WEBVTT

NOTE duration:"01:04:28.7100000"

NOTE recognizability:0.809

NOTE language:en-us

NOTE Confidence: 0.783684954

00:00:00.000 --> 00:00:03.100 The Cancer Center grand rounds.

NOTE Confidence: 0.783684954

00:00:03.100 --> 00:00:04.750 I'm Barbara Burtness,

NOTE Confidence: 0.783684954

00:00:04.750 --> 00:00:06.950 and I'm really extraordinarily

NOTE Confidence: 0.783684954

00:00:06.950 --> 00:00:09.831 thrilled to be introducing agato

NOTE Confidence: 0.783684954

00:00:09.831 --> 00:00:13.275 smuggler Jessica as our speaker today.

NOTE Confidence: 0.783684954

00:00:13.280 --> 00:00:15.695 She is an associate professor of genome

NOTE Confidence: 0.783684954

00:00:15.695 --> 00:00:18.159 maintenance at the Rockefeller University.

NOTE Confidence: 0.783684954

00:00:18.160 --> 00:00:21.009 She received her PhD from Rockefeller and

NOTE Confidence: 0.783684954

00:00:21.009 --> 00:00:24.539 her MD from Wild Cornell Medical College.

NOTE Confidence: 0.783684954

00:00:24.540 --> 00:00:26.688 Following a residency in

NOTE Confidence: 0.783684954

00:00:26.688 --> 00:00:28.836 clinical pathology at MGH,

NOTE Confidence: 0.783684954

00:00:28.840 --> 00:00:31.227 she joined Harvard Medical School as a

NOTE Confidence: 0.783684954

00:00:31.227 --> 00:00:33.539 postdoctoral fellow in Stephen Elledge's lab.

NOTE Confidence: 0.783684954

00:00:33.540 --> 00:00:36.018 She's the recipient of numerous awards,

NOTE Confidence: 0.783684954

00:00:36.020 --> 00:00:38.220 including the Irma T Herschel Research Award,

NOTE Confidence: 0.783684954

00:00:38.220 --> 00:00:39.784 the Rita Allen Foundation

NOTE Confidence: 0.783684954

00:00:39.784 --> 00:00:40.957 Scholars Program Grant,

NOTE Confidence: 0.783684954

00:00:40.960 --> 00:00:43.438 the Burroughs welcome Fund Career Award,

NOTE Confidence: 0.783684954

00:00:43.440 --> 00:00:45.800 AV Foundation Translational Research Award,

NOTE Confidence: 0.783684954

00:00:45.800 --> 00:00:49.466 and the Herald Weintraub graduate student.

NOTE Confidence: 0.783684954

00:00:49.470 --> 00:00:52.368 Her lab focuses on DNA repair mechanisms,

NOTE Confidence: 0.783684954

00:00:52.370 --> 00:00:54.898 particularly those involved with

NOTE Confidence: 0.783684954

00:00:54.898 --> 00:00:57.426 interstrand crosslink repair pathways,

NOTE Confidence: 0.783684954

00:00:57.430 --> 00:00:59.035 and she's interested in identifying

NOTE Confidence: 0.783684954

00:00:59.035 --> 00:01:01.261 new genes that are involved in this

NOTE Confidence: 0.783684954

00:01:01.261 --> 00:01:03.256 repair process in order to reveal the

NOTE Confidence: 0.783684954

00:01:03.256 --> 00:01:05.070 mechanisms at play in human diseases

NOTE Confidence: 0.783684954

00:01:05.070 --> 00:01:06.545 that result from deficiencies in

NOTE Confidence: 0.783684954

00:01:06.550 --> 00:01:09.330 interest strand cross link repair.

NOTE Confidence: 0.783684954

00:01:09.330 --> 00:01:11.880 This includes Fanconi anemia and

NOTE Confidence: 0.783684954

00:01:11.880 --> 00:01:13.920 kerio megalith interstitial nephritis.

NOTE Confidence: 0.783684954

00:01:13.920 --> 00:01:15.459 To this end,

NOTE Confidence: 0.783684954

00:01:15.459 --> 00:01:18.024 she successfully identified SLX 4,

NOTE Confidence: 0.783684954

00:01:18.030 --> 00:01:21.257 red 51 and U BE2T is interstrand

NOTE Confidence: 0.783684954

00:01:21.257 --> 00:01:22.640 crosslink repair factors,

NOTE Confidence: 0.783684954

00:01:22.640 --> 00:01:25.120 as well as developed a mouse model of

NOTE Confidence: 0.783684954

00:01:25.120 --> 00:01:27.180 Carrie Magalog interstitial nephritis.

NOTE Confidence: 0.783684954

00:01:27.180 --> 00:01:29.145 And recently she's begun studies

NOTE Confidence: 0.783684954

00:01:29.145 --> 00:01:30.717 revolving around how replication

NOTE Confidence: 0.783684954

00:01:30.717 --> 00:01:32.532 stress is addressed by cells

NOTE Confidence: 0.783684954

00:01:32.532 --> 00:01:33.896 to promote genome stability.

NOTE Confidence: 0.783684954

00:01:33.900 --> 00:01:36.210 She also has a deep interest in

NOTE Confidence: 0.783684954

00:01:36.210 --> 00:01:37.970 those cancers which arise in

NOTE Confidence: 0.783684954

00:01:37.970 --> 00:01:39.725 patients who have DNA repair.

NOTE Confidence: 0.783684954

00:01:39.730 --> 00:01:39.979 Defects.

NOTE Confidence: 0.783684954

00:01:39.979 --> 00:01:41.722 And it's because of this that I've

NOTE Confidence: 0.783684954

00:01:41.722 --> 00:01:42.849 had the extraordinary pleasure

NOTE Confidence: 0.783684954

00:01:42.849 --> 00:01:44.577 of beginning to work with her

NOTE Confidence: 0.783684954

00:01:44.577 --> 00:01:46.427 on the stand up to cancer Grant,

NOTE Confidence: 0.783684954

00:01:46.430 --> 00:01:48.290 which looks at Fanconi anemia,

NOTE Confidence: 0.783684954

00:01:48.290 --> 00:01:50.794 associated head neck cancer.

NOTE Confidence: 0.783684954

00:01:50.794 --> 00:01:51.420 So.

NOTE Confidence: 0.783684954

00:01:51.420 --> 00:01:52.575 Like I said,

NOTE Confidence: 0.783684954

00:01:52.575 --> 00:01:54.500 if you wanna come up.

NOTE Confidence: 0.783684954

00:01:54.500 --> 00:01:56.812 This plaque is to thank you for for

NOTE Confidence: 0.783684954

00:01:56.812 --> 00:01:59.119 coming to give grand rounds in person,

NOTE Confidence: 0.783684954

00:01:59.120 --> 00:02:01.001 which many people have not

NOTE Confidence: 0.783684954

00:02:01.001 --> 00:02:02.306 been willing to do recently.

NOTE Confidence: 0.856249615

00:02:04.650 --> 00:02:05.594 And we're really looking

NOTE Confidence: 0.856249615

00:02:05.594 --> 00:02:06.538 forward to your talk.

4

NOTE Confidence: 0.817401898

00:02:06.650 --> 00:02:10.052 Thank you so much. Yes, thank you.

NOTE Confidence: 0.817401898

00:02:10.052 --> 00:02:12.278 Well, thank you Barbara for first

NOTE Confidence: 0.817401898

00:02:12.278 --> 00:02:15.056 of all for inviting me all of you

NOTE Confidence: 0.817401898

00:02:15.056 --> 00:02:17.444 for coming to hear the lecture and

NOTE Confidence: 0.817401898

00:02:17.444 --> 00:02:20.163 all of you on zoom for joining in.

NOTE Confidence: 0.817401898

00:02:20.163 --> 00:02:22.774 And it's really my pleasure to to

NOTE Confidence: 0.817401898

00:02:22.774 --> 00:02:25.765 be here and it's been fantastic to

NOTE Confidence: 0.817401898

00:02:25.765 --> 00:02:28.550 work with Barbara and and learning

NOTE Confidence: 0.817401898

00:02:28.550 --> 00:02:31.532 from her more about the the clinical

NOTE Confidence: 0.817401898

00:02:31.532 --> 00:02:34.781 aspects of what we do and hopefully

NOTE Confidence: 0.817401898

00:02:34.781 --> 00:02:37.474 bringing some new therapies to

NOTE Confidence: 0.817401898

00:02:37.474 --> 00:02:40.532 these patients eventually, OK, so.

NOTE Confidence: 0.817401898

00:02:40.532 --> 00:02:43.906 I will talk about DNA interstrand crosslinks

NOTE Confidence: 0.817401898

00:02:43.906 --> 00:02:47.579 and I'll just remind you though that oh,

NOTE Confidence: 0.817401898

00:02:47.580 --> 00:02:49.532 these are my disclosures.

NOTE Confidence: 0.817401898

00:02:49.532 --> 00:02:54.520 I'll just remind you that DNA repair.

NOTE Confidence: 0.817401898

00:02:54.520 --> 00:02:57.383 It's really essential for a lot of

NOTE Confidence: 0.817401898

00:02:57.383 --> 00:03:00.743 aspects of of life and depending on what

NOTE Confidence: 0.817401898

00:03:00.743 --> 00:03:04.238 kind of flavor of DNA damage you have,

NOTE Confidence: 0.817401898

00:03:04.240 --> 00:03:06.560 whether it's from the outside,

NOTE Confidence: 0.817401898

00:03:06.560 --> 00:03:09.724 from the UV light creating these dimers,

NOTE Confidence: 0.817401898

00:03:09.730 --> 00:03:11.300 or from within the cell,

NOTE Confidence: 0.817401898

00:03:11.300 --> 00:03:14.060 something that I'm quite interested in,

NOTE Confidence: 0.817401898

00:03:14.060 --> 00:03:17.460 for example, creating mismatches.

NOTE Confidence: 0.817401898

00:03:17.460 --> 00:03:20.631 There is a repair pathway that's dedicated

NOTE Confidence: 0.817401898

00:03:20.631 --> 00:03:24.487 to these and there are a number of genetic.

NOTE Confidence: 0.817401898

00:03:24.490 --> 00:03:26.990 Diseases associated with inability

NOTE Confidence: 0.817401898

00:03:26.990 --> 00:03:29.994 to repair these different lesions

NOTE Confidence: 0.817401898

00:03:29.994 --> 00:03:33.928 and they come again in many different

NOTE Confidence: 0.817401898

00:03:33.928 --> 00:03:36.620 phenotypes resulting in developmental

NOTE Confidence: 0.817401898

00:03:36.620 --> 00:03:40.025 abnormalities and the generate the

00:03:40.025 --> 00:03:43.185 generative diseases and a lot of

00:03:43.185 --> 00:03:45.660 them obviously are associated with

00:03:45.750 --> 00:03:48.720 cancer prone due to mutagenic nature

00:03:48.720 --> 00:03:51.910 of these lesions if the lesions

00:03:51.910 --> 00:03:54.150 are not properly repaired.

00:03:54.150 --> 00:03:56.712 So my favorite lesion is this interest

00:03:56.712 --> 00:04:00.083 in Cross link and I'll give you a little

00:04:00.083 --> 00:04:02.609 bit of introduction about these lesions.

00:04:02.610 --> 00:04:04.475 This is a covalent linkage

00:04:04.475 --> 00:04:06.730 of two strands of the DNA.

00:04:06.730 --> 00:04:09.508 It's repaired by the Franco anemia

00:04:09.508 --> 00:04:12.492 DNA repair pathway and I'll give you

00:04:12.492 --> 00:04:15.622 more of a of the mechanism of how this

00:04:15.622 --> 00:04:18.428 is done in in a bit in later slide,

00:04:18.428 --> 00:04:21.214 but the whole purpose of this pathway

00:04:21.214 --> 00:04:24.569 which is activated during DNA replication.

NOTE Confidence: 0.817401898

00:04:24.570 --> 00:04:27.360 Is to create 2 pristine.

NOTE Confidence: 0.817401898

00:04:27.360 --> 00:04:30.783 Double stranded DNA that can be then

NOTE Confidence: 0.817401898

00:04:30.783 --> 00:04:34.104 moved to dollars trends during during

NOTE Confidence: 0.817401898

00:04:34.104 --> 00:04:36.931 the cell division and I'll just

NOTE Confidence: 0.817401898

00:04:36.931 --> 00:04:39.430 mention I won't talk much about it

NOTE Confidence: 0.817401898

00:04:39.506 --> 00:04:42.182 but this pathway is also activated

NOTE Confidence: 0.817401898

00:04:42.182 --> 00:04:44.640 at difficult to replicate regions.

NOTE Confidence: 0.817401898

00:04:44.640 --> 00:04:48.077 So repetitive DNA are loops and there

NOTE Confidence: 0.817401898

00:04:48.077 --> 00:04:51.540 is growing evidence that at any time

NOTE Confidence: 0.817401898

00:04:51.540 --> 00:04:54.384 there is stalling of replication forks

NOTE Confidence: 0.817401898

00:04:54.476 --> 00:04:57.409 the pathway can come to to rescue.

NOTE Confidence: 0.817401898

00:04:57.410 --> 00:05:01.755 Those forks so that this this intern

NOTE Confidence: 0.817401898

00:05:01.755 --> 00:05:04.871 crossing is really our model of

NOTE Confidence: 0.817401898

00:05:04.871 --> 00:05:07.039 of how pathways activated.

NOTE Confidence: 0.817401898

00:05:07.040 --> 00:05:10.190 And the outcomes of abnormality in

NOTE Confidence: 0.817401898

00:05:10.190 --> 00:05:12.736 pathway activation or function are

NOTE Confidence: 0.817401898

00:05:12.736 --> 00:05:14.640 these genomic instability that you

NOTE Confidence: 0.817401898

00:05:14.640 --> 00:05:17.473 can heat see here in this metaphase

NOTE Confidence: 0.817401898

00:05:17.473 --> 00:05:20.131 spread where you see number of

NOTE Confidence: 0.817401898

00:05:20.131 --> 00:05:22.390 these abnormal radial chromosomes.

NOTE Confidence: 0.817401898

00:05:22.390 --> 00:05:26.334 So we see that in cells from Franconia

NOTE Confidence: 0.817401898

00:05:26.334 --> 00:05:29.768 anemia patients when they are treated

NOTE Confidence: 0.817401898

00:05:29.768 --> 00:05:33.010 with external internal crosslink causing.

NOTE Confidence: 0.712936646333333

00:05:35.150 --> 00:05:37.832 Chemicals like mydomain sincere splatsin you

NOTE Confidence: 0.712936646333333

00:05:37.832 --> 00:05:40.620 see number of abnormalities including gaps,

NOTE Confidence: 0.712936646333333

00:05:40.620 --> 00:05:43.170 breaks and these radio chromosomes

NOTE Confidence: 0.712936646333333

00:05:43.170 --> 00:05:45.720 and the radial chromosomes occur

NOTE Confidence: 0.712936646333333

00:05:45.799 --> 00:05:48.307 because of two double strand breaks

NOTE Confidence: 0.712936646333333

00:05:48.307 --> 00:05:51.730 that are that find each other and are

NOTE Confidence: 0.712936646333333

00:05:51.730 --> 00:05:54.050 joined together forming these radios.

NOTE Confidence: 0.712936646333333

00:05:54.050 --> 00:05:56.840 And obviously these radios come radio

NOTE Confidence: 0.712936646333333

00:05:56.840 --> 00:05:59.298 chromosomes can cause instability but

NOTE Confidence: 0.712936646333333

00:05:59.298 --> 00:06:02.890 can also cause death of cells when they

NOTE Confidence: 0.712936646333333

00:06:02.890 --> 00:06:06.518 are trying to the cell tries to divide.

NOTE Confidence: 0.712936646333333

00:06:06.520 --> 00:06:09.008 So. The reason why we know that this

NOTE Confidence: 0.712936646333333

00:06:09.008 --> 00:06:11.013 pathway is particularly important in

NOTE Confidence: 0.712936646333333

00:06:11.013 --> 00:06:14.072 stem cells are all these phenotypes that

NOTE Confidence: 0.712936646333333

00:06:14.144 --> 00:06:16.727 we see in patients with Fanconi anemia.

NOTE Confidence: 0.712936646333333

00:06:16.730 --> 00:06:20.010 There are many developmental

NOTE Confidence: 0.712936646333333

00:06:20.010 --> 00:06:22.490 phenotypes including these skeletal

NOTE Confidence: 0.712936646333333

00:06:22.490 --> 00:06:24.590 abnormalities that you see here,

NOTE Confidence: 0.712936646333333

00:06:24.590 --> 00:06:26.422 but pretty much any,

NOTE Confidence: 0.712936646333333

00:06:26.422 --> 00:06:30.639 any system can be affected and that's seen in

NOTE Confidence: 0.712936646333333

00:06:30.639 --> 00:06:34.660 patients who are truly null for this pathway.

NOTE Confidence: 0.712936646333333

00:06:34.660 --> 00:06:37.208 Majority of patients will present with Pence,

NOTE Confidence: 0.712936646333333

00:06:37.210 --> 00:06:37.737 Cytopenia.

NOTE Confidence: 0.712936646333333

00:06:37.737 --> 00:06:40.899 Around age, median age of 10,

NOTE Confidence: 0.712936646333333

00:06:40.900 --> 00:06:43.396 and even though it's called anemia,

NOTE Confidence: 0.712936646333333

00:06:43.400 --> 00:06:46.340 all of the.

NOTE Confidence: 0.712936646333333

00:06:46.340 --> 00:06:49.130 All of the hematopoiesis can be

NOTE Confidence: 0.712936646333333

00:06:49.130 --> 00:06:51.510 affected and and actually platelets

NOTE Confidence: 0.712936646333333

00:06:51.510 --> 00:06:54.576 are usually the first to to draw.

NOTE Confidence: 0.712936646333333

00:06:54.580 --> 00:06:57.254 And then there is very this very

NOTE Confidence: 0.712936646333333

00:06:57.254 --> 00:06:59.104 interesting phenotype that will spend

NOTE Confidence: 0.712936646333333

00:06:59.104 --> 00:07:01.640 a lot of time talking about the cancer

NOTE Confidence: 0.712936646333333

00:07:01.712 --> 00:07:05.040 predisposition MSDS and AML occurs in

NOTE Confidence: 0.712936646333333

00:07:05.040 --> 00:07:08.140 the setting of pancytopenia and squamous

NOTE Confidence: 0.712936646333333

00:07:08.140 --> 00:07:11.620 cell carcinoma occurs later in life

NOTE Confidence: 0.712936646333333

00:07:11.620 --> 00:07:16.176 but still in in at young age of average 31.

NOTE Confidence: 0.712936646333333

00:07:16.180 --> 00:07:18.220 We have very young patients as

NOTE Confidence: 0.712936646333333

00:07:18.220 --> 00:07:20.729 I'll I'll show you in in future

NOTE Confidence: 0.712936646333333

00:07:20.729 --> 00:07:22.889 slides and then depending on the

NOTE Confidence: 0.712936646333333

00:07:22.889 --> 00:07:25.267 actual path of gene that's mutated.

NOTE Confidence: 0.712936646333333

00:07:25.270 --> 00:07:27.490 We can also have breast cancer,

NOTE Confidence: 0.712936646333333

00:07:27.490 --> 00:07:29.440 medulloblastoma and and

NOTE Confidence: 0.712936646333333

00:07:29.440 --> 00:07:31.390 other embryonal tumors.

NOTE Confidence: 0.712936646333333

00:07:31.390 --> 00:07:33.756 And there are other phenotypes that are

NOTE Confidence: 0.712936646333333

00:07:33.756 --> 00:07:35.905 still fairly poorly understood like

NOTE Confidence: 0.712936646333333

00:07:35.905 --> 00:07:38.045 infertility and endocrine abnormalities.

NOTE Confidence: 0.712936646333333

00:07:38.050 --> 00:07:42.234 So this is a great model in my

NOTE Confidence: 0.712936646333333

00:07:42.234 --> 00:07:46.108 mind for studying DNA repair.

NOTE Confidence: 0.712936646333333

00:07:46.110 --> 00:07:49.044 So today, I'll tell you about the first part,

NOTE Confidence: 0.712936646333333

00:07:49.050 --> 00:07:51.342 very short part about the mechanism

NOTE Confidence: 0.712936646333333

00:07:51.342 --> 00:07:52.870 of interstrand crosslink repair.

NOTE Confidence: 0.712936646333333

00:07:52.870 --> 00:07:53.292 Secondly,

NOTE Confidence: 0.712936646333333

00:07:53.292 --> 00:07:55.402 I'll talk about the identification

NOTE Confidence: 0.712936646333333

00:07:55.402 --> 00:07:56.668 of endogenous sources,

NOTE Confidence: 0.712936646333333

00:07:56.670 --> 00:07:58.826 sources of interstrand crosslink.

NOTE Confidence: 0.712936646333333

00:07:58.826 --> 00:08:02.060 And today I'll talk about the

NOTE Confidence: 0.712936646333333

00:08:02.153 --> 00:08:03.608 bone marrow side.

NOTE Confidence: 0.712936646333333

00:08:03.610 --> 00:08:05.668 But we are very much interested in

NOTE Confidence: 0.712936646333333

00:08:05.668 --> 00:08:08.000 those in the keratinocytes as well.

NOTE Confidence: 0.712936646333333

00:08:08.000 --> 00:08:11.186 And this is an ongoing work in my lab.

NOTE Confidence: 0.712936646333333

00:08:11.190 --> 00:08:13.990 And then I'll talk about the mechanism

NOTE Confidence: 0.712936646333333

00:08:13.990 --> 00:08:16.280 of tumorigenesis and Fanconi anemia.

NOTE Confidence: 0.712936646333333

00:08:16.280 --> 00:08:19.430 Especially in the squamous cell carcinoma.

NOTE Confidence: 0.712936646333333

00:08:19.430 --> 00:08:23.390 So just to give you a flavor of how

NOTE Confidence: 0.712936646333333

00:08:23.390 --> 00:08:26.910 this pathway actually functions,

NOTE Confidence: 0.712936646333333

00:08:26.910 --> 00:08:30.151 this is a very regulated process of

NOTE Confidence: 0.712936646333333

00:08:30.151 --> 00:08:33.180 repair of these of these lesions.

NOTE Confidence: 0.712936646333333

00:08:33.180 --> 00:08:35.876 So we start with the ACL that you

NOTE Confidence: 0.712936646333333

00:08:35.876 --> 00:08:38.593 that I've shown you before and this

NOTE Confidence: 0.712936646333333

00:08:38.593 --> 00:08:41.530 is the structure that we know forms

00:08:41.530 --> 00:08:43.765 when the replication forks stall

00:08:43.765 --> 00:08:46.280 at the lesion and some of this work

00:08:46.280 --> 00:08:48.199 has been done in in human cells,

00:08:48.200 --> 00:08:49.067 some of it.

00:08:49.067 --> 00:08:51.090 This work was done in Johannes Walters

00:08:51.157 --> 00:08:53.355 lab in the Xenopus egg extract system.

00:08:53.360 --> 00:08:54.588 So biochemically,

00:08:54.588 --> 00:08:57.658 it's a fairly understood pathway.

00:08:57.660 --> 00:08:59.440 What's essential in this pathway,

00:08:59.440 --> 00:09:00.904 and I'll show you the proteins

00:09:00.904 --> 00:09:02.359 that are involved in a moment,

00:09:02.360 --> 00:09:04.614 but what has to happen is that

00:09:04.614 --> 00:09:07.418 the the DNA needs to be broken,

00:09:07.420 --> 00:09:10.300 but in a very regulated way that then

00:09:10.300 --> 00:09:12.300 gets repaired through translesion

NOTE Confidence: 0.712936646333333

00:09:12.300 --> 00:09:15.305 synthesis and then through homologous

NOTE Confidence: 0.712936646333333

00:09:15.305 --> 00:09:17.108 recombination that requires

NOTE Confidence: 0.8328053432

00:09:17.182 --> 00:09:18.947 BRC 2 and other proteins.

NOTE Confidence: 0.8328053432

00:09:18.950 --> 00:09:23.269 And this eventually leads to this full

NOTE Confidence: 0.8328053432

00:09:23.269 --> 00:09:26.954 DNA repaired repaired DNA with with

NOTE Confidence: 0.8328053432

00:09:26.954 --> 00:09:30.620 two strands that are fully repaired.

NOTE Confidence: 0.8328053432

00:09:30.620 --> 00:09:34.226 So the proteins that are participating

NOTE Confidence: 0.8328053432

00:09:34.226 --> 00:09:38.040 in this pathway really has been

NOTE Confidence: 0.8328053432

00:09:38.040 --> 00:09:40.644 identified through studies of

NOTE Confidence: 0.8328053432

00:09:40.644 --> 00:09:43.248 Franco anemia patients and.

NOTE Confidence: 0.8328053432

00:09:43.250 --> 00:09:45.434 Just go to go back for a moment

NOTE Confidence: 0.8328053432

00:09:45.434 --> 00:09:47.788 to the history of this disease.

NOTE Confidence: 0.8328053432

00:09:47.790 --> 00:09:50.490 Fanconi anemia has been identified in

NOTE Confidence: 0.8328053432

00:09:50.490 --> 00:09:53.976 1927 by Guido Fanconi and described

NOTE Confidence: 0.8328053432

00:09:53.976 --> 00:09:56.300 as hereditary pancytopenia with

NOTE Confidence: 0.8328053432

00:09:56.388 --> 00:09:59.508 short stature and hyperpigmentation.

NOTE Confidence: 0.8328053432

00:09:59.510 --> 00:10:02.408 The first gene fancy was identified 92,

NOTE Confidence: 0.8328053432

00:10:02.410 --> 00:10:05.050 but even then it was known that more

NOTE Confidence: 0.8328053432

00:10:05.050 --> 00:10:07.499 than one gene will be causative

NOTE Confidence: 0.8328053432

00:10:07.499 --> 00:10:08.786 for this mutation.

NOTE Confidence: 0.8328053432

00:10:08.790 --> 00:10:11.298 And this was Buckwald lab who

NOTE Confidence: 0.8328053432

00:10:11.298 --> 00:10:12.970 identified the first gene.

NOTE Confidence: 0.8328053432

00:10:12.970 --> 00:10:15.852 And now we know that there are 22 genes

NOTE Confidence: 0.8328053432

00:10:15.852 --> 00:10:18.449 that can be mutated in Fanconi anemia

NOTE Confidence: 0.8328053432

00:10:18.449 --> 00:10:21.705 and we actually are working on on #23,

NOTE Confidence: 0.8328053432

00:10:21.705 --> 00:10:26.290 which fits very nicely in this pathway.

NOTE Confidence: 0.8328053432

00:10:26.290 --> 00:10:29.517 And the this data is actually showing

NOTE Confidence: 0.8328053432

00:10:29.517 --> 00:10:32.592 the percentage of of patients with

NOTE Confidence: 0.8328053432

00:10:32.592 --> 00:10:35.272 different mutations in different genes

NOTE Confidence: 0.8328053432

00:10:35.272 --> 00:10:38.608 and this is from our International

NOTE Confidence: 0.8328053432

00:10:38.608 --> 00:10:40.784 Franconia registry that I,

NOTE Confidence: 0.8328053432

00:10:40.790 --> 00:10:44.800 I run at at the Rockefeller University.

NOTE Confidence: 0.8328053432

00:10:44.800 --> 00:10:47.815 And you can see that Frank a mutations franc

NOTE Confidence: 0.8328053432

00:10:47.815 --> 00:10:50.877 and Frank G mutations are the most common.

NOTE Confidence: 0.8328053432

00:10:50.880 --> 00:10:53.743 More majority of the diseases of this

NOTE Confidence: 0.8328053432

00:10:53.743 --> 00:10:56.310 disease is autosomal recessive we have.

NOTE Confidence: 0.8328053432

00:10:56.310 --> 00:10:58.220 Language which is excellent and

NOTE Confidence: 0.8328053432

00:10:58.220 --> 00:11:00.718 then uh thank our that we've

NOTE Confidence: 0.8328053432

00:11:00.718 --> 00:11:02.758 discovered right 51 mutations.

NOTE Confidence: 0.8328053432

00:11:02.760 --> 00:11:04.650 These are always the Novo dominant

NOTE Confidence: 0.8328053432

00:11:04.650 --> 00:11:07.525 and we have a number of patients now

NOTE Confidence: 0.8328053432

00:11:07.525 --> 00:11:09.460 with different mutations and and

NOTE Confidence: 0.8328053432

00:11:09.460 --> 00:11:12.541 rat 51 and all of them have the same

NOTE Confidence: 0.8328053432

00:11:12.541 --> 00:11:14.529 dominant function and they're all

NOTE Confidence: 0.8328053432

00:11:14.529 --> 00:11:16.744 denovo presumably because right 51

NOTE Confidence: 0.8328053432

00:11:16.744 --> 00:11:19.329 is necessary during biosis and we

NOTE Confidence: 0.8328053432

17

00:11:19.329 --> 00:11:21.771 would never recover any any patients,

NOTE Confidence: 0.8328053432

00:11:21.780 --> 00:11:24.676 any transmission really through

NOTE Confidence: 0.8328053432

00:11:24.676 --> 00:11:26.848 through the germline.

NOTE Confidence: 0.8328053432

00:11:26.850 --> 00:11:27.217 OK.

NOTE Confidence: 0.8328053432

00:11:27.217 --> 00:11:29.419 And this registry that I've mentioned

NOTE Confidence: 0.8328053432

00:11:29.419 --> 00:11:31.256 has been really instrumental for

NOTE Confidence: 0.8328053432

00:11:31.256 --> 00:11:33.608 our work and it was started in

NOTE Confidence: 0.8328053432

00:11:33.610 --> 00:11:36.807 1982 by Arlene Auerbach who's still

NOTE Confidence: 0.8328053432

00:11:36.807 --> 00:11:38.792 participates in the lab meetings

NOTE Confidence: 0.8328053432

00:11:38.792 --> 00:11:41.991 and has a lot to say about about

NOTE Confidence: 0.8328053432

00:11:41.991 --> 00:11:44.283 the disease and has been really

NOTE Confidence: 0.8328053432

00:11:44.364 --> 00:11:47.304 wonderful in in in helping us through

NOTE Confidence: 0.8328053432

00:11:47.304 --> 00:11:50.022 this through some of these studies.

NOTE Confidence: 0.8328053432

00:11:50.022 --> 00:11:54.028 So now I'll spend really few just few

NOTE Confidence: 0.8328053432

00:11:54.028 --> 00:11:55.882 minutes on the proteins themselves.

NOTE Confidence: 0.8328053432

00:11:55.882 --> 00:11:57.880 Just to give you a gift,

NOTE Confidence: 0.8328053432

00:11:57.880 --> 00:12:01.176 again a flavor for the for this pathway.

NOTE Confidence: 0.8328053432

00:12:01.180 --> 00:12:03.676 So majority of the proteins whose

NOTE Confidence: 0.8328053432

00:12:03.676 --> 00:12:06.659 genes are mutated in Fanconi patients

NOTE Confidence: 0.8328053432

00:12:06.660 --> 00:12:09.540 form this large core complex.

NOTE Confidence: 0.8328053432

00:12:09.540 --> 00:12:12.078 All of the colored proteins are

NOTE Confidence: 0.8328053432

00:12:12.078 --> 00:12:14.352 actually those that have mutations

NOTE Confidence: 0.8328053432

00:12:14.352 --> 00:12:16.545 in Fanconi in Fanconi patients.

NOTE Confidence: 0.8328053432

00:12:16.545 --> 00:12:19.766 And you can see that this core complex

NOTE Confidence: 0.8328053432

00:12:19.766 --> 00:12:22.419 is situated that this cross link as

NOTE Confidence: 0.8328053432

00:12:22.419 --> 00:12:25.659 if it was identifying the the damage.

NOTE Confidence: 0.8328053432

00:12:25.660 --> 00:12:26.743 It's actually unclear.

NOTE Confidence: 0.8328053432

00:12:26.743 --> 00:12:28.187 How that's exactly done?

NOTE Confidence: 0.844819513636364

00:12:30.280 --> 00:12:33.928 The key to this core complex is that

NOTE Confidence: 0.844819513636364

00:12:33.928 --> 00:12:37.280 it has this E3 ubiquitin ligase fancl

NOTE Confidence: 0.844819513636364

00:12:37.280 --> 00:12:40.652 and with Frank T, which is the E2,

NOTE Confidence: 0.844819513636364

00:12:40.652 --> 00:12:43.342 they the whole purpose of this core

NOTE Confidence: 0.844819513636364

00:12:43.342 --> 00:12:46.135 we we understand now that the whole

NOTE Confidence: 0.844819513636364

00:12:46.135 --> 00:12:48.509 purpose is to ubiquitinated Frankie

NOTE Confidence: 0.844819513636364

00:12:48.509 --> 00:12:51.215 and Frankie 2 and that process

NOTE Confidence: 0.844819513636364

00:12:51.215 --> 00:12:52.835 through beautiful structural studies

NOTE Confidence: 0.844819513636364

00:12:52.835 --> 00:12:55.128 that have been done in the past.

NOTE Confidence: 0.844819513636364

00:12:55.130 --> 00:12:56.926 Semoran Pablo Ditches lab

NOTE Confidence: 0.844819513636364

00:12:56.926 --> 00:12:59.620 shows that the Fanki and Frank.

NOTE Confidence: 0.844819513636364

00:12:59.620 --> 00:13:03.684 Who forms a clamp around the the crosslink?

NOTE Confidence: 0.844819513636364

00:13:03.690 --> 00:13:05.362 Actually there are more,

NOTE Confidence: 0.844819513636364

00:13:05.362 --> 00:13:07.452 probably more clamps around as

NOTE Confidence: 0.844819513636364

00:13:07.452 --> 00:13:09.895 shown by the Dean slab that sort

NOTE Confidence: 0.844819513636364

00:13:09.895 --> 00:13:12.420 of decorate this cross link.

NOTE Confidence: 0.844819513636364

00:13:12.420 --> 00:13:12.935 Eventually,

NOTE Confidence: 0.844819513636364

00:13:12.935 --> 00:13:17.055 and this is again not quite worked out,

NOTE Confidence: 0.844819513636364

00:13:17.060 --> 00:13:19.982 the proteins that are important for

NOTE Confidence: 0.844819513636364

00:13:19.982 --> 00:13:22.794 in making these incisions come in

NOTE Confidence: 0.844819513636364

00:13:22.794 --> 00:13:25.140 and one of the important proteins

NOTE Confidence: 0.844819513636364

00:13:25.140 --> 00:13:28.519 here is this SLX 4 which acts as a

NOTE Confidence: 0.844819513636364

00:13:28.519 --> 00:13:30.694 scaffold for three different nucleases.

NOTE Confidence: 0.844819513636364

00:13:30.694 --> 00:13:34.523 And it's quite amazing how the three

NOTE Confidence: 0.844819513636364

00:13:34.523 --> 00:13:36.760 nucleases are associated with one

NOTE Confidence: 0.844819513636364

00:13:36.760 --> 00:13:39.820 protein and frank P is or a cell.

NOTE Confidence: 0.844819513636364

00:13:39.820 --> 00:13:43.320 X4 is essential not only for scaffolding.

NOTE Confidence: 0.844819513636364

00:13:43.320 --> 00:13:46.336 But for the function of the of these

NOTE Confidence: 0.844819513636364

00:13:46.336 --> 00:13:48.276 other nucleases without this slex

NOTE Confidence: 0.844819513636364

00:13:48.276 --> 00:13:50.866 4 none of the nucleus is actually

NOTE Confidence: 0.844819513636364

00:13:50.940 --> 00:13:53.190 are functional within the cell.

NOTE Confidence: 0.844819513636364

00:13:53.190 --> 00:13:54.882 They have full in vitro function

NOTE Confidence: 0.844819513636364

00:13:54.882 --> 00:13:56.550 but not not cellular function.

NOTE Confidence: 0.844819513636364

00:13:56.550 --> 00:13:59.370 So it's it's fascinating but in

NOTE Confidence: 0.844819513636364

00:13:59.370 --> 00:14:02.785 this case XPF is the one that's

NOTE Confidence: 0.844819513636364

00:14:02.785 --> 00:14:04.270 making the incisions.

NOTE Confidence: 0.844819513636364

00:14:04.270 --> 00:14:06.496 I'll also mention the protein that

NOTE Confidence: 0.844819513636364

00:14:06.496 --> 00:14:09.130 that or disease that Barbara mentioned

NOTE Confidence: 0.844819513636364

00:14:09.130 --> 00:14:11.290 the carrier Magali Constitution

NOTE Confidence: 0.844819513636364

00:14:11.290 --> 00:14:13.450 nephritis which has mutations.

NOTE Confidence: 0.844819513636364

00:14:13.450 --> 00:14:16.984 In fan one and Fan 1 gene codes

NOTE Confidence: 0.844819513636364

00:14:16.984 --> 00:14:19.516 for this another nuclease and this

NOTE Confidence: 0.844819513636364

00:14:19.516 --> 00:14:21.599 system which can also unhook,

NOTE Confidence: 0.844819513636364

00:14:21.600 --> 00:14:24.912 but it can unhook this this cross link

NOTE Confidence: 0.844819513636364

00:14:24.912 --> 00:14:28.155 outside of S phase and we're still

NOTE Confidence: 0.844819513636364

00:14:28.155 --> 00:14:31.032 very much interested in knowing how

NOTE Confidence: 0.844819513636364

00:14:31.032 --> 00:14:34.287 how that affects the the the function

NOTE Confidence: 0.844819513636364

00:14:34.287 --> 00:14:38.646 especially in the kidney and and the liver.

NOTE Confidence: 0.844819513636364

00:14:38.650 --> 00:14:39.242 Eventually,

NOTE Confidence: 0.844819513636364

00:14:39.242 --> 00:14:41.018 after these, uh,

NOTE Confidence: 0.844819513636364

00:14:41.018 --> 00:14:43.386 these incisions are made,

NOTE Confidence: 0.844819513636364

00:14:43.390 --> 00:14:46.490 you bring in translesion polymerases

NOTE Confidence: 0.844819513636364

00:14:46.490 --> 00:14:50.340 and they are used to to replicate

NOTE Confidence: 0.844819513636364

00:14:50.340 --> 00:14:52.810 across this unhooked lesion.

NOTE Confidence: 0.844819513636364

00:14:52.810 --> 00:14:55.790 And that's actually probably

NOTE Confidence: 0.844819513636364

00:14:55.790 --> 00:14:58.770 not a mutagenic process.

NOTE Confidence: 0.844819513636364

00:14:58.770 --> 00:15:02.746 It's mostly a Posada that that can

NOTE Confidence: 0.844819513636364

00:15:02.750 --> 00:15:05.930 that can repair this this lesion.

NOTE Confidence: 0.844819513636364

00:15:05.930 --> 00:15:07.850 And eventually, as I mentioned,

NOTE Confidence: 0.844819513636364

00:15:07.850 --> 00:15:09.926 there's a whole homologous.

NOTE Confidence: 0.844819513636364

00:15:09.926 --> 00:15:12.521 Combination pathway that is involved

NOTE Confidence: 0.844819513636364

00:15:12.521 --> 00:15:15.669 in a repair of of the double strand

NOTE Confidence: 0.844819513636364

00:15:15.669 --> 00:15:18.470 break and here all of your proteins,

NOTE Confidence: 0.844819513636364

00:15:18.470 --> 00:15:20.050 favorite proteins that are

NOTE Confidence: 0.844819513636364

00:15:20.050 --> 00:15:22.025 associated with breast and ovarian

NOTE Confidence: 0.844819513636364

00:15:22.025 --> 00:15:23.783 cancer when they're mutated when

NOTE Confidence: 0.844819513636364

00:15:23.783 --> 00:15:25.733 the genus mutated in one copy.

NOTE Confidence: 0.844819513636364

00:15:25.740 --> 00:15:29.596 So BRC 2, power B2B,

NOTE Confidence: 0.844819513636364

00:15:29.596 --> 00:15:30.152 RC1,

NOTE Confidence: 0.844819513636364

00:15:30.152 --> 00:15:35.200 rad 51 are are functioning in this in this

NOTE Confidence: 0.844819513636364

00:15:35.200 --> 00:15:39.176 pathway and eventually we go back to SLX.

NOTE Confidence: 0.844819513636364

00:15:39.180 --> 00:15:42.738 Or and associated Mercedes one and

NOTE Confidence: 0.844819513636364

00:15:42.738 --> 00:15:47.132 the selects one where the repair needs

NOTE Confidence: 0.844819513636364

00:15:47.132 --> 00:15:50.948 to be completed using these these

NOTE Confidence: 0.844819513636364

00:15:50.948 --> 00:15:54.126 nucleases or a bloom healer case.

NOTE Confidence: 0.844819513636364

00:15:54.130 --> 00:15:56.482 I will also mention that there is

NOTE Confidence: 0.844819513636364

00:15:56.482 --> 00:15:58.112 another another pathway that's and

NOTE Confidence: 0.844819513636364

00:15:58.112 --> 00:16:00.328 the reason why the RCA two and Route

NOTE Confidence: 0.844819513636364

00:16:00.395 --> 00:16:02.201 51 are necessary at these cross

NOTE Confidence: 0.844819513636364

00:16:02.201 --> 00:16:04.328 links and that's to protect these

NOTE Confidence: 0.844819513636364

00:16:04.328 --> 00:16:07.082 cross links from from nucleases and

NOTE Confidence: 0.844819513636364

00:16:07.082 --> 00:16:10.180 our lab has shown that it's there.

NOTE Confidence: 0.844819513636364

00:16:10.180 --> 00:16:13.281 There is a protection against DNA to

NOTE Confidence: 0.844819513636364

00:16:13.281 --> 00:16:16.644 and Warner and other labs before us

NOTE Confidence: 0.844819513636364

00:16:16.644 --> 00:16:19.560 have shown for especially the Jason

NOTE Confidence: 0.818846877727273

00:16:19.655 --> 00:16:22.102 lab that there is also protection

NOTE Confidence: 0.818846877727273

00:16:22.102 --> 00:16:24.292 against MRE 11 at stalled.

NOTE Confidence: 0.818846877727273

00:16:24.300 --> 00:16:25.890 Forks for example,

NOTE Confidence: 0.818846877727273

00:16:25.890 --> 00:16:29.070 after hydroxyurea and other other damage.

NOTE Confidence: 0.818846877727273

00:16:29.070 --> 00:16:31.640 So I this is this is all I I have

NOTE Confidence: 0.818846877727273

00:16:31.718 --> 00:16:34.052 to say about the mechanism of

NOTE Confidence: 0.818846877727273

00:16:34.052 --> 00:16:36.390 of function of these proteins.

NOTE Confidence: 0.818846877727273

00:16:36.390 --> 00:16:39.006 There are still a lot of details that

NOTE Confidence: 0.818846877727273

00:16:39.006 --> 00:16:41.846 need to be that need to be filled in,

NOTE Confidence: 0.818846877727273

00:16:41.850 --> 00:16:44.412 but we have an idea of how

NOTE Confidence: 0.818846877727273

00:16:44.412 --> 00:16:46.450 how this pathway functions.

NOTE Confidence: 0.818846877727273

00:16:46.450 --> 00:16:48.498 And the only other thing that I say

00:16:48.498 --> 00:16:50.589 I'll say about this is that it's

00:16:50.589 --> 00:16:52.630 really a very well regulated process,

00:16:52.630 --> 00:16:54.640 so you make double strand breaks.

00:16:54.640 --> 00:16:56.730 But they are immediately being

00:16:56.730 --> 00:16:58.820 shuttled to the proper repair.

00:16:58.820 --> 00:17:00.920 OK, so we'll talk about what happens

00:17:00.920 --> 00:17:03.589 in the in the third part of my talk,

00:17:03.590 --> 00:17:05.015 we'll, we'll talk about what

00:17:05.015 --> 00:17:06.776 happens when this repair is abnormal

00:17:06.776 --> 00:17:08.474 and the brakes are still made,

00:17:08.480 --> 00:17:10.660 but they are inappropriately repaired.

00:17:13.440 --> 00:17:15.060 So in the second part,

00:17:15.060 --> 00:17:16.820 I'll talk about the endogenous

00:17:16.820 --> 00:17:19.000 sources of interest and cross links.

00:17:19.000 --> 00:17:22.840 So I showed you that the Franconia pathway

NOTE Confidence: 0.85237806

00:17:22.840 --> 00:17:25.508 is necessary for repair of I CL's,

NOTE Confidence: 0.85237806

00:17:25.508 --> 00:17:27.275 but you may ask, well,

NOTE Confidence: 0.85237806

00:17:27.275 --> 00:17:30.485 where are these IC's coming from?

NOTE Confidence: 0.85237806

00:17:30.490 --> 00:17:32.255 Obviously in the in the

NOTE Confidence: 0.85237806

00:17:32.255 --> 00:17:34.020 clinic we are very much.

NOTE Confidence: 0.753543265

00:17:36.700 --> 00:17:40.137 Aware of cisplatin and mitomycin C and

NOTE Confidence: 0.753543265

00:17:40.137 --> 00:17:42.686 interest rate crosslinks occur after

NOTE Confidence: 0.753543265

00:17:42.686 --> 00:17:45.668 treatment with these with these agents,

NOTE Confidence: 0.753543265

00:17:45.670 --> 00:17:46.830 although there are other

NOTE Confidence: 0.753543265

00:17:46.830 --> 00:17:48.280 lesions that occur as well,

NOTE Confidence: 0.753543265

00:17:48.280 --> 00:17:51.440 right intrastrand crosslinks and others.

NOTE Confidence: 0.753543265

00:17:51.440 --> 00:17:54.576 The exogenous damage also can come from

NOTE Confidence: 0.753543265

00:17:54.576 --> 00:17:58.018 bacterial metabolites, and there are.

NOTE Confidence: 0.753543265

00:17:58.020 --> 00:18:02.045 There are E coli strains that are

NOTE Confidence: 0.753543265

00:18:02.045 --> 00:18:04.191 making ICL inducing. Chemicals.

NOTE Confidence: 0.753543265

00:18:04.191 --> 00:18:06.296 It can come from acetyl,

NOTE Confidence: 0.753543265

00:18:06.300 --> 00:18:07.758 aldehyde, from ethanol.

NOTE Confidence: 0.753543265

00:18:07.758 --> 00:18:10.674 It can come from tobacco smoke,

NOTE Confidence: 0.753543265

00:18:10.680 --> 00:18:12.420 which is full of formaldehyde,

NOTE Confidence: 0.753543265

00:18:12.420 --> 00:18:14.540 acrolein and other mutagens.

NOTE Confidence: 0.753543265

00:18:14.540 --> 00:18:17.190 But formaldehyde and acrolein are

NOTE Confidence: 0.753543265

00:18:17.190 --> 00:18:20.260 very good into strong cross linkers.

NOTE Confidence: 0.753543265

00:18:20.260 --> 00:18:22.695 But we are particularly interested

NOTE Confidence: 0.753543265

00:18:22.695 --> 00:18:25.670 in sources of endogenous DNA damage

NOTE Confidence: 0.753543265

00:18:25.670 --> 00:18:28.448 and really beautiful work that I'll

NOTE Confidence: 0.753543265

00:18:28.448 --> 00:18:31.310 describe a little bit in the two

NOTE Confidence: 0.753543265

00:18:31.310 --> 00:18:34.198 slides that are coming up have shown

NOTE Confidence: 0.753543265

00:18:34.198 --> 00:18:37.390 that endogenous toxic metabolites

NOTE Confidence: 0.753543265

00:18:37.390 --> 00:18:40.582 formaldehyde and acetaldehyde are

NOTE Confidence: 0.753543265

00:18:40.582 --> 00:18:43.774 particularly important in the bone

NOTE Confidence: 0.753543265

00:18:43.774 --> 00:18:47.224 marrow and definitely contribute to bone

NOTE Confidence: 0.753543265

00:18:47.321 --> 00:18:49.976 marrow failure in Franconia patients.

NOTE Confidence: 0.753543265

00:18:49.976 --> 00:18:51.784 And in mouse models,

NOTE Confidence: 0.753543265

00:18:51.790 --> 00:18:55.726 so let me just introduce them.

NOTE Confidence: 0.753543265

00:18:55.730 --> 00:18:58.466 This work was done mostly by

NOTE Confidence: 0.753543265

00:18:58.470 --> 00:19:02.110 KJ Patel's group in the UK and

NOTE Confidence: 0.753543265

00:19:02.110 --> 00:19:05.028 they've defined LDH 2 and ADH 5.

NOTE Confidence: 0.753543265

00:19:05.030 --> 00:19:07.240 These are alcohol and aldehyde

NOTE Confidence: 0.753543265

00:19:07.240 --> 00:19:09.008 dehydrogenases as being important

NOTE Confidence: 0.753543265

00:19:09.008 --> 00:19:11.468 for this first tier of protection.

NOTE Confidence: 0.753543265

00:19:11.470 --> 00:19:14.476 So they remove the toxins from

NOTE Confidence: 0.753543265

00:19:14.476 --> 00:19:18.091 the cell and that prevents I CL

NOTE Confidence: 0.753543265

00:19:18.091 --> 00:19:21.085 DNA damage and of course the.

NOTE Confidence: 0.753543265

00:19:21.090 --> 00:19:23.050 Frankonia pathway is a second

NOTE Confidence: 0.753543265

00:19:23.050 --> 00:19:24.226 tier of protection.

NOTE Confidence: 0.753543265

00:19:24.230 --> 00:19:26.625 Whatever has been incorporated as

NOTE Confidence: 0.753543265

00:19:26.625 --> 00:19:29.729 cross links will be removed as well.

NOTE Confidence: 0.753543265

00:19:29.730 --> 00:19:33.123 So let me just give you a a shore

NOTE Confidence: 0.753543265

00:19:33.123 --> 00:19:36.784 segue and talk about a LDH 2 and ADH 5.

NOTE Confidence: 0.753543265

00:19:36.790 --> 00:19:39.726 So a LDH 2 is necessary for removal

NOTE Confidence: 0.753543265

00:19:39.726 --> 00:19:42.746 of acetyl aldehyde which is which can

NOTE Confidence: 0.753543265

00:19:42.746 --> 00:19:45.690 come from ethanol from the outside,

NOTE Confidence: 0.753543265

00:19:45.690 --> 00:19:48.890 but also from metabolism,

NOTE Confidence: 0.753543265

00:19:48.890 --> 00:19:50.490 intracellular metabolism.

NOTE Confidence: 0.753543265

00:19:50.490 --> 00:19:54.372 And LDH 2 is responsible for

NOTE Confidence: 0.753543265

00:19:54.372 --> 00:19:56.960 detoxifying it to acetate.

NOTE Confidence: 0.753543265

00:19:56.960 --> 00:20:00.859 And a KG Patels group has described

NOTE Confidence: 0.753543265

00:20:00.859 --> 00:20:03.642 LDH 2 knockouts when combined

NOTE Confidence: 0.753543265

00:20:03.642 --> 00:20:05.858 with Fangy 2 knockouts.

NOTE Confidence: 0.753543265

00:20:05.860 --> 00:20:08.302 The mouse for the first time

NOTE Confidence: 0.753543265

00:20:08.302 --> 00:20:10.467 really developed bone marrow fell

NOTE Confidence: 0.753543265

00:20:10.467 --> 00:20:11.859 failure and leukemia.

00:20:11.860 --> 00:20:15.318 So the mouse model without just fancd

00:20:15.318 --> 00:20:18.549 2 mouse model does not develop.

00:20:18.550 --> 00:20:21.238 Bank bone marrow failure or leukemia.

00:20:21.240 --> 00:20:24.450 It has mild hematopoietic dysfunction,

00:20:24.450 --> 00:20:27.354 but it's nothing that you consider

00:20:27.354 --> 00:20:29.290 a bone marrow failure.

00:20:29.290 --> 00:20:31.730 In humans combination of FANK

00:20:31.730 --> 00:20:34.170 mutations and usually it's frank,

00:20:34.170 --> 00:20:37.730 a mutation and a LDH 2 star 2

00:20:37.730 --> 00:20:39.641 which is the dysfunctional.

00:20:39.641 --> 00:20:43.498 Variant of LDH 2 causes early onset

00:20:43.498 --> 00:20:46.865 of Fanconi anemia phenotype and there

00:20:46.865 --> 00:20:50.091 is a really beautiful paper from

00:20:50.091 --> 00:20:53.668 the Takata group that have that has

00:20:53.668 --> 00:20:56.798 shown that and that was published

00:20:56.798 --> 00:20:59.348 in 2013 which really solidified

NOTE Confidence: 0.753543265

00:20:59.348 --> 00:21:02.929 our thinking about this this as a

NOTE Confidence: 0.753543265

00:21:02.929 --> 00:21:05.419 as a modifier of Fanconi anemia.

NOTE Confidence: 0.753543265

00:21:05.420 --> 00:21:08.535 And I also will mention that together

NOTE Confidence: 0.753543265

00:21:08.535 --> 00:21:11.469 with Chris Vakoc's lab we showed that.

NOTE Confidence: 0.753543265

00:21:11.470 --> 00:21:15.610 Somatic Aldh 2 mutation silencing

NOTE Confidence: 0.753543265

00:21:15.610 --> 00:21:19.330 in AML's results in in dependency

NOTE Confidence: 0.753543265

00:21:19.330 --> 00:21:21.642 on the Fanconi anemia.

NOTE Confidence: 0.753543265

00:21:21.650 --> 00:21:24.618 So when when Chris's lab and they

NOTE Confidence: 0.753543265

00:21:24.618 --> 00:21:27.875 are at Cold Spring Harbor did a

NOTE Confidence: 0.753543265

00:21:27.875 --> 00:21:30.701 screen and showed in number of

NOTE Confidence: 0.753543265

00:21:30.710 --> 00:21:33.870 AML's dependency on Fanconi anemia.

NOTE Confidence: 0.753543265

00:21:33.870 --> 00:21:35.998 He called us up and and asked what

NOTE Confidence: 0.753543265

00:21:35.998 --> 00:21:38.277 what should I look at why are they dying?

NOTE Confidence: 0.753543265

00:21:38.280 --> 00:21:40.870 And I said well just look at LDH 2 I

NOTE Confidence: 0.7890958325

00:21:40.950 --> 00:21:42.965 bet it's. Yeah, 2 and that's what

NOTE Confidence: 0.7890958325

00:21:42.965 --> 00:21:44.729 that's what it turns out to be.

NOTE Confidence: 0.7890958325

00:21:44.730 --> 00:21:47.178 We just helped him a little bit but

NOTE Confidence: 0.7890958325

00:21:47.178 --> 00:21:49.974 some of some of AML's depend on on

NOTE Confidence: 0.7890958325

00:21:49.974 --> 00:21:52.380 Franconia because of the of the

NOTE Confidence: 0.7890958325

00:21:52.466 --> 00:21:56.214 silencing of LH2 which I think is quite

NOTE Confidence: 0.7890958325

00:21:56.214 --> 00:21:58.567 interesting and has implications for

NOTE Confidence: 0.7890958325

00:21:58.567 --> 00:22:01.458 for therapies for these for these AML.

NOTE Confidence: 0.7890958325

00:22:01.460 --> 00:22:04.920 So then ADH five came.

NOTE Confidence: 0.7890958325

00:22:04.920 --> 00:22:09.112 And that that was also from KJ Patel's

NOTE Confidence: 0.7890958325

00:22:09.112 --> 00:22:13.117 work that ADH five is necessary for.

NOTE Confidence: 0.7890958325

00:22:13.120 --> 00:22:15.336 I mean this is this has been known

NOTE Confidence: 0.7890958325

00:22:15.336 --> 00:22:17.607 that has been known that ADH five

NOTE Confidence: 0.7890958325

00:22:17.607 --> 00:22:19.728 is necessary for detoxification of

NOTE Confidence: 0.7890958325

00:22:19.728 --> 00:22:22.548 formaldehyde through this through this

NOTE Confidence: 0.7890958325

00:22:22.548 --> 00:22:25.960 pathway and again they create a DH,

NOTE Confidence: 0.7890958325

00:22:25.960 --> 00:22:28.172 five -, 22 negative mice and they

00:22:28.172 --> 00:22:30.148 had bone marrow failure but also

00:22:30.148 --> 00:22:31.596 had gromel glomerular damage.

00:22:31.600 --> 00:22:33.600 That's actually poorly understood

00:22:33.600 --> 00:22:36.336 still and there is this.

00:22:36.336 --> 00:22:39.690 Uh new digenic human disease of

00:22:39.809 --> 00:22:44.275 LDH 2 ADH 5 double knockouts or

00:22:44.275 --> 00:22:46.558 the dysfunctional alleles which

00:22:46.558 --> 00:22:48.030 have bone marrow failure,

00:22:48.030 --> 00:22:49.182 myelodysplastic syndrome,

00:22:49.182 --> 00:22:51.486 foot for some reason,

00:22:51.490 --> 00:22:53.800 foot skeletal abnormalities

00:22:53.800 --> 00:22:56.110 and also neurodegeneration.

00:22:56.110 --> 00:22:59.169 So now you have phenotypes that are

00:22:59.169 --> 00:23:02.210 associated with ACL's and creation of

00:23:02.210 --> 00:23:05.490 I CL's in multiple different tissues.

NOTE Confidence: 0.7890958325

00:23:05.490 --> 00:23:07.858 Including in the brain and we if somebody

NOTE Confidence: 0.7890958325

00:23:07.858 --> 00:23:09.849 is interested in knowing why the brain,

NOTE Confidence: 0.7890958325

00:23:09.850 --> 00:23:12.460 we can discuss that later.

NOTE Confidence: 0.7890958325

00:23:12.460 --> 00:23:14.470 But there that really shows

NOTE Confidence: 0.7890958325

00:23:14.470 --> 00:23:18.180 us that there is a lot of.

NOTE Confidence: 0.7890958325

00:23:18.180 --> 00:23:18.576 Well,

NOTE Confidence: 0.7890958325

00:23:18.576 --> 00:23:21.348 the cells have a lot of different

NOTE Confidence: 0.7890958325

00:23:21.348 --> 00:23:23.595 pathways for as this first tier

NOTE Confidence: 0.7890958325

00:23:23.595 --> 00:23:26.594 of protection and my lab has been

NOTE Confidence: 0.7890958325

00:23:26.594 --> 00:23:28.730 interested in identifying other

NOTE Confidence: 0.7890958325

00:23:28.730 --> 00:23:31.691 pathways in different cells as cell

NOTE Confidence: 0.7890958325

00:23:31.691 --> 00:23:34.274 types and we started with with cells

NOTE Confidence: 0.7890958325

00:23:34.274 --> 00:23:36.936 of jurkat cells which are T cell

NOTE Confidence: 0.7890958325

00:23:36.936 --> 00:23:39.170 leukemia cells to figure this out.

NOTE Confidence: 0.7890958325

00:23:39.170 --> 00:23:41.282 So our hypothesis was that there

NOTE Confidence: 0.7890958325

00:23:41.282 --> 00:23:43.746 would be more of these detoxification

00:23:43.746 --> 00:23:46.680 path pathways in the cells and

00:23:46.680 --> 00:23:48.670 by understanding what that is.

00:23:48.670 --> 00:23:51.245 They might actually be equipped

00:23:51.245 --> 00:23:54.392 with understanding of what can we

00:23:54.392 --> 00:23:56.802 increase to have some preventive

00:23:56.802 --> 00:23:59.400 measures in in Fanconi anemia.

00:23:59.400 --> 00:24:02.249 So this is work from Munjung Jung

00:24:02.249 --> 00:24:05.301 who's now a a assistant professor

00:24:05.301 --> 00:24:08.220 at Hopkins and she was a clinical

00:24:08.220 --> 00:24:10.966 scholar in my lab and she did

00:24:10.966 --> 00:24:12.778 a metabolism focus screen.

00:24:12.780 --> 00:24:18.230 So this is crisper screen or that she.

00:24:18.230 --> 00:24:20.134 Performed in jurkat cells.

00:24:20.134 --> 00:24:22.990 And she took Frankie to positive

00:24:23.080 --> 00:24:24.892 and negative jurkat cells.

NOTE Confidence: 0.7890958325

00:24:24.892 --> 00:24:27.418 And the whole purpose was to

NOTE Confidence: 0.7890958325

00:24:27.418 --> 00:24:30.086 identify the genes that are dropping

NOTE Confidence: 0.7890958325

00:24:30.086 --> 00:24:32.702 out from fangy to negative cells.

NOTE Confidence: 0.7890958325

00:24:32.710 --> 00:24:34.534 So these are essential,

NOTE Confidence: 0.7890958325

00:24:34.534 --> 00:24:37.611 would be essential for faculty to cells.

NOTE Confidence: 0.7890958325

00:24:37.611 --> 00:24:39.998 And you can see that there are

NOTE Confidence: 0.7890958325

00:24:39.998 --> 00:24:42.253 lots of genes that that dropped

NOTE Confidence: 0.7890958325

00:24:42.253 --> 00:24:45.044 out and some of them were actually

NOTE Confidence: 0.7890958325

00:24:45.044 --> 00:24:47.449 consistent with what we know.

NOTE Confidence: 0.7890958325

00:24:47.450 --> 00:24:51.498 So these are these cells, SLC 7A.

NOTE Confidence: 0.7890958325

00:24:51.498 --> 00:24:53.942 11 and Assoc 3A2.

NOTE Confidence: 0.7890958325

00:24:53.942 --> 00:24:57.316 They form a complex that is responsible

NOTE Confidence: 0.7890958325

00:24:57.316 --> 00:25:00.599 for cysteine movement across the cell

NOTE Confidence: 0.7890958325

00:25:00.599 --> 00:25:03.947 membrane and that feeds into glutathione,

NOTE Confidence: 0.7890958325

00:25:03.950 --> 00:25:05.994 which is important for

NOTE Confidence: 0.7890958325

37

00:25:05.994 --> 00:25:07.016 formaldehyde detoxification,

NOTE Confidence: 0.7890958325

00:25:07.020 --> 00:25:08.112 so that fit.

NOTE Confidence: 0.7890958325

00:25:08.112 --> 00:25:11.121 There was also a we did get a

NOTE Confidence: 0.7890958325

00:25:11.121 --> 00:25:12.577 DH5 in the screen,

NOTE Confidence: 0.7890958325

00:25:12.580 --> 00:25:15.694 but the gene that we concentrate

NOTE Confidence: 0.7890958325

00:25:15.694 --> 00:25:19.830 on concentrated on was a LH9A1.

NOTE Confidence: 0.7890958325

00:25:19.830 --> 00:25:23.596 Eight out of 10 guides scored in

NOTE Confidence: 0.7890958325

00:25:23.596 --> 00:25:27.026 this in this assay and the rest

NOTE Confidence: 0.7890958325

00:25:27.026 --> 00:25:29.490 of the work was really based on a

NOTE Confidence: 0.753777993

00:25:29.490 --> 00:25:32.934 LH9A1. This is a aldehyde dehydrogenases

NOTE Confidence: 0.753777993

00:25:32.934 --> 00:25:35.230 in metabolizes amino aldehydes,

NOTE Confidence: 0.753777993

00:25:35.230 --> 00:25:38.107 at least in vitro and it's highly

NOTE Confidence: 0.753777993

00:25:38.107 --> 00:25:40.447 expressed in liver, muscle and kidney.

NOTE Confidence: 0.753777993

00:25:40.447 --> 00:25:43.912 And the idea here is that it will there

NOTE Confidence: 0.753777993

00:25:43.912 --> 00:25:46.712 will be tax toxic metabolite that is

NOTE Confidence: 0.753777993

00:25:46.712 --> 00:25:49.740 now detoxified by AL DH9A1 and this.

NOTE Confidence: 0.753777993

00:25:49.740 --> 00:25:52.020 If you don't have aldh 91,

NOTE Confidence: 0.753777993

00:25:52.020 --> 00:25:53.615 the toxic metabolite will create

NOTE Confidence: 0.753777993

00:25:53.615 --> 00:25:55.920 DNA damage and you don't have if

NOTE Confidence: 0.753777993

00:25:55.920 --> 00:25:57.555 you don't have Franconia pathway,

NOTE Confidence: 0.753777993

00:25:57.560 --> 00:26:00.297 these cells would die and get transformed.

NOTE Confidence: 0.753777993

00:26:00.300 --> 00:26:02.220 But if you have Franconia pathway,

NOTE Confidence: 0.753777993

00:26:02.220 --> 00:26:05.390 you would have cell survival.

NOTE Confidence: 0.753777993

00:26:05.390 --> 00:26:08.555 So umm munjung has validated

NOTE Confidence: 0.753777993

00:26:08.555 --> 00:26:11.087 this in multiple assays,

NOTE Confidence: 0.753777993

00:26:11.090 --> 00:26:14.354 and there is a bio archives paper that

NOTE Confidence: 0.753777993

00:26:14.354 --> 00:26:17.470 we've we put out there competition.

NOTE Confidence: 0.753777993

00:26:17.470 --> 00:26:21.310 Assays cells that didn't have a

NOTE Confidence: 0.753777993

00:26:21.310 --> 00:26:25.478 two and a LDH 9A1 did much more

NOTE Confidence: 0.753777993

00:26:25.478 --> 00:26:28.389 poorly and growth assays.

NOTE Confidence: 0.753777993

00:26:28.390 --> 00:26:30.889 She also could show that there were

NOTE Confidence: 0.753777993

00:26:30.889 --> 00:26:33.049 increased numbers of apoptotic cells,

NOTE Confidence: 0.753777993

00:26:33.050 --> 00:26:36.788 increased DNA damage through gamma H2AX.

NOTE Confidence: 0.753777993

00:26:36.790 --> 00:26:38.470 And increased chromosome breakage.

NOTE Confidence: 0.753777993

00:26:38.470 --> 00:26:41.569 So this is where we can look at

NOTE Confidence: 0.753777993

00:26:41.570 --> 00:26:43.542 without exogenous DNA damage.

NOTE Confidence: 0.753777993

00:26:43.542 --> 00:26:47.095 Look at numbers of breaks that are

NOTE Confidence: 0.753777993

00:26:47.095 --> 00:26:49.660 occurring in the double knockouts

NOTE Confidence: 0.753777993

00:26:49.660 --> 00:26:52.182 in different different clones and we

NOTE Confidence: 0.753777993

00:26:52.182 --> 00:26:55.341 can see that there is a increase of

NOTE Confidence: 0.753777993

00:26:55.341 --> 00:26:57.861 of chromosome breakage if we don't

NOTE Confidence: 0.753777993

00:26:57.861 --> 00:27:01.990 have a LDH 9A1 Infinity 2 cells.

NOTE Confidence: 0.753777993

00:27:01.990 --> 00:27:04.490 She also used human hematopoietic

NOTE Confidence: 0.753777993

00:27:04.490 --> 00:27:07.730 stem cells depleted Frank A with SH.

NOTE Confidence: 0.753777993

00:27:07.730 --> 00:27:11.114 RNA's did a knockout with of LDH 9A1

NOTE Confidence: 0.753777993

00:27:11.114 --> 00:27:14.006 and those could make fewer colonies.

NOTE Confidence: 0.753777993

00:27:14.010 --> 00:27:15.396 But what happened?

NOTE Confidence: 0.753777993

00:27:15.396 --> 00:27:18.168 We made a mouse expecting some

NOTE Confidence: 0.753777993

00:27:18.168 --> 00:27:20.991 level of of bone marrow failure

NOTE Confidence: 0.753777993

00:27:20.991 --> 00:27:23.817 and we've seen phenotypes so these

NOTE Confidence: 0.753777993

00:27:23.817 --> 00:27:26.625 mice are born smaller than fanki.

NOTE Confidence: 0.753777993

00:27:26.630 --> 00:27:28.390 Negative mice which are already

NOTE Confidence: 0.753777993

00:27:28.390 --> 00:27:29.798 small have increased number

NOTE Confidence: 0.753777993

00:27:29.798 --> 00:27:31.750 of eye abnormalities at birth,

NOTE Confidence: 0.753777993

00:27:31.750 --> 00:27:33.479 which has been seen as a DNA.

NOTE Confidence: 0.753777993

00:27:33.480 --> 00:27:36.504 Damage outcome and they have increased

NOTE Confidence: 0.753777993

00:27:36.504 --> 00:27:39.649 number of variant tumors in aged mice,

NOTE Confidence: 0.753777993

00:27:39.650 --> 00:27:42.926 but really very mild hematopoietic defect.

NOTE Confidence: 0.753777993

00:27:42.930 --> 00:27:46.002 So that tells us that there will be

NOTE Confidence: 0.753777993

00:27:46.002 --> 00:27:48.206 differences also between mice and

NOTE Confidence: 0.753777993

00:27:48.206 --> 00:27:50.912 men in how the these detoxification

NOTE Confidence: 0.753777993

00:27:50.912 --> 00:27:52.330 pathways are working.

NOTE Confidence: 0.753777993

00:27:52.330 --> 00:27:55.012 And This is why we when we are modeling

NOTE Confidence: 0.753777993

00:27:55.012 --> 00:27:57.333 things in the mouse with in this in

NOTE Confidence: 0.753777993

00:27:57.333 --> 00:27:59.246 this pathway I think it's important

NOTE Confidence: 0.753777993

00:27:59.246 --> 00:28:01.605 to to do things and in parallel

NOTE Confidence: 0.753777993

00:28:01.610 --> 00:28:04.270 in human system and in the mouse.

NOTE Confidence: 0.753777993

00:28:04.270 --> 00:28:06.320 And and compare and contrast

NOTE Confidence: 0.753777993

00:28:06.320 --> 00:28:08.370 because there will be differences

NOTE Confidence: 0.753777993

00:28:08.441 --> 00:28:10.891 and whatever we model in the mouse

NOTE Confidence: 0.753777993

00:28:10.891 --> 00:28:13.618 actually might not be as as important

NOTE Confidence: 0.753777993

00:28:13.618 --> 00:28:16.120 in humans and and vice versa.

NOTE Confidence: 0.910159725

00:28:18.240 --> 00:28:19.910 So the last question that

NOTE Confidence: 0.910159725

00:28:19.910 --> 00:28:22.116 we wanted to ask is, well,

NOTE Confidence: 0.910159725

00:28:22.116 --> 00:28:24.796 we've identified the the enzyme,

NOTE Confidence: 0.910159725

00:28:24.800 --> 00:28:27.120 but what's really the,

NOTE Confidence: 0.910159725

00:28:27.120 --> 00:28:29.540 the problem, what's the source,

NOTE Confidence: 0.910159725

00:28:29.540 --> 00:28:32.060 what's the toxic metabolite that these

NOTE Confidence: 0.910159725

00:28:32.060 --> 00:28:34.679 cells are dealing with so much junk

NOTE Confidence: 0.910159725

00:28:34.679 --> 00:28:36.828 did a suppressor screen as we are,

NOTE Confidence: 0.910159725

00:28:36.830 --> 00:28:39.160 we are geneticists at heart.

NOTE Confidence: 0.910159725

00:28:39.160 --> 00:28:43.108 So she took the double negative cells

NOTE Confidence: 0.910159725

00:28:43.108 --> 00:28:47.149 frankly to a LH9A1 double knockouts and.

NOTE Confidence: 0.910159725

00:28:47.149 --> 00:28:50.549 I redid the screen the the same method

NOTE Confidence: 0.910159725

00:28:50.549 --> 00:28:53.549 with using the same metabolism library,

NOTE Confidence: 0.910159725

00:28:53.550 --> 00:28:56.154 but now wanted to see the cells

NOTE Confidence: 0.910159725

00:28:56.154 --> 00:28:58.490 that are actually growing better.

NOTE Confidence: 0.910159725

00:28:58.490 --> 00:29:02.066 So now we are knocking out some other

NOTE Confidence: 0.910159725

00:29:02.066 --> 00:29:05.212 gene that is necessary for production

NOTE Confidence: 0.910159725

00:29:05.212 --> 00:29:10.318 of our of our toxic metabolite.

NOTE Confidence: 0.910159725

00:29:10.320 --> 00:29:13.572 And the Omni gene that we've

NOTE Confidence: 0.910159725

00:29:13.572 --> 00:29:16.426 identified is this ATP 13A3.

NOTE Confidence: 0.910159725

00:29:16.426 --> 00:29:19.951 We've actually identified a LDH 9A1 itself,

NOTE Confidence: 0.910159725

00:29:19.951 --> 00:29:22.093 but that's we think is actually

00:29:22.093 --> 00:29:23.820 through reversion mutations.

00:29:23.820 --> 00:29:28.032 So these are now we are creating a mutant

00:29:28.032 --> 00:29:31.116 and a LDH 91 that reverts the function.

00:29:31.120 --> 00:29:34.392 So we in a way it shows that

00:29:34.392 --> 00:29:37.420 our screen worked in both ways,

00:29:37.420 --> 00:29:39.310 but this gene is quite interesting

00:29:39.310 --> 00:29:40.570 because this is now.

00:29:40.570 --> 00:29:44.028 A protein that's necessary codes for a

00:29:44.028 --> 00:29:46.690 protein that's necessary for polyamine,

00:29:46.690 --> 00:29:48.460 for example spermine.

00:29:50.650 --> 00:29:53.115 Movement through the from between

00:29:53.115 --> 00:29:55.580 different membranes and if we

00:29:55.666 --> 00:29:57.856 have high level of spermine,

00:29:57.860 --> 00:29:59.960 we know at least this is

00:29:59.960 --> 00:30:02.000 what we think would happen.

00:30:02.000 --> 00:30:04.728 We would get high levels of I mean

00:30:04.728 --> 00:30:07.537 the proper now and as I mentioned I'll

00:30:07.540 --> 00:30:10.192 ADH 9A1 is involved in detoxification

00:30:10.192 --> 00:30:12.640 of amino propanol and propanol

00:30:12.640 --> 00:30:15.760 can lead to acrolein and cells.

00:30:15.760 --> 00:30:17.846 We actually haven't yet shown that this

00:30:17.846 --> 00:30:20.445 these are this is what happens in the system.

00:30:20.450 --> 00:30:22.718 But everything that we have is consistent

00:30:22.718 --> 00:30:27.518 with this, with this hypothesis, so.

00:30:27.520 --> 00:30:32.342 If we have triple mutants, these cells,

00:30:32.342 --> 00:30:35.499 these cells now can grow much better,

00:30:35.500 --> 00:30:39.652 presumably because we are sequestering the

00:30:39.652 --> 00:30:44.359 polyamines outside of the away from the DNA,

00:30:44.360 --> 00:30:49.360 not creating these these crosslinks.

00:30:49.360 --> 00:30:53.491 So I think this is a a an example

00:30:53.491 --> 00:30:55.479 of how we are.

NOTE Confidence: 0.861485793333333

00:30:55.480 --> 00:30:58.070 Identifying endogenous types of DNA

NOTE Confidence: 0.861485793333333

00:30:58.070 --> 00:31:01.204 damage that are necessary for crosslink

NOTE Confidence: 0.861485793333333

00:31:01.204 --> 00:31:04.389 repair for that are necessary to be

NOTE Confidence: 0.861485793333333

00:31:04.389 --> 00:31:07.114 repaired by franklinia pathway and

NOTE Confidence: 0.861485793333333

00:31:07.114 --> 00:31:10.004 other pathways of crosslink repair.

NOTE Confidence: 0.861485793333333

00:31:10.010 --> 00:31:14.734 And really adding to this idea of

NOTE Confidence: 0.861485793333333

00:31:14.734 --> 00:31:19.170 how the first tier of protection is

NOTE Confidence: 0.861485793333333

00:31:19.170 --> 00:31:22.020 necessary to to protect the the genome,

NOTE Confidence: 0.861485793333333

00:31:22.020 --> 00:31:25.000 not creating interstrand crosslinks.

NOTE Confidence: 0.861485793333333

00:31:25.000 --> 00:31:27.748 And that eventually obviously is necessary

NOTE Confidence: 0.861485793333333

00:31:27.748 --> 00:31:30.770 for normal cell and organ function.

NOTE Confidence: 0.861485793333333

00:31:30.770 --> 00:31:32.210 So with that,

NOTE Confidence: 0.861485793333333

00:31:32.210 --> 00:31:35.090 I'll move to the last topic,

NOTE Confidence: 0.861485793333333

00:31:35.090 --> 00:31:37.808 which is cancer and Fanconi anemia,

NOTE Confidence: 0.861485793333333

00:31:37.810 --> 00:31:42.190 children and young adults.

NOTE Confidence: 0.861485793333333

00:31:42.190 --> 00:31:45.196 And when you think about Franco

NOTE Confidence: 0.861485793333333

00:31:45.196 --> 00:31:46.198 anemia pathway,

NOTE Confidence: 0.861485793333333

00:31:46.200 --> 00:31:47.194 there are,

NOTE Confidence: 0.861485793333333

00:31:47.194 --> 00:31:50.176 I already mentioned that there are

NOTE Confidence: 0.861485793333333

00:31:50.176 --> 00:31:52.596 different types of of tumors that

NOTE Confidence: 0.861485793333333

00:31:52.596 --> 00:31:55.618 can form and one of the tumors that

NOTE Confidence: 0.861485793333333

00:31:55.618 --> 00:31:58.408 we think about are these embryonal

NOTE Confidence: 0.861485793333333

00:31:58.408 --> 00:32:02.721 tumors and AML that are forming when

NOTE Confidence: 0.861485793333333

00:32:02.721 --> 00:32:05.006 homology directed repair is absent.

NOTE Confidence: 0.861485793333333

00:32:05.010 --> 00:32:08.240 So these are patients who

NOTE Confidence: 0.861485793333333

00:32:08.240 --> 00:32:11.470 have beers biallelic BRC 2.

NOTE Confidence: 0.861485793333333

00:32:11.470 --> 00:32:14.571 Or probably 2 mutations and they are

NOTE Confidence: 0.861485793333333

00:32:14.571 --> 00:32:17.339 identified early age you know they

NOTE Confidence: 0.861485793333333

00:32:17.339 --> 00:32:20.045 they have they developed these tumors

NOTE Confidence: 0.861485793333333

00:32:20.045 --> 00:32:22.928 within the first five years of of

NOTE Confidence: 0.861485793333333

47

00:32:22.928 --> 00:32:25.949 their life and we actually have a

NOTE Confidence: 0.861485793333333

00:32:25.949 --> 00:32:28.254 mouse model of of medulloblastoma

NOTE Confidence: 0.861485793333333

00:32:28.254 --> 00:32:30.188 that is quite interesting but

NOTE Confidence: 0.861485793333333

00:32:30.188 --> 00:32:31.868 not ready for prime time.

NOTE Confidence: 0.861485793333333

00:32:31.870 --> 00:32:34.600 But the the reason why we are

NOTE Confidence: 0.861485793333333

00:32:34.600 --> 00:32:36.698 interested again in these tumors

NOTE Confidence: 0.861485793333333

00:32:36.698 --> 00:32:39.230 is because we want to understand

NOTE Confidence: 0.861485793333333

00:32:39.230 --> 00:32:41.670 why the granule progenitor.

NOTE Confidence: 0.861485793333333

00:32:41.670 --> 00:32:44.351 Cells or the cells that lead to

NOTE Confidence: 0.861485793333333

00:32:44.351 --> 00:32:46.060 neuroblastoma or tulips tumors,

NOTE Confidence: 0.861485793333333

00:32:46.060 --> 00:32:49.636 why do they really need BRC 2 function?

NOTE Confidence: 0.861485793333333

00:32:49.640 --> 00:32:52.004 What's so special about these cells

NOTE Confidence: 0.861485793333333

00:32:52.004 --> 00:32:55.439 that require BRC 2 function or probably

NOTE Confidence: 0.861485793333333

00:32:55.439 --> 00:32:57.815 2 function homologous recombination.

NOTE Confidence: 0.861485793333333

00:32:57.820 --> 00:33:00.214 So that's something that we are

NOTE Confidence: 0.861485793333333

00:33:00.214 --> 00:33:02.500 we are continuing to develop.

NOTE Confidence: 0.861485793333333

00:33:02.500 --> 00:33:04.695 But outside of homologous recombination

NOTE Confidence: 0.861485793333333

00:33:04.695 --> 00:33:07.600 when the ICL repair is abnormal,

NOTE Confidence: 0.861485793333333

00:33:07.600 --> 00:33:10.862 so these are patients with mutations in

NOTE Confidence: 0.861485793333333

00:33:10.862 --> 00:33:15.427 any of the core complex fanki FANGY 2 SLX 4.

NOTE Confidence: 0.861485793333333

00:33:15.430 --> 00:33:16.920 We don't have yet patients

NOTE Confidence: 0.861485793333333

00:33:16.920 --> 00:33:18.410 who have tumors with XPF,

NOTE Confidence: 0.861485793333333

00:33:18.410 --> 00:33:22.980 but that's more of a problem of the PF

NOTE Confidence: 0.861485793333333

00:33:22.980 --> 00:33:26.370 being necessary also in other tissues.

NOTE Confidence: 0.861485793333333

00:33:26.370 --> 00:33:29.442 These patients develop AML's and also

NOTE Confidence: 0.861485793333333

00:33:29.442 --> 00:33:31.490 develop squamous cell carcinomas

NOTE Confidence: 0.861485793333333

00:33:31.564 --> 00:33:34.124 and today we'll concentrate on

NOTE Confidence: 0.861485793333333

00:33:34.124 --> 00:33:35.660 squamous cell carcinomas.

NOTE Confidence: 0.861485793333333

00:33:35.660 --> 00:33:39.182 So this is a knowledgeable audience

NOTE Confidence: 0.861485793333333

00:33:39.182 --> 00:33:42.032 about squamous cell carcinomas and

NOTE Confidence: 0.861485793333333

00:33:42.032 --> 00:33:45.044 we'll concentrate on head and neck.

NOTE Confidence: 0.861485793333333

00:33:45.050 --> 00:33:46.726 And in sporadic cases,

NOTE Confidence: 0.861485793333333

00:33:46.726 --> 00:33:49.819 you have two types of of head

NOTE Confidence: 0.861485793333333

00:33:49.819 --> 00:33:51.289 and neck cancers.

NOTE Confidence: 0.861485793333333

00:33:51.290 --> 00:33:55.826 One of them is HPV associated

NOTE Confidence: 0.917541422

00:33:55.830 --> 00:33:58.002 that we want to spend too

NOTE Confidence: 0.917541422

00:33:58.002 --> 00:33:59.450 much time talking about.

NOTE Confidence: 0.917541422

00:33:59.450 --> 00:34:03.070 The other one is a HPV negative

NOTE Confidence: 0.917541422

00:34:03.070 --> 00:34:05.770 and that those tumors are

NOTE Confidence: 0.917541422

00:34:05.770 --> 00:34:07.757 associated with carcinogens that

NOTE Confidence: 0.917541422

00:34:07.757 --> 00:34:09.959 are present in tobacco and alcohol.

NOTE Confidence: 0.917541422

00:34:09.960 --> 00:34:15.014 And I would also claim that endogenous.

NOTE Confidence: 0.917541422

00:34:15.020 --> 00:34:18.656 Aldehydes will play a role in here as well.

NOTE Confidence: 0.917541422

00:34:18.660 --> 00:34:21.495 And maybe for franconi patients who might

NOTE Confidence: 0.917541422

00:34:21.495 --> 00:34:24.405 not be exposed to alcohol and tobacco

NOTE Confidence: 0.917541422

00:34:24.405 --> 00:34:27.200 as much as the general population are,

NOTE Confidence: 0.917541422

00:34:27.200 --> 00:34:29.510 those indulgence aldehydes will be important.

NOTE Confidence: 0.846388969333333

00:34:32.070 --> 00:34:34.966 The the truth about head and neck cancer

NOTE Confidence: 0.846388969333333

00:34:34.966 --> 00:34:38.187 is that the patients are diagnosed late,

NOTE Confidence: 0.846388969333333

00:34:38.190 --> 00:34:41.230 the survival is still poor and it's not

NOTE Confidence: 0.846388969333333

00:34:41.230 --> 00:34:43.629 really decreasing and if it's decreasing

NOTE Confidence: 0.846388969333333

00:34:43.629 --> 00:34:45.987 it's it's just because there's more,

NOTE Confidence: 0.846388969333333

00:34:45.990 --> 00:34:50.394 there are more HPV positive cancers

NOTE Confidence: 0.846388969333333

00:34:50.394 --> 00:34:56.000 and again the treatment can be quite

NOTE Confidence: 0.846388969333333

00:34:56.000 --> 00:34:59.024 horrendous for for the patients and

NOTE Confidence: 0.846388969333333

00:34:59.024 --> 00:35:01.210 really learning from from Barbara.

NOTE Confidence: 0.846388969333333

00:35:01.210 --> 00:35:04.876 The the need is really to stratify these

NOTE Confidence: 0.846388969333333

00:35:04.876 --> 00:35:08.062 patients to also to identify novel

NOTE Confidence: 0.846388969333333

00:35:08.062 --> 00:35:11.268 therapeutics that might not be DNA damaging.

NOTE Confidence: 0.846388969333333

00:35:11.270 --> 00:35:16.438 So we, my lab got interested in these

NOTE Confidence: 0.846388969333333

00:35:16.438 --> 00:35:20.144 tumors because of our registry and tumors

NOTE Confidence: 0.846388969333333

00:35:20.144 --> 00:35:23.323 and Fanconi anemia patients just observing

NOTE Confidence: 0.846388969333333

00:35:23.323 --> 00:35:27.026 the patients who are becoming young adults,

NOTE Confidence: 0.846388969333333

00:35:27.030 --> 00:35:29.286 especially bone after bone marrow transplant.

NOTE Confidence: 0.846388969333333

00:35:29.290 --> 00:35:31.950 But even without the bone marrow transplant,

NOTE Confidence: 0.846388969333333

00:35:31.950 --> 00:35:34.738 many of these patients have developed

NOTE Confidence: 0.846388969333333

00:35:34.738 --> 00:35:38.322 cancer and in 2003 there was a paper

NOTE Confidence: 0.846388969333333

00:35:38.322 --> 00:35:41.228 from the registry when I wasn't.

NOTE Confidence: 0.846388969333333

00:35:41.230 --> 00:35:45.465 Yet there but showing that patients with

NOTE Confidence: 0.846388969333333

00:35:45.465 --> 00:35:50.109 Fanconi anemia had 700 at least 700 fold

NOTE Confidence: 0.846388969333333

00:35:50.109 --> 00:35:53.472 increase of of tumorigenesis in in the

NOTE Confidence: 0.846388969333333

00:35:53.472 --> 00:35:56.040 head and neck cancer in head and neck

NOTE Confidence: 0.846388969333333

00:35:56.118 --> 00:36:01.215 area and for vulvar cancer and for for

NOTE Confidence: 0.846388969333333

00:36:01.215 --> 00:36:04.485 cervical cancer and anal cancer there

NOTE Confidence: 0.846388969333333

00:36:04.485 --> 00:36:06.909 were thousandfold increases in these.

NOTE Confidence: 0.846388969333333

00:36:06.910 --> 00:36:11.033 So these are cancers that are squamous cell

NOTE Confidence: 0.846388969333333

00:36:11.033 --> 00:36:14.438 carcinomas in Fanconi anemia patients.

NOTE Confidence: 0.846388969333333

00:36:14.440 --> 00:36:17.220 And they are very there.

NOTE Confidence: 0.846388969333333

00:36:17.220 --> 00:36:20.798 There are present in the tongue

NOTE Confidence: 0.846388969333333

00:36:20.798 --> 00:36:22.686 gingiva and buccal mucosa,

NOTE Confidence: 0.846388969333333

00:36:22.690 --> 00:36:25.298 some pharynx and larynx,

NOTE Confidence: 0.846388969333333

00:36:25.298 --> 00:36:30.072 but a lot of cancers in in the oral cavity.

NOTE Confidence: 0.846388969333333

00:36:30.080 --> 00:36:32.439 We do have some esophageal cancers as

NOTE Confidence: 0.846388969333333

00:36:32.439 --> 00:36:34.939 well and those are quite interesting,

NOTE Confidence: 0.846388969333333

00:36:34.940 --> 00:36:39.259 but all of them have similar similar

NOTE Confidence: 0.846388969333333

00:36:39.259 --> 00:36:41.233 genetic or molecular characteristics.

NOTE Confidence: 0.846388969333333

00:36:41.233 --> 00:36:45.856 So here is our and this is now I'll describe

NOTE Confidence: 0.846388969333333

00:36:45.856 --> 00:36:49.400 work and I'll go fairly quickly through it.

NOTE Confidence: 0.846388969333333

00:36:49.400 --> 00:36:52.820 Work through that was recently published.

NOTE Confidence: 0.846388969333333

00:36:52.820 --> 00:36:55.820 This is our cohort of patients who were

NOTE Confidence: 0.846388969333333

00:36:55.820 --> 00:36:57.776 whose tumors were sequenced and you

NOTE Confidence: 0.846388969333333

00:36:57.776 --> 00:37:00.338 can see that the agent diagnosis is.

NOTE Confidence: 0.846388969333333

00:37:00.340 --> 00:37:03.298 On median of 31 years old,

NOTE Confidence: 0.846388969333333

00:37:03.300 --> 00:37:05.901 but we have some 13 year old 16 year

NOTE Confidence: 0.846388969333333

00:37:05.901 --> 00:37:09.104 olds with head and neck cancer that's

NOTE Confidence: 0.846388969333333

00:37:09.104 --> 00:37:10.996 extremely aggressive and extremely

NOTE Confidence: 0.846388969333333

00:37:11.067 --> 00:37:13.734 difficult to treat since we cannot use

NOTE Confidence: 0.846388969333333

00:37:13.734 --> 00:37:16.176 this platin for for these patients

NOTE Confidence: 0.846388969333333

00:37:16.176 --> 00:37:18.768 and they are radiation sensitive as

NOTE Confidence: 0.846388969333333

00:37:18.768 --> 00:37:21.686 well as as patients although not that

NOTE Confidence: 0.846388969333333

00:37:21.686 --> 00:37:24.399 radiation can still be used carefully

NOTE Confidence: 0.846388969333333

00:37:24.400 --> 00:37:26.661 you can see that these patients don't

NOTE Confidence: 0.846388969333333

00:37:26.661 --> 00:37:30.272 do well at all much worse than the.

NOTE Confidence: 0.846388969333333

00:37:30.272 --> 00:37:33.830 Sporadic cancers and patients who are

NOTE Confidence: 0.846388969333333

00:37:33.941 --> 00:37:37.685 here and survive long usually are

NOTE Confidence: 0.846388969333333

00:37:37.685 --> 00:37:40.940 patients who had successful surgical

NOTE Confidence: 0.846388969333333

00:37:40.940 --> 00:37:45.504 resection of their of their primary tumor.

NOTE Confidence: 0.846388969333333

00:37:45.510 --> 00:37:47.774 Or occasionally radiation therapy

NOTE Confidence: 0.846388969333333

00:37:47.774 --> 00:37:50.604 that actually was was successful.

NOTE Confidence: 0.846388969333333

00:37:50.610 --> 00:37:51.115 OK,

NOTE Confidence: 0.846388969333333

00:37:51.115 --> 00:37:54.145 so we were very much interested

NOTE Confidence: 0.846388969333333

00:37:54.145 --> 00:37:56.570 in understanding the molecular

NOTE Confidence: 0.846388969333333

00:37:56.570 --> 00:37:59.570 pathogenesis in these tumors and we

NOTE Confidence: 0.846388969333333

00:37:59.570 --> 00:38:02.681 showed that majority of these tumors

NOTE Confidence: 0.846388969333333

00:38:02.681 --> 00:38:05.962 were HPV negative instead majority of

NOTE Confidence: 0.846388969333333

00:38:05.962 --> 00:38:09.760 them had P53 mutations and the P53

NOTE Confidence: 0.846388969333333

00:38:09.760 --> 00:38:12.680 mutations were of variety, nonsense,

NOTE Confidence: 0.846388969333333

00:38:12.680 --> 00:38:16.730 missense, frame shifts and deletions.

NOTE Confidence: 0.846388969333333

00:38:16.730 --> 00:38:20.546 But P53 was pretty much the only Gina gene

NOTE Confidence: 0.846388969333333

00:38:20.546 --> 00:38:24.306 that was mutated through point mutations,

NOTE Confidence: 0.846388969333333

00:38:24.310 --> 00:38:24.802 OK.

NOTE Confidence: 0.846388969333333

00:38:24.802 --> 00:38:27.754 All the other changes were actually

NOTE Confidence: 0.846388969333333

00:38:27.754 --> 00:38:30.097 changes that were associated

NOTE Confidence: 0.846388969333333

00:38:30.097 --> 00:38:32.428 with structural variants.

NOTE Confidence: 0.846388969333333

00:38:32.430 --> 00:38:34.974 So here you can see that these are

NOTE Confidence: 0.846388969333333

00:38:34.974 --> 00:38:37.513 number of mutations in across different

NOTE Confidence: 0.846388969333333

00:38:37.513 --> 00:38:40.249 cancers through TCG data from TCG

NOTE Confidence: 0.813067026666667

00:38:40.324 --> 00:38:42.580 data and I inserted our Fanconi

NOTE Confidence: 0.813067026666667

00:38:42.580 --> 00:38:44.758 tumors and they have point mutations,

NOTE Confidence: 0.813067026666667

00:38:44.758 --> 00:38:46.428 the number of point mutations.

NOTE Confidence: 0.813067026666667

00:38:46.430 --> 00:38:49.254 It's pretty low and these tumors are lower

NOTE Confidence: 0.813067026666667

00:38:49.254 --> 00:38:52.216 than in sporadic head and neck cancers.

NOTE Confidence: 0.813067026666667

00:38:52.220 --> 00:38:54.948 And if we look at the what kind

NOTE Confidence: 0.813067026666667

00:38:54.948 --> 00:38:56.620 of signatures are present,

NOTE Confidence: 0.813067026666667

00:38:56.620 --> 00:38:58.924 there is no homology,

NOTE Confidence: 0.813067026666667

00:38:58.924 --> 00:39:02.964 directed repair or smoking signature and a

NOTE Confidence: 0.813067026666667

00:39:02.964 --> 00:39:06.844 lot of these are signatures of cell division.

NOTE Confidence: 0.813067026666667

00:39:06.850 --> 00:39:08.810 So the reason why we think that

NOTE Confidence: 0.813067026666667

00:39:08.810 --> 00:39:11.410 they have smaller, fewer.

NOTE Confidence: 0.813067026666667

00:39:11.410 --> 00:39:14.595 Mutations is because they are

NOTE Confidence: 0.813067026666667

00:39:14.595 --> 00:39:17.143 present in younger patients.

NOTE Confidence: 0.813067026666667

00:39:17.150 --> 00:39:20.069 And instead what we see is this

NOTE Confidence: 0.813067026666667

00:39:20.069 --> 00:39:22.067 huge genomic instability where this

NOTE Confidence: 0.813067026666667

00:39:22.067 --> 00:39:24.747 is a circus plot and all of these,

NOTE Confidence: 0.813067026666667

00:39:24.750 --> 00:39:27.198 all of these.

NOTE Confidence: 0.813067026666667

00:39:27.200 --> 00:39:29.668 Lines indicate translocations and

NOTE Confidence: 0.813067026666667

00:39:29.668 --> 00:39:32.753 structural variants that are present

NOTE Confidence: 0.813067026666667

00:39:32.753 --> 00:39:36.359 in in these tumors and if we look at

NOTE Confidence: 0.813067026666667

00:39:36.359 --> 00:39:39.194 number of structural variants across

NOTE Confidence: 0.813067026666667

00:39:39.194 --> 00:39:42.506 these tumors the there is about 2 to

NOTE Confidence: 0.813067026666667

00:39:42.506 --> 00:39:44.688 threefold increase when we compare

NOTE Confidence: 0.813067026666667

00:39:44.688 --> 00:39:47.708 it to HPV negative tumors and HPV

NOTE Confidence: 0.813067026666667

00:39:47.708 --> 00:39:50.168 positive tumors have very few of

NOTE Confidence: 0.813067026666667

00:39:50.168 --> 00:39:52.372 these since they already mutated

NOTE Confidence: 0.813067026666667

00:39:52.372 --> 00:39:56.146 P53 and RB and really don't have to

NOTE Confidence: 0.813067026666667

00:39:56.146 --> 00:39:58.636 rely on these structural variants.

NOTE Confidence: 0.813067026666667

00:39:58.640 --> 00:40:01.598 And this is comparable to the

NOTE Confidence: 0.813067026666667

00:40:01.598 --> 00:40:04.180 structural variants that we see in

NOTE Confidence: 0.813067026666667

00:40:04.180 --> 00:40:07.160 BRC 2 or BRC 1 tumors which have

NOTE Confidence: 0.813067026666667

00:40:07.160 --> 00:40:11.580 high levels of structural variation.

NOTE Confidence: 0.813067026666667

00:40:11.580 --> 00:40:14.568 As far as types of type of of structural

NOTE Confidence: 0.813067026666667

00:40:14.568 --> 00:40:16.440 variance, we see number of them,

NOTE Confidence: 0.813067026666667

00:40:16.440 --> 00:40:18.752 we see deletions, translocations,

NOTE Confidence: 0.813067026666667

00:40:18.752 --> 00:40:20.900 inversions, all of them are increased.

NOTE Confidence: 0.813067026666667

00:40:20.900 --> 00:40:23.475 And if you take proportion

NOTE Confidence: 0.813067026666667

00:40:23.475 --> 00:40:25.020 of structural variance,

NOTE Confidence: 0.813067026666667

00:40:25.020 --> 00:40:27.756 actually the on the there is a slight

NOTE Confidence: 0.813067026666667

00:40:27.756 --> 00:40:29.839 increase of tandem duplication.

NOTE Confidence: 0.813067026666667

00:40:29.840 --> 00:40:32.744 So pretty much across all structural

NOTE Confidence: 0.813067026666667

00:40:32.744 --> 00:40:35.540 variants there is an increase.

NOTE Confidence: 0.813067026666667

00:40:35.540 --> 00:40:39.224 Which is consistent with breaks being

NOTE Confidence: 0.813067026666667

00:40:39.224 --> 00:40:43.147 made when the DNA when Fanconi pathway

NOTE Confidence: 0.813067026666667

00:40:43.147 --> 00:40:46.081 cannot function and these breaks being

NOTE Confidence: 0.813067026666667

00:40:46.081 --> 00:40:48.812 being repaired inappropriately and

NOTE Confidence: 0.813067026666667

00:40:48.812 --> 00:40:51.628 it's and and to show you the extent

NOTE Confidence: 0.813067026666667

00:40:51.628 --> 00:40:54.121 of how inappropriate this repair

NOTE Confidence: 0.813067026666667

00:40:54.121 --> 00:40:57.693 is we used number of techniques of

NOTE Confidence: 0.813067026666667

00:40:57.693 --> 00:41:00.563 long read sequencing and you can see

NOTE Confidence: 0.813067026666667

00:41:00.563 --> 00:41:03.490 that pieces of chromosomes are from

NOTE Confidence: 0.813067026666667

00:41:03.490 --> 00:41:05.498 different chromosomes chromosome 8.

NOTE Confidence: 0.813067026666667

00:41:05.500 --> 00:41:06.388 For 1511,

NOTE Confidence: 0.813067026666667

00:41:06.388 --> 00:41:09.052 they're all sort of strung together

NOTE Confidence: 0.813067026666667

00:41:09.052 --> 00:41:11.647 in the in in these tumors,

NOTE Confidence: 0.813067026666667

00:41:11.650 --> 00:41:14.875 creating these completely

NOTE Confidence: 0.813067026666667

00:41:14.875 --> 00:41:18.100 abnormal abnormal structures.

NOTE Confidence: 0.813067026666667

00:41:18.100 --> 00:41:21.430 So we also asked how these

NOTE Confidence: 0.813067026666667

59

00:41:21.430 --> 00:41:23.494 DNA molecules come together,

NOTE Confidence: 0.813067026666667

00:41:23.494 --> 00:41:25.558 whether there's something special

NOTE Confidence: 0.813067026666667

00:41:25.558 --> 00:41:28.536 about them and it's many of you know

NOTE Confidence: 0.813067026666667

00:41:28.536 --> 00:41:31.059 if you have double strand break you,

NOTE Confidence: 0.813067026666667

00:41:31.060 --> 00:41:32.975 it can be repaired through

NOTE Confidence: 0.813067026666667

00:41:32.975 --> 00:41:34.124 three different mechanism,

NOTE Confidence: 0.813067026666667

00:41:34.130 --> 00:41:36.638 non homologous end joining,

NOTE Confidence: 0.813067026666667

00:41:36.638 --> 00:41:38.519 microhomology mediated repair

NOTE Confidence: 0.813067026666667

00:41:38.519 --> 00:41:41.330 and single strand annealing.

NOTE Confidence: 0.813067026666667

00:41:41.330 --> 00:41:43.790 And all of these,

NOTE Confidence: 0.813067026666667

00:41:43.790 --> 00:41:47.480 all of these should be functional

NOTE Confidence: 0.813067026666667

00:41:47.603 --> 00:41:49.900 in Franconia negative cells.

NOTE Confidence: 0.813067026666667

00:41:49.900 --> 00:41:53.300 And indeed when we look at the junctions

NOTE Confidence: 0.813067026666667

00:41:53.378 --> 00:41:55.318 in franconi associated squamous

NOTE Confidence: 0.813067026666667

00:41:55.318 --> 00:41:58.228 cell carcinoma that are shown on

NOTE Confidence: 0.813067026666667

00:41:58.313 --> 00:42:00.965 the left and sporadic HPV negative,

NOTE Confidence: 0.813067026666667

00:42:00.970 --> 00:42:04.042 we see the same repair mechanism

NOTE Confidence: 0.813067026666667

00:42:04.042 --> 00:42:07.359 being active mostly on homologous non

NOTE Confidence: 0.813067026666667

00:42:07.359 --> 00:42:11.751 homologous end joining and MJ and that's the.

NOTE Confidence: 0.813067026666667

00:42:11.751 --> 00:42:14.186 The percentages are are identical.

NOTE Confidence: 0.813067026666667

00:42:14.190 --> 00:42:16.212 So the interpretation of this is

NOTE Confidence: 0.813067026666667

00:42:16.212 --> 00:42:18.285 that whenever there is a break

NOTE Confidence: 0.813067026666667

00:42:18.285 --> 00:42:19.945 that's formed in these tumors,

NOTE Confidence: 0.813067026666667

00:42:19.950 --> 00:42:22.884 it's being repaired just by sticking

NOTE Confidence: 0.813067026666667

00:42:22.884 --> 00:42:25.860 the the ends together and random

NOTE Confidence: 0.813067026666667

00:42:25.860 --> 00:42:28.644 fashion that results in these high

NOTE Confidence: 0.813067026666667

00:42:28.644 --> 00:42:31.349 number of structural variants.

NOTE Confidence: 0.813067026666667

00:42:31.350 --> 00:42:34.036 We also asked where these breaks

NOTE Confidence: 0.813067026666667

00:42:34.036 --> 00:42:36.266 occur and specifically we were

NOTE Confidence: 0.813067026666667

00:42:36.266 --> 00:42:39.188 interested to in in knowing whether

NOTE Confidence: 0.813067026666667

00:42:39.188 --> 00:42:41.818 they occur at repetitive sites.

NOTE Confidence: 0.834055263333333

00:42:41.820 --> 00:42:45.630 And there is some increase that's

00:42:45.630 --> 00:42:47.535 statistically significant in

00:42:47.540 --> 00:42:50.960 sign elements, so I'll repeat.

00:42:50.960 --> 00:42:55.076 Had higher number of of breaks,

00:42:55.080 --> 00:42:58.720 but when we look at the whole genome

00:42:58.720 --> 00:43:02.176 we can see that the brakes and here

00:43:02.176 --> 00:43:05.465 I'm showing where all of this breaks

00:43:05.465 --> 00:43:10.055 out and structural variant ends are.

00:43:10.060 --> 00:43:12.499 I think when they're being placed in the in

00:43:12.499 --> 00:43:14.969 the genome across all of the chromosomes,

00:43:14.970 --> 00:43:17.770 you can see that there is the brakes

00:43:17.770 --> 00:43:20.270 are occurring throughout the genome.

00:43:20.270 --> 00:43:23.906 But you do see that parts of some of

00:43:23.906 --> 00:43:27.124 the genes are being hit multiple times.

00:43:27.124 --> 00:43:29.910 And that's really the the way we

00:43:29.986 --> 00:43:32.428 think about it is that there is

NOTE Confidence: 0.834055263333333

00:43:32.428 --> 00:43:34.702 mutagenesis across and then on top

NOTE Confidence: 0.834055263333333

00:43:34.702 --> 00:43:37.347 of that there's a selection of

NOTE Confidence: 0.834055263333333

00:43:37.347 --> 00:43:40.065 particular genes that help the tumors.

NOTE Confidence: 0.834055263333333

00:43:40.070 --> 00:43:43.598 Growth for example EGFR here is is being

NOTE Confidence: 0.834055263333333

00:43:43.598 --> 00:43:46.855 amplified and so are other sites you know,

NOTE Confidence: 0.834055263333333

00:43:46.860 --> 00:43:48.435 but one here.

NOTE Confidence: 0.834055263333333

00:43:48.435 --> 00:43:52.433 This is the EGFR and and also

NOTE Confidence: 0.834055263333333

00:43:52.433 --> 00:43:55.588 others the outcome of this.

NOTE Confidence: 0.834055263333333

00:43:55.590 --> 00:43:59.510 Is that these tumors have very high copy

NOTE Confidence: 0.834055263333333

00:43:59.510 --> 00:44:02.936 number variance and this is just one tumor,

NOTE Confidence: 0.834055263333333

00:44:02.940 --> 00:44:04.200 this is Ascot plot.

NOTE Confidence: 0.834055263333333

00:44:04.200 --> 00:44:06.090 So this is a little specific

NOTE Confidence: 0.834055263333333

00:44:06.163 --> 00:44:08.168 copy number where total alleles

NOTE Confidence: 0.834055263333333

00:44:08.168 --> 00:44:10.569 obviously in the cells should be 2,

NOTE Confidence: 0.834055263333333

00:44:10.570 --> 00:44:13.186 the alternative allele should be one.

NOTE Confidence: 0.834055263333333

00:44:13.190 --> 00:44:16.200 But you can see that there are

NOTE Confidence: 0.834055263333333

00:44:16.200 --> 00:44:18.443 number of amplifications and their

NOTE Confidence: 0.834055263333333

00:44:18.443 --> 00:44:20.628 amplifications and genes that we

NOTE Confidence: 0.834055263333333

00:44:20.628 --> 00:44:23.589 all know from from tumor pathways.

NOTE Confidence: 0.834055263333333

00:44:23.590 --> 00:44:25.680 Pick three CA make cycling.

NOTE Confidence: 0.834055263333333

00:44:25.680 --> 00:44:28.776 One that's that's amplified in many

NOTE Confidence: 0.834055263333333

00:44:28.776 --> 00:44:32.224 of these tumors and then there are

NOTE Confidence: 0.834055263333333

00:44:32.224 --> 00:44:34.052 deletions and tumor suppressors

NOTE Confidence: 0.834055263333333

00:44:34.052 --> 00:44:37.270 like CDK and two way and P53.

NOTE Confidence: 0.834055263333333

00:44:37.270 --> 00:44:42.276 So this is a pretty representative look

NOTE Confidence: 0.834055263333333

00:44:42.276 --> 00:44:45.844 at the at the tumor of Fanconi anemia

NOTE Confidence: 0.834055263333333

00:44:45.844 --> 00:44:49.110 patients and this is a different way

NOTE Confidence: 0.834055263333333

00:44:49.110 --> 00:44:51.978 of representing it where all of the.

NOTE Confidence: 0.834055263333333

00:44:51.980 --> 00:44:55.540 The rows are the the genes that are

NOTE Confidence: 0.834055263333333

00:44:55.540 --> 00:44:59.025 mutated and the columns are single tumor

NOTE Confidence: 0.834055263333333

00:44:59.025 --> 00:45:01.455 that we've sequenced from Fanconi patients.

NOTE Confidence: 0.834055263333333

00:45:01.460 --> 00:45:04.288 And you can see that orange or

NOTE Confidence: 0.834055263333333

00:45:04.288 --> 00:45:05.932 amplifications and deletions in

NOTE Confidence: 0.834055263333333

00:45:05.932 --> 00:45:08.110 blue and multiple of these pathways

NOTE Confidence: 0.834055263333333

00:45:08.110 --> 00:45:10.499 are mutated in each of the genes.

NOTE Confidence: 0.834055263333333

00:45:10.500 --> 00:45:13.632 And if you look at pick three CA and

NOTE Confidence: 0.834055263333333

00:45:13.632 --> 00:45:16.904 Mick Amplifications 54% of these

NOTE Confidence: 0.834055263333333

00:45:16.904 --> 00:45:19.644 tumors have Co Co amplification

NOTE Confidence: 0.834055263333333

00:45:19.644 --> 00:45:22.610 of these two of these two.

NOTE Confidence: 0.834055263333333

00:45:22.610 --> 00:45:24.908 Oncogenes, so this is a very,

NOTE Confidence: 0.834055263333333

00:45:24.910 --> 00:45:27.178 this might explain part of why

NOTE Confidence: 0.834055263333333

00:45:27.178 --> 00:45:29.091 these tumors are aggressive but

NOTE Confidence: 0.834055263333333

00:45:29.091 --> 00:45:31.083 there are other reasons they they

NOTE Confidence: 0.834055263333333

00:45:31.083 --> 00:45:33.390 they might be aggressive as well.

NOTE Confidence: 0.834055263333333

00:45:33.390 --> 00:45:36.400 So to just summarize what

NOTE Confidence: 0.834055263333333

00:45:36.400 --> 00:45:38.808 happens in franconi tumors?

NOTE Confidence: 0.834055263333333

00:45:38.810 --> 00:45:40.600 We have.

NOTE Confidence: 0.834055263333333

00:45:40.600 --> 00:45:43.350 Franconia pathway that protects cells

NOTE Confidence: 0.834055263333333

00:45:43.350 --> 00:45:46.666 from creating DNA breaks when DNA

NOTE Confidence: 0.834055263333333

00:45:46.666 --> 00:45:49.046 interstrand crosslinks are present and

NOTE Confidence: 0.834055263333333

00:45:49.046 --> 00:45:52.617 if you have DNA breaks the structural

NOTE Confidence: 0.834055263333333

00:45:52.617 --> 00:45:55.247 variants follow and eventually all

NOTE Confidence: 0.834055263333333

00:45:55.247 --> 00:45:58.385 of them lead to high copy number

NOTE Confidence: 0.834055263333333

00:45:58.385 --> 00:46:01.120 variation in these in these tumors.

NOTE Confidence: 0.834055263333333

00:46:01.120 --> 00:46:03.408 And there is also I wanted to mention

NOTE Confidence: 0.834055263333333

00:46:03.408 --> 00:46:05.367 there is a paper that recently

NOTE Confidence: 0.834055263333333

00:46:05.367 --> 00:46:07.347 came out from Jean Souliers Lab

NOTE Confidence: 0.834055263333333

00:46:07.410 --> 00:46:10.900 who looked at AML's and and AML's.

NOTE Confidence: 0.834055263333333

00:46:10.900 --> 00:46:14.920 They also see structural variant formation,

NOTE Confidence: 0.834055263333333

00:46:14.920 --> 00:46:16.831 fewer structural variants,

NOTE Confidence: 0.834055263333333

00:46:16.831 --> 00:46:21.712 and they also see P53 pathway being abnormal.

NOTE Confidence: 0.834055263333333

00:46:21.712 --> 00:46:24.640 But actually P53 itself is not mutated,

NOTE Confidence: 0.834055263333333

00:46:24.640 --> 00:46:27.356 it's through the MDM 4 pathway that

NOTE Confidence: 0.834055263333333

00:46:27.360 --> 00:46:29.917 that there is suppression of P53.

NOTE Confidence: 0.834055263333333

00:46:29.917 --> 00:46:34.819 So in the bone marrow similar

NOTE Confidence: 0.821754858888889

00:46:34.820 --> 00:46:36.185 events are happening.

NOTE Confidence: 0.821754858888889

00:46:36.185 --> 00:46:38.915 Maybe it's at a slightly smaller,

NOTE Confidence: 0.821754858888889

00:46:38.920 --> 00:46:41.240 smaller scale, which I don't.

NOTE Confidence: 0.821754858888889

00:46:41.240 --> 00:46:43.730 Alright, understand.

NOTE Confidence: 0.821754858888889

00:46:43.730 --> 00:46:46.583 And might have to do with the timing of

NOTE Confidence: 0.821754858888889

00:46:46.583 --> 00:46:49.250 these tumors and time to evolution of

NOTE Confidence: 0.821754858888889

00:46:49.250 --> 00:46:51.760 of and presentation of these tumors.

NOTE Confidence: 0.821754858888889

00:46:51.760 --> 00:46:54.820 So knowing what we know

NOTE Confidence: 0.821754858888889

00:46:54.820 --> 00:46:56.656 about frankonia tumors,

NOTE Confidence: 0.821754858888889

00:46:56.660 --> 00:47:00.590 we then turned to sporadic cancers

NOTE Confidence: 0.821754858888889

00:47:00.590 --> 00:47:04.739 and we were wondering whether the.

NOTE Confidence: 0.821754858888889

00:47:04.740 --> 00:47:07.540 Structural variants that are present

NOTE Confidence: 0.821754858888889

00:47:07.540 --> 00:47:10.340 in sporadic HPV negative tumors.

NOTE Confidence: 0.821754858888889

00:47:10.340 --> 00:47:12.181 I showed you that there are still

NOTE Confidence: 0.821754858888889

00:47:12.181 --> 00:47:13.905 some of them and they're shown

NOTE Confidence: 0.821754858888889

00:47:13.905 --> 00:47:15.657 here on the right hand side.

NOTE Confidence: 0.821754858888889

00:47:15.660 --> 00:47:17.510 These are all HPV negative

NOTE Confidence: 0.821754858888889

00:47:17.510 --> 00:47:19.360 TCG head and neck cancers.

NOTE Confidence: 0.821754858888889

00:47:19.360 --> 00:47:20.750 You can see that there's

NOTE Confidence: 0.821754858888889

00:47:20.750 --> 00:47:22.140 plenty of orange and blue.

NOTE Confidence: 0.821754858888889

00:47:22.140 --> 00:47:23.700 So there are quite a lot

NOTE Confidence: 0.821754858888889

00:47:23.700 --> 00:47:24.740 of copy number variants,

NOTE Confidence: 0.821754858888889

00:47:24.740 --> 00:47:27.380 not as many as in in Fanconi tumors,

NOTE Confidence: 0.821754858888889

00:47:27.380 --> 00:47:29.810 but still.

NOTE Confidence: 0.821754858888889

00:47:29.810 --> 00:47:31.289 A high number.

NOTE Confidence: 0.821754858888889

00:47:31.289 --> 00:47:34.247 So we were wondering whether what

NOTE Confidence: 0.821754858888889

00:47:34.247 --> 00:47:37.202 we find in Fanconi tumors might

NOTE Confidence: 0.821754858888889

00:47:37.202 --> 00:47:40.830 apply to to head and neck cancer

NOTE Confidence: 0.821754858888889

00:47:40.830 --> 00:47:43.532 and sporadic and sporadic cases.

NOTE Confidence: 0.821754858888889

00:47:43.532 --> 00:47:48.882 And what we decided to do is to look at

NOTE Confidence: 0.821754858888889

00:47:48.882 --> 00:47:52.640 a copy number variants and stratify tumors.

NOTE Confidence: 0.821754858888889

00:47:52.640 --> 00:47:56.400 So now these are the TCG TCG data

NOTE Confidence: 0.821754858888889

00:47:56.400 --> 00:47:59.693 HPV negative tumors and stratify

NOTE Confidence: 0.821754858888889

00:47:59.693 --> 00:48:02.409 them into top quartile.

NOTE Confidence: 0.821754858888889

00:48:02.410 --> 00:48:04.450 Tumors with a high number

NOTE Confidence: 0.821754858888889

00:48:04.450 --> 00:48:06.082 of copy number variants,

NOTE Confidence: 0.821754858888889

00:48:06.090 --> 00:48:07.143 so top quartile,

NOTE Confidence: 0.821754858888889

00:48:07.143 --> 00:48:10.320 and then compare them to the low quartile,

NOTE Confidence: 0.821754858888889

00:48:10.320 --> 00:48:13.626 the top 1/4 of tumors with

NOTE Confidence: 0.821754858888889

00:48:13.626 --> 00:48:17.030 the low copy number variants,

NOTE Confidence: 0.821754858888889

00:48:17.030 --> 00:48:19.970 and we could correlate the

NOTE Confidence: 0.821754858888889

00:48:19.970 --> 00:48:23.330 number of pack years with the

NOTE Confidence: 0.821754858888889

00:48:23.330 --> 00:48:25.430 level of copy number variants.

NOTE Confidence: 0.821754858888889

00:48:25.430 --> 00:48:27.970 So the higher smoking history,

NOTE Confidence: 0.821754858888889

00:48:27.970 --> 00:48:30.870 the higher copy number variants.

NOTE Confidence: 0.821754858888889

00:48:30.870 --> 00:48:33.712 And when we looked at signatures that

NOTE Confidence: 0.821754858888889

00:48:33.712 --> 00:48:36.668 were present and in these two we could

NOTE Confidence: 0.821754858888889

00:48:36.668 --> 00:48:39.080 also show that the top quartile.

NOTE Confidence: 0.821754858888889

00:48:39.080 --> 00:48:45.242 Had about twofold increase in signatures

NOTE Confidence: 0.821754858888889

00:48:45.242 --> 00:48:48.520 of ID 38SBS4 and others and these

NOTE Confidence: 0.821754858888889

00:48:48.520 --> 00:48:50.490 are smoking associated in Dells,

NOTE Confidence: 0.821754858888889

00:48:50.490 --> 00:48:51.610 so that's not surprising,

NOTE Confidence: 0.821754858888889

00:48:51.610 --> 00:48:51.890 right?

NOTE Confidence: 0.821754858888889

00:48:51.890 --> 00:48:55.550 That's correlates with the pack history

NOTE Confidence: 0.821754858888889

00:48:55.550 --> 00:48:58.652 but also non homologous end joining

NOTE Confidence: 0.821754858888889

00:48:58.652 --> 00:49:00.720 and benzopyrene and acetaldehyde.

NOTE Confidence: 0.821754858888889

00:49:00.720 --> 00:49:04.200 That suggests something we we already

NOTE Confidence: 0.821754858888889

00:49:04.200 --> 00:49:07.129 know from epidemiological studies that

NOTE Confidence: 0.821754858888889

00:49:07.129 --> 00:49:09.719 smoking and drinking go together.

NOTE Confidence: 0.821754858888889

00:49:09.720 --> 00:49:12.912 So we so these patients probably

NOTE Confidence: 0.821754858888889

00:49:12.912 --> 00:49:15.907 are also enriched for for

NOTE Confidence: 0.821754858888889

00:49:15.907 --> 00:49:18.199 increased alcohol exposure.

NOTE Confidence: 0.821754858888889

00:49:18.200 --> 00:49:21.998 So taking all of this together,

NOTE Confidence: 0.821754858888889

00:49:22.000 --> 00:49:25.012 we come up with this hypothesis

NOTE Confidence: 0.821754858888889

00:49:25.012 --> 00:49:28.070 that in sporadic cancers,

NOTE Confidence: 0.821754858888889

00:49:28.070 --> 00:49:32.992 the tobacco and alcohol exposure creates

NOTE Confidence: 0.821754858888889

00:49:32.992 --> 00:49:35.680 DNA inter interesting crosslinks.

NOTE Confidence: 0.821754858888889

00:49:35.680 --> 00:49:38.680 Obviously it creates other mutagenic events,

NOTE Confidence: 0.821754858888889

00:49:38.680 --> 00:49:39.512 including P53,

NOTE Confidence: 0.821754858888889

00:49:39.512 --> 00:49:42.424 which is an early event that then

NOTE Confidence: 0.821754858888889

00:49:42.424 --> 00:49:45.119 allows structural variants to occur.

NOTE Confidence: 0.821754858888889

00:49:45.120 --> 00:49:47.760 And Franconia pathway even though

NOTE Confidence: 0.821754858888889

00:49:47.760 --> 00:49:50.860 that it's present in these in

NOTE Confidence: 0.821754858888889

00:49:50.860 --> 00:49:53.620 these tumors and maybe it might

NOTE Confidence: 0.821754858888889

00:49:53.620 --> 00:49:55.943 be somatically decreased or maybe

NOTE Confidence: 0.821754858888889

00:49:55.943 --> 00:49:58.088 there are some genetic factors

NOTE Confidence: 0.821754858888889

00:49:58.088 --> 00:50:00.876 that that are involved here,

NOTE Confidence: 0.821754858888889

00:50:00.876 --> 00:50:03.232 but frankonia pathway which

NOTE Confidence: 0.821754858888889

00:50:03.232 --> 00:50:05.460 is largely efficient.

NOTE Confidence: 0.821754858888889

00:50:05.460 --> 00:50:07.861 There isn't just enough of it and

NOTE Confidence: 0.821754858888889

00:50:07.861 --> 00:50:10.788 it's over is overwhelmed and unable to

NOTE Confidence: 0.821754858888889

00:50:10.788 --> 00:50:13.518 repair all the DNA into crosslinks.

NOTE Confidence: 0.821754858888889

00:50:13.520 --> 00:50:16.404 It's also important that P53 is is

NOTE Confidence: 0.821754858888889

00:50:16.404 --> 00:50:19.206 mutated in these so you cannot depend

NOTE Confidence: 0.821754858888889

00:50:19.206 --> 00:50:25.404 on P53 pathway to to increase the Franconia.

NOTE Confidence: 0.821754858888889

00:50:25.410 --> 00:50:27.510 Green expression kind of going in

NOTE Confidence: 0.821754858888889

00:50:27.510 --> 00:50:29.250 gene expression patterns and all

NOTE Confidence: 0.821754858888889

00:50:29.250 --> 00:50:30.894 of this results in DNA breaks,

NOTE Confidence: 0.821754858888889

00:50:30.900 --> 00:50:33.690 structural variants and the same

NOTE Confidence: 0.821754858888889

00:50:33.690 --> 00:50:37.640 pathway leading to copy number alterations.

NOTE Confidence: 0.821754858888889

00:50:37.640 --> 00:50:38.864 So taken together,

NOTE Confidence: 0.821754858888889

00:50:38.864 --> 00:50:41.720 you know when we look at the

NOTE Confidence: 0.8395544615

00:50:41.810 --> 00:50:44.882 FRANKLINIA pathway function or if we

NOTE Confidence: 0.8395544615

00:50:44.882 --> 00:50:48.499 have patients with low pathway function,

NOTE Confidence: 0.8395544615

00:50:48.500 --> 00:50:50.838 they have very high levels of head

NOTE Confidence: 0.8395544615

00:50:50.838 --> 00:50:53.290 and neck cancers and other squamous

NOTE Confidence: 0.8395544615

00:50:53.290 --> 00:50:55.269 cell carcinomas, maybe not 100%,

NOTE Confidence: 0.8395544615

00:50:55.269 --> 00:50:57.740 but if they Long live long enough,

NOTE Confidence: 0.8395544615

00:50:57.740 --> 00:51:01.960 very high levels and if we have

NOTE Confidence: 0.8395544615

00:51:01.960 --> 00:51:03.860 full function we are protected.

NOTE Confidence: 0.8395544615

00:51:03.860 --> 00:51:06.002 However, there are a number of

NOTE Confidence: 0.8395544615

00:51:06.002 --> 00:51:07.610 genetic modifiers whether it's a.

NOTE Confidence: 0.8395544615

00:51:07.610 --> 00:51:07.780 The

NOTE Confidence: 0.687288722

00:51:10.670 --> 00:51:13.410 H2CTA4DC GSTM one and others,

NOTE Confidence: 0.687288722

00:51:13.410 --> 00:51:16.015 as well as these environmental

NOTE Confidence: 0.687288722

00:51:16.015 --> 00:51:18.620 modifiers of alcohol tobacco that

NOTE Confidence: 0.687288722

00:51:18.701 --> 00:51:21.546 is making this pathway functionally

NOTE Confidence: 0.687288722

00:51:21.550 --> 00:51:24.455 inefficient leading to to higher

NOTE Confidence: 0.687288722

00:51:24.455 --> 00:51:28.130 probability of head and neck cancer.

NOTE Confidence: 0.687288722

00:51:28.130 --> 00:51:30.910 So I'll finish and um,

NOTE Confidence: 0.687288722

00:51:30.910 --> 00:51:33.790 I'll just acknowledge my lab.

NOTE Confidence: 0.687288722

00:51:33.790 --> 00:51:36.360 This is Arlene, who's been

NOTE Confidence: 0.687288722

00:51:36.360 --> 00:51:38.930 instrumental in starting the registry.

NOTE Confidence: 0.687288722

00:51:38.930 --> 00:51:44.230 Munjung Jung has worked on a LH9A1.

NOTE Confidence: 0.687288722

00:51:44.230 --> 00:51:46.148 They work on head and neck cancers,

NOTE Confidence: 0.687288722

00:51:46.150 --> 00:51:48.498 was hugely collaborative work,

NOTE Confidence: 0.687288722

00:51:48.498 --> 00:51:52.890 and we were helped by Matthias Sanders.

NOTE Confidence: 0.687288722

00:51:52.890 --> 00:51:55.560 Working with Peter Campbell and Andrew

NOTE Confidence: 0.687288722

00:51:55.560 --> 00:51:58.138 Webster drove this work in my lab.

NOTE Confidence: 0.687288722

00:51:58.140 --> 00:51:59.592 And we had.

NOTE Confidence: 0.687288722

00:51:59.592 --> 00:52:01.528 A lot of collaborators,

00:52:01.530 --> 00:52:05.586 clinical and patient collaborators

00:52:05.586 --> 00:52:10.150 and and also other bioinformaticians

00:52:10.150 --> 00:52:13.190 who've who've helped us.

00:52:13.190 --> 00:52:18.310 And I'd like to thank my funding agencies,

00:52:18.310 --> 00:52:20.558 tons of collaborators and

00:52:20.558 --> 00:52:22.806 especially patients and families.

00:52:22.810 --> 00:52:25.234 And these are some of the young adults

00:52:25.234 --> 00:52:27.418 few years ago before the pandemic and

00:52:27.418 --> 00:52:29.878 I know that at least five of these.

00:52:29.880 --> 00:52:32.575 Adults are have passed away with with

00:52:32.575 --> 00:52:35.916 head and neck cancer and during this time.

00:52:35.920 --> 00:52:39.908 So I'll take questions.

00:52:39.910 --> 00:52:40.490 Thank you.

00:52:48.900 --> 00:52:50.134 OK. That was wonderful.

00:52:50.134 --> 00:52:51.940 For those of you who are online,

00:52:51.940 --> 00:52:55.036 please use the Q&amp;A function to to bring your

NOTE Confidence: 0.858748585714286

00:52:55.036 --> 00:52:59.430 questions and I think Jeff. Jeff, yeah.

NOTE Confidence: 0.77555748

00:52:59.430 --> 00:53:01.397 Ohh uh you can have a microphone.

NOTE Confidence: 0.800516585

00:53:01.410 --> 00:53:02.418 I think it's here.

NOTE Confidence: 0.77809263625

00:53:03.990 --> 00:53:06.270 And and maybe I'll just start

NOTE Confidence: 0.77809263625

00:53:06.270 --> 00:53:07.896 with Nadia, Dimitrova asked.

NOTE Confidence: 0.77809263625

00:53:07.896 --> 00:53:10.494 Do you see evidence of extrachromosomal

NOTE Confidence: 0.77809263625

00:53:10.494 --> 00:53:12.904 DNA circles and FA tumors to

NOTE Confidence: 0.77809263625

00:53:12.904 --> 00:53:14.380 explain the amplifications and

NOTE Confidence: 0.77809263625

00:53:14.380 --> 00:53:16.588 we haven't really looked at that,

NOTE Confidence: 0.77809263625

00:53:16.590 --> 00:53:18.767 but that would be a good idea.

NOTE Confidence: 0.77809263625

00:53:18.770 --> 00:53:22.306 We do see a lot of tandem duplications

NOTE Confidence: 0.77809263625

00:53:22.310 --> 00:53:24.725 in the in the especially Mick and

NOTE Confidence: 0.77809263625

00:53:24.725 --> 00:53:26.772 other areas that would explain

NOTE Confidence: 0.77809263625

00:53:26.772 --> 00:53:29.090 the amplifications as well. Jeff

NOTE Confidence: 0.815526265714286

00:53:29.130 --> 00:53:30.334 yeah. So that was a great talk,

NOTE Confidence: 0.815526265714286

00:53:30.340 --> 00:53:31.608 incredibly clear and insightful.

NOTE Confidence: 0.815526265714286

00:53:31.608 --> 00:53:32.876 I really appreciate it.

NOTE Confidence: 0.815526265714286

00:53:32.880 --> 00:53:34.656 I really like that last diagram.

NOTE Confidence: 0.815526265714286

00:53:34.660 --> 00:53:36.088 I know it was meant diagrammatically

NOTE Confidence: 0.815526265714286

00:53:36.088 --> 00:53:37.720 at least the way you showed it,

NOTE Confidence: 0.815526265714286

00:53:37.720 --> 00:53:38.869 but it can't.

NOTE Confidence: 0.815526265714286

00:53:38.869 --> 00:53:40.784 That doesn't stop me from

NOTE Confidence: 0.815526265714286

00:53:40.784 --> 00:53:43.897 asking do you have a way to

NOTE Confidence: 0.815526265714286

00:53:43.897 --> 00:53:45.709 quantify Fanconi anemia pathway

NOTE Confidence: 0.815526265714286

00:53:45.709 --> 00:53:47.965 function on that X axis or not.

NOTE Confidence: 0.667696745

00:53:48.010 --> 00:53:49.108 That's a really,

NOTE Confidence: 0.667696745

00:53:49.108 --> 00:53:50.938 that's a really good question.

NOTE Confidence: 0.667696745

00:53:50.940 --> 00:53:54.126 So we we have some way of doing that

NOTE Confidence: 0.667696745

00:53:54.126 --> 00:53:56.620 within the Franconia population,

NOTE Confidence: 0.667696745

00:53:56.620 --> 00:53:58.545 so something that I haven't talked about.

77

NOTE Confidence: 0.667696745

00:53:58.550 --> 00:54:01.304 We have. The registry has been

NOTE Confidence: 0.667696745

00:54:01.304 --> 00:54:03.674 amazing and we sequence now

NOTE Confidence: 0.667696745

00:54:03.674 --> 00:54:06.368 pretty much everybody who we had.

NOTE Confidence: 0.667696745

00:54:06.370 --> 00:54:10.010 The DNA for to look for phenotype,

NOTE Confidence: 0.667696745

00:54:10.010 --> 00:54:11.240 genotype correlations and

NOTE Confidence: 0.667696745

00:54:11.240 --> 00:54:13.700 there are a lot of phenotype,

NOTE Confidence: 0.667696745

00:54:13.700 --> 00:54:16.286 genotype correlations that we can tease

NOTE Confidence: 0.667696745

00:54:16.286 --> 00:54:19.898 out and we've started to describe them.

NOTE Confidence: 0.667696745

00:54:19.900 --> 00:54:22.596 And the function we can at the lower

NOTE Confidence: 0.667696745

00:54:22.596 --> 00:54:25.411 end it's hard to tease it out but

NOTE Confidence: 0.667696745

00:54:25.411 --> 00:54:27.693 you can definitely do that with

NOTE Confidence: 0.667696745

00:54:27.693 --> 00:54:29.753 number of foci with ubiquitination

NOTE Confidence: 0.667696745

00:54:29.753 --> 00:54:32.976 of fancd 2 and Frank I it's not great

NOTE Confidence: 0.667696745

00:54:32.976 --> 00:54:35.771 I think we need a better assay for

NOTE Confidence: 0.667696745

00:54:35.771 --> 00:54:38.903 for doing that on the top end I think

NOTE Confidence: 0.667696745

00:54:38.903 --> 00:54:41.810 when we have like what we see what

NOTE Confidence: 0.667696745

00:54:41.810 --> 00:54:45.010 we think fully functional pathway.

NOTE Confidence: 0.667696745

00:54:45.010 --> 00:54:47.480 It's really difficult to say

NOTE Confidence: 0.667696745

00:54:47.480 --> 00:54:51.198 whether it's 95 or or 90%.

NOTE Confidence: 0.667696745

00:54:51.198 --> 00:54:55.490 So we haven't really been able to do that.

NOTE Confidence: 0.667696745

00:54:55.490 --> 00:54:57.282 But as you saw from the second

NOTE Confidence: 0.667696745

00:54:57.282 --> 00:54:59.016 part of my talk, you know,

NOTE Confidence: 0.667696745

00:54:59.016 --> 00:55:01.067 even a little bit of DNA damage

NOTE Confidence: 0.667696745

00:55:01.067 --> 00:55:02.882 can lead to chromosome breakage

NOTE Confidence: 0.667696745

00:55:02.882 --> 00:55:05.398 like the ones that we induce when

NOTE Confidence: 0.667696745

00:55:05.398 --> 00:55:07.002 we don't have a LDH 9A1.

NOTE Confidence: 0.667696745

00:55:07.002 --> 00:55:09.737 So I think there might be ways of of

NOTE Confidence: 0.667696745

00:55:09.737 --> 00:55:12.209 doing better assay development for this.

NOTE Confidence: 0.8930388

00:55:15.900 --> 00:55:16.360 So.

NOTE Confidence: 0.8326386

00:55:20.620 --> 00:55:22.628 So if I can

NOTE Confidence: 0.846759041333333

00:55:22.640 --> 00:55:24.832 ask a question. So one of the things

NOTE Confidence: 0.846759041333333

00:55:24.832 --> 00:55:26.444 we're noticing in the virtual tumor

NOTE Confidence: 0.846759041333333

00:55:26.444 --> 00:55:28.565 board that we do for these young adults

NOTE Confidence: 0.846759041333333

00:55:28.565 --> 00:55:30.757 with head neck cancer is that they are

NOTE Confidence: 0.846759041333333

00:55:30.760 --> 00:55:33.708 really not at all responsive to immune

NOTE Confidence: 0.846759041333333

00:55:33.708 --> 00:55:35.477 checkpoint inhibition which is often

NOTE Confidence: 0.846759041333333

00:55:35.477 --> 00:55:37.397 been brought forward as as something

NOTE Confidence: 0.846759041333333

00:55:37.397 --> 00:55:39.477 that might not be so DNA damaging.

NOTE Confidence: 0.846759041333333

00:55:39.480 --> 00:55:42.189 And I wonder if you could speculate

NOTE Confidence: 0.846759041333333

00:55:42.189 --> 00:55:45.259 about that both from the perspective of?

NOTE Confidence: 0.846759041333333

00:55:45.260 --> 00:55:46.891 Sort of this global picture you've been

NOTE Confidence: 0.846759041333333

00:55:46.891 --> 00:55:48.439 talking about with structural variants,

NOTE Confidence: 0.846759041333333

00:55:48.440 --> 00:55:51.079 not some so many single nucleotide variants.

NOTE Confidence: 0.846759041333333

00:55:51.080 --> 00:55:53.336 But also, is there anything that came out

NOTE Confidence: 0.846759041333333

00:55:53.336 --> 00:55:56.040 in your gene signatures that would speak to?

NOTE Confidence: 0.846759041333333

00:55:56.040 --> 00:55:58.070 I saw NSDD one which sometimes is

NOTE Confidence: 0.846759041333333

00:55:58.070 --> 00:55:59.520 associated with immune exclusion.

NOTE Confidence: 0.846759041333333

00:55:59.520 --> 00:56:01.752 Are you getting a picture from the mutations

NOTE Confidence: 0.846759041333333

00:56:01.752 --> 00:56:03.819 of what the immune status might be?

NOTE Confidence: 0.86615868

00:56:04.720 --> 00:56:08.110 So from the mutations we we

NOTE Confidence: 0.86615868

00:56:08.110 --> 00:56:13.140 do we do see deletions in.

NOTE Confidence: 0.86615868

00:56:13.140 --> 00:56:17.800 A message. Will say.

NOTE Confidence: 0.86615868

00:56:17.800 --> 00:56:21.664 But frankly the the genome instability

NOTE Confidence: 0.86615868

00:56:21.664 --> 00:56:26.856 probably has a big part in the in the

NOTE Confidence: 0.86615868

00:56:26.856 --> 00:56:29.340 inability to have immune response right.

NOTE Confidence: 0.86615868

00:56:29.340 --> 00:56:31.893 So we are very much interested in

NOTE Confidence: 0.86615868

00:56:31.893 --> 00:56:33.989 that and we are starting to to look

NOTE Confidence: 0.86615868

00:56:33.989 --> 00:56:36.104 at that the tumor microenvironment

NOTE Confidence: 0.86615868

00:56:36.104 --> 00:56:38.339 in these tumors in particular

NOTE Confidence: 0.86615868

00:56:38.339 --> 00:56:41.212 thinking that it's it will be a good

NOTE Confidence: 0.86615868

00:56:41.212 --> 00:56:43.949 model for for understanding that.

NOTE Confidence: 0.86615868

00:56:43.950 --> 00:56:45.430 So we'll, we'll, we'll see.

NOTE Confidence: 0.86615868

00:56:45.430 --> 00:56:46.918 But it definitely looks like it

NOTE Confidence: 0.86615868

00:56:46.918 --> 00:56:51.580 would be too more suppressive, yeah.

NOTE Confidence: 0.86615868

00:56:51.580 --> 00:56:51.930 Tommy.

NOTE Confidence: 0.887544583809524

00:57:05.190 --> 00:57:07.976 Yes. So that's an interesting question and

NOTE Confidence: 0.887544583809524

00:57:07.976 --> 00:57:11.661 there is some some data in the literature

NOTE Confidence: 0.887544583809524

00:57:11.661 --> 00:57:14.370 that implicates mitochondrial DNA damage and

NOTE Confidence: 0.887544583809524

00:57:14.370 --> 00:57:16.750 Fanconi function within the mitochondria.

NOTE Confidence: 0.887544583809524

00:57:16.750 --> 00:57:19.648 I'm not sure how the fund Fanconi

NOTE Confidence: 0.887544583809524

00:57:19.650 --> 00:57:22.968 proteins would get into the mitochondria,

NOTE Confidence: 0.887544583809524

00:57:22.970 --> 00:57:26.148 but it's something that we have not.

NOTE Confidence: 0.887544583809524

00:57:26.150 --> 00:57:29.120 Explored. It would be so that,

NOTE Confidence: 0.887544583809524

00:57:29.120 --> 00:57:31.269 I'm sorry, the question was about the

NOTE Confidence: 0.887544583809524

00:57:31.269 --> 00:57:33.034 mitochondrial damage and whether there

NOTE Confidence: 0.887544583809524

00:57:33.034 --> 00:57:34.618 is increased mitochondrial damage.

NOTE Confidence: 0.887544583809524

00:57:34.620 --> 00:57:38.880 We we haven't really explored that.

NOTE Confidence: 0.887544583809524

00:57:38.880 --> 00:57:41.690 Um, and there would be.

00:57:41.690 --> 00:57:45.069 Well, it's it, it would be doable, right.

00:57:45.069 --> 00:57:47.461 I mean you just we would have to

00:57:47.461 --> 00:57:49.809 look at mitochondria specifically.

00:57:49.810 --> 00:57:52.996 The audio. That's right.

00:57:52.996 --> 00:57:54.837 A lot of these, yes.

00:57:54.837 --> 00:57:57.399 A lot of these are the

00:57:57.399 --> 00:57:58.253 detoxification enzymes.

00:57:58.260 --> 00:57:59.208 Not all of them,

00:57:59.208 --> 00:58:01.609 but many of them are within the mitochondria.

00:58:04.390 --> 00:58:05.368 The spermine? Yep.

00:58:10.720 --> 00:58:13.470 Right. Right.

00:58:17.550 --> 00:58:20.098 Right. Yeah. So there is a lot,

00:58:20.100 --> 00:58:22.782 a lot that we could explore in in this

00:58:22.782 --> 00:58:24.371 disease and mitochondrial function

00:58:24.371 --> 00:58:27.621 definitely has been brought up as as one

00:58:27.621 --> 00:58:29.889 of the places where where we should,

00:58:29.890 --> 00:58:33.918 we should look more.

00:58:33.920 --> 00:58:36.496 There was one question,

00:58:36.496 --> 00:58:39.824 is there a bias toward either focal or

00:58:39.824 --> 00:58:42.585 ARM level copy number alterations or

00:58:42.585 --> 00:58:45.618 both equally in FA tumors when compared

00:58:45.618 --> 00:58:48.460 to HPV negative head and neck cancers.

00:58:48.460 --> 00:58:50.440 So we see, we see both,

00:58:50.440 --> 00:58:54.146 I don't know if if we really compare them

00:58:54.146 --> 00:58:57.240 so we can say whether it's equal or not,

00:58:57.240 --> 00:59:01.384 but we see, we see we see some ARM

00:59:01.384 --> 00:59:04.270 level copy number alterations as well.

00:59:04.270 --> 00:59:06.430 But majority I would say,

00:59:06.430 --> 00:59:07.950 are the focal type.

00:59:13.900 --> 00:59:18.050 OK, yes. It seems that.

00:59:21.650 --> 00:59:24.288 Particular these metabolic enzymes.

NOTE Confidence: 0.541407036

00:59:26.610 --> 00:59:30.520 Essentially necessary to collect cells of the

NOTE Confidence: 0.42764593028

00:59:30.670 --> 00:59:33.910 dehydrogenases ID. Also very common.

NOTE Confidence: 0.505000965

00:59:36.490 --> 00:59:38.760 Biosynthesis inhibitors.

NOTE Confidence: 0.76317863875

00:59:42.030 --> 00:59:43.734 Do you think, well, what are your insights

NOTE Confidence: 0.712604940909091

00:59:43.750 --> 00:59:45.904 on a particular reason why blood

NOTE Confidence: 0.712604940909091

00:59:45.904 --> 00:59:48.240 cells would be more susceptible?

NOTE Confidence: 0.923196818333333

00:59:50.760 --> 00:59:53.250 Right. So one possibility is that

NOTE Confidence: 0.923196818333333

00:59:53.250 --> 00:59:56.319 they are really not more susceptible,

NOTE Confidence: 0.923196818333333

00:59:56.320 --> 00:59:58.018 they are just the there are

NOTE Confidence: 0.923196818333333

00:59:58.018 --> 00:59:59.944 fewer of them and they exhaust

NOTE Confidence: 0.923196818333333

00:59:59.944 --> 01:00:02.116 faster than any other stem cells,

NOTE Confidence: 0.923196818333333

01:00:02.120 --> 01:00:04.040 right, so that that's let's

NOTE Confidence: 0.923196818333333

01:00:04.040 --> 01:00:05.960 leave that as a possibility.

NOTE Confidence: 0.923196818333333

01:00:05.960 --> 01:00:11.215 The other is we know for formaldehyde.

NOTE Confidence: 0.923196818333333

01:00:11.215 --> 01:00:15.625 That. Very high levels of formal

01:00:15.625 --> 01:00:18.870 formaldehyde can be formed close to the

01:00:18.870 --> 01:00:21.582 DNA during the differentiation process.

01:00:21.582 --> 01:00:26.568 So one hypothesis is that you're

01:00:26.568 --> 01:00:29.458 having differentiation that happens

01:00:29.458 --> 01:00:32.888 during very few replication cycles,

01:00:32.890 --> 01:00:36.090 and that vulnerability of two

01:00:36.090 --> 01:00:38.650 formaldehyde is very high.

01:00:38.650 --> 01:00:40.740 Umm.

01:00:40.740 --> 01:00:43.610 So that's a possibility in coratina sites

01:00:43.610 --> 01:00:46.779 when we do an assay for for example

01:00:46.779 --> 01:00:50.223 whether ADH two or ADH 5 or important

01:00:50.223 --> 01:00:52.738 in with human characteristics sides,

01:00:52.740 --> 01:00:55.806 there doesn't seem to be that dependency

01:00:55.806 --> 01:00:58.896 within the fungi 2 or frank a negative.

01:00:58.900 --> 01:01:01.665 But we when we start playing with

01:01:01.665 --> 01:01:04.108 lipids metabolism they show up.

NOTE Confidence: 0.923196818333333

01:01:04.108 --> 01:01:08.468 And then it makes sense because it's the the,

NOTE Confidence: 0.923196818333333

01:01:08.470 --> 01:01:11.030 the lipid metabolism is very important in the

NOTE Confidence: 0.923196818333333

01:01:11.030 --> 01:01:14.020 in the as a barrier in correcting the sites.

NOTE Confidence: 0.923196818333333

01:01:14.020 --> 01:01:15.320 So some of it,

NOTE Confidence: 0.923196818333333

01:01:15.320 --> 01:01:19.560 I I do believe that some of it will come to

NOTE Confidence: 0.923196818333333

01:01:19.560 --> 01:01:22.690 specific functions or a particular stem cell.

NOTE Confidence: 0.923196818333333

01:01:22.690 --> 01:01:24.550 Um, and I think just more

NOTE Confidence: 0.923196818333333

01:01:24.550 --> 01:01:26.910 needs to be done to understand,

NOTE Confidence: 0.923196818333333

01:01:26.910 --> 01:01:29.060 to understand that one of

NOTE Confidence: 0.923196818333333

01:01:29.060 --> 01:01:30.780 the challenges is that.

NOTE Confidence: 0.923196818333333

01:01:30.780 --> 01:01:34.217 It's very hard to identify how much

NOTE Confidence: 0.923196818333333

01:01:34.217 --> 01:01:37.311 of these aldehydes are present and

NOTE Confidence: 0.923196818333333

01:01:37.311 --> 01:01:40.365 especially within the DNA it's just

NOTE Confidence: 0.923196818333333

01:01:40.365 --> 01:01:43.790 very difficult to to quantify these.

NOTE Confidence: 0.923196818333333

01:01:43.790 --> 01:01:45.590 But it's an I think it's

NOTE Confidence: 0.923196818333333

01:01:45.590 --> 01:01:46.960 a very interesting area.

NOTE Confidence: 0.698426

01:01:49.730 --> 01:01:54.170 OK, Ryan. Yeah, great talk about it.

NOTE Confidence: 0.698426

01:01:54.170 --> 01:01:55.839 This morning, your copy number,

NOTE Confidence: 0.698426

01:01:55.840 --> 01:01:57.160 your copy number, application

NOTE Confidence: 0.698426

01:01:57.160 --> 01:01:59.228 analysis. Have you ever

NOTE Confidence: 0.67262543

01:01:59.380 --> 01:02:00.472 have you looked at the sequences

NOTE Confidence: 0.67262543

01:02:00.472 --> 01:02:01.200 of those copy numbers?

NOTE Confidence: 0.67262543

01:02:01.200 --> 01:02:02.796 Are they mutating in each copy number?

NOTE Confidence: 0.67262543

01:02:02.800 --> 01:02:03.850 And what do you think

NOTE Confidence: 0.67262543

01:02:03.850 --> 01:02:04.690 driving that copy number,

NOTE Confidence: 0.67262543

01:02:04.690 --> 01:02:07.009 especially the amplification?

NOTE Confidence: 0.67262543

01:02:07.010 --> 01:02:08.678 Do you think it's like a DNA repair

NOTE Confidence: 0.6206159728

01:02:08.690 --> 01:02:11.090 pathway, like pull Theta

NOTE Confidence: 0.6206159728

01:02:11.090 --> 01:02:12.419 or something like that?

NOTE Confidence: 0.6206159728

01:02:12.420 --> 01:02:13.570 Yes. So let me just,

NOTE Confidence: 0.6206159728

01:02:13.570 --> 01:02:16.126 I don't know if I left.

NOTE Confidence: 0.6206159728

01:02:16.130 --> 01:02:18.770 Oh, I can't escape, OK.

NOTE Confidence: 0.6206159728

01:02:18.770 --> 01:02:23.243 Well, I won't try to find slides for this.

NOTE Confidence: 0.6206159728

01:02:23.250 --> 01:02:26.754 So we as far as you mean like

NOTE Confidence: 0.6206159728

01:02:26.754 --> 01:02:29.679 point mutations within the within

NOTE Confidence: 0.6206159728

01:02:29.679 --> 01:02:31.626 the amplified regions,

NOTE Confidence: 0.6206159728

01:02:31.630 --> 01:02:34.087 we don't really see any kind of.

NOTE Confidence: 0.827191321428571

01:02:36.390 --> 01:02:37.743 Aggregation of mutations

NOTE Confidence: 0.827191321428571

01:02:37.743 --> 01:02:39.547 like at the junctions.

NOTE Confidence: 0.827191321428571

01:02:39.550 --> 01:02:41.980 Let's say we've looked at that.

NOTE Confidence: 0.827191321428571

01:02:41.980 --> 01:02:45.988 Um, and the way I some of these

NOTE Confidence: 0.827191321428571

01:02:45.988 --> 01:02:47.659 amplifications occur through

NOTE Confidence: 0.827191321428571

01:02:47.659 --> 01:02:50.499 probably or are consistent with

NOTE Confidence: 0.827191321428571

01:02:50.499 --> 01:02:54.004 let's say that with stalling at the,

NOTE Confidence: 0.827191321428571

01:02:54.004 --> 01:02:56.860 at the at the cross link or

NOTE Confidence: 0.827191321428571

01:02:56.954 --> 01:02:59.829 some other lesion and reversal?

NOTE Confidence: 0.827191321428571

01:02:59.830 --> 01:03:03.113 So we do see these inversions that

NOTE Confidence: 0.827191321428571

01:03:03.113 --> 01:03:06.305 that are associated would be expected

NOTE Confidence: 0.827191321428571

01:03:06.305 --> 01:03:09.130 to be associated with replication.

NOTE Confidence: 0.827191321428571

01:03:09.130 --> 01:03:11.596 Some of them are tandem duplications

NOTE Confidence: 0.827191321428571

01:03:11.596 --> 01:03:14.878 and I think a nice system to figure

NOTE Confidence: 0.827191321428571

01:03:14.878 --> 01:03:17.745 this out is actually in a system

NOTE Confidence: 0.827191321428571

01:03:17.745 --> 01:03:20.610 where you have tester sequences

NOTE Confidence: 0.827191321428571

01:03:20.610 --> 01:03:24.959 and stalling through tester that

NOTE Confidence: 0.827191321428571

01:03:24.959 --> 01:03:26.842 that would be one place where you

NOTE Confidence: 0.827191321428571

01:03:26.842 --> 01:03:29.022 could model some of these, I think.

NOTE Confidence: 0.827191321428571

01:03:29.022 --> 01:03:30.833 I guess I was thinking of all these

NOTE Confidence: 0.827191321428571

01:03:30.833 --> 01:03:31.690 reversion mutations that arise

NOTE Confidence: 0.827191321428571

01:03:31.690 --> 01:03:33.790 like in Fanconi anemia perhaps

NOTE Confidence: 0.827191321428571

01:03:33.790 --> 01:03:34.830 you know the copy

NOTE Confidence: 0.773251861111111

01:03:34.840 --> 01:03:35.988 numbers. They're sampling different

NOTE Confidence: 0.773251861111111

01:03:35.988 --> 01:03:37.540 genetic states so they can, you

NOTE Confidence: 0.88679877

01:03:37.550 --> 01:03:39.950 know, sort of revert to a.

NOTE Confidence: 0.88679877

01:03:39.950 --> 01:03:41.870 I have a lot to say about the,

NOTE Confidence: 0.88679877

01:03:41.870 --> 01:03:44.024 the copy, not the the reversions

NOTE Confidence: 0.88679877

01:03:44.024 --> 01:03:46.685 in Fanconi because we have a whole

NOTE Confidence: 0.88679877

01:03:46.685 --> 01:03:48.995 another paper that's coming soon on

NOTE Confidence: 0.88679877

01:03:48.995 --> 01:03:51.549 mosaicism in the blood and a lot of

NOTE Confidence: 0.88679877

01:03:51.549 --> 01:03:54.460 these mutations are actually somatic

NOTE Confidence: 0.88679877

01:03:54.460 --> 01:03:58.441 recombination events that are UMPD,

NOTE Confidence: 0.88679877

01:03:58.441 --> 01:04:01.069 their uniparental disomy events.

NOTE Confidence: 0.88679877

01:04:01.070 --> 01:04:02.174 So there are, yes,

NOTE Confidence: 0.88679877

01:04:02.174 --> 01:04:03.830 there are point mutations and there

NOTE Confidence: 0.88679877

01:04:03.886 --> 01:04:05.728 are other things happening you know,

NOTE Confidence: 0.88679877

01:04:05.730 --> 01:04:08.310 splice site.

NOTE Confidence: 0.88679877

01:04:08.310 --> 01:04:09.650 New splice site mutations

NOTE Confidence: 0.88679877

01:04:09.650 --> 01:04:10.990 and things like that,

NOTE Confidence: 0.88679877

01:04:10.990 --> 01:04:15.031 but a lot of them are are full uniparental

NOTE Confidence: 0.88679877

01:04:15.031 --> 01:04:18.319 disomy through mitotic recombination.

NOTE Confidence: 0.88679877

01:04:18.320 --> 01:04:20.050 Which I think is interesting.

NOTE Confidence: 0.88679877

01:04:20.050 --> 01:04:21.210 Thank you.

NOTE Confidence: 0.88679877

01:04:21.210 --> 01:04:22.633 Thank you very much.

NOTE Confidence: 0.88679877

01:04:22.633 --> 01:04:23.479 Thank you.

NOTE Confidence: 0.606702535

01:04:26.530 --> 01:04:28.710 Um, for the fellows I think you're.