WEBVTT

NOTE duration:”00:31:25”

NOTE recognizability:0.934

NOTE language:en-us

NOTE Confidence: 0.8817718625

00:00:00.000 --> 00:00:01.880 Doctor Alexei Abizov is

NOTE Confidence: 0.8817718625

00:00:01.880 --> 00:00:03.760 a physicist by training.

NOTE Confidence: 0.8817718625

00:00:03.760 --> 00:00:06.553 In 2002 he graduated from the Moscow

NOTE Confidence: 0.8817718625

00:00:06.553 --> 00:00:08.880 Institute of Physics and Technology.

NOTE Confidence: 0.8817718625

00:00:08.880 --> 00:00:12.237 And by the way, I think that we heard

NOTE Confidence: 0.8817718625

00:00:12.237 --> 00:00:17.066 that before where he obtained same place

NOTE Confidence: 0.8817718625

00:00:17.066 --> 00:00:19.994 where he obtained his BS&amp;MS degrees.

NOTE Confidence: 0.8817718625

00:00:19.994 --> 00:00:21.979 He then conducted graduate studies

NOTE Confidence: 0.8817718625

00:00:21.979 --> 00:00:24.400 in biology and in 2008 received

NOTE Confidence: 0.8817718625

00:00:24.400 --> 00:00:27.000 his PhD in computational biology

NOTE Confidence: 0.8817718625

00:00:27.000 --> 00:00:28.560 from Northeastern University.

NOTE Confidence: 0.8817718625

00:00:28.560 --> 00:00:31.010 In Boston, after working as a scientist

NOTE Confidence: 0.8817718625

00:00:31.010 --> 00:00:33.398 at Yale University for almost six years,

NOTE Confidence: 0.8817718625

00:00:33.400 --> 00:00:35.220 he opened his laboratory at

NOTE Confidence: 0.8817718625

00:00:35.220 --> 00:00:37.040 the Mayo Clinic in Rochester,

NOTE Confidence: 0.8817718625

00:00:37.040 --> 00:00:39.245 and his laboratory is purely

NOTE Confidence: 0.8817718625

00:00:39.245 --> 00:00:41.009 analytical and studies variations

NOTE Confidence: 0.8817718625

00:00:41.009 --> 00:00:43.728 in mutation in human cells and how

NOTE Confidence: 0.8817718625

00:00:43.728 --> 00:00:46.080 they can affect health and disease.

NOTE Confidence: 0.8817718625

00:00:46.080 --> 00:00:48.440 He was a member of the 1000 Genomes

NOTE Confidence: 0.8817718625

00:00:48.440 --> 00:00:50.037 Project and then Code Consortium

NOTE Confidence: 0.8817718625

00:00:50.037 --> 00:00:52.751 and was one of the leaders of the

NOTE Confidence: 0.8817718625

00:00:52.751 --> 00:00:54.559 brain Somatic Mosaicism Network,

NOTE Confidence: 0.8817718625

00:00:54.560 --> 00:00:56.320 and he's currently a member of the 2nd.

NOTE Confidence: 0.927749986666667

00:00:58.720 --> 00:01:01.184 All right, I'm actually a second scientist

NOTE Confidence: 0.927749986666667

00:01:01.184 --> 00:01:03.916 talking here who is not like organic person,

NOTE Confidence: 0.927749986666667

00:01:03.920 --> 00:01:06.836 so I'm more like studying genomics,

NOTE Confidence: 0.927749986666667

00:01:06.840 --> 00:01:09.788 but I hope I could do some and you

NOTE Confidence: 0.927749986666667

00:01:09.788 --> 00:01:11.426 will see how we can contribute to

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NOTE Confidence: 0.927749986666667

00:01:11.426 --> 00:01:13.010 general knowledge from different areas

NOTE Confidence: 0.927749986666667

00:01:13.010 --> 00:01:14.960 and from different angles of studies.

NOTE Confidence: 0.927749986666667

00:01:14.960 --> 00:01:16.960 So as was discussed today,

NOTE Confidence: 0.927749986666667

00:01:16.960 --> 00:01:19.360 Organo is a quite powerful system.

NOTE Confidence: 0.927749986666667

00:01:19.360 --> 00:01:22.141 So you can do them for many organs and

NOTE Confidence: 0.927749986666667

00:01:22.141 --> 00:01:25.450 they actually give a promise to not only to

NOTE Confidence: 0.927749986666667

00:01:25.450 --> 00:01:28.267 recreate the organs but also use it as a.

NOTE Confidence: 0.927749986666667

00:01:28.270 --> 00:01:31.376 As a model where you can study development

NOTE Confidence: 0.927749986666667

00:01:31.376 --> 00:01:33.906 and different phenomenons in human.

NOTE Confidence: 0.927749986666667

00:01:33.910 --> 00:01:39.574 So one of the thing in organoids which

NOTE Confidence: 0.927749986666667

00:01:39.574 --> 00:01:42.070 didn't was not highlighted that much

NOTE Confidence: 0.927749986666667

00:01:42.070 --> 00:01:44.667 today is that organoids allow you to

NOTE Confidence: 0.927749986666667

00:01:44.667 --> 00:01:46.541 actually do genetic manipulation in

NOTE Confidence: 0.927749986666667

00:01:46.541 --> 00:01:49.301 the in the system and then see which

NOTE Confidence: 0.927749986666667

00:01:49.368 --> 00:01:51.874 effect is going to give a downstream

NOTE Confidence: 0.927749986666667
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00:01:51.874 --> 00:01:53.586 on development or organ growth.

NOTE Confidence: 0.927749986666667

00:01:53.586 --> 00:01:55.812 And typically how it's done if you

NOTE Confidence: 0.927749986666667

00:01:55.812 --> 00:01:57.810 have like some kind of cell car,

NOTE Confidence: 0.927749986666667

00:01:57.810 --> 00:02:00.282 so typically it's IPS line so you can

NOTE Confidence: 0.927749986666667

00:02:00.282 --> 00:02:02.374 CRISPR edit it and introduce edit.

NOTE Confidence: 0.927749986666667

00:02:02.374 --> 00:02:05.582 But since the CRISPR is not 100% efficient,

NOTE Confidence: 0.927749986666667

00:02:05.582 --> 00:02:07.490 not all of the cells will have the edit,

NOTE Confidence: 0.927749986666667

00:02:07.490 --> 00:02:09.186 so some of them will, some of them won't.

NOTE Confidence: 0.927749986666667

00:02:09.186 --> 00:02:10.470 So typically what people do is

NOTE Confidence: 0.927749986666667

00:02:10.516 --> 00:02:11.329 a clonal selection,

NOTE Confidence: 0.927749986666667

00:02:11.330 --> 00:02:15.512 select a pure edited colony and what

NOTE Confidence: 0.927749986666667

00:02:15.512 --> 00:02:17.498 what can happen during this process

NOTE Confidence: 0.927749986666667

00:02:17.498 --> 00:02:20.109 which is not very obvious all the time.

NOTE Confidence: 0.927749986666667

00:02:20.110 --> 00:02:22.546 Is that actually our cells have mutation.

NOTE Confidence: 0.927749986666667

00:02:22.550 --> 00:02:24.294 So you can have in the initial culture

NOTE Confidence: 0.927749986666667

00:02:24.294 --> 00:02:25.845 you can have cells with a mutation

NOTE Confidence: 0.927749986666667

00:02:25.845 --> 00:02:27.947 and then on top of what you have cells

NOTE Confidence: 0.927749986666667

00:02:27.947 --> 00:02:29.423 which can be edited to unedited.

NOTE Confidence: 0.927749986666667

00:02:29.430 --> 00:02:31.008 And when you do clonal selection

NOTE Confidence: 0.927749986666667

00:02:31.008 --> 00:02:33.341 you can get a colony which may have

NOTE Confidence: 0.927749986666667

00:02:33.341 --> 00:02:34.866 no edit but with mutation.

NOTE Confidence: 0.927749986666667

00:02:34.870 --> 00:02:36.798 Or it can have edit and mutation or

NOTE Confidence: 0.927749986666667

00:02:36.798 --> 00:02:38.828 it may have edit and no mutation.

NOTE Confidence: 0.927749986666667

00:02:38.830 --> 00:02:41.375 So it's actually creates heterogeneity

NOTE Confidence: 0.927749986666667

00:02:41.375 --> 00:02:44.750 during this process of clonal selection.

NOTE Confidence: 0.927749986666667

00:02:44.750 --> 00:02:46.470 Of course if it's only one single mutation,

NOTE Confidence: 0.927749986666667

00:02:46.470 --> 00:02:47.370 maybe you don't care,

NOTE Confidence: 0.927749986666667

00:02:47.370 --> 00:02:49.055 but then the question is like how

NOTE Confidence: 0.927749986666667

00:02:49.055 --> 00:02:50.219 much everything is different.

NOTE Confidence: 0.927749986666667

00:02:50.220 --> 00:02:54.117 And we collaborated with a few labs and

NOTE Confidence: 0.927749986666667

00:02:54.117 --> 00:02:56.173 there were a few labs at Mayo Clinic,

NOTE Confidence: 0.927749986666667

00:02:56.180 --> 00:03:00.806 at Flores Lab at Yale and in Oklahoma.

NOTE Confidence: 0.927749986666667

00:03:00.806 --> 00:03:04.537 So we collected data for those experiments.

NOTE Confidence: 0.927749986666667

00:03:04.540 --> 00:03:05.880 We conducted whole genome sequence

NOTE Confidence: 0.927749986666667

00:03:05.880 --> 00:03:08.068 and of the clones and we just simply

NOTE Confidence: 0.927749986666667

00:03:08.068 --> 00:03:09.916 compared them and ask a simple questions

NOTE Confidence: 0.927749986666667

00:03:09.964 --> 00:03:12.148 how much is the clones which are being

NOTE Confidence: 0.927749986666667

00:03:12.148 --> 00:03:14.100 conducted analysis how much is a similar,

NOTE Confidence: 0.927749986666667

00:03:14.100 --> 00:03:15.804 it turn out that pretty much

NOTE Confidence: 0.927749986666667

00:03:15.804 --> 00:03:16.656 they're all different.

NOTE Confidence: 0.927749986666667

00:03:16.660 --> 00:03:18.907 So there is nothing which is similar.

NOTE Confidence: 0.927749986666667

00:03:18.910 --> 00:03:21.750 And for example as it is shown here,

NOTE Confidence: 0.927749986666667

00:03:21.750 --> 00:03:23.670 so there are three clones which are derived

NOTE Confidence: 0.927749986666667

00:03:23.670 --> 00:03:25.067 after CRISPR experiments and they're

NOTE Confidence: 0.927749986666667

00:03:25.067 --> 00:03:27.104 different here in the copy number variation.

NOTE Confidence: 0.927749986666667

00:03:27.110 --> 00:03:29.670 So this is the coverage across whole genome,

NOTE Confidence: 0.927749986666667

00:03:29.670 --> 00:03:30.210 across genome.

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NOTE Confidence: 0.927749986666667

00:03:30.210 --> 00:03:32.845 And then you can see that here the coverage

NOTE Confidence: 0.927749986666667

00:03:32.845 --> 00:03:35.305 drops which is means heterozygous deletion,

NOTE Confidence: 0.927749986666667

00:03:35.310 --> 00:03:36.390 one of it was deleted,

NOTE Confidence: 0.927749986666667

00:03:36.390 --> 00:03:38.422 so in this line it was deleted and

NOTE Confidence: 0.927749986666667

00:03:38.422 --> 00:03:40.200 this line is completely normal.

NOTE Confidence: 0.927749986666667

00:03:40.200 --> 00:03:41.478 So, and this is quite large,

NOTE Confidence: 0.927749986666667

00:03:41.480 --> 00:03:42.548 this is kilobases,

NOTE Confidence: 0.927749986666667

00:03:42.548 --> 00:03:43.972 multiple kilobases that's that

NOTE Confidence: 0.927749986666667

00:03:43.972 --> 00:03:45.040 has been deleted

NOTE Confidence: 0.921859566666667

00:03:45.100 --> 00:03:46.368 in other experiments it's

NOTE Confidence: 0.921859566666667

00:03:46.368 --> 00:03:47.636 pretty much just say.

NOTE Confidence: 0.921859566666667

00:03:47.640 --> 00:03:50.146 So here is extremely large deletion which

NOTE Confidence: 0.921859566666667

00:03:50.146 --> 00:03:52.480 is manifested only in one of the lines.

NOTE Confidence: 0.921859566666667

00:03:52.480 --> 00:03:55.456 Here there is a small deletion and then

NOTE Confidence: 0.921859566666667

00:03:55.456 --> 00:03:57.840 also manifested and and the same here.

NOTE Confidence: 0.921859566666667
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00:03:57.840 --> 00:04:00.080 All of this variations which are shown here,

NOTE Confidence: 0.921859566666667

00:04:00.080 --> 00:04:02.408 they actually were present in the

NOTE Confidence: 0.921859566666667

00:04:02.408 --> 00:04:04.461 initial culture in the initial

NOTE Confidence: 0.921859566666667

00:04:04.461 --> 00:04:06.596 self population that you use.

NOTE Confidence: 0.921859566666667

00:04:06.600 --> 00:04:08.644 So and if you can do exactly.

NOTE Confidence: 0.921859566666667

00:04:08.650 --> 00:04:10.855 If you can do similar analysis for

NOTE Confidence: 0.921859566666667

00:04:10.855 --> 00:04:12.715 the point mutation and you discover

NOTE Confidence: 0.921859566666667

00:04:12.715 --> 00:04:15.077 them so you can see hundreds of them

NOTE Confidence: 0.921859566666667

00:04:15.077 --> 00:04:17.205 uniquely in each clone and IPS line.

NOTE Confidence: 0.921859566666667

00:04:17.210 --> 00:04:19.418 So this effect is manifested. Why?

NOTE Confidence: 0.921859566666667

00:04:19.418 --> 00:04:22.042 Because we actually do a single cell clone,

NOTE Confidence: 0.921859566666667

00:04:22.050 --> 00:04:24.367 so we now there is this bottleneck

NOTE Confidence: 0.921859566666667

00:04:24.367 --> 00:04:26.127 during analysis when you analyze

NOTE Confidence: 0.921859566666667

00:04:26.127 --> 00:04:28.245 single cell or isolate single cell.

NOTE Confidence: 0.921859566666667

00:04:28.250 --> 00:04:31.208 So a simple conclusion from this

NOTE Confidence: 0.921859566666667

00:04:31.208 --> 00:04:33.810 kind of various experiments that

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NOTE Confidence: 0.921859566666667

00:04:33.810 --> 00:04:36.050 clone and conculturing actually.

NOTE Confidence: 0.921859566666667

00:04:36.050 --> 00:04:38.171 Results to in non isogenic lines that

NOTE Confidence: 0.921859566666667

00:04:38.171 --> 00:04:40.213 the promise of doing CRISPR that

NOTE Confidence: 0.921859566666667

00:04:40.213 --> 00:04:42.349 you can actually can get perfectly

NOTE Confidence: 0.921859566666667

00:04:42.349 --> 00:04:44.485 isogenic and only one mutation that

NOTE Confidence: 0.921859566666667

00:04:44.485 --> 00:04:46.205 you introduced will be affecting

NOTE Confidence: 0.921859566666667

00:04:46.210 --> 00:04:47.714 differences in your analysis.

NOTE Confidence: 0.921859566666667

00:04:47.714 --> 00:04:49.970 However the step of cloning results

NOTE Confidence: 0.921859566666667

00:04:50.030 --> 00:04:51.680 in differences and people have

NOTE Confidence: 0.921859566666667

00:04:51.680 --> 00:04:53.330 to take this into account.

NOTE Confidence: 0.929726842857143

00:04:55.540 --> 00:04:59.344 But I think more, maybe excitingly

NOTE Confidence: 0.929726842857143

00:04:59.344 --> 00:05:01.520 importantly for us to understand that

NOTE Confidence: 0.929726842857143

00:05:01.520 --> 00:05:03.060 actually all cells are different.

NOTE Confidence: 0.929726842857143

00:05:03.060 --> 00:05:04.660 So no two cells even

NOTE Confidence: 0.929726842857143

00:05:04.660 --> 00:05:05.940 from the same individual,

NOTE Confidence: 0.929726842857143
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00:05:05.940 --> 00:05:07.697 from the same culture as the same.

NOTE Confidence: 0.929726842857143

00:05:07.700 --> 00:05:10.020 So this example I gave you in culture,

NOTE Confidence: 0.929726842857143

00:05:10.020 --> 00:05:12.924 but pretty much the same is true for

NOTE Confidence: 0.929726842857143

00:05:12.924 --> 00:05:15.345 cells in our body, in every person.

NOTE Confidence: 0.929726842857143

00:05:15.345 --> 00:05:16.820 So all cells are different.

NOTE Confidence: 0.929726842857143

00:05:16.820 --> 00:05:20.138 And this is called somatic mosaicism.

NOTE Confidence: 0.929726842857143

00:05:20.140 --> 00:05:22.090 Somatic mosaicism gained a lot

NOTE Confidence: 0.929726842857143

00:05:22.090 --> 00:05:23.650 of attention recent years.

NOTE Confidence: 0.929726842857143

00:05:23.650 --> 00:05:26.688 Because we had a boost in technology,

NOTE Confidence: 0.929726842857143

00:05:26.690 --> 00:05:28.825 everyone knows of you development

NOTE Confidence: 0.929726842857143

00:05:28.825 --> 00:05:30.960 of sequencing technologies and also

NOTE Confidence: 0.929726842857143

00:05:31.030 --> 00:05:32.890 there were approaches to study

NOTE Confidence: 0.929726842857143

00:05:32.890 --> 00:05:34.690 mutation to the single cell level.

NOTE Confidence: 0.929726842857143

00:05:34.690 --> 00:05:36.280 However, the ideas of the somatic

NOTE Confidence: 0.929726842857143

00:05:36.280 --> 00:05:37.850 mosaic and they actually quite old.

NOTE Confidence: 0.929726842857143

00:05:37.850 --> 00:05:40.156 The first mentioning was in 2004.

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NOTE Confidence: 0.929726842857143

00:05:40.156 --> 00:05:42.886 The conceptual idea was expressed

NOTE Confidence: 0.929726842857143

00:05:42.890 --> 00:05:45.690 in 2040 that first time it was

NOTE Confidence: 0.929726842857143

00:05:45.690 --> 00:05:47.551 published phrase somatic mosaic

NOTE Confidence: 0.929726842857143

00:05:47.551 --> 00:05:49.297 in scientific literature.

NOTE Confidence: 0.929726842857143

00:05:49.300 --> 00:05:51.715 In in 1945 that was the first

NOTE Confidence: 0.929726842857143

00:05:51.715 --> 00:05:53.874 time we expressed ideas that this

NOTE Confidence: 0.929726842857143

00:05:53.874 --> 00:05:55.619 can happen in a human.

NOTE Confidence: 0.929726842857143

00:05:55.620 --> 00:05:59.120 So I want to share with you

NOTE Confidence: 0.929726842857143

00:05:59.120 --> 00:06:01.388 today talk about two projects,

NOTE Confidence: 0.929726842857143

00:06:01.388 --> 00:06:04.040 one of them related to development

NOTE Confidence: 0.929726842857143

00:06:04.120 --> 00:06:07.960 and the other one related to agent.

NOTE Confidence: 0.929726842857143

00:06:07.960 --> 00:06:12.010 So what does the semantic Moses

NOTE Confidence: 0.929726842857143

00:06:12.010 --> 00:06:12.934 mean development.

NOTE Confidence: 0.929726842857143

00:06:12.940 --> 00:06:14.060 We as a mammal,

NOTE Confidence: 0.929726842857143

00:06:14.060 --> 00:06:16.517 so we developed from a single cell and

NOTE Confidence: 0.929726842857143
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00:06:16.517 --> 00:06:19.259 we follow very defined developmental path.

NOTE Confidence: 0.929726842857143

00:06:19.260 --> 00:06:21.756 So fertilize deck first produce a

NOTE Confidence: 0.929726842857143

00:06:21.756 --> 00:06:23.420 blastosis and blastosis differentiate

NOTE Confidence: 0.929726842857143

00:06:23.480 --> 00:06:25.178 inter in and outer cell mass.

NOTE Confidence: 0.929726842857143

00:06:25.180 --> 00:06:26.870 Then inner cell mass differentiate

NOTE Confidence: 0.929726842857143

00:06:26.870 --> 00:06:29.435 into 3 drum layers and outer cell

NOTE Confidence: 0.929726842857143

00:06:29.435 --> 00:06:31.055 mass mostly produces placenta.

NOTE Confidence: 0.929726842857143

00:06:31.060 --> 00:06:33.832 And then there is a cell migration

NOTE Confidence: 0.929726842857143

00:06:33.832 --> 00:06:35.580 intermixing and making organs.

NOTE Confidence: 0.929726842857143

00:06:35.580 --> 00:06:37.749 If we look at this process in a little

NOTE Confidence: 0.929726842857143

00:06:37.749 --> 00:06:40.295 bit more details this is how it looks like.

NOTE Confidence: 0.929726842857143

00:06:40.300 --> 00:06:42.743 So this is a fertilize deck and

NOTE Confidence: 0.929726842857143

00:06:42.743 --> 00:06:44.686 this is differentiation pass which

NOTE Confidence: 0.929726842857143

00:06:44.686 --> 00:06:46.710 happens to different tissues so.

NOTE Confidence: 0.929726842857143

00:06:46.710 --> 00:06:47.450 For example,

NOTE Confidence: 0.929726842857143

00:06:47.450 --> 00:06:50.040 there is a blood tissue eventually developed,

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NOTE Confidence: 0.929726842857143

00:06:50.040 --> 00:06:52.950 so brain tissue and any other

NOTE Confidence: 0.929726842857143

00:06:52.950 --> 00:06:55.840 tissues and and and cell commitments.

NOTE Confidence: 0.929726842857143

00:06:55.840 --> 00:07:00.278 So this process is this picture

NOTE Confidence: 0.929726842857143

00:07:00.278 --> 00:07:01.796 reflects your development,

NOTE Confidence: 0.929726842857143

00:07:01.800 --> 00:07:04.360 how this happened and differentiation.

NOTE Confidence: 0.929726842857143

00:07:04.360 --> 00:07:04.836 However,

NOTE Confidence: 0.929726842857143

00:07:04.836 --> 00:07:07.692 together and in parallel with the

NOTE Confidence: 0.929726842857143

00:07:07.692 --> 00:07:09.720 differentiation another thing happens,

NOTE Confidence: 0.929726842857143

00:07:09.720 --> 00:07:11.040 cells acquire mutation,

NOTE Confidence: 0.929726842857143

00:07:11.040 --> 00:07:12.360 so they divide,

NOTE Confidence: 0.929726842857143

00:07:12.360 --> 00:07:14.724 they acquire mutation and they also

NOTE Confidence: 0.929726842857143

00:07:14.724 --> 00:07:15.118 differentiate.

NOTE Confidence: 0.929726842857143

00:07:15.120 --> 00:07:17.538 So these two processes are coupled.

NOTE Confidence: 0.929726842857143

00:07:17.540 --> 00:07:20.686 And in fact mutations can happen

NOTE Confidence: 0.929726842857143

00:07:20.686 --> 00:07:22.498 at a different stage of development.

NOTE Confidence: 0.929726842857143
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00:07:22.500 --> 00:07:23.780 If they happened really late,

NOTE Confidence: 0.929726842857143

00:07:23.780 --> 00:07:26.120 they may may be present only in brain and

NOTE Confidence: 0.929726842857143

00:07:26.120 --> 00:07:28.454 not present in the blood or vice versa.

NOTE Confidence: 0.929726842857143

00:07:28.460 --> 00:07:31.348 So a lot of analysis that currently being

NOTE Confidence: 0.929726842857143

00:07:31.348 --> 00:07:33.817 conducted in in medicine and genetics,

NOTE Confidence: 0.929726842857143

00:07:33.820 --> 00:07:35.348 we simply take blood,

NOTE Confidence: 0.929726842857143

00:07:35.348 --> 00:07:37.388 analyze it and and asking a question

NOTE Confidence: 0.929726842857143

00:07:37.388 --> 00:07:38.498 can we see something there.

NOTE Confidence: 0.929726842857143

00:07:38.500 --> 00:07:40.010 But doesn't necessarily guarantee you

NOTE Confidence: 0.929726842857143

00:07:40.010 --> 00:07:41.759 that mutation whatever you see in

NOTE Confidence: 0.929726842857143

00:07:41.759 --> 00:07:43.295 the blood can be found in the brain.

NOTE Confidence: 0.929726842857143

00:07:43.300 --> 00:07:45.400 So this is 1 aspect why it's

NOTE Confidence: 0.929726842857143

00:07:45.400 --> 00:07:47.010 important to study mosaicism.

NOTE Confidence: 0.929726842857143

00:07:47.010 --> 00:07:48.474 And 2nd aspect is,

NOTE Confidence: 0.929726842857143

00:07:48.474 --> 00:07:50.304 since these two processes are

NOTE Confidence: 0.929726842857143

00:07:50.304 --> 00:07:51.789 actually coupled development

NOTE Confidence: 0.929726842857143

00:07:51.789 --> 00:07:53.889 and acquisition of mutations,

NOTE Confidence: 0.929726842857143

00:07:53.890 --> 00:07:57.058 you can ask a question can we use one

NOTE Confidence: 0.929726842857143

00:07:57.058 --> 00:07:59.590 process like let's say mutations to

NOTE Confidence: 0.929726842857143

00:07:59.590 --> 00:08:01.770 infer something about the development.

NOTE Confidence: 0.929726842857143

00:08:01.770 --> 00:08:03.545 So specifically you can think

NOTE Confidence: 0.929726842857143

00:08:03.545 --> 00:08:04.965 of the following idea.

NOTE Confidence: 0.929726842857143

00:08:04.970 --> 00:08:06.930 So in mice when we do lineage

NOTE Confidence: 0.929726842857143

00:08:06.930 --> 00:08:07.770 tracing and try

NOTE Confidence: 0.931611761428571

00:08:07.835 --> 00:08:09.327 to define cell ancestry,

NOTE Confidence: 0.931611761428571

00:08:09.330 --> 00:08:11.090 so people typically use

NOTE Confidence: 0.931611761428571

00:08:11.090 --> 00:08:12.653 genetically modified mice, so.

NOTE Confidence: 0.931611761428571

00:08:12.653 --> 00:08:13.868 What is it shown here?

NOTE Confidence: 0.931611761428571

00:08:13.870 --> 00:08:16.705 So this is the first cell that I got

NOTE Confidence: 0.931611761428571

00:08:16.705 --> 00:08:19.746 is start dividing and at some point

NOTE Confidence: 0.931611761428571

00:08:19.746 --> 00:08:22.204 you can activate expression of let's

NOTE Confidence: 0.931611761428571

00:08:22.204 --> 00:08:24.472 say green fluorescent protein and like

NOTE Confidence: 0.931611761428571

00:08:24.472 --> 00:08:26.350 cartoonishly you will get such a result.

NOTE Confidence: 0.931611761428571

00:08:26.350 --> 00:08:28.240 Like you can usually see that

NOTE Confidence: 0.931611761428571

00:08:28.240 --> 00:08:30.398 there is some area in the mouse

NOTE Confidence: 0.931611761428571

00:08:30.398 --> 00:08:32.426 which is have some abnormal color.

NOTE Confidence: 0.931611761428571

00:08:32.426 --> 00:08:35.309 So obviously we cannot do that in human.

NOTE Confidence: 0.931611761428571

00:08:35.310 --> 00:08:37.314 In human is basically not permissible

NOTE Confidence: 0.931611761428571

00:08:37.314 --> 00:08:39.510 to make a genetic modification.

NOTE Confidence: 0.931611761428571

00:08:39.510 --> 00:08:41.654 However, you can use this idea of mutation

NOTE Confidence: 0.931611761428571

00:08:41.654 --> 00:08:43.709 because once the mutation happen in a cell,

NOTE Confidence: 0.931611761428571

00:08:43.710 --> 00:08:45.240 all progenies of a cell

NOTE Confidence: 0.931611761428571

00:08:45.240 --> 00:08:46.464 will inherit that mutation.

NOTE Confidence: 0.931611761428571

00:08:46.470 --> 00:08:47.590 And we know that majority,

NOTE Confidence: 0.931611761428571

00:08:47.590 --> 00:08:48.810 absolute majority of the mutation

NOTE Confidence: 0.931611761428571

00:08:48.810 --> 00:08:50.030 not going to do anything.

NOTE Confidence: 0.931611761428571

00:08:50.030 --> 00:08:53.110 So they're just purely marks of development.

NOTE Confidence: 0.931611761428571

00:08:53.110 --> 00:08:54.226 So like as it's shown here,

NOTE Confidence: 0.931611761428571

00:08:54.230 --> 00:08:55.710 so let's say you have a First Division,

NOTE Confidence: 0.931611761428571

00:08:55.710 --> 00:08:58.110 you will have mutation A1A2,

NOTE Confidence: 0.931611761428571

00:08:58.110 --> 00:08:59.150 then you have next division,

NOTE Confidence: 0.931611761428571

00:08:59.150 --> 00:09:00.548 let's say you have beta mutation,

NOTE Confidence: 0.931611761428571

00:09:00.550 --> 00:09:01.282 you have gamma.

NOTE Confidence: 0.931611761428571

00:09:01.282 --> 00:09:03.569 And then let's say we will take this cell,

NOTE Confidence: 0.931611761428571

00:09:03.570 --> 00:09:04.810 it will have three mutations.

NOTE Confidence: 0.931611761428571

00:09:04.810 --> 00:09:06.651 So all of the Progenies will inherit

NOTE Confidence: 0.931611761428571

00:09:06.651 --> 00:09:07.803 this unique combination is going

NOTE Confidence: 0.931611761428571

00:09:07.803 --> 00:09:09.330 to be like a bar code for a cell,

NOTE Confidence: 0.931611761428571

00:09:09.330 --> 00:09:11.222 like 3 unique mutations.

NOTE Confidence: 0.931611761428571

00:09:11.222 --> 00:09:15.050 And then in the adult person given that

NOTE Confidence: 0.931611761428571

00:09:15.050 --> 00:09:16.850 if you can analyze multiple cells,

NOTE Confidence: 0.931611761428571

00:09:16.850 --> 00:09:19.834 you can actually infer and see it and

NOTE Confidence: 0.931611761428571

00:09:19.834 --> 00:09:21.489 reconstruct ancestor of the cells.

NOTE Confidence: 0.931611761428571

00:09:21.490 --> 00:09:24.834 So we try to capitalize on this idea

NOTE Confidence: 0.931611761428571

00:09:24.834 --> 00:09:27.922 and study what can we and try to see

NOTE Confidence: 0.931611761428571

00:09:27.922 --> 00:09:29.650 what we can say about development.

NOTE Confidence: 0.931611761428571

00:09:29.650 --> 00:09:31.246 So specifically we did the following.

NOTE Confidence: 0.931611761428571

00:09:31.250 --> 00:09:34.010 So we took a person.

NOTE Confidence: 0.931611761428571

00:09:34.010 --> 00:09:37.166 So we did multiple skin biopsies

NOTE Confidence: 0.931611761428571

00:09:37.170 --> 00:09:40.302 from a person from different areas we

NOTE Confidence: 0.931611761428571

00:09:40.302 --> 00:09:42.562 extracted fibroblast cells and from

NOTE Confidence: 0.931611761428571

00:09:42.562 --> 00:09:45.230 fibroblast cells we derived IPS lines.

NOTE Confidence: 0.931611761428571

00:09:45.230 --> 00:09:47.810 So here we leverage the property

NOTE Confidence: 0.931611761428571

00:09:47.810 --> 00:09:51.089 of IPS lines that they are clonal.

NOTE Confidence: 0.931611761428571

00:09:51.090 --> 00:09:53.338 So every IPS line that you derive it

NOTE Confidence: 0.931611761428571

00:09:53.338 --> 00:09:56.210 will be a perfect clone of one single cell.

NOTE Confidence: 0.931611761428571

00:09:56.210 --> 00:09:58.016 So you can think of IPS line

NOTE Confidence: 0.931611761428571

00:09:58.016 --> 00:09:59.580 as basically a single cell.

NOTE Confidence: 0.931611761428571

00:09:59.580 --> 00:10:02.631 Which we analyze and then we discovered

NOTE Confidence: 0.931611761428571

00:10:02.631 --> 00:10:05.817 mutation in this single cells and

NOTE Confidence: 0.931611761428571

00:10:05.820 --> 00:10:08.571 by sharing of the mutation we can

NOTE Confidence: 0.931611761428571

00:10:08.571 --> 00:10:10.899 reconstruct ancest is 3 of the cells.

NOTE Confidence: 0.931611761428571

00:10:10.900 --> 00:10:12.384 So if they if they share mutation

NOTE Confidence: 0.931611761428571

00:10:12.384 --> 00:10:13.860 means they had a common ancestor,

NOTE Confidence: 0.931611761428571

00:10:13.860 --> 00:10:15.060 if they don't they don't.

NOTE Confidence: 0.931611761428571

00:10:15.060 --> 00:10:18.336 And then like you do simple phylogeny,

NOTE Confidence: 0.931611761428571

00:10:18.340 --> 00:10:20.052 I mean in fact it's not was the

NOTE Confidence: 0.931611761428571

00:10:20.052 --> 00:10:21.915 simple but I'm not going to go

NOTE Confidence: 0.931611761428571

00:10:21.915 --> 00:10:22.740 into technical details.

NOTE Confidence: 0.931611761428571

00:10:22.740 --> 00:10:24.860 So what did we find at the end?

NOTE Confidence: 0.931611761428571

00:10:24.860 --> 00:10:27.032 So this is a patient with

NOTE Confidence: 0.931611761428571

00:10:27.032 --> 00:10:28.118 a Tourette syndrome.

NOTE Confidence: 0.931611761428571

00:10:28.120 --> 00:10:30.226 So here so each branch basically

NOTE Confidence: 0.931611761428571

00:10:30.226 --> 00:10:32.471 represents your single cell and these

NOTE Confidence: 0.931611761428571

00:10:32.471 --> 00:10:34.426 three represents you their ancestry

NOTE Confidence: 0.931611761428571

00:10:34.426 --> 00:10:36.720 that we reconstructed from the mutation.

NOTE Confidence: 0.931611761428571

00:10:36.720 --> 00:10:39.036 So this is in our model.

NOTE Confidence: 0.931611761428571

00:10:39.040 --> 00:10:41.280 This is as I got which divided

NOTE Confidence: 0.931611761428571

00:10:41.280 --> 00:10:43.422 into 2 branches and mutations are

NOTE Confidence: 0.931611761428571

00:10:43.422 --> 00:10:45.313 shown by letters so ABCD.

NOTE Confidence: 0.931611761428571

00:10:45.313 --> 00:10:47.504 And we used Latin letters for this

NOTE Confidence: 0.931611761428571

00:10:47.504 --> 00:10:50.036 branch and brick letters for this branch.

NOTE Confidence: 0.931611761428571

00:10:50.040 --> 00:10:52.038 So OK so we reconstructed this.

NOTE Confidence: 0.931611761428571

00:10:52.040 --> 00:10:53.520 Is there anything interesting?

NOTE Confidence: 0.931611761428571

00:10:53.520 --> 00:10:55.740 So this bars over here show

NOTE Confidence: 0.94780115

00:10:55.804 --> 00:10:58.096 you the frequency of this mutations.

NOTE Confidence: 0.94780115

00:10:58.100 --> 00:10:59.660 In cells from different tissues.

NOTE Confidence: 0.94780115

00:10:59.660 --> 00:11:01.208 So red is blood,

NOTE Confidence: 0.94780115

00:11:01.208 --> 00:11:04.140 blue is saliva and yellow is urine.

NOTE Confidence: 0.94780115

00:11:04.140 --> 00:11:06.800 So what we see right away is that this for

NOTE Confidence: 0.94780115

00:11:06.863 --> 00:11:09.455 mutations which marks this entire branch,

NOTE Confidence: 0.94780115

00:11:09.460 --> 00:11:13.442 they're present in 9180 and 69% of cells

NOTE Confidence: 0.94780115

00:11:13.442 --> 00:11:16.480 and cells from this accordingly they will

NOTE Confidence: 0.94780115

00:11:16.567 --> 00:11:19.870 be at much smaller fraction, 2 to 10%.

NOTE Confidence: 0.94780115

00:11:19.870 --> 00:11:21.970 So right away we notice that

NOTE Confidence: 0.94780115

00:11:21.970 --> 00:11:23.987 there is a huge asymmetry.

NOTE Confidence: 0.94780115

00:11:23.990 --> 00:11:26.260 SO2 blastomers, they already not

NOTE Confidence: 0.94780115

00:11:26.260 --> 00:11:28.950 contributing equally to the adult body.

NOTE Confidence: 0.94780115

00:11:28.950 --> 00:11:31.827 So that was really surprising to us.

NOTE Confidence: 0.94780115

00:11:31.830 --> 00:11:33.696 And this asymmetry to some extent

NOTE Confidence: 0.94780115

00:11:33.696 --> 00:11:35.510 projected to the following divisions,

NOTE Confidence: 0.94780115

00:11:35.510 --> 00:11:36.594 so divisions.

NOTE Confidence: 0.94780115

00:11:36.594 --> 00:11:40.388 So we thought maybe it's just something.

NOTE Confidence: 0.94780115

00:11:40.390 --> 00:11:42.266 So we call this dominant lineage and

NOTE Confidence: 0.94780115

00:11:42.266 --> 00:11:44.390 then we call this recessive lineage.

NOTE Confidence: 0.94780115

00:11:44.390 --> 00:11:45.590 So we thought maybe this is

NOTE Confidence: 0.94780115

00:11:45.590 --> 00:11:46.750 something related to a patient,

NOTE Confidence: 0.94780115

00:11:46.750 --> 00:11:49.750 maybe it's maybe overall not a big deal.

NOTE Confidence: 0.94780115

00:11:49.750 --> 00:11:52.114 So we actually recruited another just

NOTE Confidence: 0.94780115

00:11:52.114 --> 00:11:54.927 healthy individual and did pretty much the

NOTE Confidence: 0.94780115

00:11:54.927 --> 00:11:57.267 same analysis and found identical result.

NOTE Confidence: 0.94780115

00:11:57.270 --> 00:11:59.535 So we reconstructed this lineages

NOTE Confidence: 0.94780115

00:11:59.535 --> 00:12:02.180 and one branch was dominating and

NOTE Confidence: 0.94780115

00:12:02.180 --> 00:12:05.990 the other one was really recessive.

NOTE Confidence: 0.94780115

00:12:05.990 --> 00:12:08.012 There was some some slight differences

NOTE Confidence: 0.94780115

00:12:08.012 --> 00:12:10.707 that there was a lot of mutation here.

NOTE Confidence: 0.94780115

00:12:10.710 --> 00:12:11.240 But however,

NOTE Confidence: 0.94780115

00:12:11.240 --> 00:12:12.830 the overall effect was the same.

NOTE Confidence: 0.94780115

00:12:12.830 --> 00:12:17.950 So we published that study earlier in 2021.

NOTE Confidence: 0.94780115

00:12:17.950 --> 00:12:18.310 Yeah,

NOTE Confidence: 0.94780115

00:12:18.310 --> 00:12:21.200 it was early 2021 and this result was

NOTE Confidence: 0.94780115

00:12:21.200 --> 00:12:23.010 partially replicated by three follow

NOTE Confidence: 0.94780115

00:12:23.071 --> 00:12:25.027 up studies just few months later.

NOTE Confidence: 0.94780115

00:12:25.030 --> 00:12:27.874 Why I say partially is that as a

NOTE Confidence: 0.94780115

00:12:27.874 --> 00:12:29.562 studies using slightly different

NOTE Confidence: 0.94780115

00:12:29.562 --> 00:12:31.265 approach obtains the same result but

NOTE Confidence: 0.94780115

00:12:31.265 --> 00:12:34.750 not in all of the individuals so.

NOTE Confidence: 0.94780115

00:12:34.750 --> 00:12:36.650 Roughly half of the individuals

NOTE Confidence: 0.94780115

00:12:36.650 --> 00:12:38.550 where such linear construction was

NOTE Confidence: 0.94780115

00:12:38.615 --> 00:12:40.750 conducted have this strong asymmetry,

NOTE Confidence: 0.94780115

00:12:40.750 --> 00:12:42.325 and another half doesn't have

NOTE Confidence: 0.94780115

00:12:42.325 --> 00:12:43.270 the strong asymmetry,

NOTE Confidence: 0.94780115

00:12:43.270 --> 00:12:44.670 and we don't know exactly what it means.

NOTE Confidence: 0.94780115

00:12:44.670 --> 00:12:46.490 It could be that this is a

NOTE Confidence: 0.94780115

00:12:46.490 --> 00:12:47.670 finistic variation between people,

NOTE Confidence: 0.94780115

00:12:47.670 --> 00:12:49.574 or it could be that we simply

NOTE Confidence: 0.94780115

00:12:49.574 --> 00:12:50.390 in those individuals.

NOTE Confidence: 0.94780115

00:12:50.390 --> 00:12:51.390 We haven't found it yet.

NOTE Confidence: 0.94780115

00:12:51.390 --> 00:12:52.254 This is a symmetry.

NOTE Confidence: 0.94780115

00:12:52.254 --> 00:12:53.870 You just need to sample more cells.

NOTE Confidence: 0.94780115

00:12:53.870 --> 00:12:54.145 Obviously,

NOTE Confidence: 0.94780115

00:12:54.145 --> 00:12:56.345 the more cells you sample from a person,

NOTE Confidence: 0.94780115

00:12:56.350 --> 00:12:58.054 the more power you have to

NOTE Confidence: 0.94780115

00:12:58.054 --> 00:12:59.190 find such a symmetries.

NOTE Confidence: 0.94780115

00:12:59.190 --> 00:12:59.684 So.

NOTE Confidence: 0.94780115

00:12:59.684 --> 00:13:02.154 But what is the interpretation

NOTE Confidence: 0.94780115

00:13:02.154 --> 00:13:03.636 of this asymmetry?

NOTE Confidence: 0.94780115

00:13:03.640 --> 00:13:04.424 Technically speaking,

NOTE Confidence: 0.94780115

00:13:04.424 --> 00:13:07.560 you can think about two effect effect #1.

NOTE Confidence: 0.94780115

00:13:07.560 --> 00:13:11.676 So if the blastomer divides and creates 2

NOTE Confidence: 0.94780115

00:13:11.676 --> 00:13:14.840 lineages initially is I got this divide.

NOTE Confidence: 0.94780115

00:13:14.840 --> 00:13:18.536 So it could be that one lineage

NOTE Confidence: 0.94780115

00:13:18.536 --> 00:13:19.800 somehow has an advantage.

NOTE Confidence: 0.94780115

00:13:19.800 --> 00:13:22.248 Maybe it proliferates faster or maybe

NOTE Confidence: 0.94780115

00:13:22.248 --> 00:13:24.360 the other lineage proliferates slower.

NOTE Confidence: 0.94780115

00:13:24.360 --> 00:13:26.355 So this is what happens in reality.

NOTE Confidence: 0.94780115

00:13:26.360 --> 00:13:27.936 But when we construct.

NOTE Confidence: 0.94780115

00:13:27.936 --> 00:13:30.300 When we make a retrospective reconstruction,

NOTE Confidence: 0.94780115

00:13:30.300 --> 00:13:31.500 because we actually don't

NOTE Confidence: 0.94780115

00:13:31.500 --> 00:13:32.700 have information about time,

NOTE Confidence: 0.94780115

00:13:32.700 --> 00:13:35.340 we only have information about ancestry,

NOTE Confidence: 0.94780115

00:13:35.340 --> 00:13:36.824 it looks to us that there was

NOTE Confidence: 0.94780115

00:13:36.824 --> 00:13:38.227 only two divisions and we assume

NOTE Confidence: 0.94780115

00:13:38.227 --> 00:13:39.417 there was scenario like this.

NOTE Confidence: 0.94780115

00:13:39.420 --> 00:13:39.683 However,

NOTE Confidence: 0.94780115

00:13:39.683 --> 00:13:41.524 in fact may have been this case

NOTE Confidence: 0.94780115

00:13:41.524 --> 00:13:43.225 where for three divisions in this

NOTE Confidence: 0.94780115

00:13:43.225 --> 00:13:45.220 lineage there was only two of this.

NOTE Confidence: 0.94780115

00:13:45.220 --> 00:13:46.156 This is just cartoonish,

NOTE Confidence: 0.94780115

00:13:46.156 --> 00:13:48.259 but showing you that there is some asymmetry,

NOTE Confidence: 0.94780115

00:13:48.260 --> 00:13:50.045 like internal properties,

NOTE Confidence: 0.94780115

00:13:50.045 --> 00:13:53.020 that's possible explanation number one.

NOTE Confidence: 0.94780115

00:13:53.020 --> 00:13:56.990 Another one maybe that.

NOTE Confidence: 0.94780115

00:13:56.990 --> 00:13:59.630 This lineage which we call recessive

NOTE Confidence: 0.94780115

00:13:59.630 --> 00:14:01.772 cells of this lineage have some

NOTE Confidence: 0.94780115

00:14:01.772 --> 00:14:03.200 intrinsic property where which

NOTE Confidence: 0.949646106666667

00:14:03.267 --> 00:14:05.670 for example leads them to higher apoptosis.

NOTE Confidence: 0.949646106666667

00:14:05.670 --> 00:14:07.590 So so this cells.

NOTE Confidence: 0.949646106666667

00:14:07.590 --> 00:14:09.767 So in reality they this cell divided

NOTE Confidence: 0.949646106666667

00:14:09.767 --> 00:14:12.360 into 2 but that cell didn't survive

NOTE Confidence: 0.949646106666667

00:14:12.360 --> 00:14:14.742 and maybe this cell didn't survive.

NOTE Confidence: 0.949646106666667

00:14:14.750 --> 00:14:16.796 So then every time we divide

NOTE Confidence: 0.949646106666667

00:14:16.796 --> 00:14:18.686 it acquires mutation and start

NOTE Confidence: 0.949646106666667

00:14:18.686 --> 00:14:20.976 with some mutation and one

NOTE Confidence: 0.949646106666667

00:14:20.976 --> 00:14:22.350 retrospectively we reconstruct.

NOTE Confidence: 0.949646106666667

00:14:22.350 --> 00:14:23.883 Then it looks to us that it

NOTE Confidence: 0.949646106666667

00:14:23.883 --> 00:14:25.070 was one single mutation,

NOTE Confidence: 0.949646106666667

00:14:25.070 --> 00:14:27.149 was one single division with many mutation.

NOTE Confidence: 0.949646106666667

00:14:27.150 --> 00:14:28.308 But in fact it was not

NOTE Confidence: 0.915076654545455

00:14:31.870 --> 00:14:33.875 here that the cells which

NOTE Confidence: 0.915076654545455

00:14:33.875 --> 00:14:36.390 we put with a question mark,

NOTE Confidence: 0.915076654545455

00:14:36.390 --> 00:14:38.394 they don't necessarily may up up

NOTE Confidence: 0.915076654545455

00:14:38.394 --> 00:14:40.750 toes or maybe happen something else.

NOTE Confidence: 0.915076654545455

00:14:40.750 --> 00:14:42.310 Particularly they may go to placenta

NOTE Confidence: 0.915076654545455

00:14:42.310 --> 00:14:44.120 and since we are not something

NOTE Confidence: 0.915076654545455

00:14:44.120 --> 00:14:45.910 placenta from the living individuals,

NOTE Confidence: 0.915076654545455

00:14:45.910 --> 00:14:48.744 we are not able to observe it.

NOTE Confidence: 0.915076654545455

00:14:48.744 --> 00:14:50.429 And this possibility is quite

NOTE Confidence: 0.915076654545455

00:14:50.429 --> 00:14:52.268 exciting because it may suggest

NOTE Confidence: 0.915076654545455

00:14:52.268 --> 00:14:53.426 the following scenario.

NOTE Confidence: 0.915076654545455

00:14:53.430 --> 00:14:54.746 At this point we cannot prove it.

NOTE Confidence: 0.915076654545455

00:14:54.750 --> 00:14:57.094 But this is on the level of hypothesis

NOTE Confidence: 0.915076654545455

00:14:57.094 --> 00:14:59.502 that two cells from the very beginning

NOTE Confidence: 0.915076654545455

00:14:59.502 --> 00:15:01.830 could be already unequal in their fate,

NOTE Confidence: 0.915076654545455

00:15:01.830 --> 00:15:03.950 and one of them, one of the cell,

NOTE Confidence: 0.915076654545455

00:15:03.950 --> 00:15:05.665 one of the blastomer from the beginning,

NOTE Confidence: 0.915076654545455

00:15:05.670 --> 00:15:07.025 already knows that it will

NOTE Confidence: 0.915076654545455

00:15:07.025 --> 00:15:08.109 mostly make a placenta,

NOTE Confidence: 0.915076654545455

00:15:08.110 --> 00:15:09.592 and the other blastomer will know

NOTE Confidence: 0.915076654545455

00:15:09.592 --> 00:15:11.427 that it mostly will make a dull body.

NOTE Confidence: 0.915076654545455

00:15:11.430 --> 00:15:13.270 And then during this development,

NOTE Confidence: 0.915076654545455

00:15:13.270 --> 00:15:15.302 so this will organize,

NOTE Confidence: 0.915076654545455

00:15:15.302 --> 00:15:18.350 the development will go this way.

NOTE Confidence: 0.915076654545455

00:15:18.350 --> 00:15:20.960 And that's why when we are

NOTE Confidence: 0.915076654545455

00:15:20.960 --> 00:15:22.265 analyzing leaving individual,

NOTE Confidence: 0.945285407142857

00:15:24.830 --> 00:15:26.894 one of the lineage will be

NOTE Confidence: 0.945285407142857

00:15:26.894 --> 00:15:28.270 underrepresented and the other

NOTE Confidence: 0.945285407142857

00:15:28.336 --> 00:15:30.670 lineage will be overrepresented. So

NOTE Confidence: 0.916010616875

00:15:33.110 --> 00:15:34.550 that's that's about development.

NOTE Confidence: 0.916010616875

00:15:34.550 --> 00:15:37.114 And then let me slightly shift gears

NOTE Confidence: 0.916010616875

00:15:37.114 --> 00:15:38.829 and go about somatic mutation.

NOTE Confidence: 0.916010616875

00:15:38.830 --> 00:15:40.948 What can we infer about aging?

NOTE Confidence: 0.951231854545455

00:15:44.000 --> 00:15:46.244 This project was conducted in frame

NOTE Confidence: 0.951231854545455

00:15:46.244 --> 00:15:48.320 of brain somatic Moses network.

NOTE Confidence: 0.951231854545455

00:15:48.320 --> 00:15:51.160 This network was established by

NOTE Confidence: 0.951231854545455

00:15:51.160 --> 00:15:53.410 NIMH National Institute of Mental

NOTE Confidence: 0.951231854545455

00:15:53.410 --> 00:15:56.107 Health with the aim of understanding

NOTE Confidence: 0.951231854545455

00:15:56.107 --> 00:15:58.352 how much somatic mutations can

NOTE Confidence: 0.951231854545455

00:15:58.352 --> 00:16:00.840 contribute to neurological diseases.

NOTE Confidence: 0.951231854545455

00:16:00.840 --> 00:16:02.910 So there were six diseases targeted

NOTE Confidence: 0.951231854545455

00:16:02.910 --> 00:16:05.709 and the idea will discover all of the

NOTE Confidence: 0.951231854545455

00:16:05.709 --> 00:16:08.200 type of somatic mutations in the brain.

NOTE Confidence: 0.951231854545455

00:16:08.200 --> 00:16:10.258 But today I will mostly focus

NOTE Confidence: 0.951231854545455

00:16:10.258 --> 00:16:11.630 on the three diseases.

NOTE Confidence: 0.951231854545455

00:16:11.630 --> 00:16:13.316 Simply because for this for brains

NOTE Confidence: 0.951231854545455

00:16:13.316 --> 00:16:15.338 with these diseases we had whole genome

NOTE Confidence: 0.951231854545455

00:16:15.338 --> 00:16:17.305 sequencing data and for others we don't.

NOTE Confidence: 0.951231854545455

00:16:17.310 --> 00:16:19.296 And we actually like really whole

NOTE Confidence: 0.951231854545455

00:16:19.296 --> 00:16:21.233 genome data because we can analyze

NOTE Confidence: 0.951231854545455

00:16:21.233 --> 00:16:23.449 entire genome and it gives us a lot

NOTE Confidence: 0.951231854545455

00:16:23.516 --> 00:16:25.665 of information and also I will be

NOTE Confidence: 0.951231854545455

00:16:25.665 --> 00:16:29.030 focusing mostly on point mutations.

NOTE Confidence: 0.951231854545455

00:16:29.030 --> 00:16:33.455 So when we started this project in 2015,

NOTE Confidence: 0.951231854545455

00:16:33.455 --> 00:16:35.870 I believe at that time the question

NOTE Confidence: 0.951231854545455

00:16:35.870 --> 00:16:38.023 number one was can we discover

NOTE Confidence: 0.951231854545455

00:16:38.023 --> 00:16:39.758 some ASIC mutations or not.

NOTE Confidence: 0.951231854545455

00:16:39.760 --> 00:16:42.064 The approach in this project was

NOTE Confidence: 0.951231854545455

00:16:42.064 --> 00:16:44.016 different from that lineage tracing

NOTE Confidence: 0.951231854545455

00:16:44.016 --> 00:16:46.495 I just talked about because here we

NOTE Confidence: 0.951231854545455

00:16:46.495 --> 00:16:48.320 did not analyze individual cells.

NOTE Confidence: 0.951231854545455

00:16:48.320 --> 00:16:50.084 So here we took a brain and

NOTE Confidence: 0.951231854545455

00:16:50.084 --> 00:16:51.479 analyzed bulk of the brain.

NOTE Confidence: 0.951231854545455

00:16:51.480 --> 00:16:52.293 And last question,

NOTE Confidence: 0.951231854545455

00:16:52.293 --> 00:16:53.919 can we see some mutations there?

NOTE Confidence: 0.951231854545455

00:16:53.920 --> 00:16:55.860 So obviously we cannot see

NOTE Confidence: 0.951231854545455

00:16:55.860 --> 00:16:57.800 mutations which are extremely rare.

NOTE Confidence: 0.951231854545455

00:16:57.800 --> 00:17:00.164 We can only see relatively frequent

NOTE Confidence: 0.951231854545455

00:17:00.164 --> 00:17:01.664 mutations and the question was

NOTE Confidence: 0.951231854545455

00:17:01.664 --> 00:17:03.320 how do we actually discover them.

NOTE Confidence: 0.951231854545455

00:17:03.320 --> 00:17:06.360 So just briefly what we did,

NOTE Confidence: 0.951231854545455

00:17:06.360 --> 00:17:09.828 we simulated somatic mutations by mixing.

NOTE Confidence: 0.951231854545455

00:17:09.830 --> 00:17:12.310 Different samples with different genomes.

NOTE Confidence: 0.951231854545455

00:17:12.310 --> 00:17:16.522 So this way variations which I inherited

NOTE Confidence: 0.951231854545455

00:17:16.522 --> 00:17:19.000 will be present as a frequency

NOTE Confidence: 0.951231854545455

00:17:19.070 --> 00:17:21.010 which is not in 100% of cells,

NOTE Confidence: 0.951231854545455

00:17:21.010 --> 00:17:22.385 just a fraction of cells,

NOTE Confidence: 0.951231854545455

00:17:22.390 --> 00:17:24.475 and this thereby will simulate

NOTE Confidence: 0.951231854545455

00:17:24.475 --> 00:17:25.309 somatic mutations.

NOTE Confidence: 0.951231854545455

00:17:25.310 --> 00:17:26.834 The Long story short,

NOTE Confidence: 0.951231854545455

00:17:26.834 --> 00:17:28.358 basically nonexistent methods allow

NOTE Confidence: 0.951231854545455

00:17:28.358 --> 00:17:30.835 us to do comprehensive and accurate

NOTE Confidence: 0.951231854545455

00:17:30.835 --> 00:17:33.670 discovery of somatic mutations at that time,

NOTE Confidence: 0.951231854545455

00:17:33.670 --> 00:17:35.860 so we actually had to develop

NOTE Confidence: 0.951231854545455

00:17:35.860 --> 00:17:36.955 some new approaches.

NOTE Confidence: 0.951231854545455

00:17:36.960 --> 00:17:38.878 So we set up a big experiments,

NOTE Confidence: 0.951231854545455

00:17:38.880 --> 00:17:41.698 so we did that in the in the

NOTE Confidence: 0.951231854545455

00:17:41.698 --> 00:17:43.543 consortium and we generated tons

NOTE Confidence: 0.951231854545455

00:17:43.543 --> 00:17:45.769 of call predictions from many labs

NOTE Confidence: 0.951231854545455

00:17:45.769 --> 00:17:47.869 and we made elaborate efforts to

NOTE Confidence: 0.951231854545455

00:17:47.869 --> 00:17:49.916 validate as many sites as possible.

NOTE Confidence: 0.951231854545455

00:17:49.920 --> 00:17:51.480 So here basically showing you

NOTE Confidence: 0.951231854545455

00:17:51.480 --> 00:17:53.040 a validation for 400 sites.

NOTE Confidence: 0.951231854545455

00:17:53.040 --> 00:17:54.942 So every column corresponds to A1

NOTE Confidence: 0.951231854545455

00:17:54.942 --> 00:17:56.586 mutation and every row corresponds

NOTE Confidence: 0.951231854545455

00:17:56.586 --> 00:17:58.805 to a different type of data we

NOTE Confidence: 0.951231854545455

00:17:58.805 --> 00:18:00.289 collected for this mutation.

NOTE Confidence: 0.951231854545455

00:18:00.290 --> 00:18:01.850 So we for this call,

NOTE Confidence: 0.951231854545455

00:18:01.850 --> 00:18:03.938 so we did the multiple sequencing

NOTE Confidence: 0.951231854545455

00:18:03.938 --> 00:18:05.330 of the brain regions,

NOTE Confidence: 0.951231854545455

00:18:05.330 --> 00:18:06.646 we did multiple replicas,

NOTE Confidence: 0.951231854545455

00:18:06.646 --> 00:18:08.850 we did multiple validation and so on.

NOTE Confidence: 0.951231854545455

00:18:08.850 --> 00:18:11.530 So as you can see from this experiment,

NOTE Confidence: 0.951231854545455

00:18:11.530 --> 00:18:13.924 majority of the things we find we

NOTE Confidence: 0.951231854545455

00:18:13.924 --> 00:18:15.390 eventually deemed false positive

NOTE Confidence: 0.951231854545455

00:18:15.390 --> 00:18:17.290 and only small fractions were

NOTE Confidence: 0.951231854545455

00:18:17.290 --> 00:18:18.778 true real thematic mutations.

NOTE Confidence: 0.951231854545455

00:18:18.778 --> 00:18:20.638 And based on this experiment

NOTE Confidence: 0.951231854545455

00:18:20.638 --> 00:18:22.835 I'm not going to overload you

NOTE Confidence: 0.951231854545455

00:18:22.835 --> 00:18:24.247 with the technical details,

NOTE Confidence: 0.951231854545455

00:18:24.250 --> 00:18:26.563 but at the end we came up with a

NOTE Confidence: 0.951231854545455

00:18:26.563 --> 00:18:29.040 way how we can discover mutations.

NOTE Confidence: 0.951231854545455

00:18:29.040 --> 00:18:30.780 From just sequencing brain

NOTE Confidence: 0.951231854545455

00:18:30.780 --> 00:18:32.520 bulk at high coverage,

NOTE Confidence: 0.951231854545455

00:18:32.520 --> 00:18:36.794 so few of the kind of snippets of what does

NOTE Confidence: 0.951231854545455

00:18:36.794 --> 00:18:39.780 the what was the key in this discovery.

NOTE Confidence: 0.951231854545455

00:18:39.780 --> 00:18:43.062 So we had to adjust existing methods

NOTE Confidence: 0.951231854545455

00:18:43.062 --> 00:18:45.408 to become more sensitive to find

NOTE Confidence: 0.951231854545455

00:18:45.408 --> 00:18:47.520 mutations at the lower frequency.

NOTE Confidence: 0.951231854545455

00:18:47.520 --> 00:18:50.236 So we had to use accessibility marks.

NOTE Confidence: 0.936899133333333

00:18:50.240 --> 00:18:52.224 What does it mean? Our genome has a

NOTE Confidence: 0.936899133333333

00:18:52.224 --> 00:18:54.289 lot of repeats so we actually had

NOTE Confidence: 0.936899133333333

00:18:54.289 --> 00:18:56.592 to throw about 25% of the genome.

NOTE Confidence: 0.936899133333333

00:18:56.592 --> 00:19:00.031 Where reads we are using short reads I'm not

NOTE Confidence: 0.936899133333333

00:19:00.031 --> 00:19:02.587 able to reliably call somatic mutations.

NOTE Confidence: 0.936899133333333

00:19:02.590 --> 00:19:06.510 And then what was important we have

NOTE Confidence: 0.936899133333333

00:19:06.510 --> 00:19:09.590 to use panel of normal mask which

NOTE Confidence: 0.936899133333333

00:19:09.590 --> 00:19:12.330 is we see for reproducible errors

NOTE Confidence: 0.936899133333333

00:19:12.330 --> 00:19:13.710 across multiple samples.

NOTE Confidence: 0.936899133333333

00:19:13.710 --> 00:19:16.050 So this was a quick three key steps

NOTE Confidence: 0.936899133333333

00:19:16.050 --> 00:19:18.340 and eventually one of the lab in the

NOTE Confidence: 0.936899133333333

00:19:18.340 --> 00:19:19.988 brain somatic mosaicism developed.

NOTE Confidence: 0.949756584615385

00:19:22.650 --> 00:19:23.958 Artificial intelligence approach,

NOTE Confidence: 0.949756584615385

00:19:23.958 --> 00:19:26.138 a machine learning approach to

NOTE Confidence: 0.949756584615385

00:19:26.138 --> 00:19:28.368 make a final filtering step.

NOTE Confidence: 0.949756584615385

00:19:28.370 --> 00:19:30.938 So at the end, so this is performance

NOTE Confidence: 0.949756584615385

00:19:30.938 --> 00:19:32.649 assessment of our performance,

NOTE Confidence: 0.949756584615385

00:19:32.650 --> 00:19:36.706 how we see it for our developed approach.

NOTE Confidence: 0.949756584615385

00:19:36.706 --> 00:19:39.550 So now mutations between frequency of

NOTE Confidence: 0.949756584615385

00:19:39.632 --> 00:19:41.850 about 20% of frequency and about 2%

NOTE Confidence: 0.949756584615385

00:19:41.850 --> 00:19:44.886 of frequency can be discovered with

NOTE Confidence: 0.949756584615385

00:19:44.886 --> 00:19:47.760 relatively high sensitivity of about 70%.

NOTE Confidence: 0.949756584615385

00:19:47.760 --> 00:19:49.158 So we are missing a lot.

NOTE Confidence: 0.949756584615385

00:19:49.160 --> 00:19:50.665 And we're missing a lot because we

NOTE Confidence: 0.949756584615385

00:19:50.665 --> 00:19:52.146 have to throw out this repetitive

NOTE Confidence: 0.949756584615385

00:19:52.146 --> 00:19:53.194 region of the genome.

NOTE Confidence: 0.949756584615385

00:19:53.200 --> 00:19:55.372 But we can guarantee that what

NOTE Confidence: 0.949756584615385

00:19:55.372 --> 00:19:58.650 we find in in that 75% of the

NOTE Confidence: 0.949756584615385

00:19:58.650 --> 00:20:01.000 genome is actually quite accurate.

NOTE Confidence: 0.949756584615385

00:20:01.000 --> 00:20:03.600 Accuracy is about so false.

NOTE Confidence: 0.949756584615385

00:20:03.600 --> 00:20:07.040 Positive rate is around 5%.

NOTE Confidence: 0.949756584615385

00:20:07.040 --> 00:20:09.280 So what do we find?

NOTE Confidence: 0.949756584615385

00:20:09.280 --> 00:20:12.360 So we analyzed 131 brains.

NOTE Confidence: 0.949756584615385

00:20:12.360 --> 00:20:13.640 There were normal brains,

NOTE Confidence: 0.949756584615385

00:20:13.640 --> 00:20:14.920 brains with stress syndrome,

NOTE Confidence: 0.949756584615385

00:20:14.920 --> 00:20:16.069 ASD and schizophrenia.

NOTE Confidence: 0.949756584615385

00:20:16.069 --> 00:20:17.984 So those are shown here.

NOTE Confidence: 0.949756584615385

00:20:17.990 --> 00:20:20.654 And since we find only relatively

NOTE Confidence: 0.949756584615385

00:20:20.654 --> 00:20:21.986 high frequency mutations,

NOTE Confidence: 0.949756584615385

00:20:21.990 --> 00:20:24.443 so we don't see all like

NOTE Confidence: 0.949756584615385

00:20:24.443 --> 00:20:25.708 hundreds and thousands of them,

NOTE Confidence: 0.949756584615385

00:20:25.710 --> 00:20:27.785 we see relatively small number

NOTE Confidence: 0.949756584615385

00:20:27.785 --> 00:20:30.430 between 20 to 40 per brain.

NOTE Confidence: 0.949756584615385

00:20:30.430 --> 00:20:32.344 And this number is quite consistent

NOTE Confidence: 0.949756584615385

00:20:32.344 --> 00:20:34.455 across all of the cohorts across

NOTE Confidence: 0.949756584615385

00:20:34.455 --> 00:20:36.390 normal and the disease cohort.

NOTE Confidence: 0.949756584615385

00:20:36.390 --> 00:20:40.390 So that was kind of in some sense expected.

NOTE Confidence: 0.949756584615385

00:20:40.390 --> 00:20:42.170 So however what was unexpected

NOTE Confidence: 0.949756584615385

00:20:42.170 --> 00:20:43.950 that there are few brains.

NOTE Confidence: 0.949756584615385

00:20:43.950 --> 00:20:46.267 Where mutation burden is much much high.

NOTE Confidence: 0.949756584615385

00:20:46.270 --> 00:20:47.890 So please pay attention that

NOTE Confidence: 0.949756584615385

00:20:47.890 --> 00:20:49.186 this is log scale.

NOTE Confidence: 0.949756584615385

00:20:49.190 --> 00:20:51.998 So like here the count of mutation is roughly

NOTE Confidence: 0.949756584615385

00:20:51.998 --> 00:20:54.626 2000 that we detected in A1 single brain.

NOTE Confidence: 0.949756584615385

00:20:54.630 --> 00:20:56.790 So we call this brain hypermutables.

NOTE Confidence: 0.949756584615385

00:20:56.790 --> 00:20:59.392 Initially we saw that maybe something

NOTE Confidence: 0.949756584615385

00:20:59.392 --> 00:21:01.648 wrong with the data and we did all

NOTE Confidence: 0.949756584615385

00:21:01.648 --> 00:21:03.880 the possible checks so here it just.

NOTE Confidence: 0.949756584615385

00:21:03.880 --> 00:21:05.525 Showing you that they are not outlined

NOTE Confidence: 0.949756584615385

00:21:05.525 --> 00:21:07.637 in terms of phasing it to the haplotypes.

NOTE Confidence: 0.949756584615385

00:21:07.640 --> 00:21:08.905 They are not outlined in

NOTE Confidence: 0.949756584615385

00:21:08.905 --> 00:21:09.917 terms of mutation spectrum.

NOTE Confidence: 0.949756584615385

00:21:09.920 --> 00:21:11.824 They are not outlined in terms of like

NOTE Confidence: 0.949756584615385

00:21:11.824 --> 00:21:14.077 as a more refined mutation spectrum,

NOTE Confidence: 0.949756584615385

00:21:14.080 --> 00:21:14.418 everything.

NOTE Confidence: 0.949756584615385

00:21:14.418 --> 00:21:16.446 What we could actually point out

NOTE Confidence: 0.949756584615385

00:21:16.446 --> 00:21:18.320 that these are real mutation.

NOTE Confidence: 0.949756584615385

00:21:18.320 --> 00:21:21.078 So these brains in fact have much

NOTE Confidence: 0.949756584615385

00:21:21.078 --> 00:21:23.879 higher count of detective mutation.

NOTE Confidence: 0.949756584615385

00:21:23.880 --> 00:21:25.480 So interestingly enough that

NOTE Confidence: 0.949756584615385

00:21:25.480 --> 00:21:28.340 if we now put age together with

NOTE Confidence: 0.949756584615385

00:21:28.340 --> 00:21:30.275 the count of this mutation,

NOTE Confidence: 0.949756584615385

00:21:30.280 --> 00:21:32.360 we see a positive correlation.

NOTE Confidence: 0.949756584615385

00:21:32.360 --> 00:21:33.320 So here what we saw,

NOTE Confidence: 0.949756584615385

00:21:33.320 --> 00:21:35.800 we show the age of the brain and

NOTE Confidence: 0.949756584615385

00:21:35.800 --> 00:21:38.360 here is a mutation count that we

NOTE Confidence: 0.949756584615385

00:21:38.360 --> 00:21:40.830 detected and we see the positive

NOTE Confidence: 0.949756584615385

00:21:40.830 --> 00:21:43.480 increase that aging brains have.

NOTE Confidence: 0.949756584615385

00:21:43.480 --> 00:21:46.560 All the brains have higher fraction of

NOTE Confidence: 0.949756584615385

00:21:46.560 --> 00:21:49.819 brains with increased mutation count,

NOTE Confidence: 0.949756584615385

00:21:49.819 --> 00:21:52.198 so obvious association.

NOTE Confidence: 0.949756584615385

00:21:52.200 --> 00:21:53.532 And then the question we was

NOTE Confidence: 0.949756584615385

00:21:53.532 --> 00:21:55.159 of course how do we explain it?

NOTE Confidence: 0.949756584615385

00:21:55.160 --> 00:21:57.800 What does it mean?

NOTE Confidence: 0.949756584615385

00:21:57.800 --> 00:22:02.315 So two brains here which are circled.

NOTE Confidence: 0.949756584615385

00:22:02.320 --> 00:22:04.030 They actually had a one missions

NOTE Confidence: 0.949756584615385

00:22:04.030 --> 00:22:06.213 mutation in the NRAS gene and then Ras

NOTE Confidence: 0.949756584615385

00:22:06.213 --> 00:22:08.400 is a quite well known cancer driver gene.

NOTE Confidence: 0.949756584615385

00:22:08.400 --> 00:22:11.640 So it it was damage and mutation over there.

NOTE Confidence: 0.949756584615385

00:22:11.640 --> 00:22:15.195 So this brain had a mutation in the anthorgy.

NOTE Confidence: 0.949756584615385

00:22:15.200 --> 00:22:18.038 So this actually also quite famous

NOTE Confidence: 0.949756584615385

00:22:18.040 --> 00:22:19.993 cancer driver gene and this one the

NOTE Confidence: 0.949756584615385

00:22:19.993 --> 00:22:21.813 brain with the highest mutation count

NOTE Confidence: 0.949756584615385

00:22:21.813 --> 00:22:23.962 actually if you look at the copy

NOTE Confidence: 0.949756584615385

00:22:24.024 --> 00:22:25.869 number profile across the genome.

NOTE Confidence: 0.949756584615385

00:22:25.870 --> 00:22:27.146 So this is cortex,

NOTE Confidence: 0.949756584615385

00:22:27.146 --> 00:22:29.830 this is hippocampus and this is chromosome.

NOTE Confidence: 0.949756584615385

00:22:29.830 --> 00:22:32.329 So what you can see that cortex

NOTE Confidence: 0.949756584615385

00:22:32.329 --> 00:22:33.400 is absolutely normal

NOTE Confidence: 0.903622213846154

00:22:33.468 --> 00:22:34.908 and then hippocampus.

NOTE Confidence: 0.903622213846154

00:22:34.910 --> 00:22:37.270 So there is a gain of chromosome 7.

NOTE Confidence: 0.903622213846154

00:22:37.270 --> 00:22:38.700 It's mosaic, so it's not

NOTE Confidence: 0.903622213846154

00:22:38.700 --> 00:22:40.510 present in all of the sand,

NOTE Confidence: 0.903622213846154

00:22:40.510 --> 00:22:43.030 all of the cells and loss of chromosome 10.

NOTE Confidence: 0.903622213846154

00:22:43.030 --> 00:22:45.750 So it's also mosaic.

NOTE Confidence: 0.903622213846154

00:22:45.750 --> 00:22:47.864 This is actually gain seven loss 10.

NOTE Confidence: 0.903622213846154

00:22:47.870 --> 00:22:50.186 It's a classical example of glioblastoma.

NOTE Confidence: 0.903622213846154

00:22:50.190 --> 00:22:52.512 So this is how it's often

NOTE Confidence: 0.903622213846154

00:22:52.512 --> 00:22:53.673 time being diagnosed.

NOTE Confidence: 0.903622213846154

00:22:53.680 --> 00:22:55.384 When we talked to clinicians in the Mayo

NOTE Confidence: 0.903622213846154

00:22:55.384 --> 00:22:57.994 Clinic, they said well if we see this,

NOTE Confidence: 0.903622213846154

00:22:58.000 --> 00:22:59.518 it's not enough to say it's,

NOTE Confidence: 0.903622213846154

00:22:59.520 --> 00:23:01.676 it's we diagnose it as a cancer.

NOTE Confidence: 0.903622213846154

00:23:01.680 --> 00:23:03.612 However, if you go to the third

NOTE Confidence: 0.903622213846154

00:23:03.612 --> 00:23:05.400 promoter and find mutations there,

NOTE Confidence: 0.903622213846154

00:23:05.400 --> 00:23:08.154 then we'll we'll just call it a cancer case.

NOTE Confidence: 0.903622213846154

00:23:08.160 --> 00:23:10.400 We actually went to the third promoter.

NOTE Confidence: 0.903622213846154

00:23:10.400 --> 00:23:13.118 So it was masked out as a repetitive regions.

NOTE Confidence: 0.903622213846154

00:23:13.120 --> 00:23:14.495 So that's why initially we

NOTE Confidence: 0.903622213846154

00:23:14.495 --> 00:23:15.595 didn't see this mutation.

NOTE Confidence: 0.903622213846154

00:23:15.600 --> 00:23:17.392 However, if we actually go to that

NOTE Confidence: 0.903622213846154

00:23:17.392 --> 00:23:18.779 position where this mutation happens

NOTE Confidence: 0.903622213846154

00:23:18.779 --> 00:23:20.832 to actually see it, so it's there.

NOTE Confidence: 0.903622213846154

00:23:20.832 --> 00:23:22.656 So this person has all the

NOTE Confidence: 0.903622213846154

00:23:22.656 --> 00:23:23.619 hallmarks of cancer.

NOTE Confidence: 0.903622213846154

00:23:23.620 --> 00:23:24.424 Gain of seven,

NOTE Confidence: 0.903622213846154

00:23:24.424 --> 00:23:26.900 loss of 10 and 3rd promote the mutation.

NOTE Confidence: 0.903622213846154

00:23:26.900 --> 00:23:28.952 So we think that it's probably

NOTE Confidence: 0.903622213846154

00:23:28.952 --> 00:23:31.233 undiagnosed case in the person or

NOTE Confidence: 0.903622213846154

00:23:31.233 --> 00:23:33.353 maybe misdiagnosed because that the

NOTE Confidence: 0.903622213846154

00:23:33.353 --> 00:23:35.580 official diagnosis is schizophrenia.

NOTE Confidence: 0.903622213846154

00:23:35.580 --> 00:23:38.820 So that's already we have multiple

NOTE Confidence: 0.903622213846154

00:23:38.820 --> 00:23:41.684 evidence pointing to the cancer driver

NOTE Confidence: 0.903622213846154

00:23:41.684 --> 00:23:44.148 genes and actually if you could be

NOTE Confidence: 0.903622213846154

00:23:44.148 --> 00:23:46.497 late all of the mutations we have.

NOTE Confidence: 0.903622213846154

00:23:46.500 --> 00:23:48.090 So these are all mutations

NOTE Confidence: 0.903622213846154

00:23:48.090 --> 00:23:49.680 in the cancer driver genes.

NOTE Confidence: 0.903622213846154

00:23:49.680 --> 00:23:51.270 Typically we see them in the

NOTE Confidence: 0.903622213846154

00:23:51.270 --> 00:23:52.800 brains which are hyper mutable.

NOTE Confidence: 0.903622213846154

00:23:52.800 --> 00:23:54.048 So there are few brains which

NOTE Confidence: 0.903622213846154

00:23:54.048 --> 00:23:54.880 are non hyper mutable.

NOTE Confidence: 0.903622213846154

00:23:54.880 --> 00:23:56.555 Sometimes we see mutations in

NOTE Confidence: 0.903622213846154

00:23:56.555 --> 00:23:58.230 the cancer driver genes but

NOTE Confidence: 0.903622213846154

00:23:58.295 --> 00:24:00.923 typically there and this is a

NOTE Confidence: 0.903622213846154

00:24:00.923 --> 00:24:02.237 statistically significant enrichment.

NOTE Confidence: 0.903622213846154

00:24:02.240 --> 00:24:04.039 So now we have association with age

NOTE Confidence: 0.903622213846154

00:24:04.039 --> 00:24:06.249 and then we have association with the

NOTE Confidence: 0.903622213846154

00:24:06.249 --> 00:24:08.319 mutations in the cancer driver genes.

NOTE Confidence: 0.903622213846154

00:24:08.320 --> 00:24:09.993 So we think that likely what we

NOTE Confidence: 0.903622213846154

00:24:09.993 --> 00:24:11.760 observe is the following scenario.

NOTE Confidence: 0.903622213846154

00:24:11.760 --> 00:24:13.596 In a normal brain we have

NOTE Confidence: 0.903622213846154

00:24:13.596 --> 00:24:14.820 a diversity of clones.

NOTE Confidence: 0.903622213846154

00:24:14.820 --> 00:24:16.773 And then if we randomly pick up one clone,

NOTE Confidence: 0.903622213846154

00:24:16.780 --> 00:24:18.096 this is just a two dish example.

NOTE Confidence: 0.903622213846154

00:24:18.100 --> 00:24:20.206 Mutation in that clone will be

NOTE Confidence: 0.903622213846154

00:24:20.206 --> 00:24:21.908 at relatively low frequency and

NOTE Confidence: 0.903622213846154

00:24:21.908 --> 00:24:23.748 we are not going to be able to

NOTE Confidence: 0.903622213846154

00:24:23.748 --> 00:24:25.618 see them by sequence and bulk.

NOTE Confidence: 0.903622213846154

00:24:25.620 --> 00:24:26.069 However,

NOTE Confidence: 0.903622213846154

00:24:26.069 --> 00:24:28.763 if you gain some proliferative advantage

NOTE Confidence: 0.903622213846154

00:24:28.763 --> 00:24:31.673 this clone start to expand and

NOTE Confidence: 0.903622213846154

00:24:31.673 --> 00:24:33.657 clonal diversity significantly drops.

NOTE Confidence: 0.903622213846154

00:24:33.660 --> 00:24:35.940 Then mutations present in one

NOTE Confidence: 0.903622213846154

00:24:35.940 --> 00:24:38.606 clone in this green line they

NOTE Confidence: 0.903622213846154

00:24:38.606 --> 00:24:40.922 will rise to the high frequency

NOTE Confidence: 0.903622213846154

00:24:40.922 --> 00:24:43.608 and then by sequence and bulk.

NOTE Confidence: 0.903622213846154

00:24:43.610 --> 00:24:45.170 We are able to detect it.

NOTE Confidence: 0.903622213846154

00:24:45.170 --> 00:24:47.498 So the question is what actually

NOTE Confidence: 0.903622213846154

00:24:47.498 --> 00:24:49.768 cell type expands because in brand

NOTE Confidence: 0.903622213846154

00:24:49.768 --> 00:24:52.015 we have multitude of cell types and

NOTE Confidence: 0.903622213846154

00:24:52.015 --> 00:24:54.486 the question is what happens there?

NOTE Confidence: 0.903622213846154

00:24:54.490 --> 00:24:56.968 So that's one case which I already

NOTE Confidence: 0.903622213846154

00:24:56.968 --> 00:24:59.703 went over it once with this game

NOTE Confidence: 0.903622213846154

00:24:59.703 --> 00:25:05.770 seven and delete loss of 10 so this.

NOTE Confidence: 0.903622213846154

00:25:05.770 --> 00:25:07.828 In hippocampus we see this unemployed is

NOTE Confidence: 0.903622213846154

00:25:07.828 --> 00:25:10.567 and all of these mutations that we detect,

NOTE Confidence: 0.903622213846154

00:25:10.570 --> 00:25:12.046 we also find it in hippocampus.

NOTE Confidence: 0.903622213846154

00:25:12.050 --> 00:25:13.610 So this plot is showing you.

NOTE Confidence: 0.903622213846154

00:25:13.610 --> 00:25:17.089 So every column corresponds to a mutation.

NOTE Confidence: 0.903622213846154

00:25:17.090 --> 00:25:19.676 There are two regions and color

NOTE Confidence: 0.903622213846154

00:25:19.676 --> 00:25:20.969 represents your frequency.

NOTE Confidence: 0.903622213846154

00:25:20.970 --> 00:25:22.710 So these mutations are shared

NOTE Confidence: 0.903622213846154

00:25:22.710 --> 00:25:24.450 between cortex and hippocampus and

NOTE Confidence: 0.903622213846154

00:25:24.506 --> 00:25:26.410 that probably developmental origin.

NOTE Confidence: 0.943913018181818

00:25:26.410 --> 00:25:28.349 So these are early one and these

NOTE Confidence: 0.943913018181818

00:25:28.349 --> 00:25:29.930 are specific to hippocampus,

NOTE Confidence: 0.943913018181818

00:25:29.930 --> 00:25:33.710 most likely reflecting this clonal expansion.

NOTE Confidence: 0.943913018181818

00:25:33.710 --> 00:25:35.852 So we think that in this case

NOTE Confidence: 0.943913018181818

00:25:35.852 --> 00:25:37.589 it's probably glial cells again.

NOTE Confidence: 0.943913018181818

00:25:37.590 --> 00:25:39.792 So this is our strong hypothesis

NOTE Confidence: 0.943913018181818

00:25:39.792 --> 00:25:41.870 which need to be proven.

NOTE Confidence: 0.943913018181818

00:25:41.870 --> 00:25:43.439 So hypothesis #1,

NOTE Confidence: 0.943913018181818

00:25:43.439 --> 00:25:46.577 if you expect inspect mutations which

NOTE Confidence: 0.943913018181818

00:25:46.577 --> 00:25:49.068 happened in cancer driver genes,

NOTE Confidence: 0.943913018181818

00:25:49.070 --> 00:25:51.466 then you will notice genes like DN,

NOTE Confidence: 0.943913018181818

00:25:51.466 --> 00:25:55.078 MT3A, tattoo ID H2 and these genes

NOTE Confidence: 0.943913018181818

00:25:55.078 --> 00:25:58.475 have been before implicated into

NOTE Confidence: 0.943913018181818

00:25:58.475 --> 00:26:00.802 their hematobological malignancy,

NOTE Confidence: 0.943913018181818

00:26:00.802 --> 00:26:03.160 basically blood cancers.

NOTE Confidence: 0.943913018181818

00:26:03.160 --> 00:26:05.045 So another possibility from this

NOTE Confidence: 0.943913018181818

00:26:05.045 --> 00:26:07.880 analysis we think that it could be

NOTE Confidence: 0.943913018181818

00:26:07.880 --> 00:26:09.900 hematopaetic cells so which are

NOTE Confidence: 0.943913018181818

00:26:09.900 --> 00:26:12.180 expanding in the blood but somehow

NOTE Confidence: 0.943913018181818

00:26:12.180 --> 00:26:14.654 they penetrate into the brain and we

NOTE Confidence: 0.943913018181818

00:26:14.654 --> 00:26:17.843 we are able to detect it by by this

NOTE Confidence: 0.943913018181818

00:26:17.843 --> 00:26:19.944 analysis particularly we know that

NOTE Confidence: 0.943913018181818

00:26:19.944 --> 00:26:22.560 aging brains actually they are more

NOTE Confidence: 0.943913018181818

00:26:22.636 --> 00:26:25.430 prone to blood brain leakage and as

NOTE Confidence: 0.943913018181818

00:26:25.430 --> 00:26:29.550 the last hypothesis that we have is.

NOTE Confidence: 0.943913018181818

00:26:29.550 --> 00:26:31.270 Comes from the brain NC7,

NOTE Confidence: 0.943913018181818

00:26:31.270 --> 00:26:33.755 where we already had mutation in the

NOTE Confidence: 0.943913018181818

00:26:33.755 --> 00:26:36.830 NRAS gene and so the plot is the same here.

NOTE Confidence: 0.943913018181818

00:26:36.830 --> 00:26:38.206 So columns represent mutation.

NOTE Confidence: 0.943913018181818

00:26:38.206 --> 00:26:40.270 But now we have different brain

NOTE Confidence: 0.943913018181818

00:26:40.333 --> 00:26:42.388 regions and different cell fractions.

NOTE Confidence: 0.943913018181818

00:26:42.390 --> 00:26:44.798 And what we saw that mutations present

NOTE Confidence: 0.943913018181818

00:26:44.798 --> 00:26:46.629 everywhere in the cortex bulk,

NOTE Confidence: 0.943913018181818

00:26:46.630 --> 00:26:48.628 they're present everywhere in stratum bulk,

NOTE Confidence: 0.943913018181818

00:26:48.630 --> 00:26:51.227 but also they were present in the

NOTE Confidence: 0.943913018181818

00:26:51.227 --> 00:26:53.064 stratum interneural fractions that we

NOTE Confidence: 0.943913018181818

00:26:53.064 --> 00:26:55.044 isolated from this region and actually

NOTE Confidence: 0.943913018181818

00:26:55.044 --> 00:26:57.806 the quite high frequency just to prove that.

NOTE Confidence: 0.943913018181818

00:26:57.806 --> 00:27:00.004 What we did, we isolated cells

NOTE Confidence: 0.943913018181818

00:27:00.004 --> 00:27:01.716 from this stratum interneurons,

NOTE Confidence: 0.943913018181818

00:27:01.720 --> 00:27:04.800 single cells, so isolated 16 of them.

NOTE Confidence: 0.943913018181818

00:27:04.800 --> 00:27:07.380 And we genotype mutations in the

NOTE Confidence: 0.943913018181818

00:27:07.380 --> 00:27:09.640 single cells, so coverage was not high.

NOTE Confidence: 0.943913018181818

00:27:09.640 --> 00:27:12.559 So our genotype inefficiency was roughly 50%.

NOTE Confidence: 0.943913018181818

00:27:12.560 --> 00:27:13.800 So half of the mutation,

NOTE Confidence: 0.943913018181818

00:27:13.800 --> 00:27:15.448 we can see half of them, we're not.

NOTE Confidence: 0.943913018181818

00:27:15.448 --> 00:27:17.392 But you quite clearly can see

NOTE Confidence: 0.943913018181818

00:27:17.392 --> 00:27:18.920 that in the 8 cells,

NOTE Confidence: 0.943913018181818

00:27:18.920 --> 00:27:21.377 they clearly have almost all of the

NOTE Confidence: 0.943913018181818

00:27:21.377 --> 00:27:23.957 mutations in this stratum in the neurons

NOTE Confidence: 0.943913018181818

00:27:23.960 --> 00:27:27.040 from from this that we discovered in bulk.

NOTE Confidence: 0.943913018181818

00:27:27.040 --> 00:27:28.480 And half of the cells you

NOTE Confidence: 0.943913018181818

00:27:28.480 --> 00:27:29.200 don't have anything.

NOTE Confidence: 0.943913018181818

00:27:29.200 --> 00:27:31.528 So it's it's an ultimate proof that first

NOTE Confidence: 0.943913018181818

00:27:31.528 --> 00:27:33.723 of all that this is quantal expansion

NOTE Confidence: 0.943913018181818

00:27:33.723 --> 00:27:36.006 in a single some all mutations present

NOTE Confidence: 0.943913018181818

00:27:36.006 --> 00:27:38.678 in a single cell in a single lineage.

NOTE Confidence: 0.943913018181818

00:27:38.680 --> 00:27:41.165 And then it strongly suggests that stratum

NOTE Confidence: 0.943913018181818

00:27:41.165 --> 00:27:43.275 interneurons may have expanded and and

NOTE Confidence: 0.943913018181818

00:27:43.275 --> 00:27:45.237 then lead to this quantal expansion.

NOTE Confidence: 0.943913018181818

00:27:45.240 --> 00:27:47.120 So to summarize, so,

NOTE Confidence: 0.943913018181818

00:27:47.120 --> 00:27:49.000 so this next hypothesis,

NOTE Confidence: 0.943913018181818

00:27:49.000 --> 00:27:50.674 this is interneurons just to summarize

NOTE Confidence: 0.943913018181818

00:27:50.674 --> 00:27:52.718 that what we think may have happened,

NOTE Confidence: 0.943913018181818

00:27:52.720 --> 00:27:54.368 this is 3 hypothesis.

NOTE Confidence: 0.943913018181818

00:27:54.368 --> 00:27:56.840 One possible origin of this quantum

NOTE Confidence: 0.943913018181818

00:27:56.920 --> 00:27:59.308 expansion is during neurogenesis,

NOTE Confidence: 0.943913018181818

00:27:59.310 --> 00:28:00.706 so where interneural generated

NOTE Confidence: 0.943913018181818

00:28:00.706 --> 00:28:03.261 in one specific area of the brain

NOTE Confidence: 0.943913018181818

00:28:03.261 --> 00:28:05.613 and then migrate and populate the

NOTE Confidence: 0.943913018181818

00:28:05.613 --> 00:28:06.789 brain during development.

NOTE Confidence: 0.943913018181818

00:28:06.790 --> 00:28:08.890 That's hypothesis #1 and then when we

NOTE Confidence: 0.943913018181818

00:28:08.890 --> 00:28:11.065 do sequencing so we are able to see it.

NOTE Confidence: 0.943913018181818

00:28:11.070 --> 00:28:13.541 Next hypothesis is that this is gluogenic

NOTE Confidence: 0.943913018181818

00:28:13.541 --> 00:28:15.350 origin probably happened late in life,

NOTE Confidence: 0.943913018181818

00:28:15.350 --> 00:28:18.350 so at some time during lifetime

NOTE Confidence: 0.943913018181818

00:28:18.350 --> 00:28:20.518 cell acquire proliferative advantage

NOTE Confidence: 0.943913018181818

00:28:20.518 --> 00:28:23.228 and then repopulate brain area.

NOTE Confidence: 0.943913018181818

00:28:23.230 --> 00:28:25.379 Is going to be localized in particular

NOTE Confidence: 0.943913018181818

00:28:25.379 --> 00:28:27.391 region and the other one that

NOTE Confidence: 0.943913018181818

00:28:27.391 --> 00:28:29.443 there is a hematopaetic origin that

NOTE Confidence: 0.943913018181818

00:28:29.443 --> 00:28:31.053 actually clonal expansion happens

NOTE Confidence: 0.943913018181818

00:28:31.053 --> 00:28:34.000 in the brain and then they penetrate

NOTE Confidence: 0.943913018181818

00:28:34.070 --> 00:28:36.625 sorry happens in the blood and then

NOTE Confidence: 0.943913018181818

00:28:36.625 --> 00:28:37.720 the cells somehow

NOTE Confidence: 0.94944192173913

00:28:37.798 --> 00:28:39.732 penetrate brain and that will

NOTE Confidence: 0.94944192173913

00:28:39.732 --> 00:28:41.598 be excited to see what they

NOTE Confidence: 0.94944192173913

00:28:41.598 --> 00:28:43.710 may do if this is the case.

NOTE Confidence: 0.94944192173913

00:28:43.710 --> 00:28:48.132 So the last thing what we did is

NOTE Confidence: 0.94944192173913

00:28:48.132 --> 00:28:50.460 there some functional relevance

NOTE Confidence: 0.94944192173913

00:28:50.460 --> 00:28:52.788 of the discovered mutations.

NOTE Confidence: 0.94944192173913

00:28:52.790 --> 00:28:54.386 Sorry, this is my own timer,

NOTE Confidence: 0.93220288

00:28:56.470 --> 00:29:00.270 I have one minute. So is the question was

NOTE Confidence: 0.939479492307692

00:29:02.350 --> 00:29:03.953 do they do do they have any

NOTE Confidence: 0.939479492307692

00:29:03.953 --> 00:29:05.348 relevance to diseases that we study?

NOTE Confidence: 0.939479492307692

00:29:05.350 --> 00:29:06.568 This neuro, psych,

NOTE Confidence: 0.939479492307692

00:29:06.568 --> 00:29:09.004 psychiatric when we did the standard

NOTE Confidence: 0.939479492307692

00:29:09.004 --> 00:29:11.535 analysis using overlap with exams and

NOTE Confidence: 0.939479492307692

00:29:11.535 --> 00:29:12.994 predicting possible functional variants.

NOTE Confidence: 0.939479492307692

00:29:12.994 --> 00:29:15.430 So we didn't really see anything specific.

NOTE Confidence: 0.939479492307692

00:29:15.430 --> 00:29:17.082 The only signal we can find is

NOTE Confidence: 0.939479492307692

00:29:17.082 --> 00:29:19.028 when we try to predict mutations,

NOTE Confidence: 0.939479492307692

00:29:19.030 --> 00:29:19.826 affected enhancers.

NOTE Confidence: 0.939479492307692

00:29:19.826 --> 00:29:22.612 So what we saw the over representation

NOTE Confidence: 0.939479492307692

00:29:22.612 --> 00:29:25.118 of mutations which create binding

NOTE Confidence: 0.939479492307692

00:29:25.118 --> 00:29:27.154 sites particularly for the

NOTE Confidence: 0.939479492307692

00:29:27.154 --> 00:29:29.029 transcription factor like Mace 1,

NOTE Confidence: 0.939479492307692

00:29:29.030 --> 00:29:32.780 Mace 2, Mace 3 and we saw that in the

NOTE Confidence: 0.939479492307692

00:29:32.886 --> 00:29:34.894 ASD this transcription factors they

NOTE Confidence: 0.939479492307692

00:29:34.894 --> 00:29:37.024 actually very important in development.

NOTE Confidence: 0.939479492307692

00:29:37.030 --> 00:29:39.255 So our hypothesis that semantic

NOTE Confidence: 0.939479492307692

00:29:39.255 --> 00:29:41.480 mutations can contribute to the

NOTE Confidence: 0.939479492307692

00:29:41.552 --> 00:29:44.420 ASD phenotype during development by

NOTE Confidence: 0.939479492307692

00:29:44.420 --> 00:29:47.380 affecting regulation or dysregulation

NOTE Confidence: 0.939479492307692

00:29:47.380 --> 00:29:49.690 of development and.

NOTE Confidence: 0.939479492307692

00:29:49.690 --> 00:29:52.330 By affecting transcription factor binding.

NOTE Confidence: 0.939479492307692

00:29:52.330 --> 00:29:55.004 All right. So my conclusions,

NOTE Confidence: 0.939479492307692

00:29:55.004 --> 00:29:56.889 conclusion slide about all this.

NOTE Confidence: 0.939479492307692

00:29:56.890 --> 00:30:00.130 So mutations actually very frequent.

NOTE Confidence: 0.939479492307692

00:30:00.130 --> 00:30:01.020 So no,

NOTE Confidence: 0.939479492307692

00:30:01.020 --> 00:30:04.138 no two cells in our basically in our

NOTE Confidence: 0.939479492307692

00:30:04.138 --> 00:30:06.210 body will ever have the same genome,

NOTE Confidence: 0.939479492307692

00:30:06.210 --> 00:30:07.490 probably from the very beginning.

NOTE Confidence: 0.938017288888889

00:30:09.570 --> 00:30:12.243 And we can use this to track cell lineages.

NOTE Confidence: 0.938017288888889

00:30:12.250 --> 00:30:14.314 So we already see the effects

NOTE Confidence: 0.938017288888889

00:30:14.314 --> 00:30:15.690 from the very beginning,

NOTE Confidence: 0.938017288888889

00:30:15.690 --> 00:30:19.738 this created lineages are not.

NOTE Confidence: 0.938017288888889

00:30:19.738 --> 00:30:21.452 Symmetrical and maybe I

NOTE Confidence: 0.938017288888889

00:30:21.452 --> 00:30:22.868 didn't highlight it enough,

NOTE Confidence: 0.938017288888889

00:30:22.870 --> 00:30:24.148 I kind of bolted it here.

NOTE Confidence: 0.938017288888889

00:30:24.150 --> 00:30:25.790 So this approach for lineage

NOTE Confidence: 0.938017288888889

00:30:25.790 --> 00:30:27.560 tracing that we have, it's,

NOTE Confidence: 0.938017288888889

00:30:27.560 --> 00:30:30.710 it was done for the living individual.

NOTE Confidence: 0.938017288888889

00:30:30.710 --> 00:30:33.394 So basically it's a way like every

NOTE Confidence: 0.938017288888889

00:30:33.394 --> 00:30:34.966 everyone sitting in the room we

NOTE Confidence: 0.938017288888889

00:30:34.966 --> 00:30:36.925 can conduct the same study and

NOTE Confidence: 0.938017288888889

00:30:36.925 --> 00:30:38.309 reconstruct your personalized history.

NOTE Confidence: 0.938017288888889

00:30:38.310 --> 00:30:39.870 What happened to you when you are really,

NOTE Confidence: 0.938017288888889

00:30:39.870 --> 00:30:43.670 really little like literally very small and.

NOTE Confidence: 0.94427896

00:30:46.910 --> 00:30:50.078 In brain we see between 20 to 60 mutations

NOTE Confidence: 0.94427896

00:30:50.078 --> 00:30:51.770 and this effect of hyper vitability

NOTE Confidence: 0.94427896

00:30:51.770 --> 00:30:53.364 is there are three hypothesis which

NOTE Confidence: 0.94427896

00:30:53.364 --> 00:30:55.012 we are in the process of trying to

NOTE Confidence: 0.94427896

00:30:55.012 --> 00:30:56.586 figure out which one of them is true.

NOTE Confidence: 0.94427896

00:30:56.590 --> 00:30:58.174 And actually maybe all three of

NOTE Confidence: 0.94427896

00:30:58.174 --> 00:31:00.230 them are true in different brains.

NOTE Confidence: 0.94427896

00:31:00.230 --> 00:31:02.900 And let me conclude by acknowledging

NOTE Confidence: 0.94427896

00:31:02.900 --> 00:31:03.790 my colleagues.

NOTE Confidence: 0.94427896

00:31:03.790 --> 00:31:06.292 Of course a lot of work is done with

NOTE Confidence: 0.94427896

00:31:06.292 --> 00:31:08.981 as I said with a Flora Walk arena and

NOTE Confidence: 0.94427896

00:31:08.981 --> 00:31:11.948 my lab is purely analytical and we

NOTE Confidence: 0.94427896

00:31:11.948 --> 00:31:14.582 rely on collaboration with other labs

NOTE Confidence: 0.94427896

00:31:14.582 --> 00:31:17.426 to generate data and analyze it and.

NOTE Confidence: 0.94427896

00:31:17.430 --> 00:31:19.329 Of course, big signs goes to BSMN

NOTE Confidence: 0.94427896

00:31:19.329 --> 00:31:21.422 because it was a big project with

NOTE Confidence: 0.94427896

00:31:21.422 --> 00:31:23.348 enrollment of more than a dozen lab.

NOTE Confidence: 0.94427896

00:31:23.350 --> 00:31:24.998 And thank you very much for your attention.