

WEBVTT

NOTE duration:"00:18:24.9680000"

NOTE language:en-us

NOTE Confidence: 0.85246646

00:00:00.000 --> 00:00:02.807 Our next speaker is Doctor Joel Gelernter.

NOTE Confidence: 0.85246646

00:00:02.810 --> 00:00:05.168 Briefly, he graduated from Yale College,

NOTE Confidence: 0.85246646

00:00:05.170 --> 00:00:07.928 went to medical school at SUNY Downstate,

NOTE Confidence: 0.85246646

00:00:07.930 --> 00:00:10.938 and then did a residency in psychiatry at

NOTE Confidence: 0.85246646

00:00:10.938 --> 00:00:13.048 Western Psychiatric Institute and Clinic,

NOTE Confidence: 0.85246646

00:00:13.050 --> 00:00:15.020 followed by a fellowship in

NOTE Confidence: 0.85246646

00:00:15.020 --> 00:00:16.596 psychiatric genetics at NIMH.

NOTE Confidence: 0.85246646

00:00:16.600 --> 00:00:18.565 He is currently the foundation's

NOTE Confidence: 0.85246646

00:00:18.565 --> 00:00:20.137 fund professor of Psychiatry,

NOTE Confidence: 0.85246646

00:00:20.140 --> 00:00:22.245 professor of genetics and Neuroscience

NOTE Confidence: 0.85246646

00:00:22.245 --> 00:00:25.119 and director of the Division of Human

NOTE Confidence: 0.85246646

00:00:25.119 --> 00:00:27.237 Genetics in Psychiatry here at Yale,

NOTE Confidence: 0.85246646

00:00:27.240 --> 00:00:29.538 where he studies the genetics of

NOTE Confidence: 0.85246646

00:00:29.538 --> 00:00:31.760 psychiatric and substance use disorders.

NOTE Confidence: 0.85246646

00:00:31.760 --> 00:00:33.210 Thank you Doctor Gordon, thank

NOTE Confidence: 0.81320304

00:00:33.210 --> 00:00:35.716 you very much and I don't have

NOTE Confidence: 0.81320304

00:00:35.716 --> 00:00:37.480 relevant conflicts of interest.

NOTE Confidence: 0.81320304

00:00:37.480 --> 00:00:39.502 So I'm going to talk about

NOTE Confidence: 0.81320304

00:00:39.502 --> 00:00:42.073 where we stand with genome wide

NOTE Confidence: 0.81320304

00:00:42.073 --> 00:00:44.369 Association studies and psychiatry.

NOTE Confidence: 0.81320304

00:00:44.370 --> 00:00:46.926 And it's just been an enormously

NOTE Confidence: 0.81320304

00:00:46.926 --> 00:00:49.562 eventful few years as large studies

NOTE Confidence: 0.81320304

00:00:49.562 --> 00:00:52.106 have taken hold in the field.

NOTE Confidence: 0.81320304

00:00:52.110 --> 00:00:54.791 This has been due to the advent

NOTE Confidence: 0.81320304

00:00:54.791 --> 00:00:57.051 of large biobanks available for

NOTE Confidence: 0.81320304

00:00:57.051 --> 00:01:00.147 research like the UK Biobank Million

NOTE Confidence: 0.81320304

00:01:00.147 --> 00:01:02.382 Veteran Program and Mega Analysis

NOTE Confidence: 0.81320304

00:01:02.382 --> 00:01:05.554 in front of those are the work from

NOTE Confidence: 0.81320304

00:01:05.554 --> 00:01:07.730 the Psychiatric Genomics Consortium.

NOTE Confidence: 0.81320304

00:01:07.730 --> 00:01:10.271 It's also the case that's what's considered
NOTE Confidence: 0.81320304

00:01:10.271 --> 00:01:12.698 a large study is evolving rapidly,
NOTE Confidence: 0.81320304

00:01:12.700 --> 00:01:15.892 so studies of over a million subjects
NOTE Confidence: 0.81320304

00:01:15.892 --> 00:01:18.979 are not at all uncommon now.
NOTE Confidence: 0.81320304

00:01:18.980 --> 00:01:21.395 So we like to identify lots of
NOTE Confidence: 0.81320304

00:01:21.395 --> 00:01:23.228 genes because that's interesting and
NOTE Confidence: 0.81320304

00:01:23.228 --> 00:01:25.755 we want to see what they encode.
NOTE Confidence: 0.81320304

00:01:25.760 --> 00:01:28.973 But we also once we have genome wide data,
NOTE Confidence: 0.81320304

00:01:28.980 --> 00:01:31.806 want to go beyond that and see what we
NOTE Confidence: 0.81320304

00:01:31.806 --> 00:01:34.772 can use that data for to learn about
NOTE Confidence: 0.81320304

00:01:34.772 --> 00:01:37.896 the biology that comes out of well powered,
NOTE Confidence: 0.81320304

00:01:37.900 --> 00:01:40.476 G was we could look at Lee Atropia
NOTE Confidence: 0.81320304

00:01:40.476 --> 00:01:42.540 shared genetics with other disorders,
NOTE Confidence: 0.81320304

00:01:42.540 --> 00:01:42.997 pathways,
NOTE Confidence: 0.81320304

00:01:42.997 --> 00:01:45.282 mechanisms and also better understanding
NOTE Confidence: 0.81320304

00:01:45.282 --> 00:01:47.860 of the meaning of diagnosis.

NOTE Confidence: 0.81320304

00:01:47.860 --> 00:01:51.244 If we look at the current state of the

NOTE Confidence: 0.81320304

00:01:51.244 --> 00:01:54.790 world of Genome Wide Association analysis,

NOTE Confidence: 0.81320304

00:01:54.790 --> 00:01:57.290 this is.

NOTE Confidence: 0.81320304

00:01:57.290 --> 00:02:00.111 Diagram that's updated regularly at the you

NOTE Confidence: 0.81320304

00:02:00.111 --> 00:02:03.098 know gene Human Genome Institute website.

NOTE Confidence: 0.81320304

00:02:03.100 --> 00:02:06.352 Now there are so many significantly

NOTE Confidence: 0.81320304

00:02:06.352 --> 00:02:09.437 map genome wide associated loci that

NOTE Confidence: 0.81320304

00:02:09.437 --> 00:02:12.314 you can only fit a few chromosomes

NOTE Confidence: 0.81320304

00:02:12.314 --> 00:02:14.128 on a single slide.

NOTE Confidence: 0.81320304

00:02:14.130 --> 00:02:16.608 But going back only 16 years,

NOTE Confidence: 0.81320304

00:02:16.610 --> 00:02:19.640 this is the first important genome

NOTE Confidence: 0.81320304

00:02:19.640 --> 00:02:22.445 wide Association study came out in

NOTE Confidence: 0.81320304

00:02:22.445 --> 00:02:25.245 science and we can focus in and look

NOTE Confidence: 0.81320304

00:02:25.332 --> 00:02:28.260 on the sample size that was only 96

NOTE Confidence: 0.81320304

00:02:28.260 --> 00:02:30.948 cases and 50 controls which amazingly

NOTE Confidence: 0.81320304

00:02:30.948 --> 00:02:34.430 still work for a somewhat complex trait.

NOTE Confidence: 0.81320304

00:02:34.430 --> 00:02:35.690 For years after that,

NOTE Confidence: 0.81320304

00:02:35.690 --> 00:02:38.062 there wasn't a whole lot of success

NOTE Confidence: 0.81320304

00:02:38.062 --> 00:02:40.122 in Genome Wide Association analysis

NOTE Confidence: 0.81320304

00:02:40.122 --> 00:02:42.780 of complex traits an all psychiatric

NOTE Confidence: 0.81320304

00:02:42.780 --> 00:02:44.668 disorders or complex trades,

NOTE Confidence: 0.81320304

00:02:44.670 --> 00:02:46.896 and there was discussion about whether

NOTE Confidence: 0.81320304

00:02:46.896 --> 00:02:48.867 complex traits just weren't amenable

NOTE Confidence: 0.81320304

00:02:48.867 --> 00:02:50.977 to genome wide Association analysis.

NOTE Confidence: 0.81320304

00:02:50.980 --> 00:02:52.996 There was some other problem that

NOTE Confidence: 0.81320304

00:02:52.996 --> 00:02:55.310 they were just too heterogeneous.

NOTE Confidence: 0.81320304

00:02:55.310 --> 00:02:58.462 It turns out that it was more than

NOTE Confidence: 0.81320304

00:02:58.462 --> 00:03:01.010 anything else, a problem of power,

NOTE Confidence: 0.81320304

00:03:01.010 --> 00:03:03.650 and that with lower sample size

NOTE Confidence: 0.81320304

00:03:03.736 --> 00:03:06.410 studies up to a few 1000 cases.

NOTE Confidence: 0.81320304

00:03:06.410 --> 00:03:07.682 For complex traits,

NOTE Confidence: 0.81320304

00:03:07.682 --> 00:03:10.226 you have to keep adding cases

NOTE Confidence: 0.81320304

00:03:10.226 --> 00:03:13.091 until you come to what appears to

NOTE Confidence: 0.81320304

00:03:13.091 --> 00:03:14.663 be an inflection point,

NOTE Confidence: 0.81320304

00:03:14.670 --> 00:03:17.554 and once you hit the inflection point,

NOTE Confidence: 0.81320304

00:03:17.560 --> 00:03:20.542 which is about 10,000 cases for schizophrenia

NOTE Confidence: 0.81320304

00:03:20.542 --> 00:03:23.339 for every set of subjects you add,

NOTE Confidence: 0.81320304

00:03:23.340 --> 00:03:25.818 you discover more risk loci regularly,

NOTE Confidence: 0.81320304

00:03:25.820 --> 00:03:28.622 and this inflection point was simply

NOTE Confidence: 0.81320304

00:03:28.622 --> 00:03:31.626 much earlier on for complex traits

NOTE Confidence: 0.81320304

00:03:31.626 --> 00:03:34.758 outside of the realm of psychiatry.

NOTE Confidence: 0.81320304

00:03:34.760 --> 00:03:37.400 This was put forward by Pat

NOTE Confidence: 0.81320304

00:03:37.400 --> 00:03:40.659 Sullivan from PGC a few years back,

NOTE Confidence: 0.81320304

00:03:40.660 --> 00:03:42.930 and it's continued to hold.

NOTE Confidence: 0.81320304

00:03:42.930 --> 00:03:45.660 Here's an example from depression work,

NOTE Confidence: 0.81320304

00:03:45.660 --> 00:03:48.474 where until a few years ago there

NOTE Confidence: 0.81320304

00:03:48.474 --> 00:03:50.650 was nothing from depression,
NOTE Confidence: 0.81320304

00:03:50.650 --> 00:03:54.274 and now we've gone up 278 risk loci,
NOTE Confidence: 0.81320304

00:03:54.280 --> 00:03:57.904 but that took a very large sample size,
NOTE Confidence: 0.81320304

00:03:57.910 --> 00:04:00.590 over 300,000.
NOTE Confidence: 0.81320304

00:04:00.590 --> 00:04:03.080 So most of the progress for
NOTE Confidence: 0.81320304

00:04:03.080 --> 00:04:05.321 psychiatric traits comes from massive
NOTE Confidence: 0.81320304

00:04:05.321 --> 00:04:07.866 meta analysis and biobank samples.
NOTE Confidence: 0.81320304

00:04:07.870 --> 00:04:11.206 Uh, the UK biobank is very well known.
NOTE Confidence: 0.8777002

00:04:11.210 --> 00:04:13.300 It has half million subjects,
NOTE Confidence: 0.8777002

00:04:13.300 --> 00:04:16.644 self report surveys on a subset of them,
NOTE Confidence: 0.8777002

00:04:16.650 --> 00:04:19.254 electronic health record linkage and a
NOTE Confidence: 0.8777002

00:04:19.254 --> 00:04:22.178 very open design where anyone can obtain
NOTE Confidence: 0.8777002

00:04:22.178 --> 00:04:24.768 access to the data and do analysis
NOTE Confidence: 0.8777002

00:04:24.844 --> 00:04:27.448 and this is generated huge numbers
NOTE Confidence: 0.8777002

00:04:27.448 --> 00:04:29.655 of very important research papers.
NOTE Confidence: 0.8777002

00:04:29.655 --> 00:04:32.445 There's 23 andme the direct to

NOTE Confidence: 0.8777002

00:04:32.445 --> 00:04:34.956 consumer Testing Company, which has

NOTE Confidence: 0.8777002

00:04:34.956 --> 00:04:38.304 millions of subjects and is growing.

NOTE Confidence: 0.8777002

00:04:38.310 --> 00:04:41.134 Despite shallow diagnostic ascertainment,

NOTE Confidence: 0.8777002

00:04:41.134 --> 00:04:45.370 it still proved to be enormously

NOTE Confidence: 0.8777002

00:04:45.474 --> 00:04:49.482 useful for common trades and then

NOTE Confidence: 0.8777002

00:04:49.482 --> 00:04:52.154 the Psychiatric Genomics consortium.

NOTE Confidence: 0.8777002

00:04:52.160 --> 00:04:54.638 In addition, there are some important

NOTE Confidence: 0.8777002

00:04:54.638 --> 00:04:56.290 academic center related biobanks,

NOTE Confidence: 0.8777002

00:04:56.290 --> 00:04:58.768 like the one at Harvard Partners,

NOTE Confidence: 0.8777002

00:04:58.770 --> 00:05:01.654 the Bio V1 led by Nancy Cox,

NOTE Confidence: 0.8777002

00:05:01.660 --> 00:05:06.028 who previously was at Yale and soon Yell.

NOTE Confidence: 0.8777002

00:05:06.030 --> 00:05:07.870 The million veteran program until

NOTE Confidence: 0.8777002

00:05:07.870 --> 00:05:10.110 recently was somewhat less well known,

NOTE Confidence: 0.8777002

00:05:10.110 --> 00:05:12.602 but in some ways it's the most

NOTE Confidence: 0.8777002

00:05:12.602 --> 00:05:14.559 useful of the bio banks,

NOTE Confidence: 0.8777002

00:05:14.560 --> 00:05:17.341 so we can look at some of the characteristics

NOTE Confidence: 0.8777002

00:05:17.341 --> 00:05:20.145 of the MVP sample large sample size

NOTE Confidence: 0.8777002

00:05:20.145 --> 00:05:22.350 they've already recruited over 800,000.

NOTE Confidence: 0.8777002

00:05:22.350 --> 00:05:24.205 The original plan was to

NOTE Confidence: 0.8777002

00:05:24.205 --> 00:05:25.689 recruit a million participants,

NOTE Confidence: 0.8777002

00:05:25.690 --> 00:05:28.480 but they are now planning to

NOTE Confidence: 0.8777002

00:05:28.480 --> 00:05:30.340 go well beyond that.

NOTE Confidence: 0.8777002

00:05:30.340 --> 00:05:32.608 Most of the larger samples that

NOTE Confidence: 0.8777002

00:05:32.608 --> 00:05:35.320 are available for study are very

NOTE Confidence: 0.8777002

00:05:35.320 --> 00:05:37.568 predominantly European ancestry samples.

NOTE Confidence: 0.8777002

00:05:37.570 --> 00:05:40.138 The MVP has very good representation

NOTE Confidence: 0.8777002

00:05:40.138 --> 00:05:42.540 from non European ancestry subjects,

NOTE Confidence: 0.8777002

00:05:42.540 --> 00:05:45.258 especially African American and Latin X,

NOTE Confidence: 0.8777002

00:05:45.260 --> 00:05:48.698 and I'm going to give an example of why

NOTE Confidence: 0.8777002

00:05:48.698 --> 00:05:51.580 that's important for gene discovery.

NOTE Confidence: 0.8777002

00:05:51.580 --> 00:05:52.945 It's mostly male.

NOTE Confidence: 0.8777002

00:05:52.945 --> 00:05:55.675 That's a disadvantage in that we

NOTE Confidence: 0.8777002

00:05:55.675 --> 00:05:58.815 can't say much about females from MVP,

NOTE Confidence: 0.8777002

00:05:58.820 --> 00:06:00.532 but it does increase.

NOTE Confidence: 0.8777002

00:06:00.532 --> 00:06:03.678 The homogeneity of the sample and increase

NOTE Confidence: 0.8777002

00:06:03.678 --> 00:06:06.678 our power for discovery among males.

NOTE Confidence: 0.8777002

00:06:06.680 --> 00:06:08.204 There is EHR linkage.

NOTE Confidence: 0.8777002

00:06:08.204 --> 00:06:12.019 The VAEHR is one of the oldest worldwide.

NOTE Confidence: 0.8777002

00:06:12.020 --> 00:06:16.016 Goes back to the 90s and so there is

NOTE Confidence: 0.8777002

00:06:16.016 --> 00:06:19.457 longitudinal repeated measured data from EHR.

NOTE Confidence: 0.8777002

00:06:19.460 --> 00:06:22.208 Depending on the phenotype.

NOTE Confidence: 0.8777002

00:06:22.210 --> 00:06:23.090 And finally,

NOTE Confidence: 0.8777002

00:06:23.090 --> 00:06:26.610 the MVP sample is relatively old and SEK.

NOTE Confidence: 0.8777002

00:06:26.610 --> 00:06:28.890 There are individuals who have

NOTE Confidence: 0.8777002

00:06:28.890 --> 00:06:31.662 used VA health services and this

NOTE Confidence: 0.8777002

00:06:31.662 --> 00:06:34.116 is in contrast to other large

NOTE Confidence: 0.8777002

00:06:34.116 --> 00:06:36.290 biobanks like the UK Biobank,
NOTE Confidence: 0.8777002

00:06:36.290 --> 00:06:39.305 which is relatively higher socioeconomic
NOTE Confidence: 0.8777002

00:06:39.305 --> 00:06:42.890 status and not quite as sick.
NOTE Confidence: 0.8777002

00:06:42.890 --> 00:06:45.487 So I'm going to give examples for
NOTE Confidence: 0.8777002

00:06:45.487 --> 00:06:47.989 gene mapping into psychiatric areas.
NOTE Confidence: 0.8777002

00:06:47.990 --> 00:06:50.810 First post Traumatic stress disorder
NOTE Confidence: 0.8777002

00:06:50.810 --> 00:06:53.630 and then alcohol use disorder.
NOTE Confidence: 0.8777002

00:06:53.630 --> 00:06:56.766 So one of the goals of collecting the
NOTE Confidence: 0.8777002

00:06:56.766 --> 00:07:00.095 MVP sample was to map disorders of
NOTE Confidence: 0.8777002

00:07:00.095 --> 00:07:02.550 relevance to the veteran population.
NOTE Confidence: 0.8777002

00:07:02.550 --> 00:07:05.220 An although PTSD is not specific
NOTE Confidence: 0.8777002

00:07:05.220 --> 00:07:06.555 to military populations,
NOTE Confidence: 0.8777002

00:07:06.560 --> 00:07:10.550 it's very important in those populations.
NOTE Confidence: 0.8777002

00:07:10.550 --> 00:07:13.413 We have the HR data relating to
NOTE Confidence: 0.8777002

00:07:13.413 --> 00:07:17.432 PTSD in the MVP and we also have PCL
NOTE Confidence: 0.8777002

00:07:17.432 --> 00:07:21.479 checklist data that we can use as a

NOTE Confidence: 0.8777002

00:07:21.479 --> 00:07:24.179 quantitative measure of PTSD symptoms.

NOTE Confidence: 0.8777002

00:07:24.180 --> 00:07:26.903 PCL is often used clinically and it

NOTE Confidence: 0.8777002

00:07:26.903 --> 00:07:29.379 breaks down into three different

NOTE Confidence: 0.8777002

00:07:29.379 --> 00:07:31.839 sub phenotypes re experiencing

NOTE Confidence: 0.8777002

00:07:31.839 --> 00:07:33.684 avoidance and hyperarousal.

NOTE Confidence: 0.8777002

00:07:33.690 --> 00:07:35.755 Which in the original clinical

NOTE Confidence: 0.8777002

00:07:35.755 --> 00:07:36.994 conception of PTSD,

NOTE Confidence: 0.8777002

00:07:37.000 --> 00:07:39.070 were thought to be important

NOTE Confidence: 0.8777002

00:07:39.070 --> 00:07:41.140 for diagnosis of the trade,

NOTE Confidence: 0.8777002

00:07:41.140 --> 00:07:42.382 even though phenomenologically

NOTE Confidence: 0.8777002

00:07:42.382 --> 00:07:44.866 they appear to be quite different,

NOTE Confidence: 0.8777002

00:07:44.870 --> 00:07:48.174 so I'm going to come back to that.

NOTE Confidence: 0.8777002

00:07:48.180 --> 00:07:51.572 But first I'm going to talk about PTSD

NOTE Confidence: 0.8777002

00:07:51.572 --> 00:07:54.035 Re experiencing which was the subject

NOTE Confidence: 0.8777002

00:07:54.035 --> 00:07:57.290 of our first paper from NVP about PTSD.

NOTE Confidence: 0.8777002

00:07:57.290 --> 00:07:58.942 So sample re experiencing
NOTE Confidence: 0.8777002

00:07:58.942 --> 00:08:00.594 item is given below.
NOTE Confidence: 0.8777002

00:08:00.600 --> 00:08:03.156 How much have you been bothered
NOTE Confidence: 0.8777002

00:08:03.156 --> 00:08:04.434 by repeated disturbing?
NOTE Confidence: 0.86981666

00:08:04.440 --> 00:08:06.724 And unwanted memories of
NOTE Confidence: 0.86981666

00:08:06.724 --> 00:08:08.437 the stressful experience.
NOTE Confidence: 0.86981666

00:08:08.440 --> 00:08:10.432 Here's the Manhattan Plot,
NOTE Confidence: 0.86981666

00:08:10.432 --> 00:08:12.922 8 distinct common variant genome
NOTE Confidence: 0.86981666

00:08:12.922 --> 00:08:15.910 wide significant regions identified.
NOTE Confidence: 0.86981666

00:08:15.910 --> 00:08:17.542 Three with very high
NOTE Confidence: 0.86981666

00:08:17.542 --> 00:08:18.358 statistical significance,
NOTE Confidence: 0.86981666

00:08:18.360 --> 00:08:20.000 and I've already described
NOTE Confidence: 0.86981666

00:08:20.000 --> 00:08:22.050 this as a Manhattan plot.
NOTE Confidence: 0.86981666

00:08:22.050 --> 00:08:25.218 This is why in this Manhattan plot only
NOTE Confidence: 0.86981666

00:08:25.218 --> 00:08:27.751 the World Trade Center is significant
NOTE Confidence: 0.86981666

00:08:27.751 --> 00:08:32.270 over $5 * 10$ to the minus South.

NOTE Confidence: 0.86981666

00:08:32.270 --> 00:08:34.854 So I'm going to focus in on only

NOTE Confidence: 0.86981666

00:08:34.854 --> 00:08:37.783 one of those results from our re

NOTE Confidence: 0.86981666

00:08:37.783 --> 00:08:40.698 experiencing G was and that is the

NOTE Confidence: 0.86981666

00:08:40.698 --> 00:08:43.585 CR H R1 region and in the upper plot

NOTE Confidence: 0.86981666

00:08:43.585 --> 00:08:45.410 this is called original Manhattan.

NOTE Confidence: 0.86981666

00:08:45.410 --> 00:08:48.077 Plot it zooming in on the Manhattan

NOTE Confidence: 0.86981666

00:08:48.077 --> 00:08:50.980 plot to show chromosome or region.

NOTE Confidence: 0.86981666

00:08:50.980 --> 00:08:53.146 We have a region of high

NOTE Confidence: 0.86981666

00:08:53.146 --> 00:08:53.868 statistical significance,

NOTE Confidence: 0.86981666

00:08:53.870 --> 00:08:56.758 but we can't pick out a risk gene,

NOTE Confidence: 0.86981666

00:08:56.760 --> 00:08:59.406 much less or risk locus that

NOTE Confidence: 0.86981666

00:08:59.406 --> 00:09:01.890 Maps higher than the others.

NOTE Confidence: 0.86981666

00:09:01.890 --> 00:09:05.172 We have an African ancestry sample

NOTE Confidence: 0.86981666

00:09:05.172 --> 00:09:08.454 below that's about 20% the size

NOTE Confidence: 0.86981666

00:09:08.454 --> 00:09:11.189 of the European ancestry sample.

NOTE Confidence: 0.86981666

00:09:11.190 --> 00:09:14.360 Not large enough to show
NOTE Confidence: 0.86981666

00:09:14.360 --> 00:09:15.628 statistical significance.
NOTE Confidence: 0.86981666

00:09:15.630 --> 00:09:18.270 But European Americans have higher LD
NOTE Confidence: 0.86981666

00:09:18.270 --> 00:09:21.210 and a common inversion in this region.
NOTE Confidence: 0.86981666

00:09:21.210 --> 00:09:22.922 African Americans have lower
NOTE Confidence: 0.86981666

00:09:22.922 --> 00:09:24.634 linkage disequilibrium genome wide,
NOTE Confidence: 0.86981666

00:09:24.640 --> 00:09:26.705 and this particular inversion in
NOTE Confidence: 0.86981666

00:09:26.705 --> 00:09:29.360 this region is much less common,
NOTE Confidence: 0.86981666

00:09:29.360 --> 00:09:31.880 and the result is that when we
NOTE Confidence: 0.86981666

00:09:31.880 --> 00:09:34.590 met it analyze the data from
NOTE Confidence: 0.86981666

00:09:34.590 --> 00:09:36.650 European and African Americans,
NOTE Confidence: 0.86981666

00:09:36.650 --> 00:09:39.387 we can now localize the signal in
NOTE Confidence: 0.86981666

00:09:39.387 --> 00:09:42.027 this region to a specific gene
NOTE Confidence: 0.86981666

00:09:42.027 --> 00:09:44.793 with about two orders of magnitude,
NOTE Confidence: 0.86981666

00:09:44.800 --> 00:09:46.950 two log units of support.
NOTE Confidence: 0.86981666

00:09:46.950 --> 00:09:50.868 So it's a pretty good localization.

NOTE Confidence: 0.86981666

00:09:50.870 --> 00:09:53.299 So I want to illustrate two points.

NOTE Confidence: 0.86981666

00:09:53.300 --> 00:09:54.200 First of all,

NOTE Confidence: 0.86981666

00:09:54.200 --> 00:09:55.700 the gene that it localizes

NOTE Confidence: 0.86981666

00:09:55.700 --> 00:09:57.460 to CRH R1 corticotropin,

NOTE Confidence: 0.86981666

00:09:57.460 --> 00:10:00.000 releasing hormone receptor one.

NOTE Confidence: 0.86981666

00:10:00.000 --> 00:10:01.890 Is Gene that participates in a

NOTE Confidence: 0.86981666

00:10:01.890 --> 00:10:03.982 pathway that's long been known to

NOTE Confidence: 0.86981666

00:10:03.982 --> 00:10:05.902 be important in stress response

NOTE Confidence: 0.86981666

00:10:05.902 --> 00:10:07.690 steroid signaling cortisol signaling?

NOTE Confidence: 0.86981666

00:10:07.690 --> 00:10:08.426 In fact,

NOTE Confidence: 0.86981666

00:10:08.426 --> 00:10:11.370 it was such a strong candidate that it

NOTE Confidence: 0.86981666

00:10:11.449 --> 00:10:14.263 was studied in prior candidate gene

NOTE Confidence: 0.86981666

00:10:14.263 --> 00:10:17.398 studies picked out based on its biology.

NOTE Confidence: 0.86981666

00:10:17.400 --> 00:10:19.101 The other thing I want to point

NOTE Confidence: 0.86981666

00:10:19.101 --> 00:10:21.299 out is the importance of having

NOTE Confidence: 0.86981666

00:10:21.299 --> 00:10:23.175 populations other than European
NOTE Confidence: 0.86981666

00:10:23.175 --> 00:10:25.532 ancestry populations because absent the
NOTE Confidence: 0.86981666

00:10:25.532 --> 00:10:27.308 contribution from African ancestry,
NOTE Confidence: 0.86981666

00:10:27.310 --> 00:10:29.766 then any of the genes in this region
NOTE Confidence: 0.86981666

00:10:29.766 --> 00:10:31.919 could really be considered to have
NOTE Confidence: 0.86981666

00:10:31.919 --> 00:10:33.395 equal statistical support and
NOTE Confidence: 0.86981666

00:10:33.395 --> 00:10:36.206 some of them are also interesting
NOTE Confidence: 0.86981666

00:10:36.206 --> 00:10:37.208 biological candidates,
NOTE Confidence: 0.86981666

00:10:37.210 --> 00:10:39.653 and this was the cover that we
NOTE Confidence: 0.86981666

00:10:39.653 --> 00:10:41.636 proposed for the Journal that
NOTE Confidence: 0.86981666

00:10:41.636 --> 00:10:42.926 was turned down.
NOTE Confidence: 0.86981666

00:10:42.930 --> 00:10:46.362 But it's a guy re experiencing
NOTE Confidence: 0.86981666

00:10:46.362 --> 00:10:48.650 the regional Association plot.
NOTE Confidence: 0.86981666

00:10:48.650 --> 00:10:51.518 Our follow up paper considered all
NOTE Confidence: 0.86981666

00:10:51.518 --> 00:10:54.909 three of the PTSD sub phenotypes,
NOTE Confidence: 0.86981666

00:10:54.910 --> 00:10:57.598 avoidance re experiencing and

NOTE Confidence: 0.86981666

00:10:57.598 --> 00:11:00.958 hyperarousal and these were analysis

NOTE Confidence: 0.86981666

00:11:00.958 --> 00:11:05.504 that were done mostly by Dan Leavy in my lab.

NOTE Confidence: 0.86981666

00:11:05.510 --> 00:11:08.438 This came out in nature genetics

NOTE Confidence: 0.86981666

00:11:08.438 --> 00:11:10.390 I think in January.

NOTE Confidence: 0.86981666

00:11:10.390 --> 00:11:12.940 So this study included many more

NOTE Confidence: 0.86981666

00:11:12.940 --> 00:11:15.790 subjects were up to over 250,000,

NOTE Confidence: 0.86981666

00:11:15.790 --> 00:11:18.430 and we considered both case control

NOTE Confidence: 0.86981666

00:11:18.430 --> 00:11:20.740 models and quantitative trait models,

NOTE Confidence: 0.86981666

00:11:20.740 --> 00:11:23.890 and we also looked at the three

NOTE Confidence: 0.86981666

00:11:23.890 --> 00:11:25.240 sub phenotypes separately.

NOTE Confidence: 0.86981666

00:11:25.240 --> 00:11:28.840 So if we look at total PSL score,

NOTE Confidence: 0.86981666

00:11:28.840 --> 00:11:30.640 that's the overall quantitative

NOTE Confidence: 0.86981666

00:11:30.640 --> 00:11:32.890 measure used to diagnose PTSD.

NOTE Confidence: 0.86981666

00:11:32.890 --> 00:11:35.520 We now 15 independent associated

NOTE Confidence: 0.86981666

00:11:35.520 --> 00:11:37.624 regions much larger sample.

NOTE Confidence: 0.86981666

00:11:37.630 --> 00:11:40.300 And in this very nice graph,
NOTE Confidence: 0.86981666

00:11:40.300 --> 00:11:42.982 which was made by Gita Pathak
NOTE Confidence: 0.86981666

00:11:42.982 --> 00:11:45.200 and Renato Paula Montes Lab,
NOTE Confidence: 0.86981666

00:11:45.200 --> 00:11:47.080 we can see the localization
NOTE Confidence: 0.86981666

00:11:47.080 --> 00:11:48.960 of risk loci by trade
NOTE Confidence: 0.7824783

00:11:49.046 --> 00:11:51.426 re experiencing avoidance and hyperarousal
NOTE Confidence: 0.7824783

00:11:51.426 --> 00:11:55.428 or PCL total or EHR define case control.
NOTE Confidence: 0.7824783

00:11:55.430 --> 00:11:58.158 You can see that we do have some
NOTE Confidence: 0.7824783

00:11:58.158 --> 00:11:59.924 genome wide significant findings
NOTE Confidence: 0.7824783

00:11:59.924 --> 00:12:02.439 for African Americans now that
NOTE Confidence: 0.7824783

00:12:02.439 --> 00:12:06.126 they tend not to localize with the
NOTE Confidence: 0.7824783

00:12:06.126 --> 00:12:08.218 genome wide significant findings.
NOTE Confidence: 0.7824783

00:12:08.220 --> 00:12:10.800 For European American subjects and
NOTE Confidence: 0.7824783

00:12:10.800 --> 00:12:13.987 that the different sub phenotypes have
NOTE Confidence: 0.7824783

00:12:13.987 --> 00:12:17.158 genomic regions, some of which coincide,
NOTE Confidence: 0.7824783

00:12:17.158 --> 00:12:20.320 and some of which are specific

NOTE Confidence: 0.7824783

00:12:20.422 --> 00:12:23.446 to a specific of sub phenotype.

NOTE Confidence: 0.8389494

00:12:25.620 --> 00:12:29.460 So now we can start to get some

NOTE Confidence: 0.8389494

00:12:29.460 --> 00:12:31.650 interesting biology out of that.

NOTE Confidence: 0.8389494

00:12:31.650 --> 00:12:33.506 This graph shows correlation

NOTE Confidence: 0.8389494

00:12:33.506 --> 00:12:35.826 phenotypic Lee between case control,

NOTE Confidence: 0.8389494

00:12:35.830 --> 00:12:38.698 total PCL and sub phenotypes and

NOTE Confidence: 0.8389494

00:12:38.698 --> 00:12:40.930 below genetic correlation or RG.

NOTE Confidence: 0.8389494

00:12:40.930 --> 00:12:44.116 And what I want to point out is that

NOTE Confidence: 0.8389494

00:12:44.116 --> 00:12:46.148 genetic genetic correlation between

NOTE Confidence: 0.8389494

00:12:46.148 --> 00:12:49.865 each of the three sub phenotype groups

NOTE Confidence: 0.8389494

00:12:49.952 --> 00:12:52.527 taken individually is very high.

NOTE Confidence: 0.8389494

00:12:52.530 --> 00:12:55.878 In each case it's over .9.

NOTE Confidence: 0.8389494

00:12:55.880 --> 00:12:58.934 So the implication is that although

NOTE Confidence: 0.8389494

00:12:58.934 --> 00:13:00.970 there are phenomenologically different

NOTE Confidence: 0.8389494

00:13:01.042 --> 00:13:03.268 that the clinical insight that they

NOTE Confidence: 0.8389494

00:13:03.268 --> 00:13:05.951 formed part of the same diagnostic
NOTE Confidence: 0.8389494

00:13:05.951 --> 00:13:08.199 construct was absolutely correct,
NOTE Confidence: 0.8389494

00:13:08.200 --> 00:13:10.132 because genetically they
NOTE Confidence: 0.8389494

00:13:10.132 --> 00:13:12.708 share similar orange origins.
NOTE Confidence: 0.8389494

00:13:12.710 --> 00:13:16.118 So this allows us to use.
NOTE Confidence: 0.8389494

00:13:16.120 --> 00:13:18.922 Genome wide genetic data to reflect
NOTE Confidence: 0.8389494

00:13:18.922 --> 00:13:21.620 back on diagnosis and nosology.
NOTE Confidence: 0.77978975

00:13:23.720 --> 00:13:27.605 So now we have large geosat PTSD.
NOTE Confidence: 0.77978975

00:13:27.610 --> 00:13:30.390 We've discovered more risk loci,
NOTE Confidence: 0.77978975

00:13:30.390 --> 00:13:33.058 genomic structural equation equation
NOTE Confidence: 0.77978975

00:13:33.058 --> 00:13:35.726 modeling also supported the.
NOTE Confidence: 0.77978975

00:13:35.730 --> 00:13:39.456 A single common factor underlying the
NOTE Confidence: 0.77978975

00:13:39.456 --> 00:13:41.940 three phenomenologically different PTSD
NOTE Confidence: 0.77978975

00:13:42.025 --> 00:13:44.805 sub phenotype factors validating the
NOTE Confidence: 0.77978975

00:13:44.805 --> 00:13:48.400 biological coherence of the PTSD syndrome.
NOTE Confidence: 0.77978975

00:13:48.400 --> 00:13:50.997 The other trade I'm going to talk

NOTE Confidence: 0.77978975

00:13:50.997 --> 00:13:53.673 about is alcohol use or alcohol use

NOTE Confidence: 0.77978975

00:13:53.673 --> 00:13:55.899 disorder risk genes that map to

NOTE Confidence: 0.77978975

00:13:55.977 --> 00:13:57.937 alcohol metabolising pathways have

NOTE Confidence: 0.77978975

00:13:57.937 --> 00:14:01.296 been well known for decades and are

NOTE Confidence: 0.77978975

00:14:01.296 --> 00:14:03.376 very easy to understand biologically.

NOTE Confidence: 0.77978975

00:14:03.380 --> 00:14:06.436 If you have a variant that interferes with

NOTE Confidence: 0.77978975

00:14:06.436 --> 00:14:09.040 the metabolism of ethanol that results

NOTE Confidence: 0.77978975

00:14:09.040 --> 00:14:11.692 in high rates of circulating acetaldehyde.

NOTE Confidence: 0.77978975

00:14:11.700 --> 00:14:14.190 The first metabolite on the most

NOTE Confidence: 0.77978975

00:14:14.190 --> 00:14:15.435 important metabolic pathway,

NOTE Confidence: 0.77978975

00:14:15.440 --> 00:14:17.520 which results in dysphoric properties,

NOTE Confidence: 0.77978975

00:14:17.520 --> 00:14:19.500 you're relatively protected from.

NOTE Confidence: 0.77978975

00:14:19.500 --> 00:14:20.985 Alcohol use disorder.

NOTE Confidence: 0.77978975

00:14:20.990 --> 00:14:25.182 The first PG CG was for alcohol use

NOTE Confidence: 0.77978975

00:14:25.182 --> 00:14:28.640 disorder which came out in late 2018,

NOTE Confidence: 0.77978975

00:14:28.640 --> 00:14:32.084 found despite a good sample size with
NOTE Confidence: 0.77978975

00:14:32.084 --> 00:14:34.759 46,000 European ancestry subjects only.
NOTE Confidence: 0.77978975

00:14:34.760 --> 00:14:37.820 This one risk locus and European
NOTE Confidence: 0.77978975

00:14:37.820 --> 00:14:38.840 ancestry subjects.
NOTE Confidence: 0.77978975

00:14:38.840 --> 00:14:42.410 Nevertheless, it made the cover of nature.
NOTE Confidence: 0.77978975

00:14:42.410 --> 00:14:42.920 Neuroscience,
NOTE Confidence: 0.77978975

00:14:42.920 --> 00:14:47.000 name of this cover diagram is plot glasses.
NOTE Confidence: 0.85018146

00:14:49.160 --> 00:14:51.570 Our follow-up study from the
NOTE Confidence: 0.85018146

00:14:51.570 --> 00:14:53.980 MVP was again much larger,
NOTE Confidence: 0.85018146

00:14:53.980 --> 00:14:56.390 and we considered both alcohol
NOTE Confidence: 0.85018146

00:14:56.390 --> 00:14:58.800 use disorder perception an audit,
NOTE Confidence: 0.85018146

00:14:58.800 --> 00:15:01.254 see which is a quantity frequency
NOTE Confidence: 0.85018146

00:15:01.254 --> 00:15:04.543 measure of alcohol use without capturing
NOTE Confidence: 0.85018146

00:15:04.543 --> 00:15:06.910 biological physiological dependence.
NOTE Confidence: 0.85018146

00:15:06.910 --> 00:15:08.725 So previously these were thought
NOTE Confidence: 0.85018146

00:15:08.725 --> 00:15:10.540 to index closely related traits,

NOTE Confidence: 0.85018146

00:15:10.540 --> 00:15:13.436 so if you drink a lot of alcohol,

NOTE Confidence: 0.85018146

00:15:13.440 --> 00:15:15.756 we might have assumed that the

NOTE Confidence: 0.85018146

00:15:15.756 --> 00:15:17.808 genetic background was similar to

NOTE Confidence: 0.85018146

00:15:17.808 --> 00:15:19.580 alcohol use disorder perception.

NOTE Confidence: 0.85018146

00:15:19.580 --> 00:15:22.268 Here's the Manhattan plot for audit.

NOTE Confidence: 0.85018146

00:15:22.270 --> 00:15:25.590 See quantity frequency measure.

NOTE Confidence: 0.85018146

00:15:25.590 --> 00:15:28.320 These analysis were led by Hong Zhao,

NOTE Confidence: 0.85018146

00:15:28.320 --> 00:15:29.880 an associate research scientist.

NOTE Confidence: 0.85018146

00:15:29.880 --> 00:15:31.440 Now in my lab.

NOTE Confidence: 0.85018146

00:15:31.440 --> 00:15:34.870 This is the meta analysis across population

NOTE Confidence: 0.85018146

00:15:34.870 --> 00:15:37.450 groups for alcohol use disorder.

NOTE Confidence: 0.85018146

00:15:37.450 --> 00:15:40.906 I won't spend a lot of time on those.

NOTE Confidence: 0.85018146

00:15:40.910 --> 00:15:42.639 What I want to spend some time

NOTE Confidence: 0.85018146

00:15:42.639 --> 00:15:44.477 on is the genetic correlation

NOTE Confidence: 0.85018146

00:15:44.477 --> 00:15:46.533 patterns by linkage disequilibrium

NOTE Confidence: 0.85018146

00:15:46.533 --> 00:15:48.589 score regression with audit.
NOTE Confidence: 0.85018146

00:15:48.590 --> 00:15:50.170 See quantity frequency measure.
NOTE Confidence: 0.85018146

00:15:50.170 --> 00:15:52.540 On the one hand and alcohol
NOTE Confidence: 0.85018146

00:15:52.609 --> 00:15:54.349 use disorder on the other.
NOTE Confidence: 0.85018146

00:15:54.350 --> 00:15:56.854 And what we can see is that there
NOTE Confidence: 0.85018146

00:15:56.854 --> 00:15:58.914 are patterns of genetic correlation
NOTE Confidence: 0.85018146

00:15:58.914 --> 00:16:01.638 are very different in important ways.
NOTE Confidence: 0.85018146

00:16:01.640 --> 00:16:03.584 So if we look at anthropometric
NOTE Confidence: 0.85018146

00:16:03.584 --> 00:16:05.435 measures we see many significant
NOTE Confidence: 0.85018146

00:16:05.435 --> 00:16:07.875 negative correlations with audit C.
NOTE Confidence: 0.85018146

00:16:07.880 --> 00:16:10.670 So audit, see higher audit C,
NOTE Confidence: 0.85018146

00:16:10.670 --> 00:16:13.150 so drinking more frequently and
NOTE Confidence: 0.85018146

00:16:13.150 --> 00:16:15.630 in higher quantity is associated
NOTE Confidence: 0.85018146

00:16:15.711 --> 00:16:17.646 to lower body mass index.
NOTE Confidence: 0.85018146

00:16:17.650 --> 00:16:18.578 Lower obesity,
NOTE Confidence: 0.85018146

00:16:18.578 --> 00:16:20.434 apparent decrease risk for

NOTE Confidence: 0.85018146
00:16:20.434 --> 00:16:21.826 coronary artery disease.
NOTE Confidence: 0.85018146
00:16:21.830 --> 00:16:26.694 This is not seen for alcohol use disorder.
NOTE Confidence: 0.85018146
00:16:26.700 --> 00:16:29.844 But if we look at psychiatric traits audit,
NOTE Confidence: 0.85018146
00:16:29.850 --> 00:16:32.994 see appears to be in a minor way,
NOTE Confidence: 0.85018146
00:16:33.000 --> 00:16:34.944 protected against major depression.
NOTE Confidence: 0.85018146
00:16:34.944 --> 00:16:37.860 But IU D is associated with
NOTE Confidence: 0.85018146
00:16:37.941 --> 00:16:40.177 risk for smoking neuroticism,
NOTE Confidence: 0.85018146
00:16:40.180 --> 00:16:41.174 bipolar disorder,
NOTE Confidence: 0.85018146
00:16:41.174 --> 00:16:41.671 schizophrenia,
NOTE Confidence: 0.85018146
00:16:41.671 --> 00:16:44.653 down the gamut of psychiatric traits,
NOTE Confidence: 0.85018146
00:16:44.660 --> 00:16:49.418 for which we have sufficient information.
NOTE Confidence: 0.85018146
00:16:49.420 --> 00:16:51.682 But once we have genome wide
NOTE Confidence: 0.85018146
00:16:51.682 --> 00:16:52.436 Association data,
NOTE Confidence: 0.85018146
00:16:52.440 --> 00:16:55.328 we can do all sorts of post GWAS
NOTE Confidence: 0.85018146
00:16:55.328 --> 00:16:57.283 insilico analysis to learn more
NOTE Confidence: 0.85018146

00:16:57.283 --> 00:16:59.593 about the biology of the disorder.
NOTE Confidence: 0.85018146

00:16:59.600 --> 00:17:02.239 I've focused only on plea atropia analysis,
NOTE Confidence: 0.85018146

00:17:02.240 --> 00:17:05.327 but there are a range of things you can
NOTE Confidence: 0.85018146

00:17:05.327 --> 00:17:09.017 do to learn about the biology of the trait.
NOTE Confidence: 0.85018146

00:17:09.020 --> 00:17:12.002 Once you have a genome wide Association
NOTE Confidence: 0.85018146

00:17:12.002 --> 00:17:14.309 analysis with good enough power.
NOTE Confidence: 0.85018146

00:17:14.310 --> 00:17:15.156 So finally,
NOTE Confidence: 0.85018146

00:17:15.156 --> 00:17:17.694 for gene identification studies like juos,
NOTE Confidence: 0.85018146

00:17:17.700 --> 00:17:19.820 larger samples are much better,
NOTE Confidence: 0.85018146

00:17:19.820 --> 00:17:21.089 provided that careful
NOTE Confidence: 0.85018146

00:17:21.089 --> 00:17:23.204 attention is paid to phenotype,
NOTE Confidence: 0.85018146

00:17:23.210 --> 00:17:24.890 the amount of alcohol consumed
NOTE Confidence: 0.85018146

00:17:24.890 --> 00:17:27.760 turns out to be a different genetic
NOTE Confidence: 0.85018146

00:17:27.760 --> 00:17:30.000 trait from alcohol dependence,
NOTE Confidence: 0.85018146

00:17:30.000 --> 00:17:32.115 most biobank samples so far
NOTE Confidence: 0.85018146

00:17:32.115 --> 00:17:33.807 are mostly European ancestry.

NOTE Confidence: 0.85018146
00:17:33.810 --> 00:17:36.645 This is a problem not just in
NOTE Confidence: 0.85018146
00:17:36.645 --> 00:17:38.899 terms of fairness and equity,
NOTE Confidence: 0.85018146
00:17:38.900 --> 00:17:41.588 but in terms of science differences
NOTE Confidence: 0.85018146
00:17:41.588 --> 00:17:42.932 and linkage disequilibrium
NOTE Confidence: 0.85018146
00:17:42.932 --> 00:17:44.320 structure by population.
NOTE Confidence: 0.85018146
00:17:44.320 --> 00:17:46.780 Are very important in helping us
NOTE Confidence: 0.85018146
00:17:46.780 --> 00:17:49.012 improve fine mapping and therefore
NOTE Confidence: 0.85018146
00:17:49.012 --> 00:17:51.056 identify what variance might
NOTE Confidence: 0.85018146
00:17:51.056 --> 00:17:53.611 really be associated to disease,
NOTE Confidence: 0.85018146
00:17:53.620 --> 00:17:57.925 and even sometimes what genes are associated.
NOTE Confidence: 0.85018146
00:17:57.930 --> 00:17:58.760 And finally,
NOTE Confidence: 0.85018146
00:17:58.760 --> 00:18:01.250 the MVP million vets program comparatively
NOTE Confidence: 0.85018146
00:18:01.250 --> 00:18:03.385 ill comparatively low SES presently
NOTE Confidence: 0.85018146
00:18:03.385 --> 00:18:05.450 uniquely valuable gene mapping resource.
NOTE Confidence: 0.85018146
00:18:05.450 --> 00:18:09.362 And with that I want to acknowledge funding
NOTE Confidence: 0.85018146

00:18:09.362 --> 00:18:12.975 from the VA an from not in an I AAA.

NOTE Confidence: 0.85018146

00:18:12.980 --> 00:18:16.910 My collaborators and the PTSD study.

NOTE Confidence: 0.85018146

00:18:16.910 --> 00:18:18.615 And collaborators in the Alcohol

NOTE Confidence: 0.85018146

00:18:18.615 --> 00:18:20.736 use study and thank you very

NOTE Confidence: 0.85018146

00:18:20.736 --> 00:18:22.148 much for your attention.

NOTE Confidence: 0.85018146

00:18:22.150 --> 00:18:24.966 I'd be happy to take questions by email.