0.8056938

00:14:50.130 --> 00:14:52.220 for a rare direction, 1 cases,

NOTE Confidence: 0.8056938

00:14:52.220 --> 00:14:54.180 two of them with deletions in the

NOTE Confidence: 0.8056938

00:14:54.180 --> 00:14:56.017 five prime region of the gene,

NOTE Confidence: 0.8056938

00:14:56.020 --> 00:14:57.475 including the promoter in the

NOTE Confidence: 0.8056938

00:14:57.475 --> 00:14:58.348 first two exons,

NOTE Confidence: 0.8056938

00:14:58.350 --> 00:15:00.373 and two of them with deletions in

NOTE Confidence: 0.8056938

00:15:00.373 --> 00:15:02.419 the three prime region of the gene,

NOTE Confidence: 0.8056938

00:15:02.420 --> 00:15:03.293 including the second,

NOTE Confidence: 0.8056938

00:15:03.293 --> 00:15:05.039 third and last from their second,

NOTE Confidence: 0.8056938

00:15:05.040 --> 00:15:07.500 third, and 4th from last exons.
NOTE Confidence: 0.8056938

00:15:07.500 --> 00:15:09.205 This is long range sequencing
NOTE Confidence: 0.8056938

00:15:09.205 --> 00:15:10.569 analysis were considering how
NOTE Confidence: 0.8056938

00:15:10.569 --> 00:15:12.331 the direction one isoforms vary
NOTE Confidence: 0.8056938

00:15:12.331 --> 00:15:14.377 between the cases and the controls,
NOTE Confidence: 0.8056938

00:15:14.380 --> 00:15:17.404 and the first thing that I want to point
NOTE Confidence: 0.8056938

00:15:17.404 --> 00:15:20.230 out about 50% of the isoforms are decreased.
NOTE Confidence: 0.8056938

00:15:20.230 --> 00:15:21.950 Inpatient neurons relative to controls,
NOTE Confidence: 0.8056938

00:15:21.950 --> 00:15:23.665 and so you can really
NOTE Confidence: 0.8056938

00:15:23.665 --> 00:15:25.037 visualize how these neurons,
NOTE Confidence: 0.8056938

00:15:25.040 --> 00:15:27.659 how I support a differin you can see in
NOTE Confidence: 0.8056938

00:15:27.659 --> 00:15:29.857 purple the differences in abundance,
NOTE Confidence: 0.8056938

00:15:29.860 --> 00:15:32.156 another about a third of the isoforms
NOTE Confidence: 0.8056938

00:15:32.156 --> 00:15:33.990 were detected in the controls,
NOTE Confidence: 0.8056938

00:15:33.990 --> 00:15:36.734 but not in the patient neurons at all.
NOTE Confidence: 0.8056938

00:15:36.740 --> 00:15:39.236 These were some of the lower

NOTE Confidence: 0.8056938
00:15:39.236 --> 00:15:40.484 abundance control isoforms.
NOTE Confidence: 0.8056938
00:15:40.490 --> 00:15:41.426 And most surprisingly,
NOTE Confidence: 0.8056938
00:15:41.426 --> 00:15:44.045 I think we had to find 31 unique
NOTE Confidence: 0.8056938
00:15:44.045 --> 00:15:46.229 mutant isoforms that we were did
NOTE Confidence: 0.8056938
00:15:46.229 --> 00:15:48.239 that we detected in a patient.
NOTE Confidence: 0.8056938
00:15:48.240 --> 00:15:50.100 Neurons formed by splicing around
NOTE Confidence: 0.8056938
00:15:50.100 --> 00:15:51.960 that three prime deletion that
NOTE Confidence: 0.7763849
00:15:52.019 --> 00:15:54.291 we never saw in control neurons that we
NOTE Confidence: 0.7763849
00:15:54.291 --> 00:15:56.666 never saw in the postmortem human brain.
NOTE Confidence: 0.7763849
00:15:56.670 --> 00:15:58.014 Aaron cloned and overexpressed
NOTE Confidence: 0.7763849
00:15:58.014 --> 00:16:00.030 some of these are most abundant
NOTE Confidence: 0.7763849
00:16:00.091 --> 00:16:01.716 wild type and mutant isoforms.
NOTE Confidence: 0.7763849
00:16:01.720 --> 00:16:04.536 She was able to show in control neurons
NOTE Confidence: 0.7763849
00:16:04.536 --> 00:16:06.780 here starting in that left most bar.
NOTE Confidence: 0.7763849
00:16:06.780 --> 00:16:09.054 This wild type control neuron activity
NOTE Confidence: 0.7763849

00:16:09.054 --> 00:16:11.290 that by knocking it down with.
NOTE Confidence: 0.7763849

00:16:11.290 --> 00:16:13.322 Four different mutant rexon,
NOTE Confidence: 0.7763849

00:16:13.322 --> 00:16:15.862 one isoforms you could decrease
NOTE Confidence: 0.7763849

00:16:15.862 --> 00:16:18.567 neural activity in control neurons.
NOTE Confidence: 0.7763849

00:16:18.570 --> 00:16:20.080 In those five prime cases,
NOTE Confidence: 0.7763849

00:16:20.080 --> 00:16:21.963 the ones that are not thought to
NOTE Confidence: 0.7763849

00:16:21.963 --> 00:16:23.805 express Newton isoforms should be able
NOTE Confidence: 0.7763849

00:16:23.805 --> 00:16:25.767 to rescue decreased normal activity by
NOTE Confidence: 0.7763849

00:16:25.767 --> 00:16:27.297 overexpressing even just One Direction.
NOTE Confidence: 0.7763849

00:16:27.300 --> 00:16:30.310 When I spoke at a time and in the hub,
NOTE Confidence: 0.7763849

00:16:30.310 --> 00:16:32.116 three prime cases, the ones that
NOTE Confidence: 0.7763849

00:16:32.116 --> 00:16:33.320 did overexpressed mutant isoforms,
NOTE Confidence: 0.7763849

00:16:33.320 --> 00:16:35.704 she was never able to rescue activity by
NOTE Confidence: 0.7763849

00:16:35.704 --> 00:16:37.530 over expression of wild type isoforms.
NOTE Confidence: 0.7763849

00:16:37.530 --> 00:16:39.180 To really, we think the phenotypes
NOTE Confidence: 0.7763849

00:16:39.180 --> 00:16:40.840 are occurring through two mechanisms.

NOTE Confidence: 0.7763849
00:16:40.840 --> 00:16:41.141 First,
NOTE Confidence: 0.7763849
00:16:41.141 --> 00:16:43.850 a loss of neurexin one dose in all cases,
NOTE Confidence: 0.7763849
00:16:43.850 --> 00:16:46.208 but then in the subset of patients on the
NOTE Confidence: 0.7763849
00:16:46.208 --> 00:16:48.370 additive effect of mutant isoforms activity.
NOTE Confidence: 0.7763849
00:16:48.370 --> 00:16:50.200 And this is something we're
NOTE Confidence: 0.7763849
00:16:50.200 --> 00:16:52.360 continuing to explore in the lab.
NOTE Confidence: 0.7763849
00:16:52.360 --> 00:16:54.360 And so with that I want to stop
NOTE Confidence: 0.7763849
00:16:54.360 --> 00:16:56.207 and thank everybody in the lab.
NOTE Confidence: 0.7763849
00:16:56.210 --> 00:16:57.585 This has been an extraordinary
NOTE Confidence: 0.7763849
00:16:57.585 --> 00:16:58.135 difficult year.
NOTE Confidence: 0.7763849
00:16:58.140 --> 00:17:00.890 And if it wasn't for all of their hard work,
NOTE Confidence: 0.7763849
00:17:00.890 --> 00:17:02.618 we really wouldn't have been able
NOTE Confidence: 0.7763849
00:17:02.618 --> 00:17:04.072 to keep these experiments rolling
NOTE Confidence: 0.7763849
00:17:04.072 --> 00:17:05.815 in the data I talked about today
NOTE Confidence: 0.7763849
00:17:05.815 --> 00:17:07.490 was really led by Christina Atron,
NOTE Confidence: 0.7763849

00:17:07.490 --> 00:17:09.254 Nadine Erin for Sean and Soak it

NOTE Confidence: 0.7763849

00:17:09.254 --> 00:17:10.683 in collaboration with our really

NOTE Confidence: 0.7763849

00:17:10.683 --> 00:17:11.610 our key collaborators.

NOTE Confidence: 0.7763849

00:17:11.610 --> 00:17:13.409 So I will thank you and turn

NOTE Confidence: 0.7763849

00:17:13.409 --> 00:17:15.261 the floor back to our moderator.