What to do with novel findings in next-generation sequencing?

Data sharing, phenotyping and solving unsolved cases

Aleš Maver

THE HUMAN VARIOME PROJECT
an NGO official partner of UNESCO
sharing data · reducing disease

4th Variant Effect Prediction Training Course
29-31 May 2019
Moscow, Russia

KIMG 50
KLINIČNI INŠTITUT ZA MEDICINSKO GENETIKO
Clinical Institute of Medical Genetics

EFQM Recognised for Excellence 4 Star - 2018
univerzitetni klinični center ljubljana

I have found a novel variant. What now?

Legacy databases and literature

Use existing sources to get the most information on your variant

Get in touch with institutions to get more information about my variant of interest

Share phenotypes in a standarized way

Use match-making to identify similar patients

You are welcome to participate!

1. Open web browser on the phone and go to this address: **etc.ch/me6t**
2. Once the question will appear, select your answer and click Vote

If it does not work

3

Q0. Does the voting work?

A. Yes

B. No

Voting link **etc.ch/me6t**

4

RESULTS

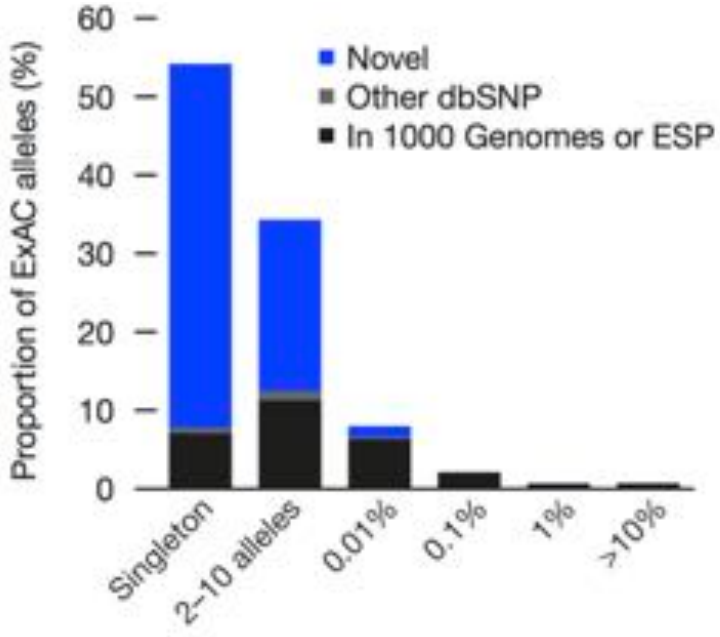
Voting link **etc.ch/me6t**

Genome sequencing constantly generates novel findings

The higher the throughput the higher the rate of identification of novel findings

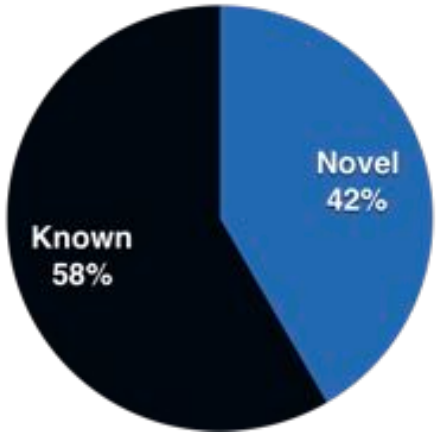
ExAC project

N=60.706



Reported clinically relevant variants in CMG database 2014-2016

(n=596 variants, in submission to ClinVar)



6

Variant interpretation

False negative

False positive

genomeweb

My GenomeWeb

Mother's Negligence Suit Against Quest's Athena Could Broadly Impact Genetic Testing Labs

Mar 14, 2016 | Turna Ray

NEW YORK (GenomeWeb) – Christian Millare had a severe seizure on Jan. 5, 2008, and died. He was two years old.

His mother Amy Williams is convinced, based on his medical records, the opinions of experts, and the published literature, that her son's life didn't have to come to such a premature end. Eight years later, Williams is suing Quest Diagnostics, one of the largest reference labs in the US, and its subsidiary Athena Diagnostics, which in 2007 tested Christian for mutations in the SCN1A gene.

In a lawsuit filed last month in the fifth judicial circuit court in Richland County, South Carolina, Williams alleges that because Athena failed to follow federal lab regulations and accurately classify the genetic mutation causing her son's epileptic seizures, he continued to receive treatment that worsened his condition and caused his death.

The Atlantic

Clinical Genetics Has a Big Problem That's Affecting People's Lives

Unreliable research can lead families to make health decisions they might regret.

Cheryl Ravelo / Reuters

ED YONG | DEC 16, 2015 | SCIENCE

For Heidi Rehm, it looked like a straightforward case. Her lab at Partners Healthcare offers tests for genetic diseases. They had received a blood sample from a fetus after a doctor conducting an ultrasound spotted signs of Noonan syndrome—an inherited disorder involving heart problems and stunted growth. The fetus turned out to have a mutation in PTPN11, a gene that affects the risk of Noonan syndrome.

admitted that their conclusions were wrong. In later work, they had found that the mutation is so common in certain ethnic groups that it couldn't possibly be responsible for a rare disease like Noonan syndrome. It wasn't pathogenic after all.

"I immediately contacted the physician to find out the story with that baby," Rehm says. "And that's when I found out that the parents had terminated it."

9

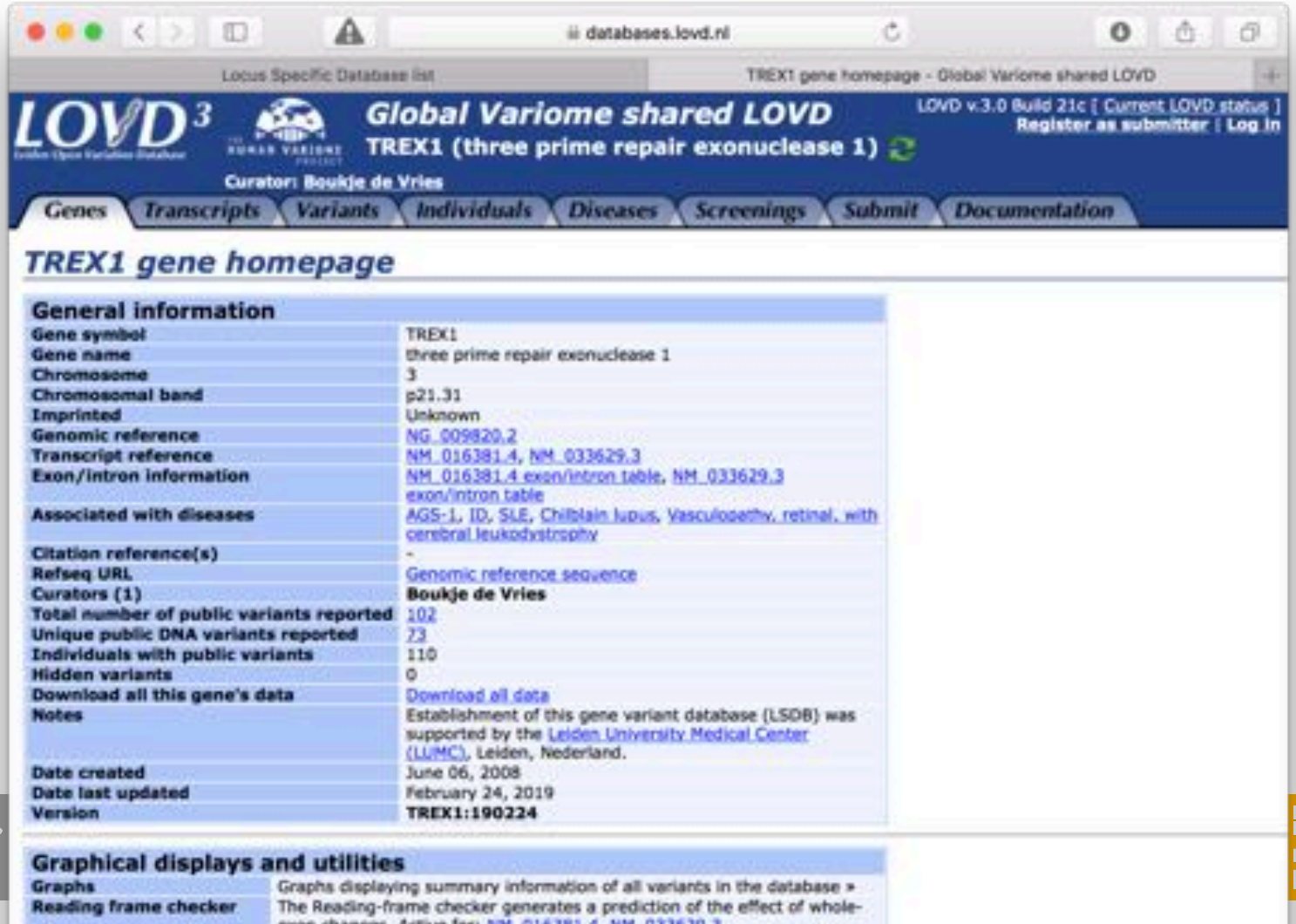
Before we start…
some essential tools we will need

GnomAD

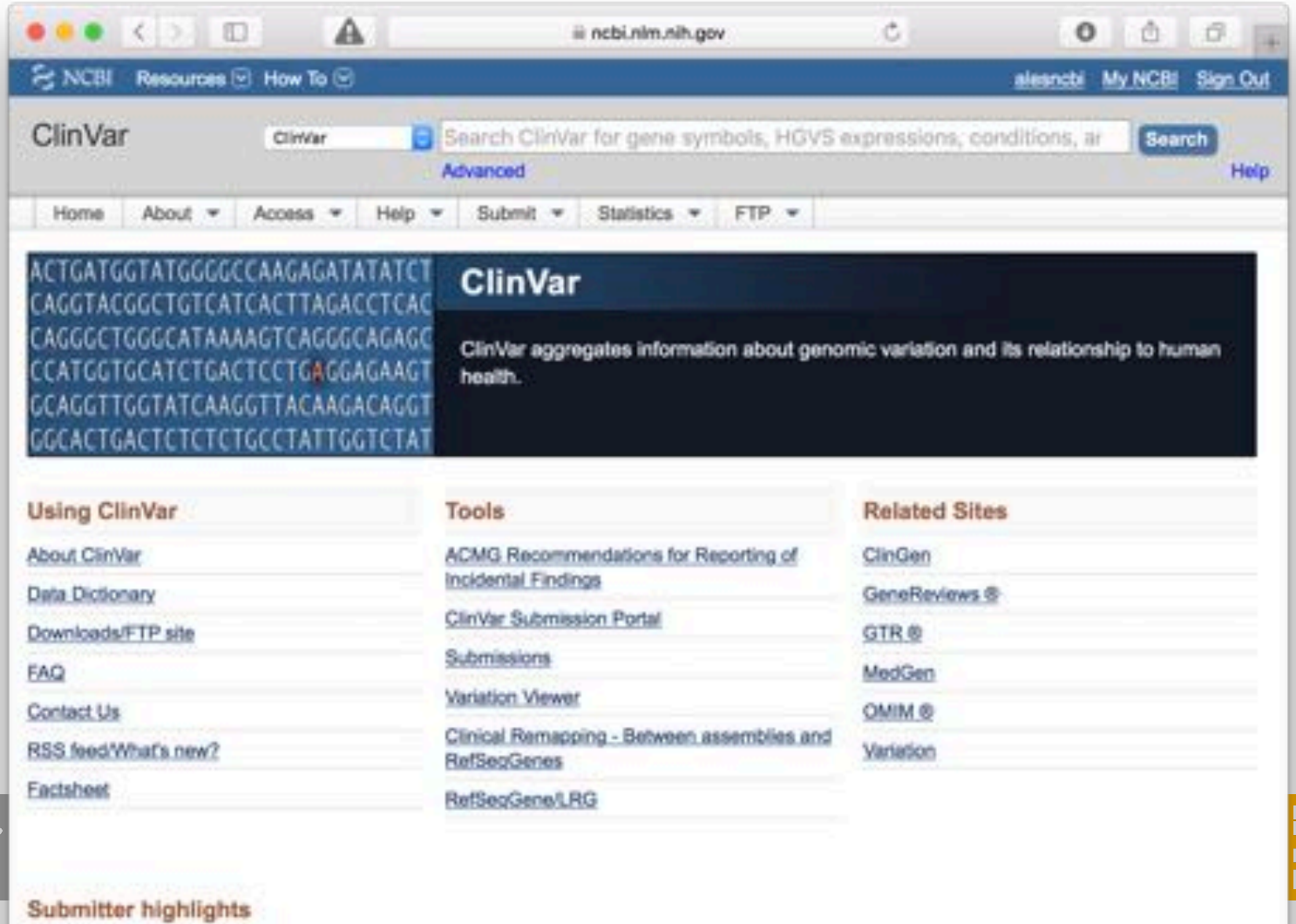
Use gnomAD to gain information on the population variation in >100.000 individuals

gnomad.broadinstitute.org

LOVD (genename.lovd.nl then click Global Variome shared LOVD)



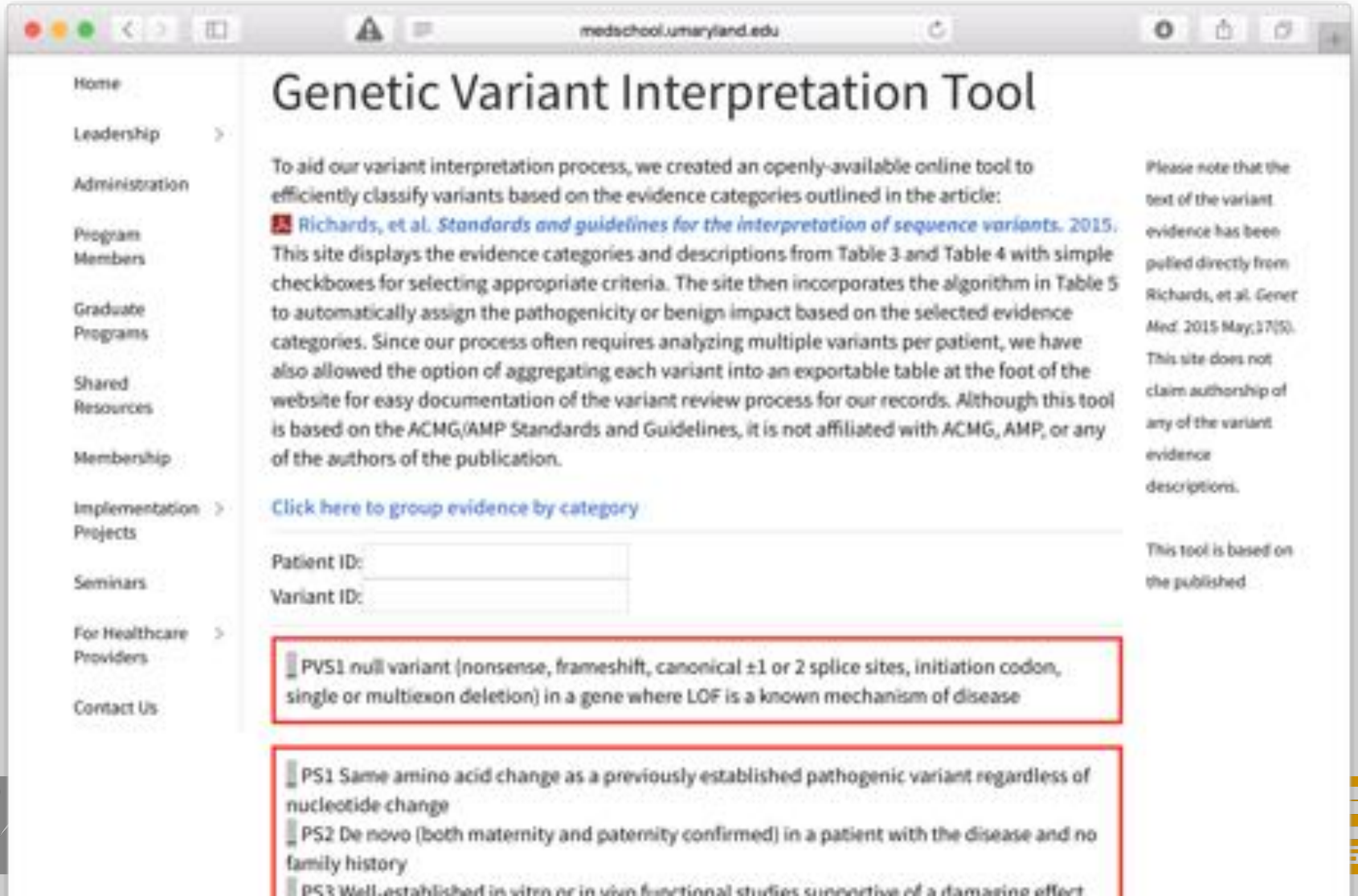
ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/)



ACMG

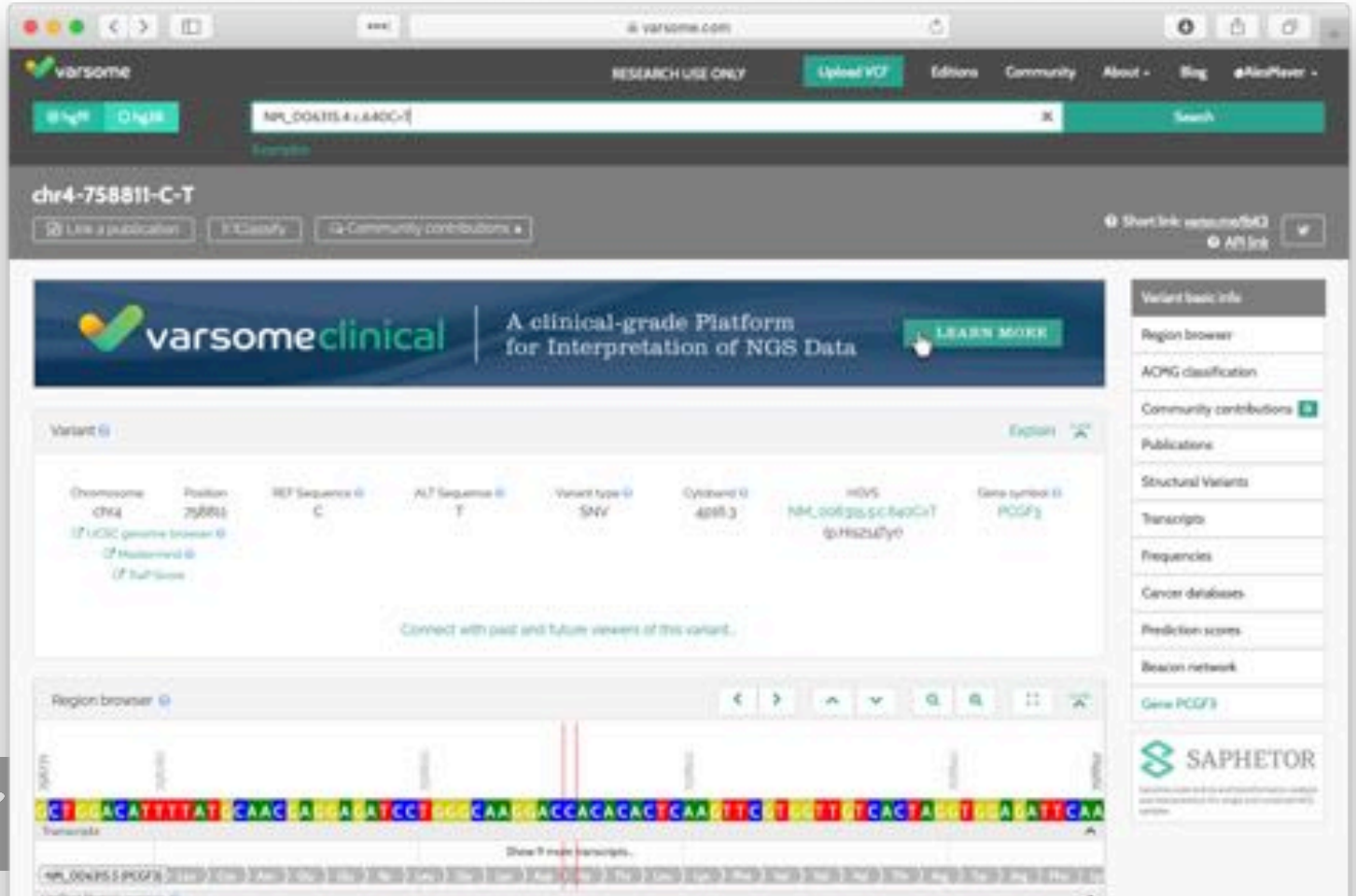
https://www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/

Google “variant interpretation tool”



Varsome – for quick variant queries

Search for your variant using the transcript coordinate
(ie. NM_144628.4:c.553dup)



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Patient with CADASIL syndrome

- A patient with suspected CADASIL syndrome was referred for genetic testing
- CADASIL syndrome is caused by heterozygous pathogenic variants in NOTCH3 gene
- You identified a novel missense variant in NOTCH3 gene

NM_000435.3:c.865G>T

The variant is novel, missense p.(Gly289Cys) and predicted as damaging by in-silico algorithms

Q1 How would you classify the NOTCH3 variant?

NM_000435.3:c.865G>T

1. Benign
2. Likely benign
3. Variant of uncertain significance
4. Likely pathogenic
5. Pathogenic

Voting link **etc.ch/me6t**

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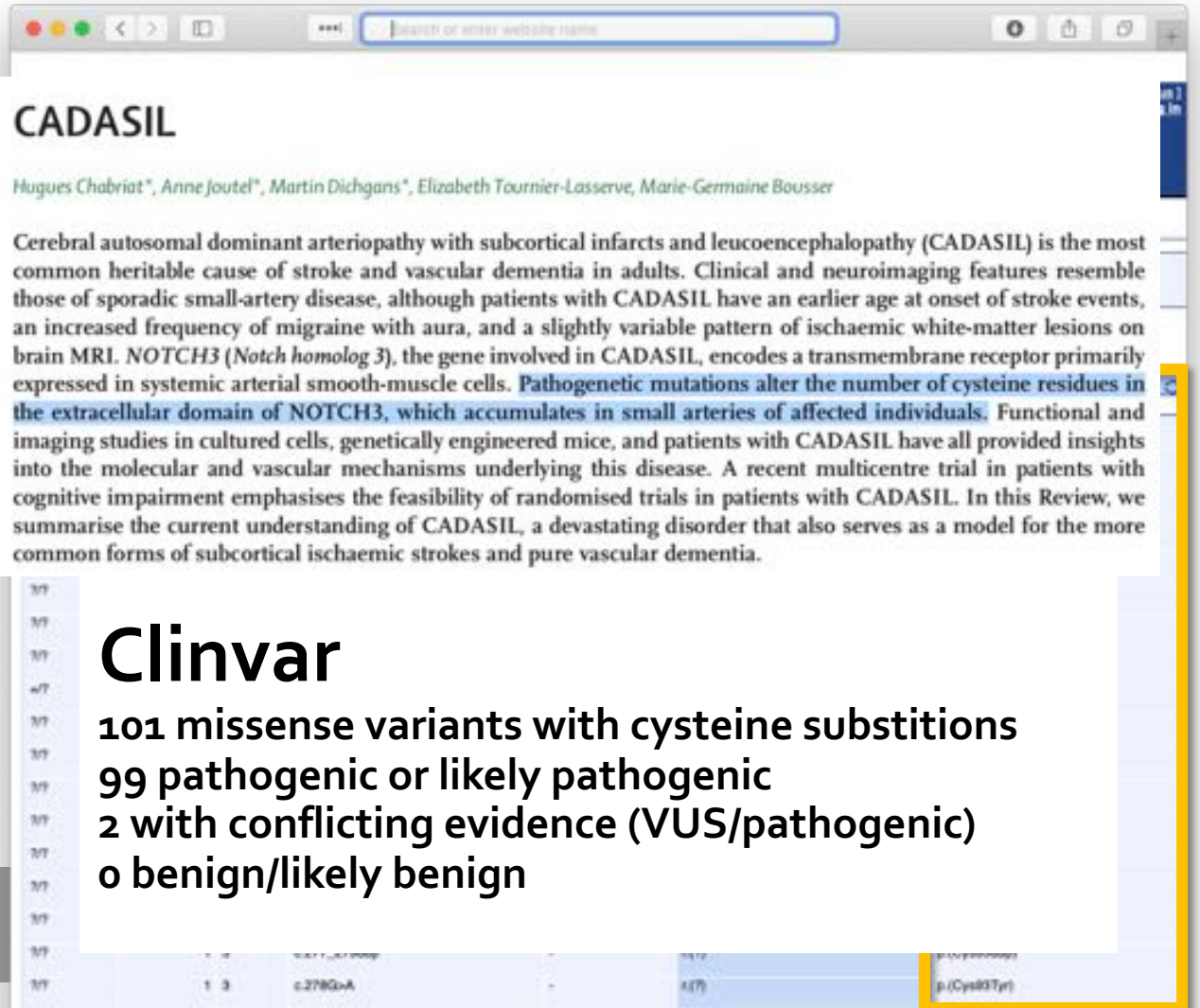
https:// directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.

Voting link **etc.ch/me6t**

Spectrum of pathogenic variation in the gene



CADASIL

Hugues Chabriat*, Anne Joutel*, Martin Dichgans*, Elizabeth Tournier-Lasserve, Marie-Germaine Bousser

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common heritable cause of stroke and vascular dementia in adults. Clinical and neuroimaging features resemble those of sporadic small-artery disease, although patients with CADASIL have an earlier age at onset of stroke events, an increased frequency of migraine with aura, and a slightly variable pattern of ischaemic white-matter lesions on brain MRI. *NOTCH3* (*Notch homolog 3*), the gene involved in CADASIL, encodes a transmembrane receptor primarily expressed in systemic arterial smooth-muscle cells. Pathogenetic mutations alter the number of cysteine residues in the extracellular domain of NOTCH3, which accumulates in small arteries of affected individuals. Functional and imaging studies in cultured cells, genetically engineered mice, and patients with CADASIL have all provided insights into the molecular and vascular mechanisms underlying this disease. A recent multicentre trial in patients with cognitive impairment emphasises the feasibility of randomised trials in patients with CADASIL. In this Review, we summarise the current understanding of CADASIL, a devastating disorder that also serves as a model for the more common forms of subcortical ischaemic strokes and pure vascular dementia.

Clinvar

101 missense variants with cysteine substitions
99 pathogenic or likely pathogenic
2 with conflicting evidence (VUS/pathogenic)
0 benign/likely benign

Cysteine substitutions are typical pathogenic variants in NOTCH3 gene

NM_000435.3:c.865G>T (p.Gly289Cys)

PM1 – Functional hotspot (Cysteine substitutions)
PM2 – Absent from controls
PP3 – Predicted pathogenic
PP4 – Phenotype typical

Likely pathogenic

Patient with a neurodevelopmental disorder

- A patient with global developmental delay is referred for whole exome sequencing
- In this patient, you identify a heterozygous stop-gain variant in RTKN gene:

NM_001015055.1:c.973C>T

RTKN gene has **not yet been associated with monogenic disease**, but the gene is expressed in the brain, the variant is absent in controls and predicted to result in a loss of function p.(Gln325Ter)

Q2 - What is your conclusion about the RTKN variant?

NM_001015055.1:c.973C>T

1. This is a likely cause of the neurodevelopmental disorder in this patient
2. We have likely found a novel gene for human disease – we need to find other patients with similar variants
3. This variant affects a gene not related to human disease, thus it is not likely a pathogenic variant
4. Heterozygous loss-of-function variants in this gene are common in the general population, thus it is unlikely to cause a severe mendelian phenotype

Voting link **etc.ch/me6t**

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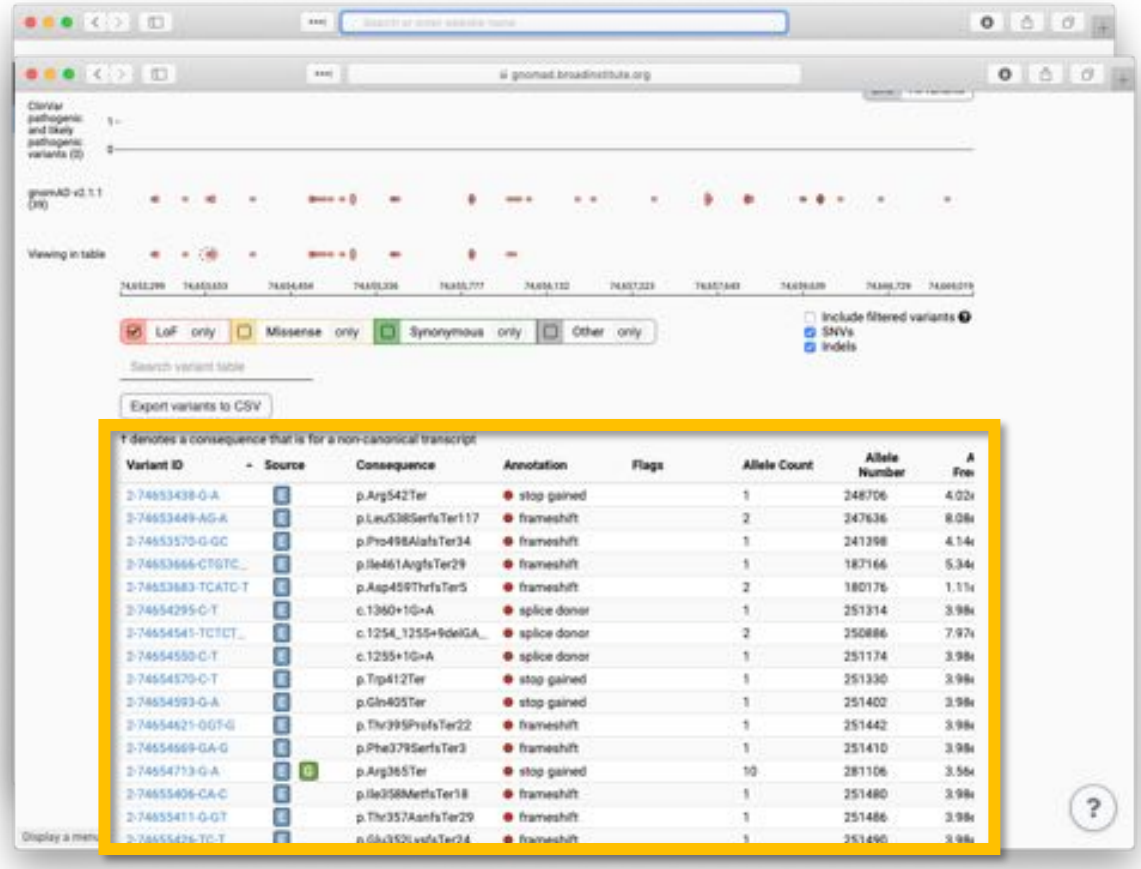
Spectrum of population variation in the gene



Heterozygous loss-of-function variants in RTKN gene are commonly observed in the general population

A heterozygous stop-gain variant in RTKN gene is thus less likely to be a cause of a severe early neurodevelopmental disorder

Patient with night blindness

- A patient with congenital stationary night blindness was referred for genetic testing
- Pathogenic heterozygous variants in NYX gene represent an established cause of night blindness
- In this patient, you identified a heterozygous in-frame duplication variant in NYX gene:

NM_022567.2 c.619_627dup

Try to find this variant in LOVD (nyx.lovd.nl) or Clinvar (https://www.ncbi.nlm.nih.gov/clinvar/)?

Q3 - How would you classify the NYX variant?

NM_022567.2 c.619_627dup

1. Benign
2. Likely benign
3. Variant of uncertain significance
4. Likely pathogenic
5. Pathogenic

Voting link **etc.ch/me6t**

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Voting link **etc.ch/me6t**

Legacy mutation databases and old nomenclature

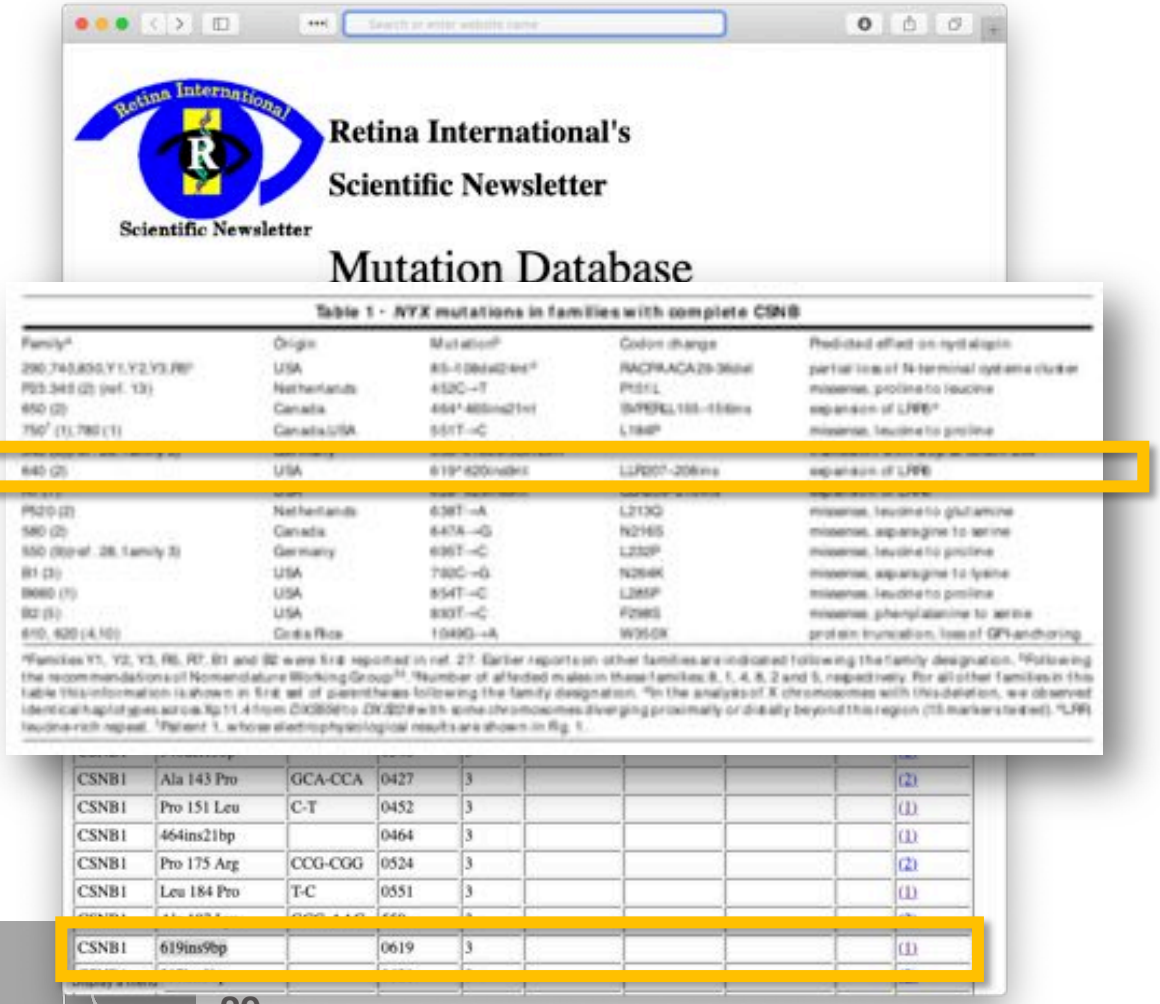
Retina International's
Scientific Newsletter
Mutation Database

Table 1 - NYX mutations in families with complete CSNB

Family	Origin	Mutation	Codon change	Predicted effect on nyctalopin
290,745,805,Y1,Y2,Y3,R6	USA	85-108del24ins	RACPRACA29-36ins	partial loss of N-terminal cysteine cluster
R03,340 (2) (ref. 13)	Netherlands	452C→T	P151L	missense, proline to leucine
650 (2)	Canada	464*465ins21nt	S(PRE)L155–156ins	expansion of LRR6*
750* (1),780 (1)	Canada,USA	551T→C	L184P	missense, leucine to proline
640 (2)	USA	619*620ins9nt	LLR207–208ins	expansion of LRR6
P520 (2)	Netherlands	638T→A	L213Q	missense, leucine to glutamine
580 (2)	Canada	647A→G	N216S	missense, asparagine to serine
550 (R)-ref. 28, family 3)	Germany	695T→C	L232P	missense, leucine to proline
B1 (3)	USA	782C→G	N284K	missense, asparagine to lysine
B660 (1)	USA	854T→C	L285P	missense, leucine to proline
B2 (5)	USA	893T→C	F298S	missense, phenylalanine to serine
610, 620 (4,10)	Costa Rica	1049G→A	W350X	protein truncation, loss of GPI-anchoring

*Families Y1, Y2, Y3, R6, R7, B1 and B2 were first reported in ref. 27. Earlier reports on other families are indicated following the family designation. †Following the recommendations of Nomenclature Working Group[32]. ‡Number of affected males in these families: 8, 1, 4, 8, 2 and 5, respectively. For all other families in this table this information is shown in first set of parentheses following the family designation. §In the analysis of X chromosomes with this deletion, we observed identical haplotypes across the 11.4-cM DXS8061c–DXS228 with some chromosomes diverging proximally or distally beyond this region (15 markers tested). ¶LRR, leucine-rich repeat. ||Patient 1, whose electrophysiological results are shown in Fig. 1.

CSNB1	Ala 143 Pro	GCA-CCA	0427	3						(2)
CSNB1	Pro 151 Leu	C-T	0452	3						(1)
CSNB1	464ins21bp		0464	3						(1)
CSNB1	Pro 175 Arg	CCG-CGG	0524	3						(2)
CSNB1	Leu 184 Pro	T-C	0551	3						(1)
CSNB1	619ins9bp		0619	3						(1)

The same variant has been reported in the original report of the NYX involvement in night blindness in year 2000

NM_022567.2 c.619_627dup

PS1 – Established pathogenic variant
PM1 – Functional hotspot (LRR6 expansion)
PM2 – Absent from controls
PP4 – Phenotype typical

Likely pathogenic

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Legacy databases and literature

LOVD ClinVar gnomAD

Use existing sources to get the most information on your variant

LOVD ClinVar UniProt

Beacon Network Geno2MP

Get in touch with institutions to get more information about my variant of interest

Share phenotypes in a standarized way

human phenotype ontology PHENOTIPS™

Use match-making to identify similar patients

PHENOME CENTRAL DECIPHER GRCh37

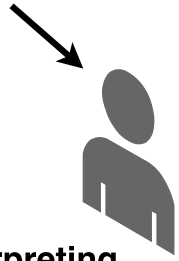
GENE MATCHER MyGene2

UDN Undiagnosed Diseases Network

Genetic variant information sharing

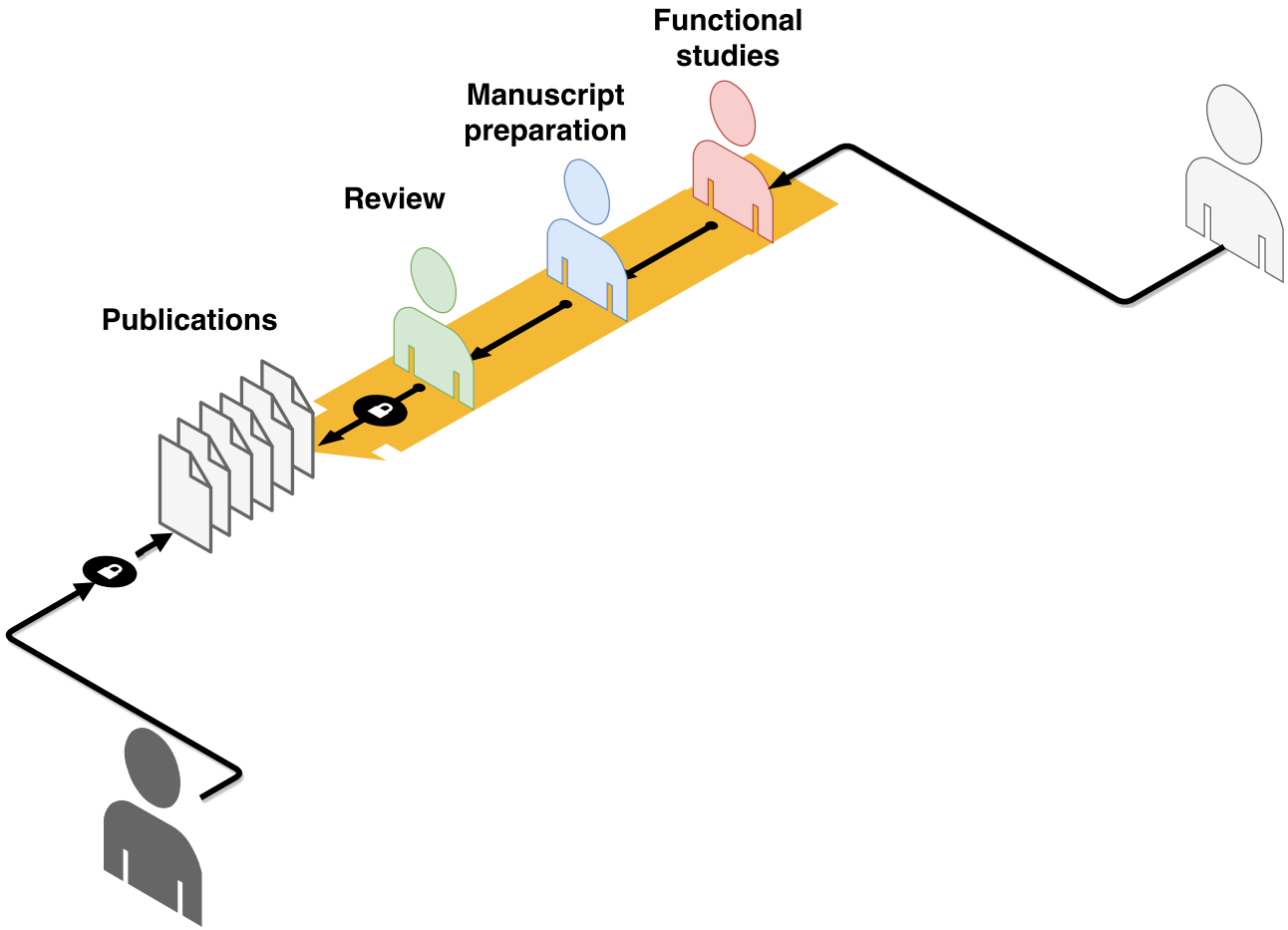
Reporting the variant

You are here



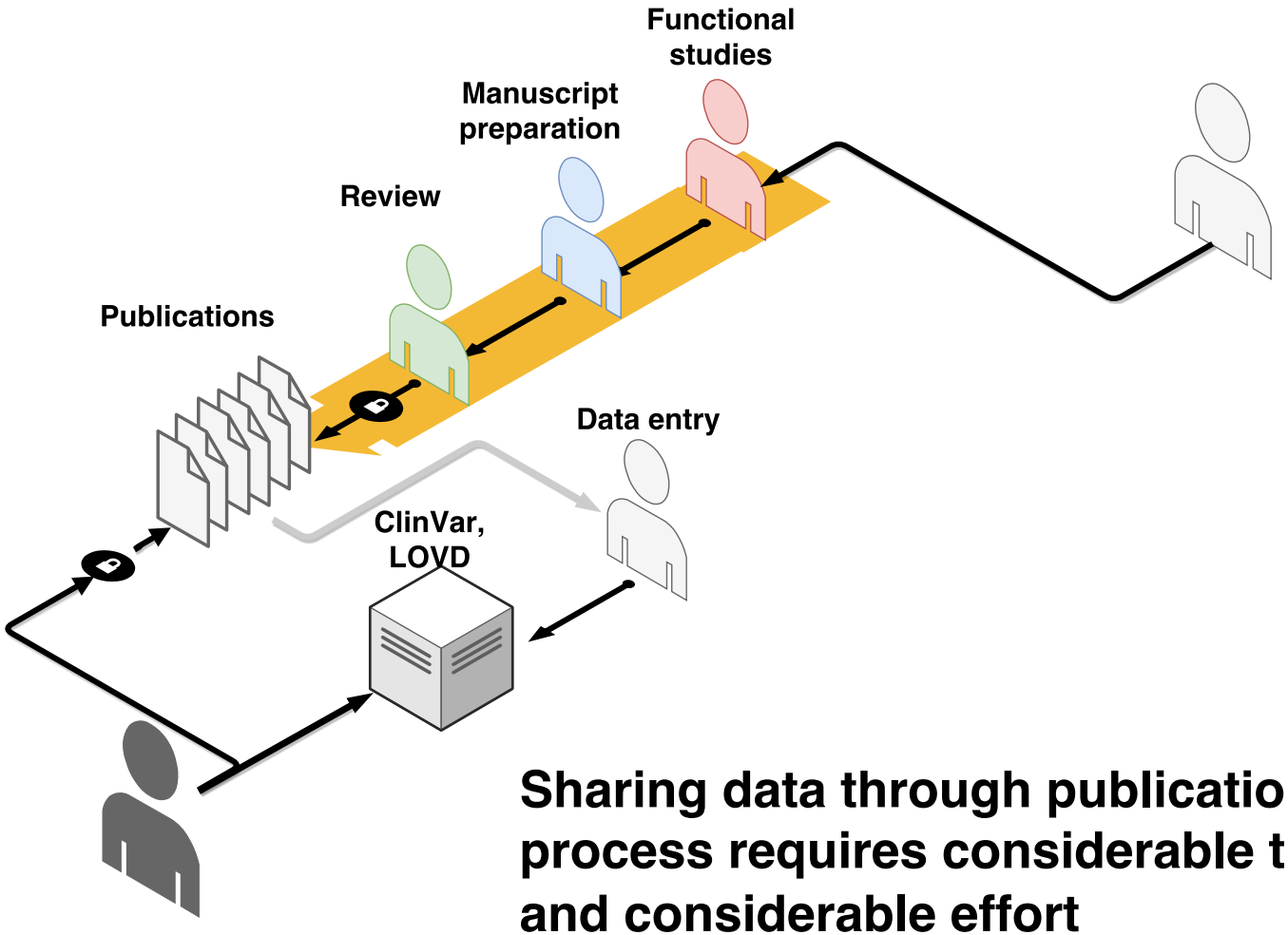
Interpreting exome/genome sequencing results

Genetic variant information sharing



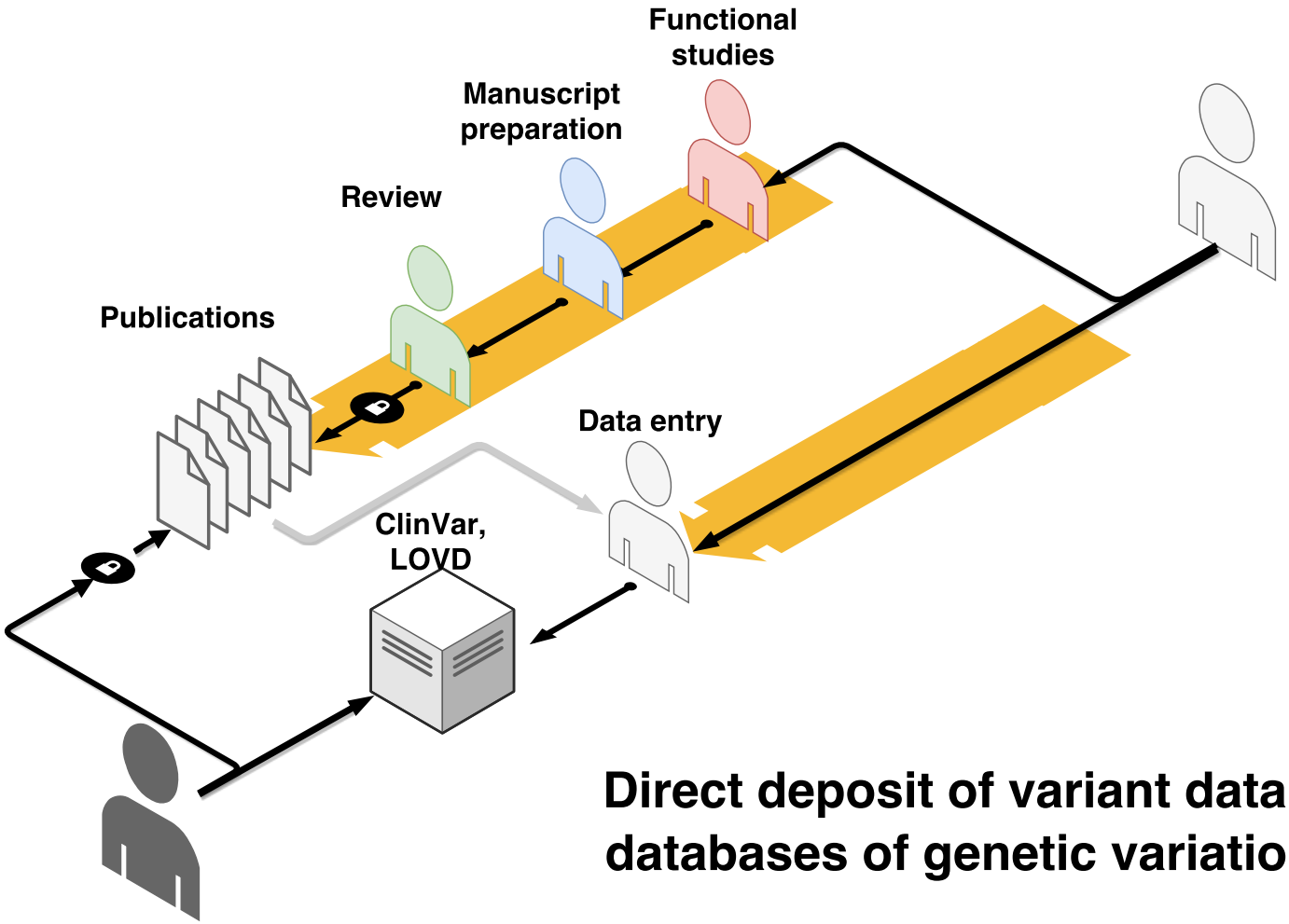
33

Genetic variant information sharing



Sharing data through publication process requires considerable time and considerable effort

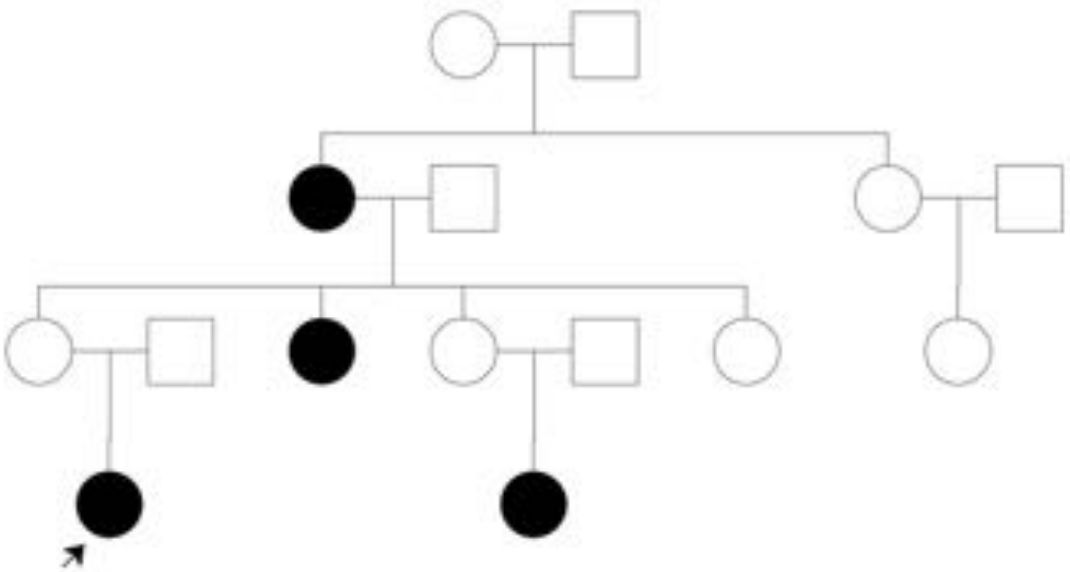
Genetic variant information sharing



Direct deposit of variant data to databases of genetic variations

Family with suspected mitochondrial disease

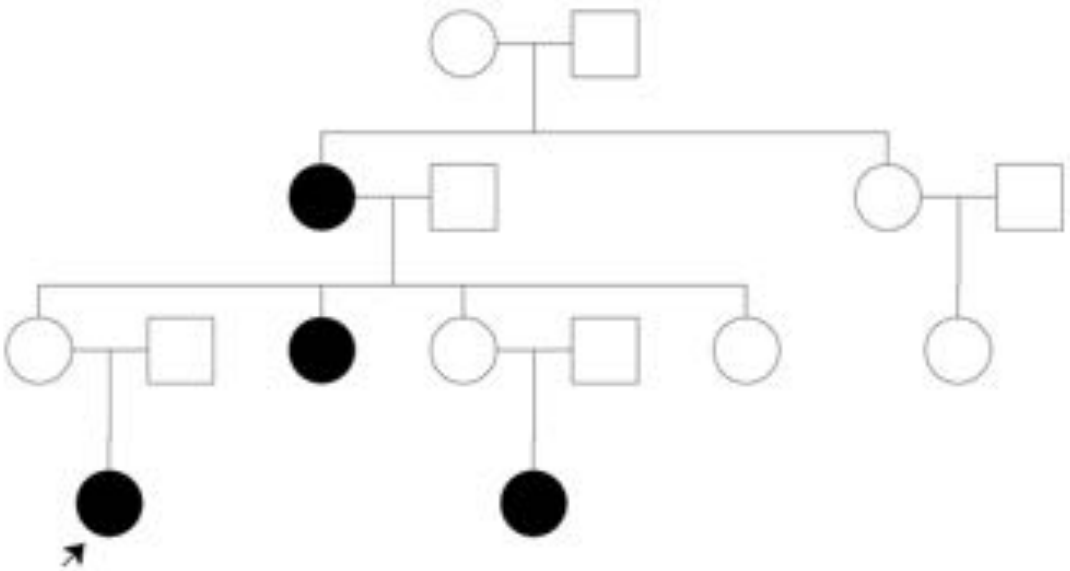
Apparent matrilinear inheritance of variable clinical presentation of seizures, renal disease and developmental delay



The proband is a girl with **seizures and developmental delay**, with a more severe clinical presentation than observed in other family members

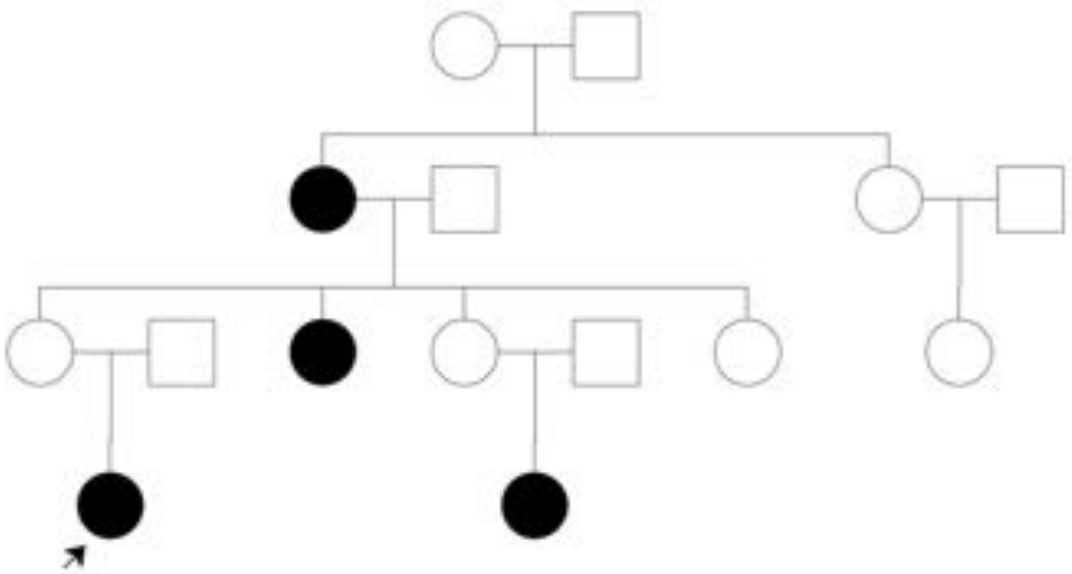
Family with suspected mitochondrial disease

Apparent matrilinear inheritance of variable clinical presentation of seizures, renal disease and developmental delay



Exome sequencing

No mitochondrially encoded pathogenic variants detected



Synonymous
variant in **ARID1B** gene
Near intron-exon junction, rare and
with possible effect on splicing

Paternal DNA sample not available for testing

The is a single report of this variant with
the **likely pathogenic** classification in ClinVar

Q4 - How would you classify the ARID1B variant?

Synonymous variant with predicted effect on splicing, absent from all control populations (gnomAD) and possibly fitting the diagnosis in the patient. Only a single assertion of Likely pathogenic in Clinvar.

1. Benign
2. Likely benign
3. Variant of uncertain significance
4. Likely pathogenic
5. Pathogenic

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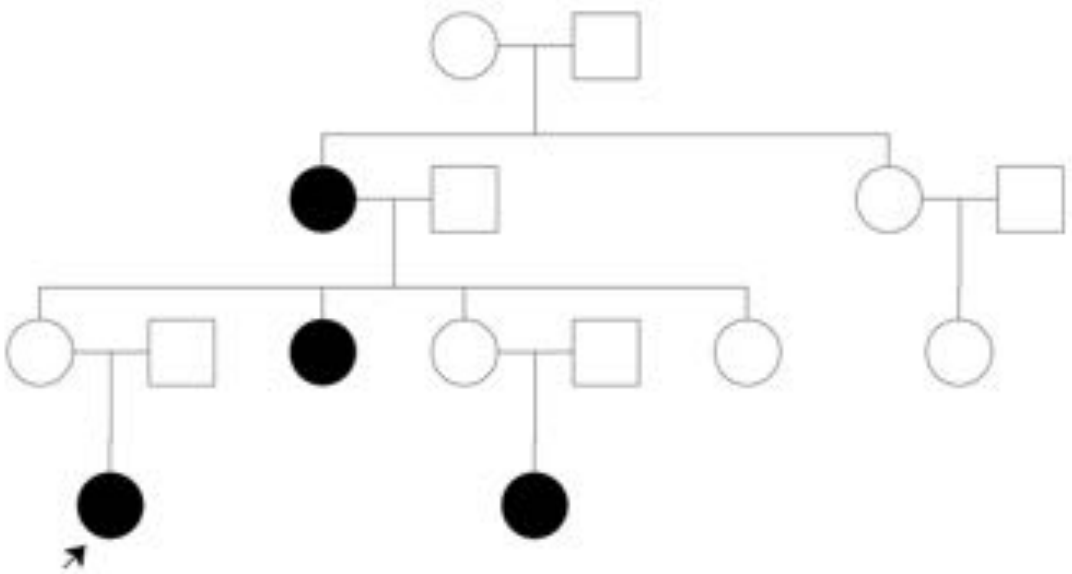

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variant in **ARID1B** gene
Near intron-exon junction, rare and
with possible effect on splicing

Paternal DNA sample not available for testing

The is a single report of this variant with
the **likely pathogenic** classification in ClinVar

Variant of uncertain significance
(PM2, PP3, PP5)

Q5 - What is your next step for this family

1. Release the report with this variant classified as a VUS
2. Perform segregation in maternal relatives
3. Try to contact the laboratory that reported it as Likely pathogenic and ask why
4. This variant is most likely benign due to it being synonymous
5. This cannot be the causative variant due to an original suspicion of mitochondrial disease

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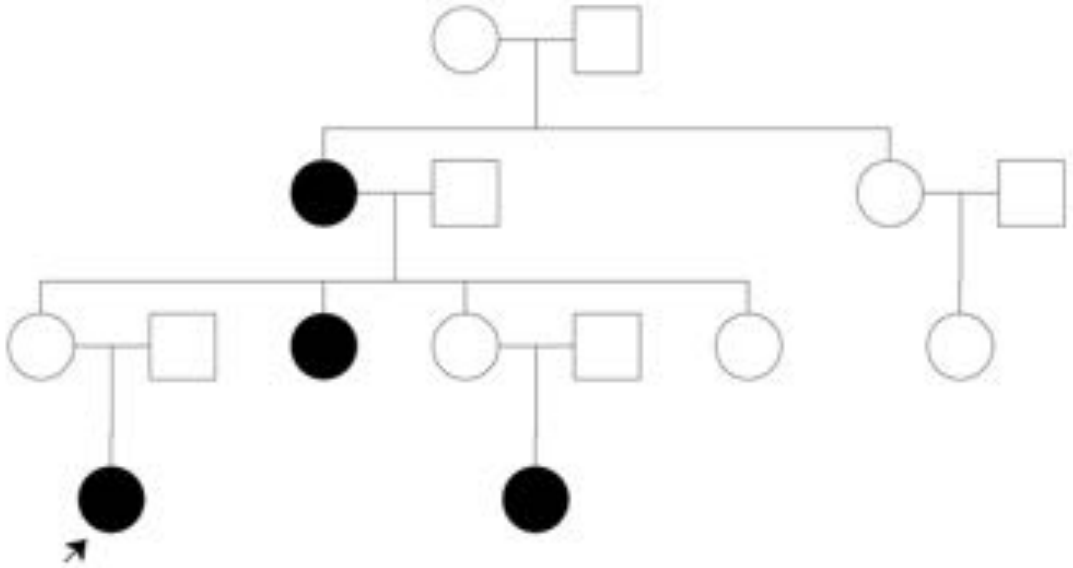

Synonymous p.Pro1370Pro
variant in **ARID1B** gene
Near intron-exon junction, rare and
possible effect on splicing

One report classifying it as a likely pathogenic variant in ClinVar

Submission Accession	Submitter	Review Status (Assertion method)	Clinical Significance (Last evaluated)
SCV000246523	Genetic Services Laboratory, University of Chicago	criteria provided, single submitter • ACMG Guidelines, 2015	Likely pathogenic (Dec 22, 2014)

One report classifying it as a likely pathogenic variant in ClinVar

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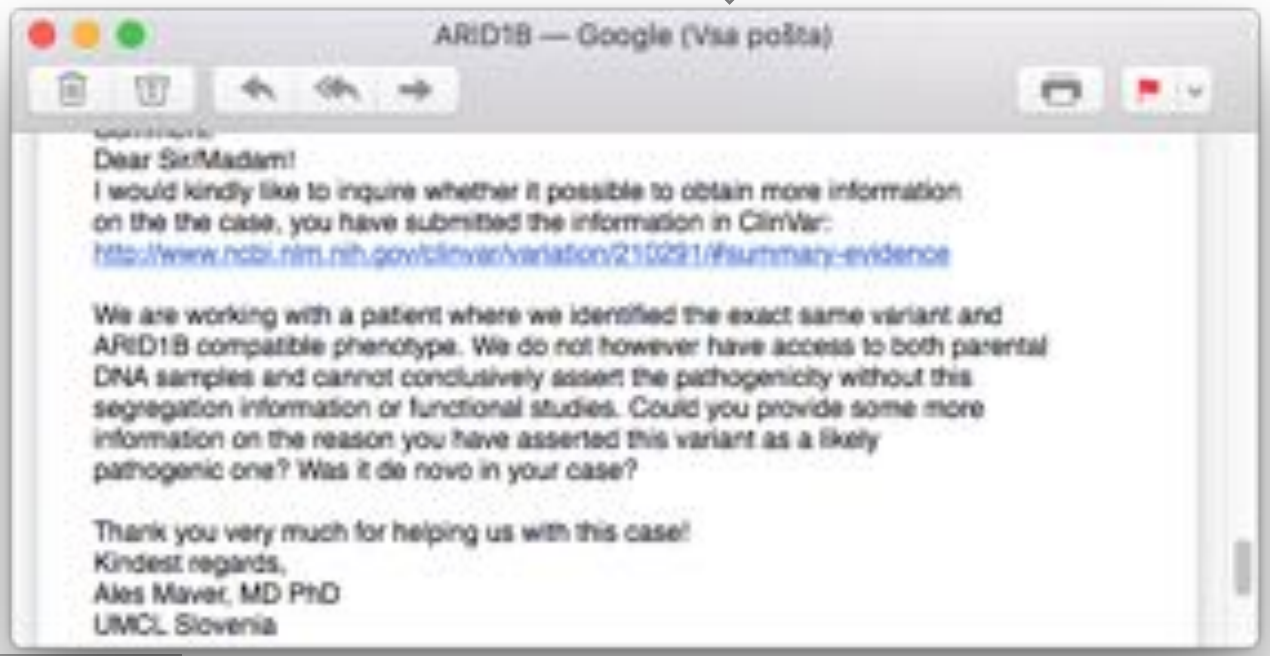

One report classifying it as a likely pathogenic variant in ClinVar

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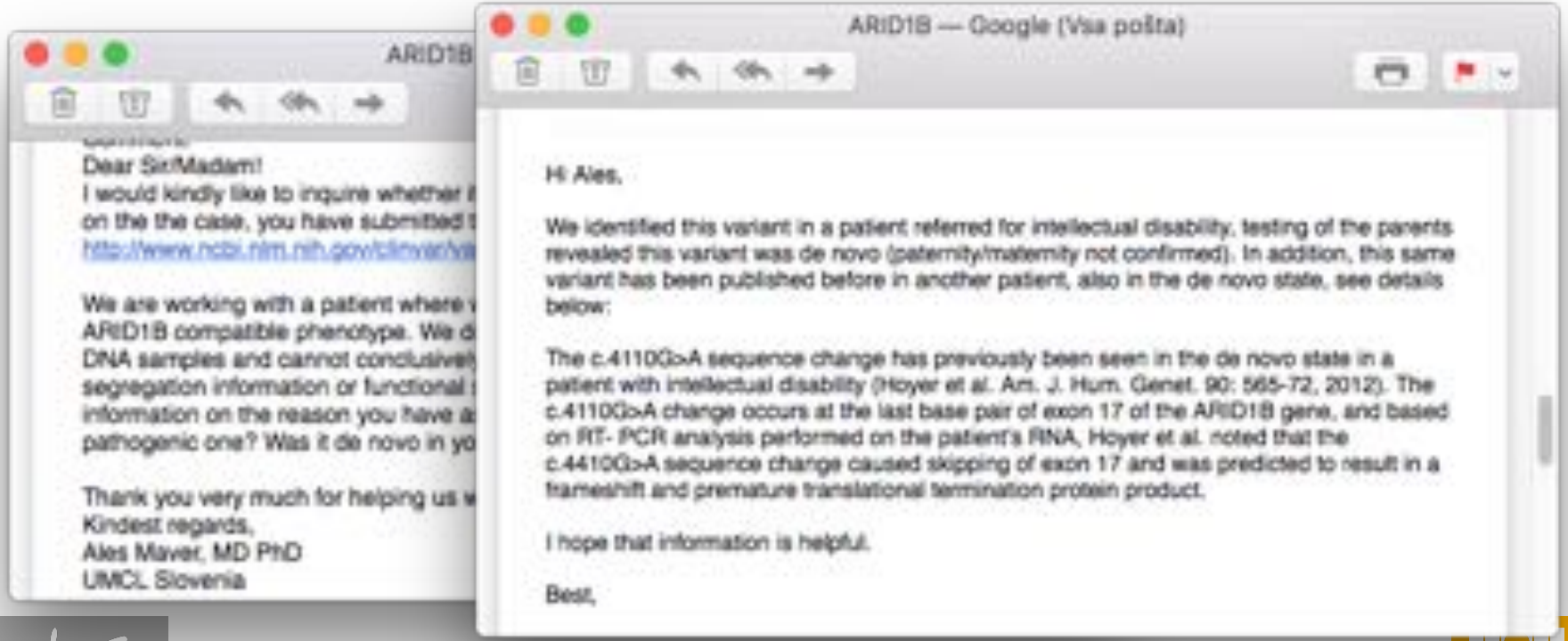

Q6 - How would you classify the ARID1B variant?

Synonymous with predicted effect on splicing, absent from all control populations (gnomAD) and possibly fitting the diagnosis in the patient.
A single assertion of Likely pathogenic in Clinvar.
Reported as de novo in two cases and functional studies have been performed.

1. Benign
2. Likely benign
3. Variant of uncertain significance
4. Likely pathogenic
5. Pathogenic

Voting link **etc.ch/me6t**

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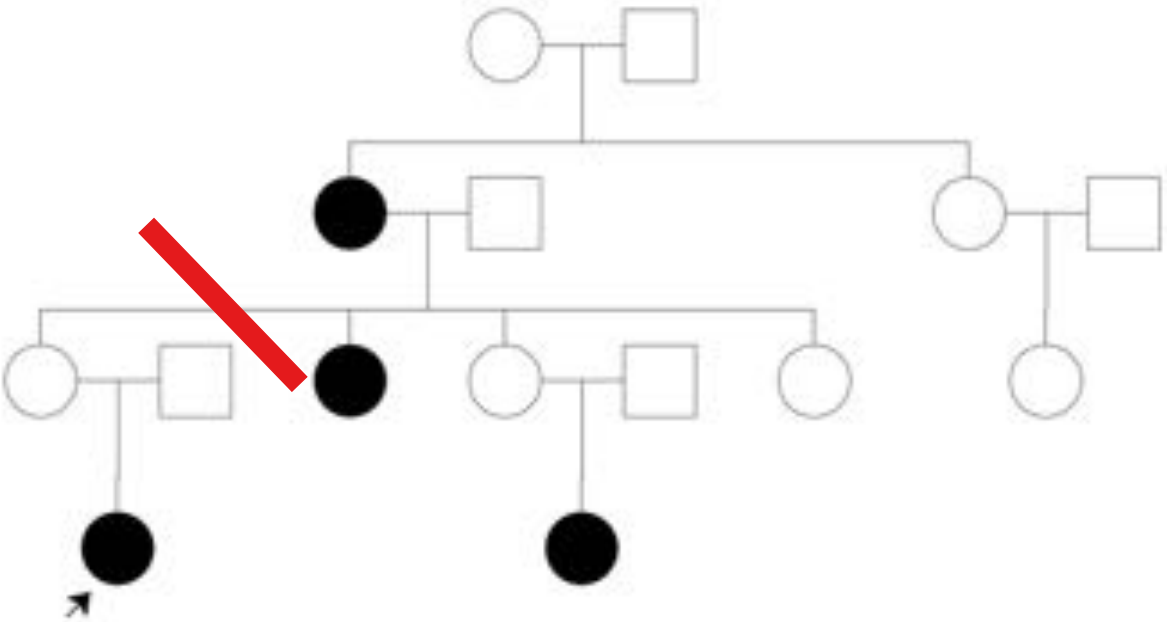
Voting link **etc.ch/me6t**

Significance of variant information exchange



Synonymous p.Pro1370Pro
variant in **ARID1B** gene
With functionally proven effect on splicing
Shown to be de novo in two cases with
similar clinical presentation

Reclassified as **Pathogenic**
(PVS1, PS1, PS2, PS3, PM2)

Establishment of **pathogenicity**
Establishment of a **diagnosis** (ARID1B
associated developmental delay)
Clarification of **inheritance**

Infant with severe dilated cardiomyopathy

- In an infant with severe dilated cardiomyopathy you discovered a rare missense homozygous variant in AARS2 gene
- Pathogenic biallelic variants in AARS2 gene cause Combined oxidative phosphorylation deficiency 8, but have recently been reported rarely in severe early onset cardiomyopathy
- There are five heterozygous carriers in gnomAD and no homozygous individuals, the variant is predicted as pathogenic in-silico, but the phenotype overlap is not clear
- Try to find out if any lab has reported this variant in ClinVar (www.ncbi.nlm.nih.gov/clinvar/)

Q7 – What will you do next about the NM_020745.3:c.985C>T variant?

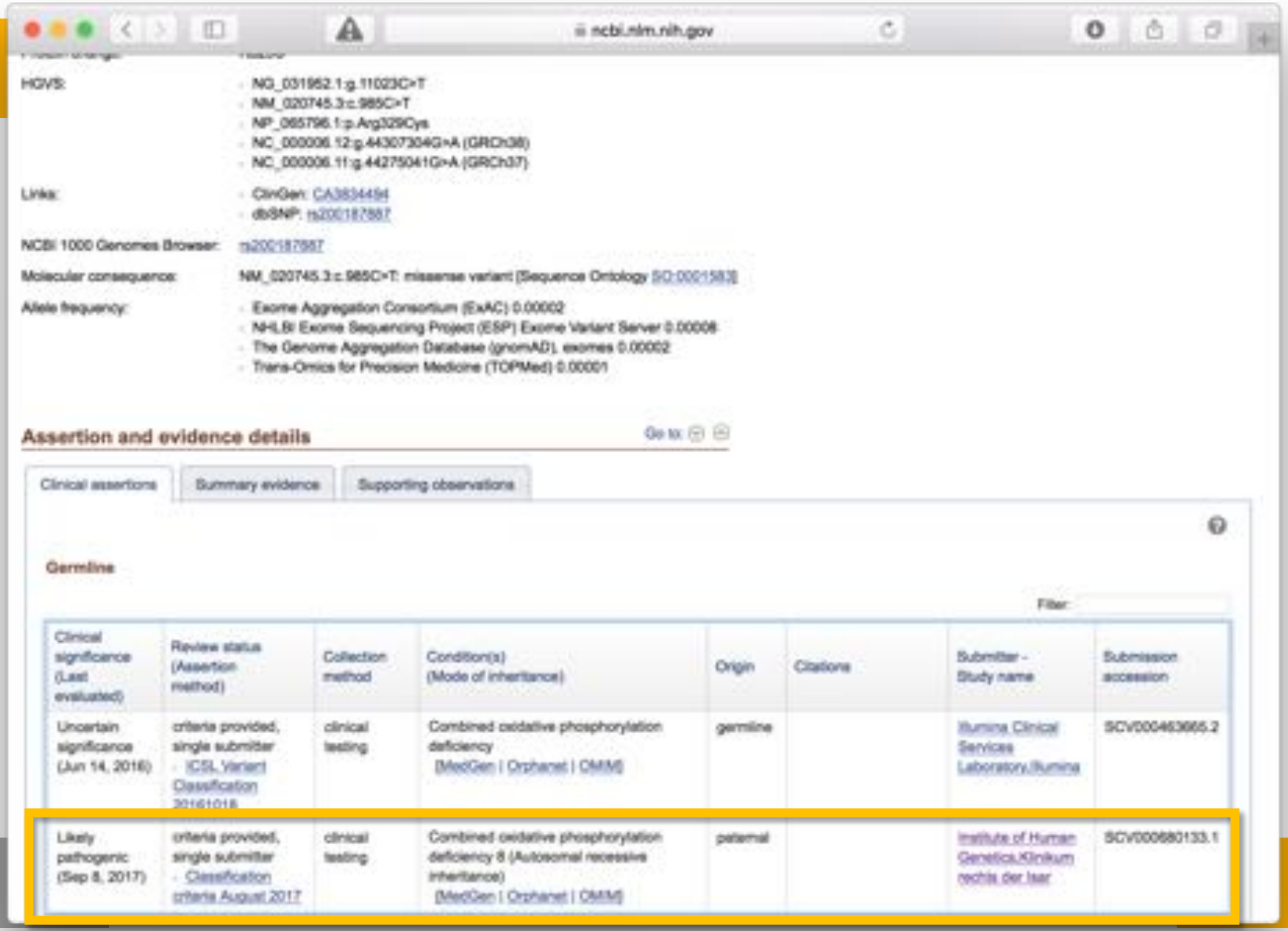
1. Report as likely pathogenic and advise parents to perform prenatal testing in further pregnancies
2. Conclude the report, reporting this variant as a VUS finding
3. Contact the Institute of Human Genetics, IHG-MRI-TUM Munich for more information
4. Contact Illumina Clinical Services lab for more information
5. Do not report this variant

Voting link **etc.ch/me6t**

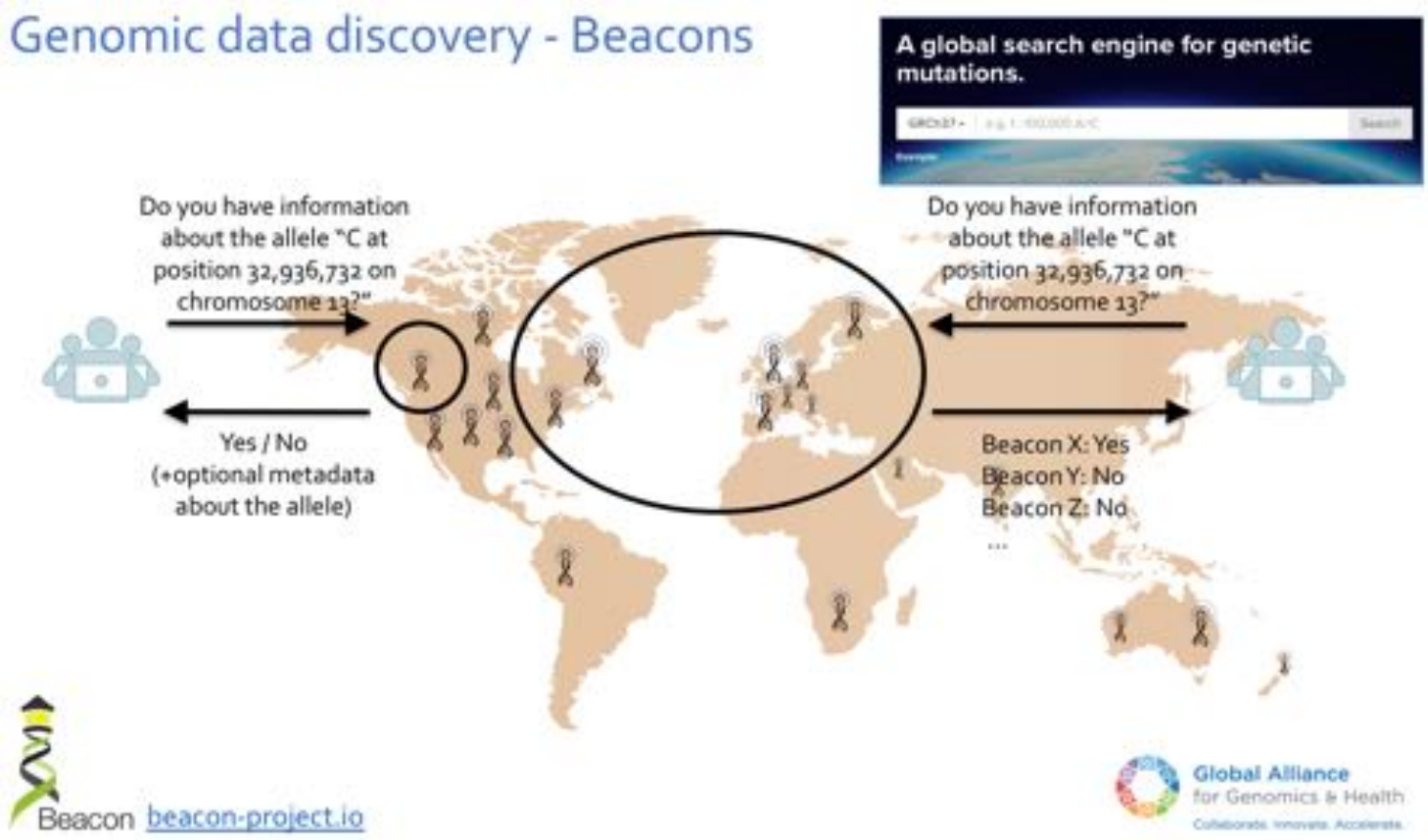
RESULTS

Voting link **etc.ch/me6t**

The ClinVar entry

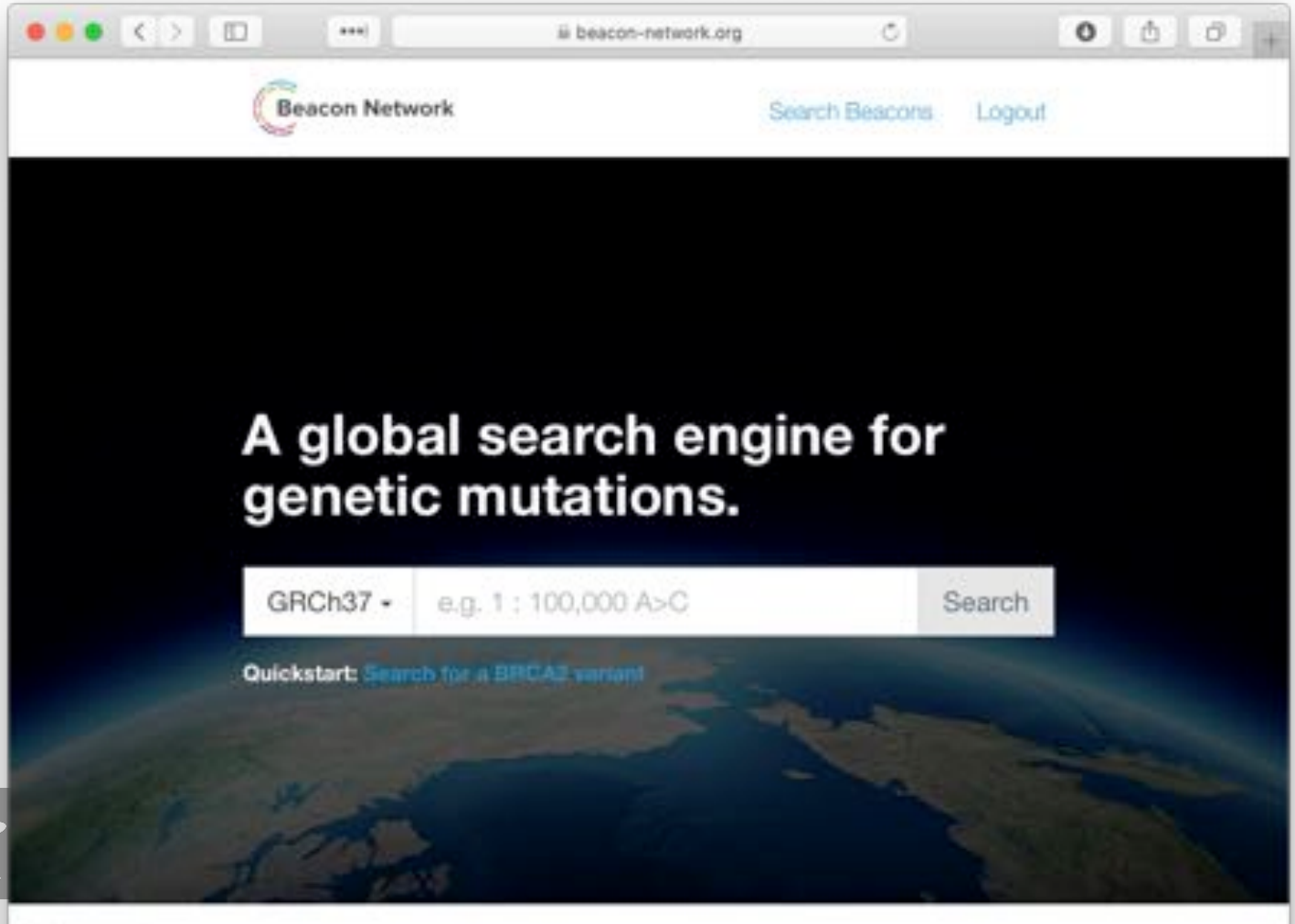


Beacon –etwork - a federated network for variant searches



Find your variant using the beacon network

beacon-network.org



Try it your self

- In a patient with intellectual disability, microcephaly and seizures you have identified a de novo variant in ACTL6B gene:

NM_016188.4 c.1027G>A

The variant is absent from gnomAD, predicted pathogenic but ACTL6B is not yet tracked in OMIM

Use the beacon network platform (beacon-network.org) to identify other laboratories that have patients with this same variant.

Q8 - Which institution will you contact about this variant (use beacon-network.org)

NM_016188.4 c.1027G>A

Genome coordinate (hg19): NC_000007.13:g.100244260C>T

1. Johns Hopkins All Children's Hospital
2. Children's Mercy hospital, Kansas
3. University Medical Center Utrecht
4. Ghent University Hospital
5. Partners HealthCare Personalized Medicine, Boston

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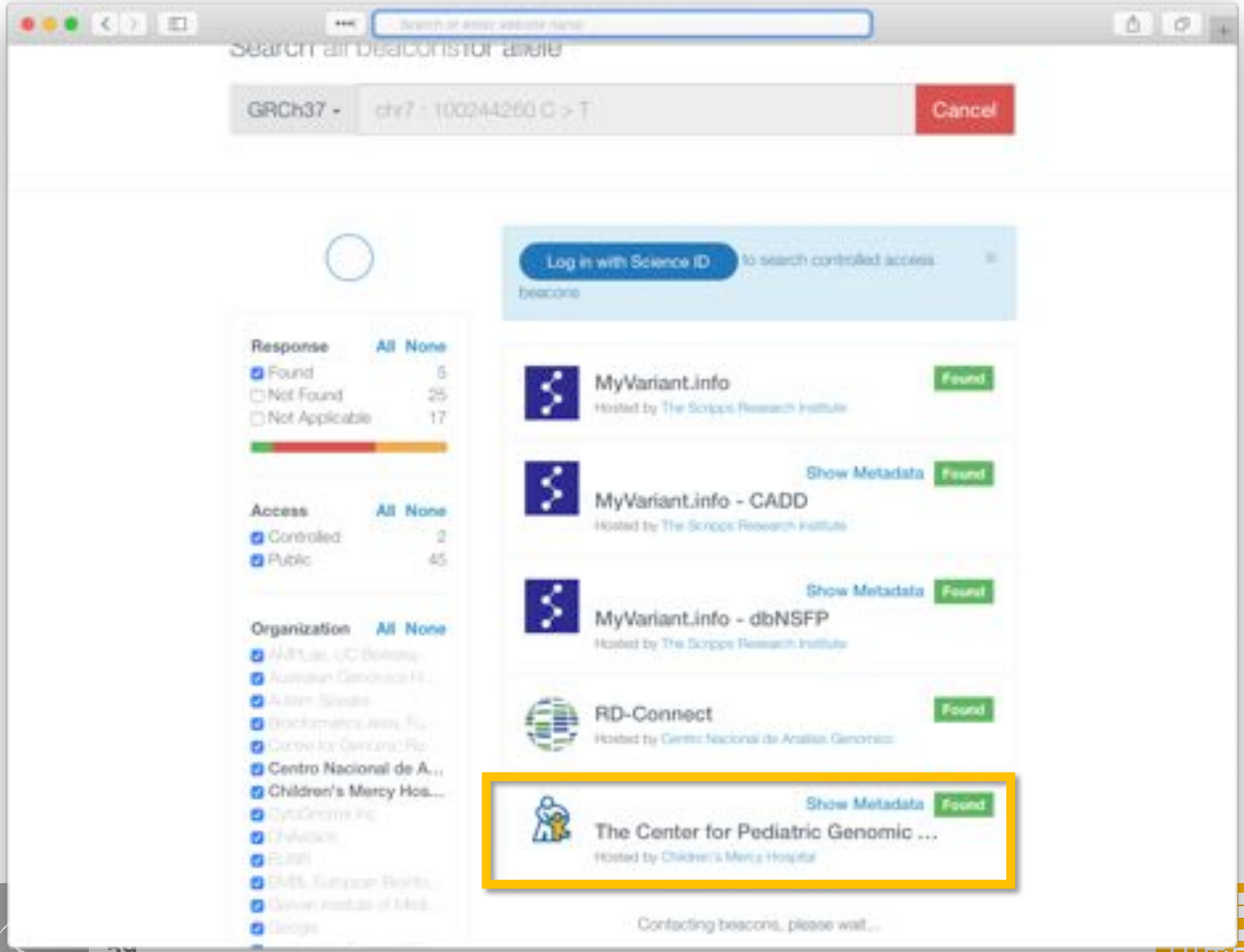
Voting link **etc.ch/me6t**


GRCh37 -
Cancel
Log in with Science ID
to search controlled access beacons
Response All None
Found 6
Not Found 25
Not Applicable 17
Access All None
Controlled 2
Public 45
Organization All None
Centro Nacional de A...
Children's Mercy Hos...
MyVariant.info
Found
Hosted by The Scripps Research Institute
Show Metadata
MyVariant.info - CADD
MyVariant.info - dbNSFP
RD-Connect
Hosted by Centro Nacional de Análisis Genómico
The Center for Pediatric Genomic ...
Hosted by Children's Mercy Hospital
Contacting beacons, please wait...

Published in 2nd May 2019

ARTICLE

Mutations in *ACTL6B* Cause Neurodevelopmental Deficits and Epilepsy and Lead to Loss of Dendrites in Human Neurons

Scott Bell,[1,33] Justine Rousseau,[2,33] Huashan Peng,[1] Zahia Aouabed,[1] Pierre Priam,[3] Jean-Francois Theroux,[1] Malvin Jefri,[1] Arnaud Tanti,[1] Hanrong Wu,[1] Ilaria Kolobova,[1] Heika Silviera,[1] Karla Manzano-Vargas,[1] Sophie Ehresmann,[2] Fadi F. Hamdan,[2] Nuwan Hettige,[1] Xin Zhang,[1] Lilit Antonyan,[1] Christina Nassif,[2] Lina Ghaloul-Gonzalez,[4] Jessica Sebastian,[4] Jerry Vockley,[4] Amber G. Begtrup,[5] Ingrid M. Wentzensen,[5] Amy Crunk,[5] Robert D. Nicholls,[4] Kristin C. Herman,[6] Joshua L. Deignan,[7] Walla Al-Hertani,[8] Stephanie Efthymiou,[9] Vincenzo Salpietro,[9] Noriko Miyake,[10] Yoshio Makita,[11] Naomichi Matsumoto,[10] Rune Østern,[12] Gunnar Houge,[13] Maria Hafström,[12] Emily Fassi,[14] Henry Houlden,[15] Jolien S. Klein Wassink-Ruiter,[16] Dominic Nelson,[17] Amy Goldstein,[18] Tabib Dabir,[19] Julien van Gils,[20] Thomas Bourgeron,[20] Richard Delorme,[21] Gregory M. Cooper,[22] Jose E. Martinez,[23] Candice R. Finnila,[22] Lionel Carmant,[23] Anne Lortie,[24] Renske Oegema,[25] Koen van Gassen,[25] Sarju G. Mehta,[26] Dagmar Huhle,[26] Rami Abou Jamra,[27]

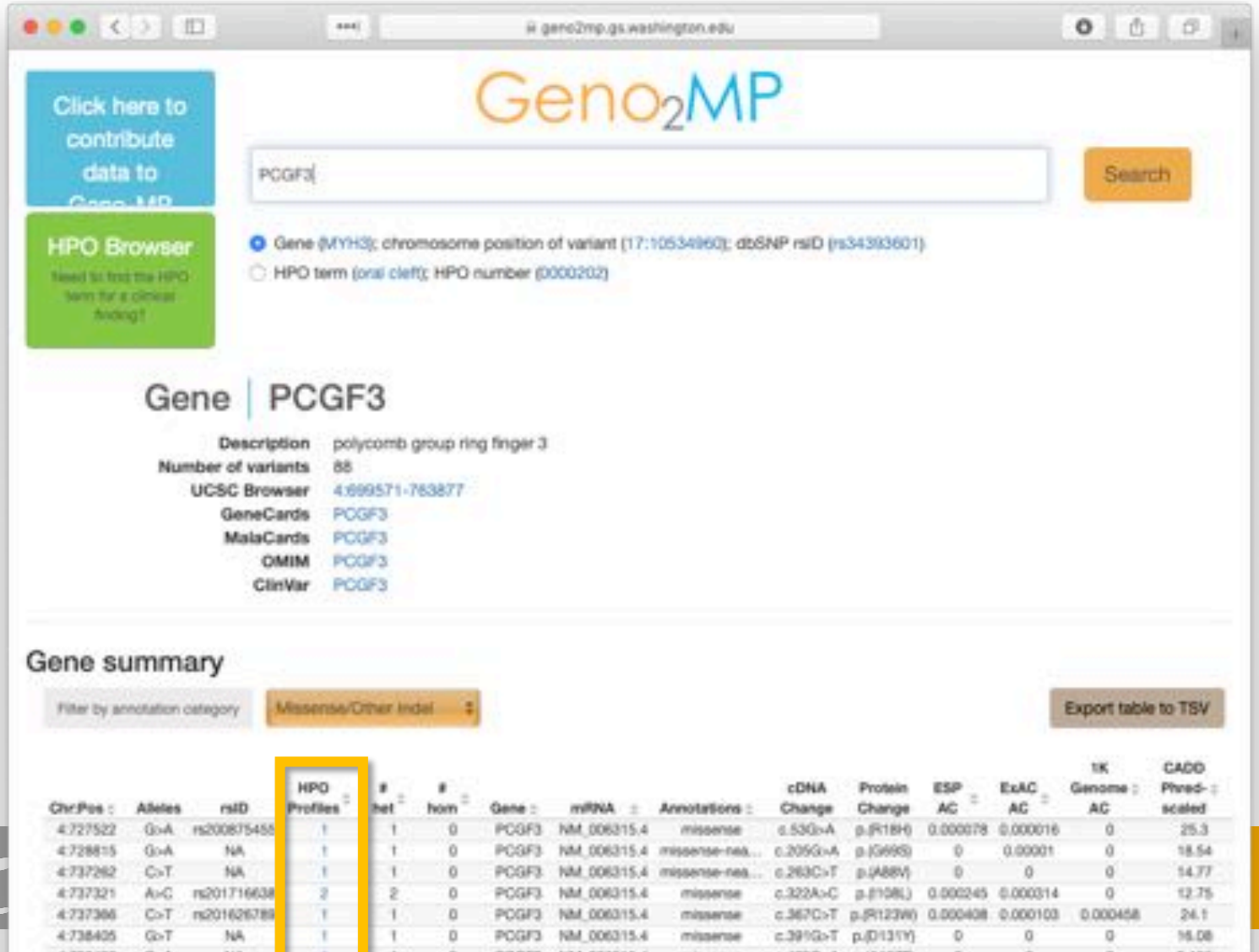
(Author list continued on next page)

We identified individuals with variations in *ACTL6B*, a component of the chromatin remodeling machinery including the BAF complex. Ten individuals harbored bi-allelic mutations and presented with global developmental delay, epileptic encephalopathy, and spasticity, and ten individuals with *de novo* heterozygous mutations displayed intellectual disability, ambulation deficits, severe language impairment, hypotonia, Rett-like stereotypies, and minor facial dysmorphisms (wide mouth, diastema, bulbous nose). Nine of these ten unrelated individuals had the identical *de novo* c.1027G>A (p.Gly343Arg) mutation. Human-derived neurons were generated that recap-

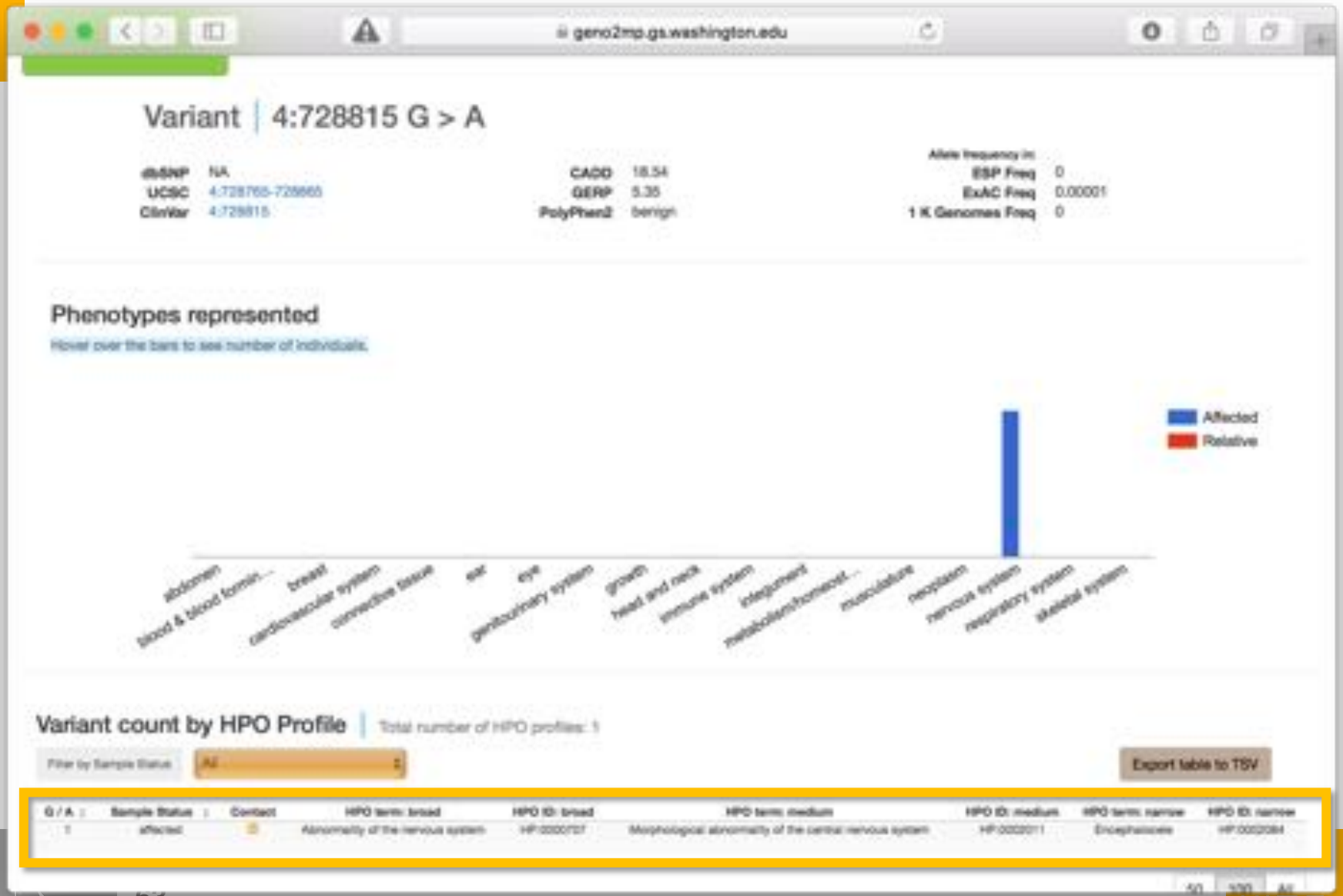
Geno2MP platform

geno2mp.gs.washington.edu

Finding variants in Geno2MP



Phenotypes in patients with the variant



Try it your self

- In a patient with features of premature aging, failure to thrive and craniosynostosis, you identified a de novo missense variant in SLC25A24 gene:

  NM_013386.4:c.650G>A, p.(Arg217His)

The variant is absent from all control populations, predicted pathogenic

Can you find a matching patient with a similar variant as this patient?

Q9 - What is the phenotype of the patient with a similar finding

1. Failure to thrive
2. Global developmental delay
3. Autism
4. Malformation of the heart and great vessels
5. Prematurely aged appearance

Go to **geno2mp.gs.washington.edu** and check if you can get some information about the NM_013386.4:c.650G>A, p.(Arg217His) variant in SLC25A24 gene

Voting link **etc.ch/me6t**

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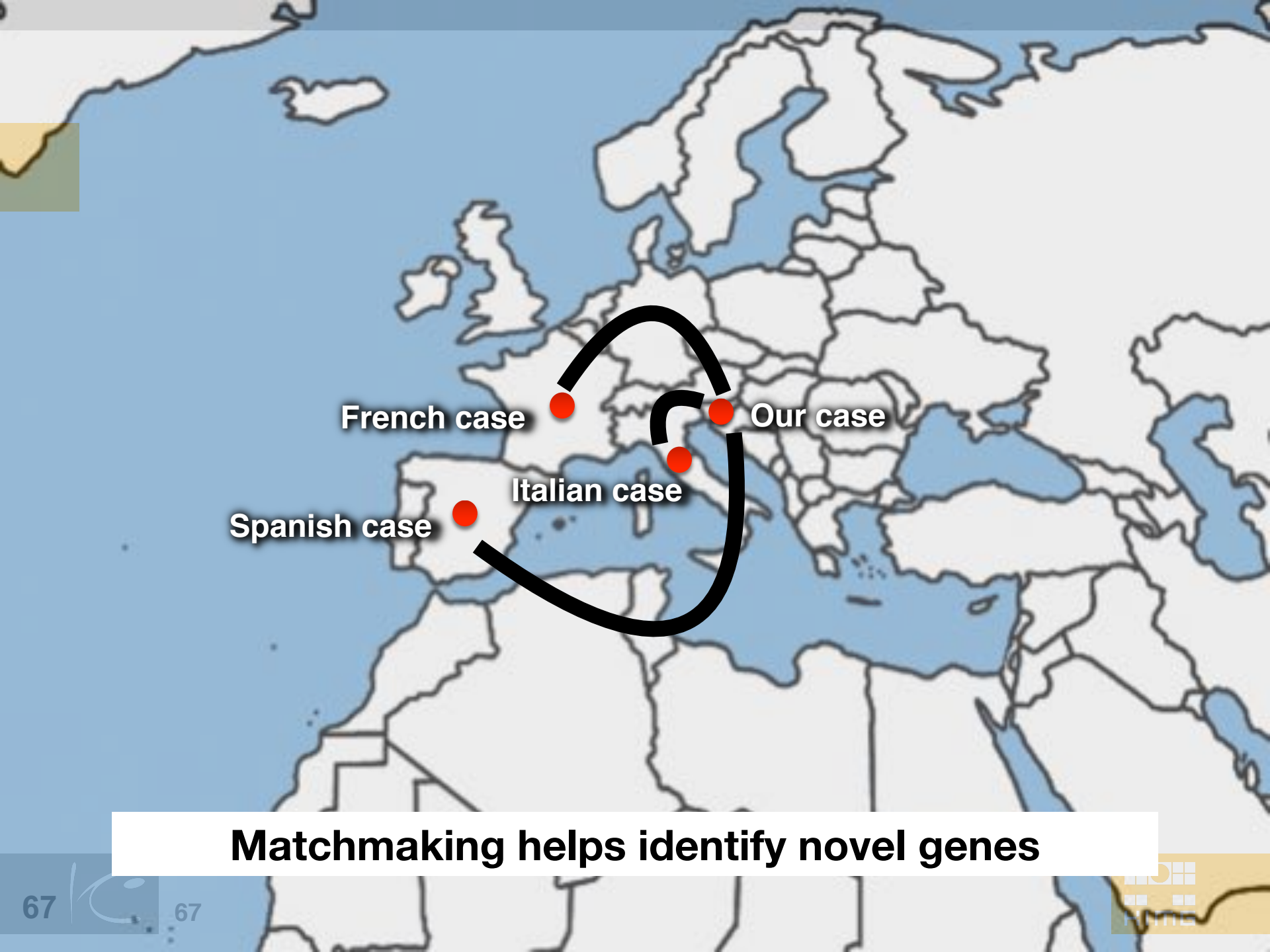
Voting link **etc.ch/me6t**



Matchmaking helps identify novel genes

67

De novo variants affecting Arg217 residue in SLC25A24 protein as the cause of a progeroid syndrome

REPORT

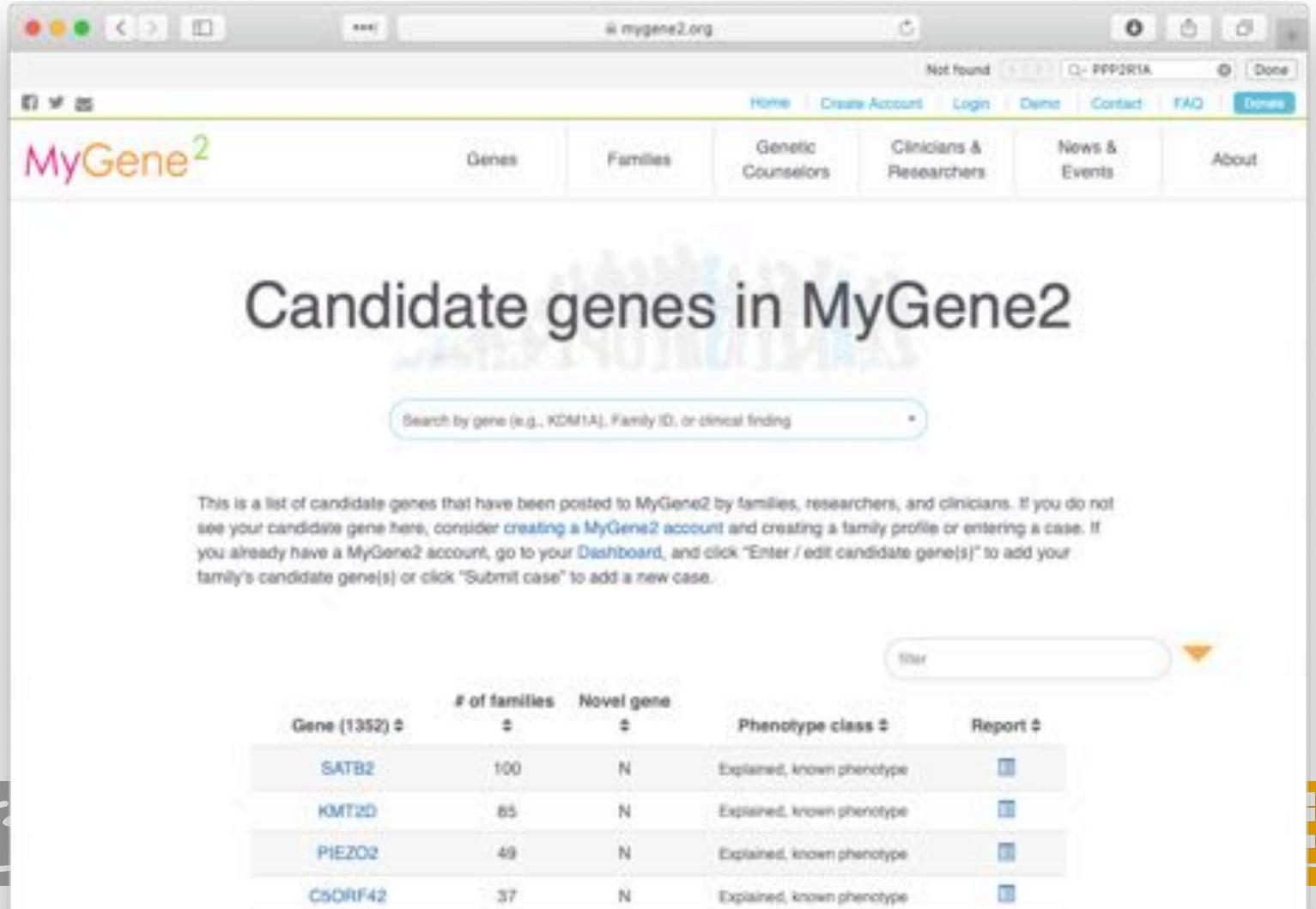
De Novo Mutations in *SLC25A24* Cause a Disorder Characterized by Early Aging, Bone Dysplasia, Characteristic Face, and Early Demise

Karin Writzl,[1,*] Ales Maver,[1] Lidija Kovačič,[2] Paula Martinez-Valero,[3,4,5] Laura Contreras,[3,4,5] Jorgina Satrustegui,[3,4,5] Marco Castori,[6] Laurence Faivre,[7,8] Pablo Lapunzina,[9] André B.P. van Kuilenburg,[10] Slobodanka Radović,[11] Christel Thauvin-Robinet,[7,8] Borut Peterlin,[1] Araceli del Arco,[4,5,12] and Raoul C. Hennekam[13]

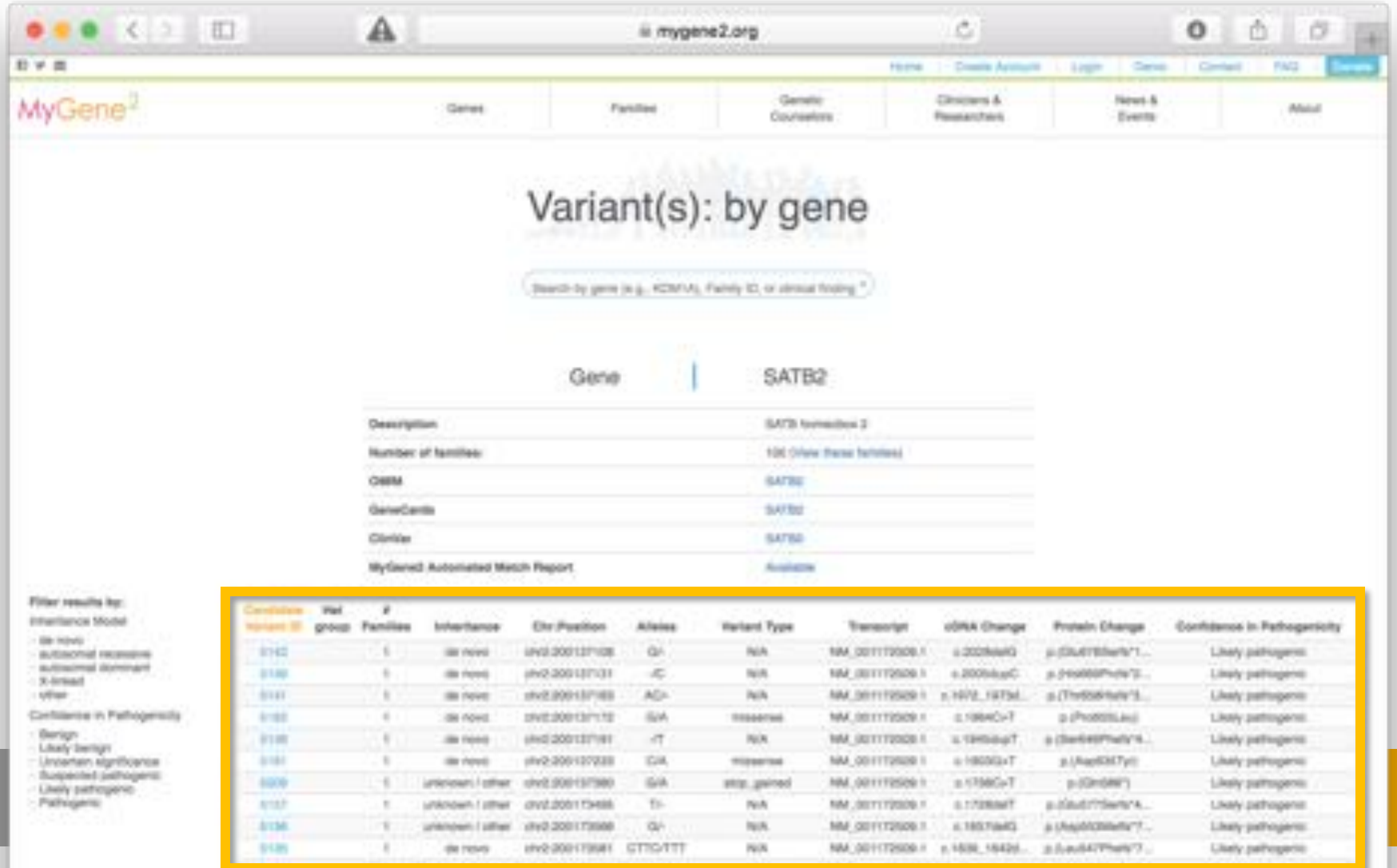
A series of simplex cases have been reported under various diagnoses sharing early aging, especially evident in congenitally decreased subcutaneous fat tissue and sparse hair, bone dysplasia of the skull and fingers, a distinctive facial gestalt, and prenatal and postnatal growth retardation. For historical reasons, we suggest naming the entity Fontaine syndrome. Exome sequencing of four unrelated affected individuals showed that all carried the *de novo* missense variant c.649C>T (p.Arg217Cys) or c.650G>A (p.Arg217His) in *SLC25A24*, a solute carrier 25 family member coding for calcium-binding mitochondrial carrier protein (SCaMC-1, also known as SLC25A24). SLC25A24 allows an electro-neutral and reversible exchange of ATP-Mg and phosphate between the cytosol and mitochondria, which is required for maintaining optimal adenine nucleotide levels in the mitochondrial matrix. Molecular dynamic simulation studies predict that p.Arg217Cys and p.Arg217His narrow the substrate cavity of the protein and disrupt transporter dynamics. *SLC25A24*-mutant fibroblasts and cells expressing p.Arg217Cys or p.Arg217His variants showed altered mitochondrial morphology, a decreased proliferation rate, increased mitochondrial membrane potential, and decreased ATP-linked mitochondrial oxygen consumption. The results suggest that the *SLC25A24* mutations lead to impaired mitochondrial ATP synthesis and cause hyperpolarization and increased proton leak in association with an impaired energy metabolism. Our findings identify *SLC25A24* mutations affecting codon 217 as the underlying genetic cause of human progeroid Fontaine syndrome.

Writzl et al, AJHG, 2017

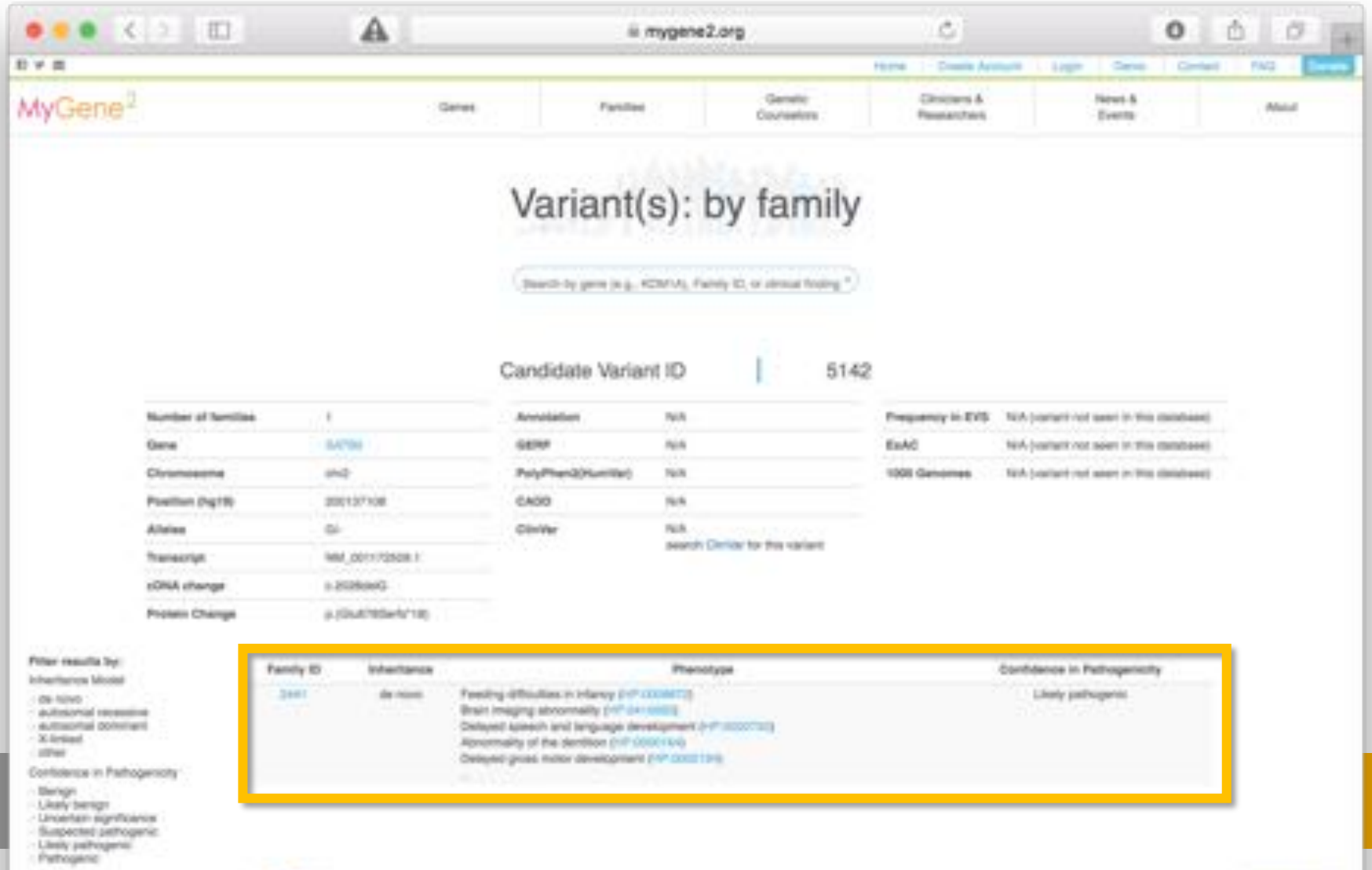
Find patient contributed information



Find patient contributed information



…and associated phenotypes



Q10 - Patient with a de novo KMT2E variant

In a patient with neurodevelopmental phenotype, you identified a de novo missense KMT2E variant. This gene/variant has not yet been reported in association with human disease. **Use MyGene2 to find out which holds true**

1. De novo missense KMT2E variants cause developmental delay
2. Biallelic variants in KMT2E cause developmental delay
3. Pathogenic variants in KMT2E cause an unrelated clinical presentation
4. There is no evidence on the role of KMT2E in human disease

Voting link etc.ch/me6t

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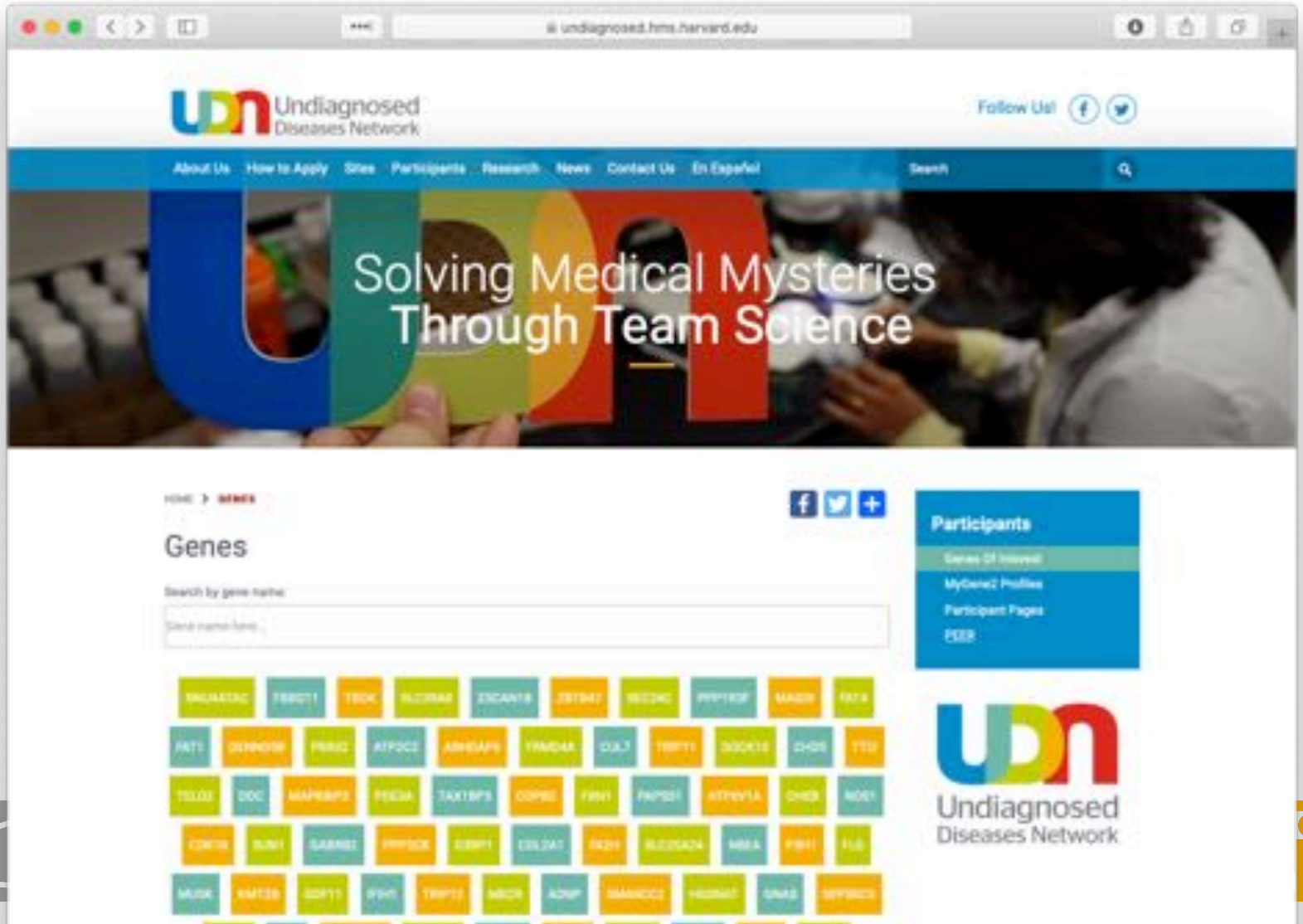
Voting link **etc.ch/me6t**

Crowd-sourced match-making



I have found a novel variant. What now?

Legacy databases and literature

Use existing sources to get the most information on your variant

Get in touch with institutions to get more information about my variant of interest

Share phenotypes in a standarized way

Use match-making to identify similar patients

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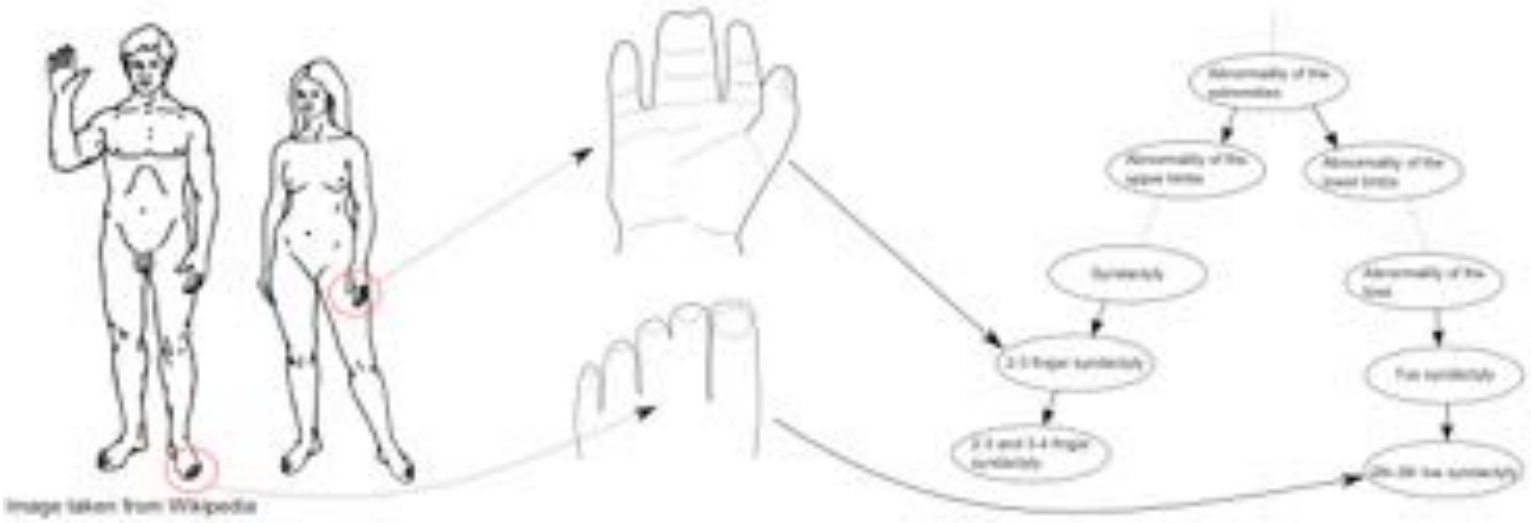
GENE MATCHER MyGene2

UDN Undiagnosed Diseases Network

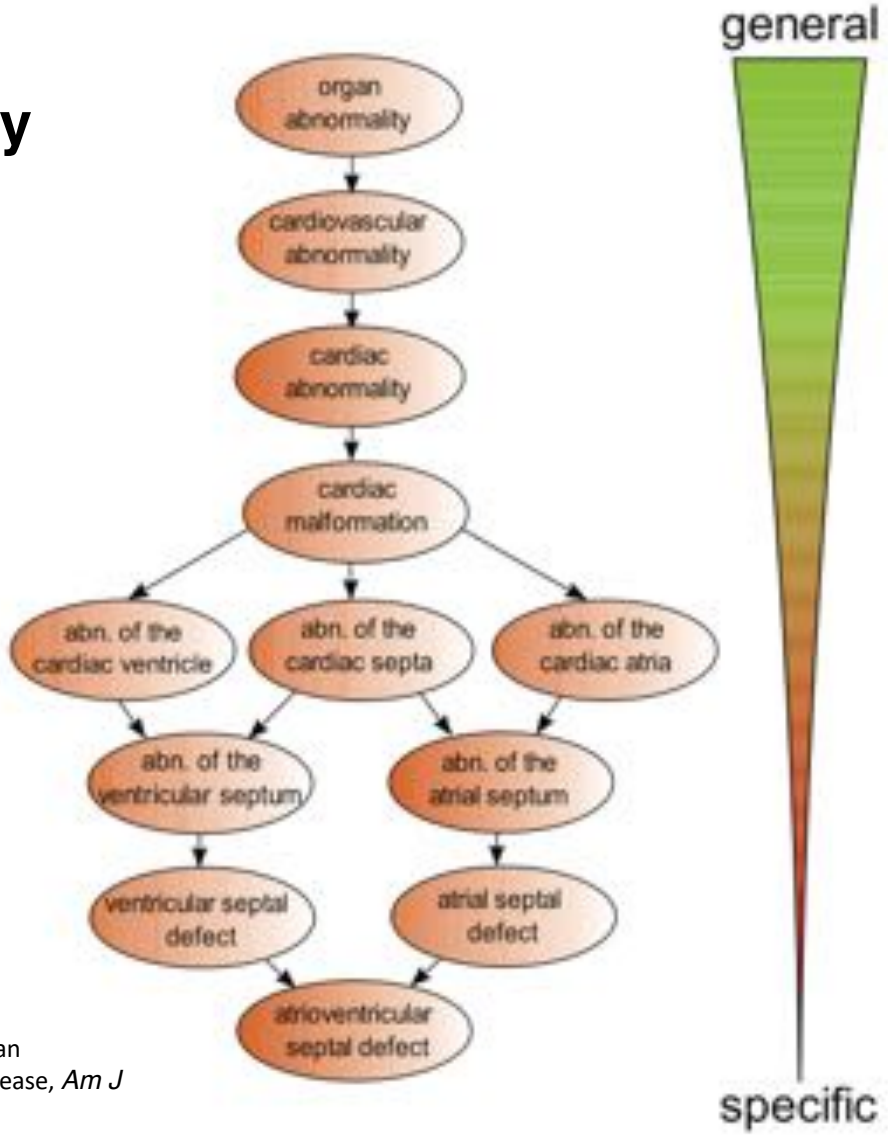
Human phenotype ontology

(http://www.human-phenotype-ontology.org)



Köhler, et al. .Nucleic acids research (2013): gkt1026.

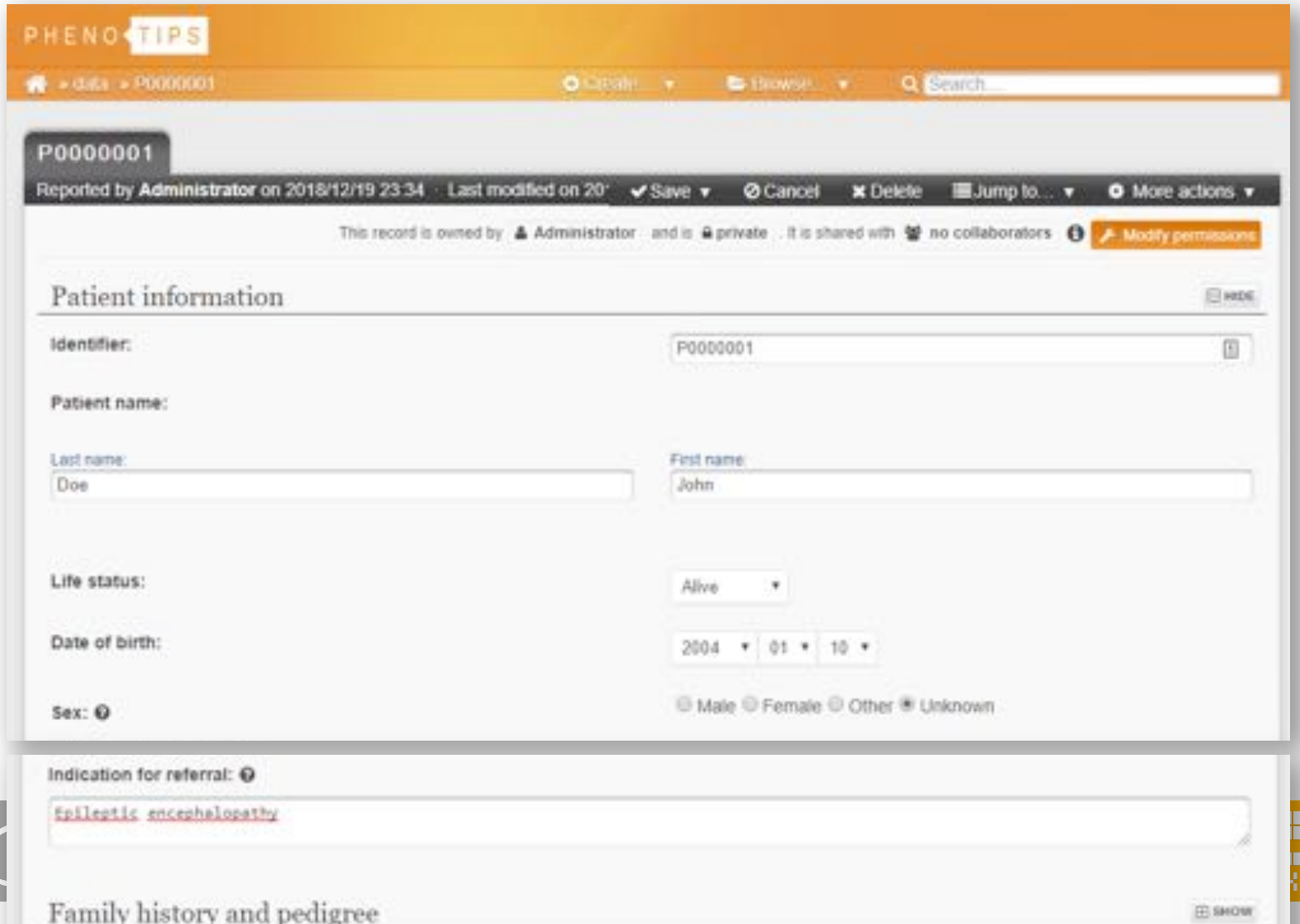
Human Phenotype Ontology



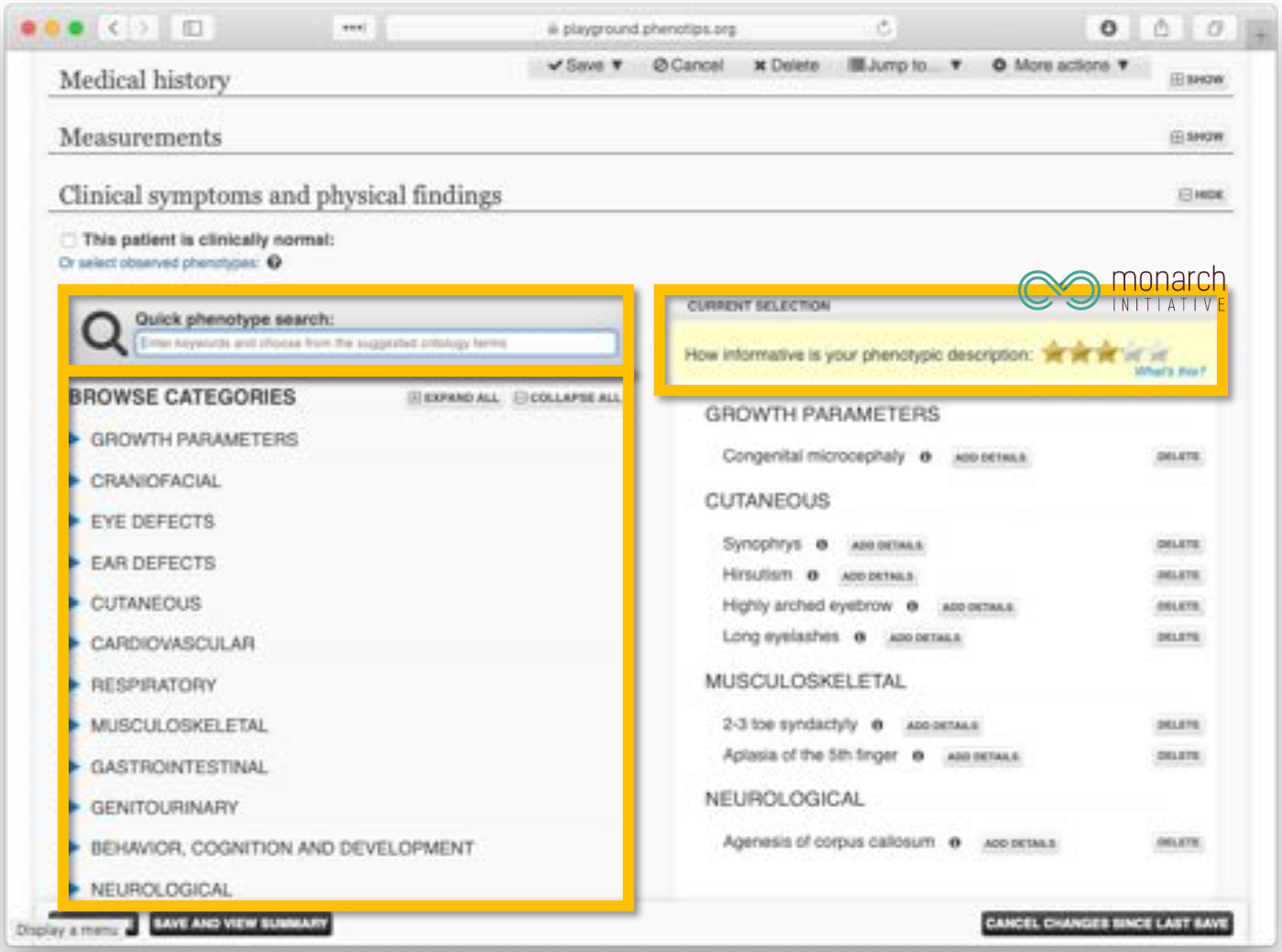
Atrioventricular septal defect

Robinson P, Köhler S, Bauer S, Seelow D, Horn D, Mundlos: The Human Phenotype Ontology: A Tool for annotating and analyzing human hereditary disease, *Am J Hum Genet. 2008 Nov*

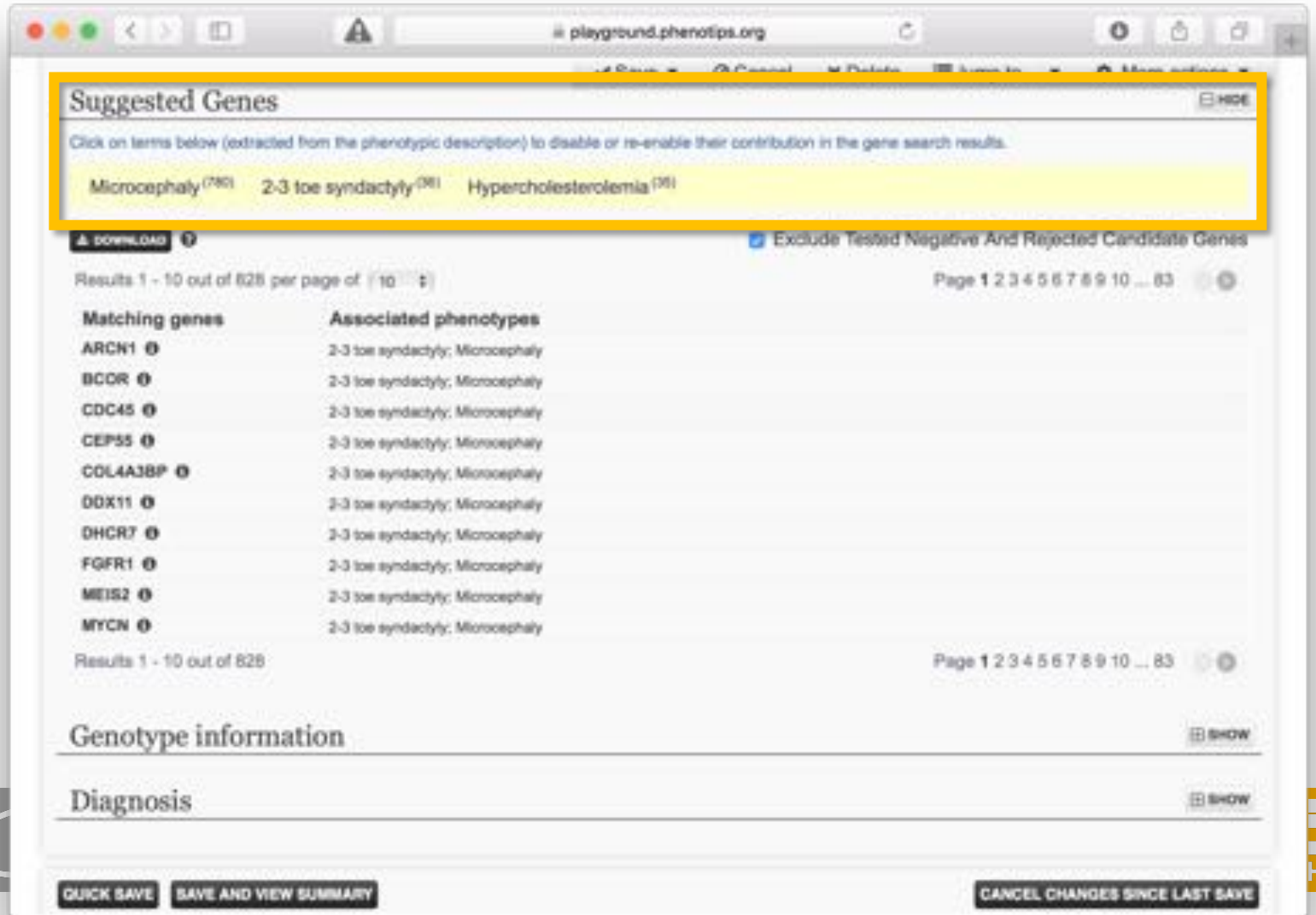
PhenoTips platform



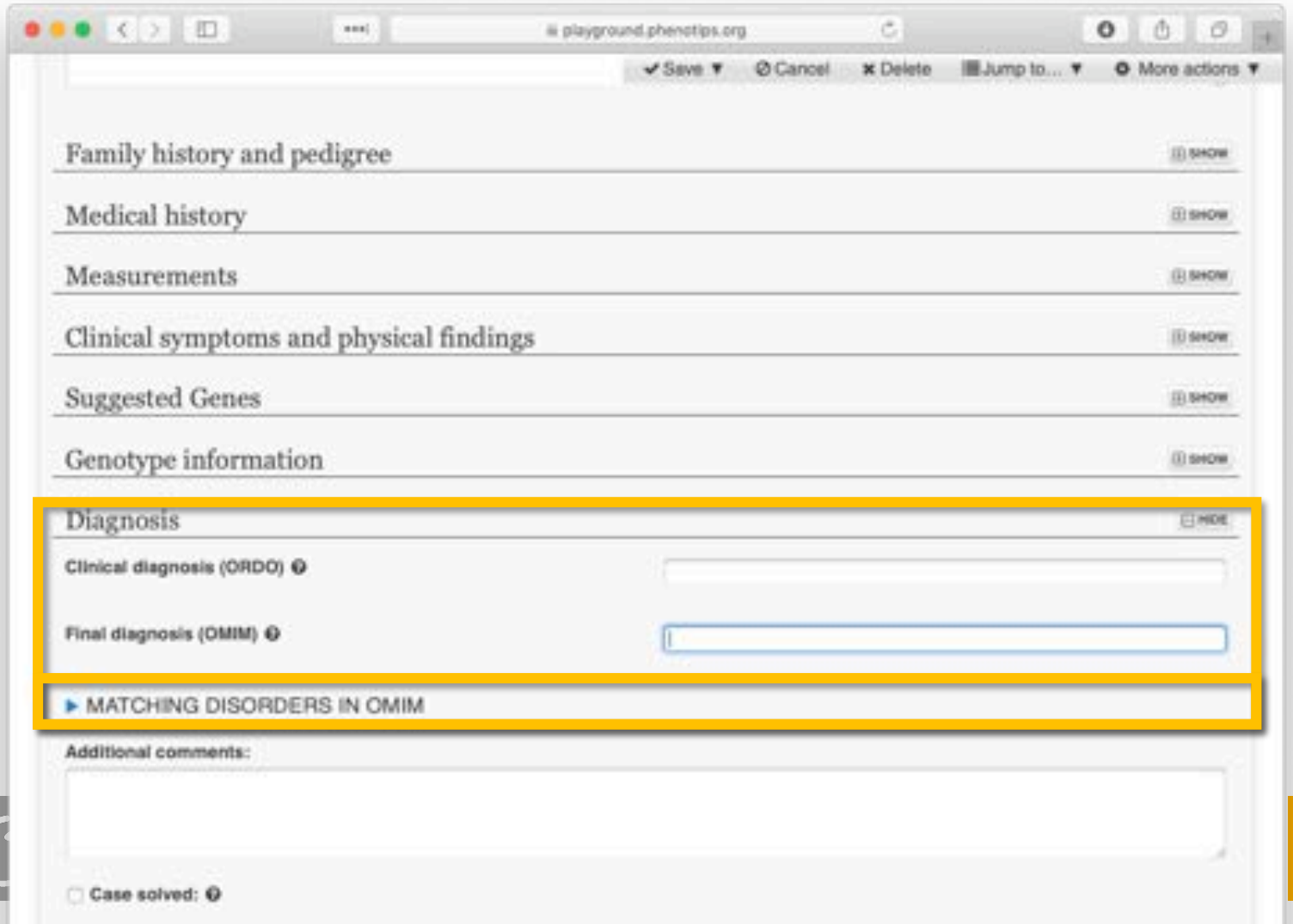
Phenotips enables streamlined collection of patients' phenotypes



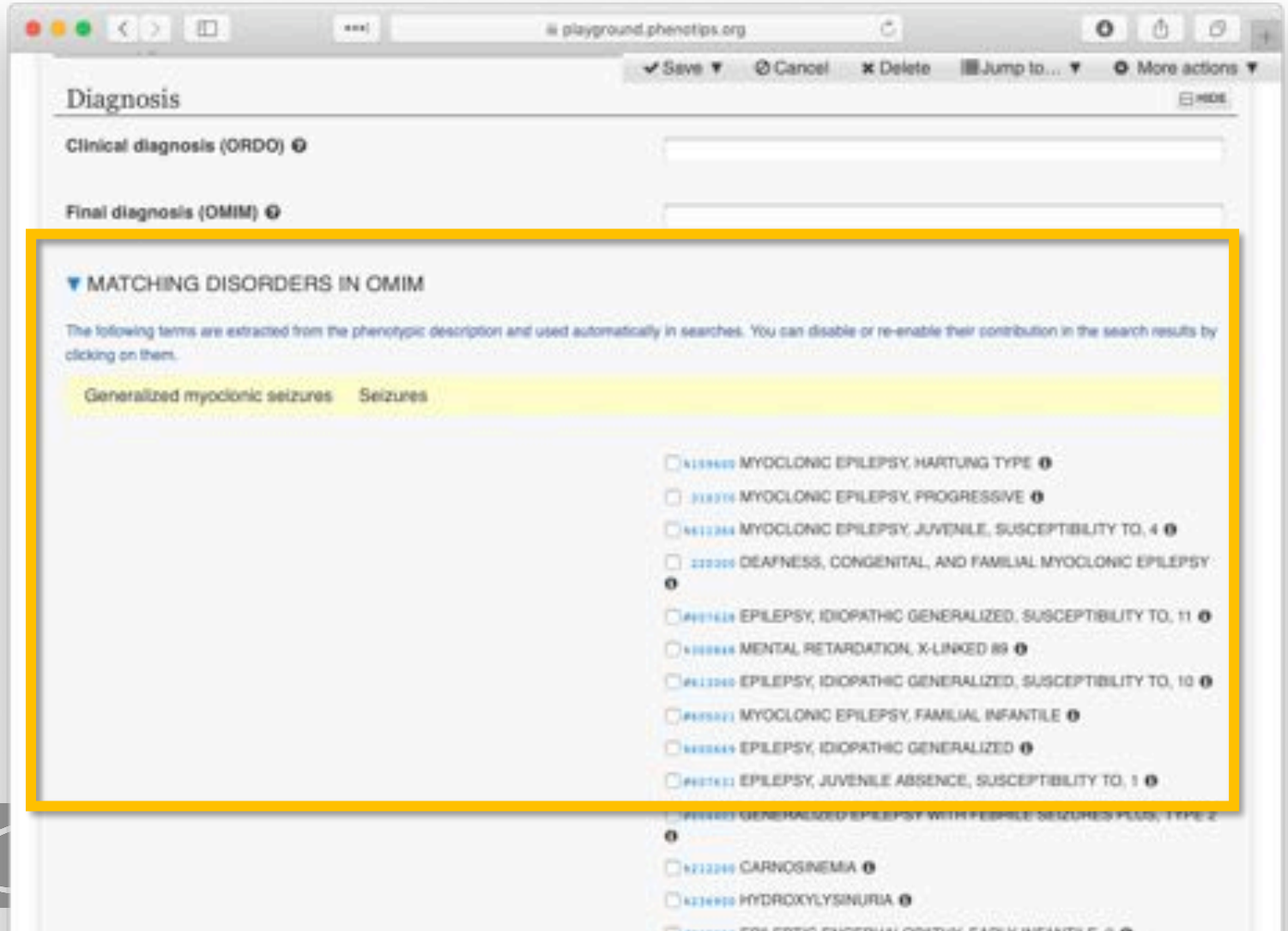
Clinical information based on HPO profiles



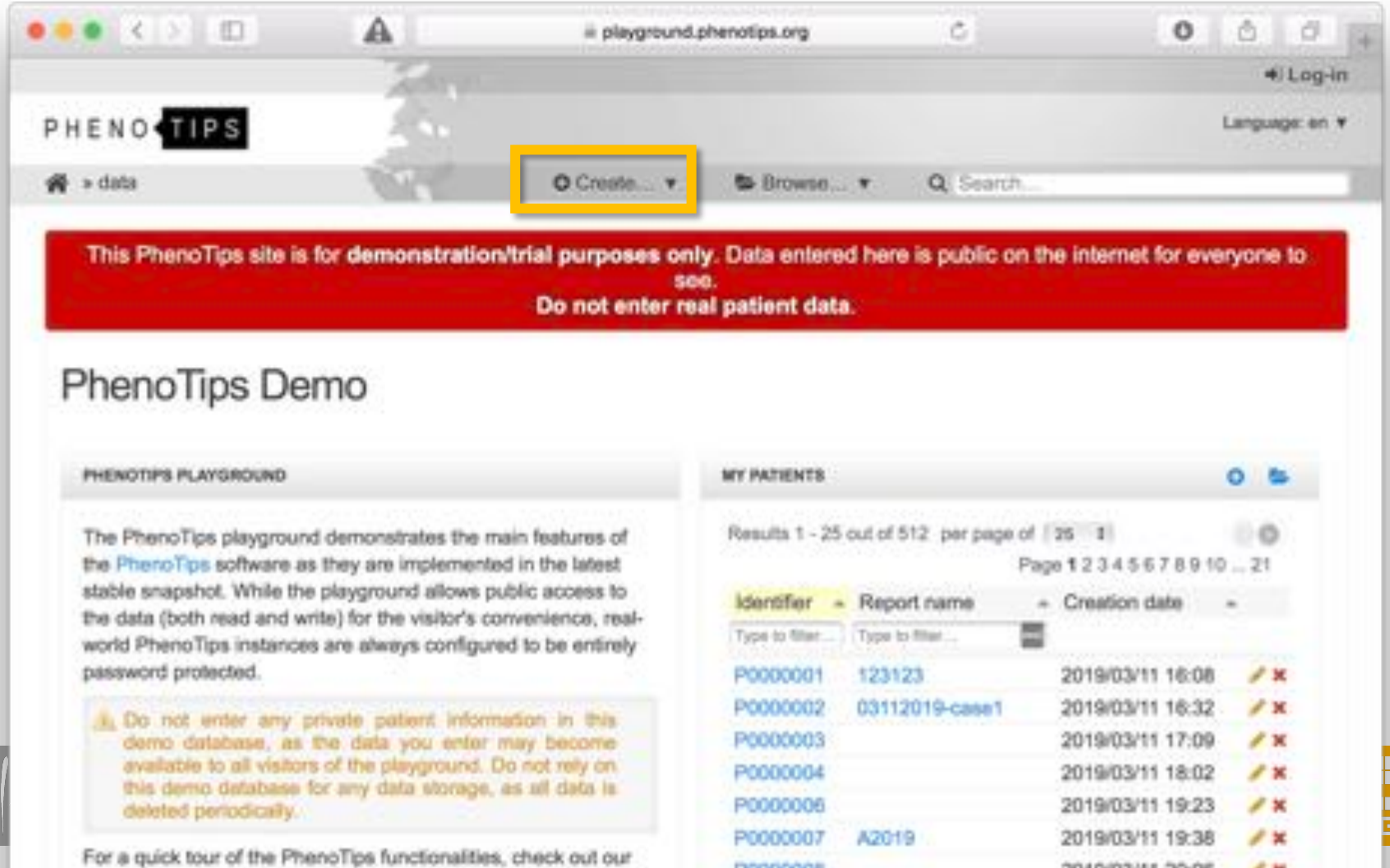
Clinical information based on HPO profiles



Clinical information based on HPO profiles



Try it: playground.phenotips.org



Patient 1

Patient 1 is a 6-year old girl born (13.2.2013) to healthy, unaffected parents. Her development is characterized by growth delay and developmental delay, including moderate intellectual disability. Her head is smaller than expected for her age.

She has several facial dysmorphic features, particularly notable features include synophrys, highly arched eyebrows, long eyelashes and low-set ears. The clinician observed that she has thick hair and that some hair extends on her back and arms (hirsutism). She has disproportionally small hands and is missing a finger on her right hand.

She also has reported hearing impairment and ventricular septal defect, that was operated in the first year.

Create a new patient using PhenoTips and fill in the basic fields. Try to diagnose your patient using the clinical signs. Using the Matching disorders in OMIM in the Diagnosis section, try to find a correct diagnosis in this patient.

Q11 - What is your diagnosis?

1. Kabuki syndrome
2. Boehring-Opitz syndrome
3. Cornelia de Lange syndrome
4. Hajdu-Cheney syndrome
5. Mucopolysaccharidosis, type 3

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Patient 1 - Diagnosis

Clinical symptoms and physical findings

GROWTH PARAMETERS

- **Head circumference for age**
  - Microcephaly (<-3SD)
- Growth delay

CRANIOFACIAL

- Anteverted nares

EAR DEFECTS

- Hearing impairment
- Low-set ears

CUTANEOUS

- Long eyelashes
- Synophrys
- Hirsutism
- Highly arched eyebrow
- Thick hair

CARDIOVASCULAR

- Ventricular septal defect

MUSCULOSKELETAL

- Oligodactyly
- Small hand

NEUROLOGICAL

- Intellectual disability

Top candidate diseases

#122470 CORNELIA DE LANGE SYNDROME 1

#610759 CORNELIA DE LANGE SYNDROME 3

#300590 CORNELIA DE LANGE SYNDROME 2

#605039 BOHRING-OPITZ SYNDROME

#610253 KLEEFSTRA SYNDROME 1

#614583 BARAITSER-WINTER SYNDROME 2

#212066 CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIa

#300867 KABUKI SYNDROME 2

#300882 CORNELIA DE LANGE SYNDROME 5

#156200 MENTAL RETARDATION, AUTOSOMAL DOMINANT 1

Sharing phenotypes is dependent on the accurate phenotyping!

Patient 2

Patient 2 is a 10-year old boy born (1.3.2009) born to healthy, unaffected parents.
The major feature observed in this patient is his overgrowth – all of his growth parameters exceed those expected at his age. His stature is tall (above 97th percentile). His head circumference is large (above 97th percentile) and he is dolichocephalic.
His development is characterized by moderate developmental delay, in particular intellectual disability.

He has distinctive facial features, he has a pointed chin, downslanting palpebral fissures and mandibular prognathia.

He also has atrial septal defect and scoliosis.

Create a new patient using PhenoTips and fill in the basic information. Try to diagnose your patient by entering the clinical signs. Using the Matching disorders in OMIM in the Diagnosis section, try to find a correct diagnosis in this patient.

Q12– what is your diagnosis?

1. Smith-Lemli-Opitz syndrome
2. Phelan McDermid syndrome
3. Cornelia de Lange syndrome
4. Kleefstra syndrome
5. Sotos syndrome

Voting link **etc.ch/me6t**

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Voting link **etc.ch/me6t**

Patient 2 - Diagnosis

Top candidate diseases

Patient 3

Patient 3 is a 30-year old woman (1.3.2009).
She was hospitalised for jaundice and chronic anemia.
Ultrasound revealed splenomegaly of unknown cause.
Laboratory tests also that her anemia is hemolytic, her levels of reticulocytes are increased and she has hyperbilirubinemia.

Create a new patient using PhenoTips and fill in the basic information. Try to diagnose your patient using the clinical signs. Using the Matching disorders in OMIM in the Diagnosis section, try to find a correct diagnosis in this patient.

Q13 – what is your diagnosis?

1. Spherocytosis
2. Thalassemia
3. Haemochromatosis
4. Porphyria
5. Diamond-Blackfan anemia

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I have found a novel variant. What now?

Legacy databases and literature

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Use existing sources to get the most information on your variant

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Beacon Network Geno2MP

Get in touch with institutions to get more information about my variant of interest

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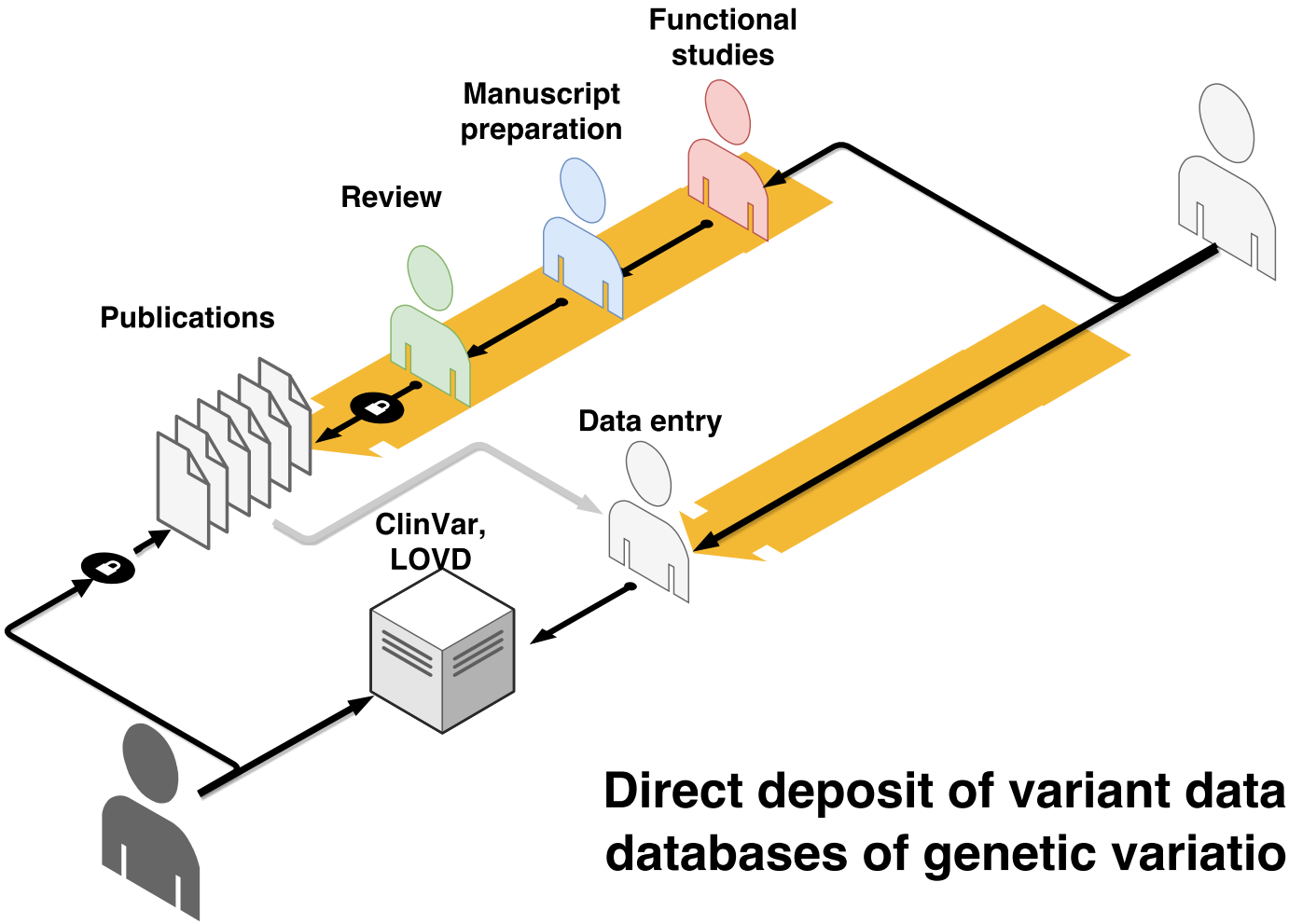
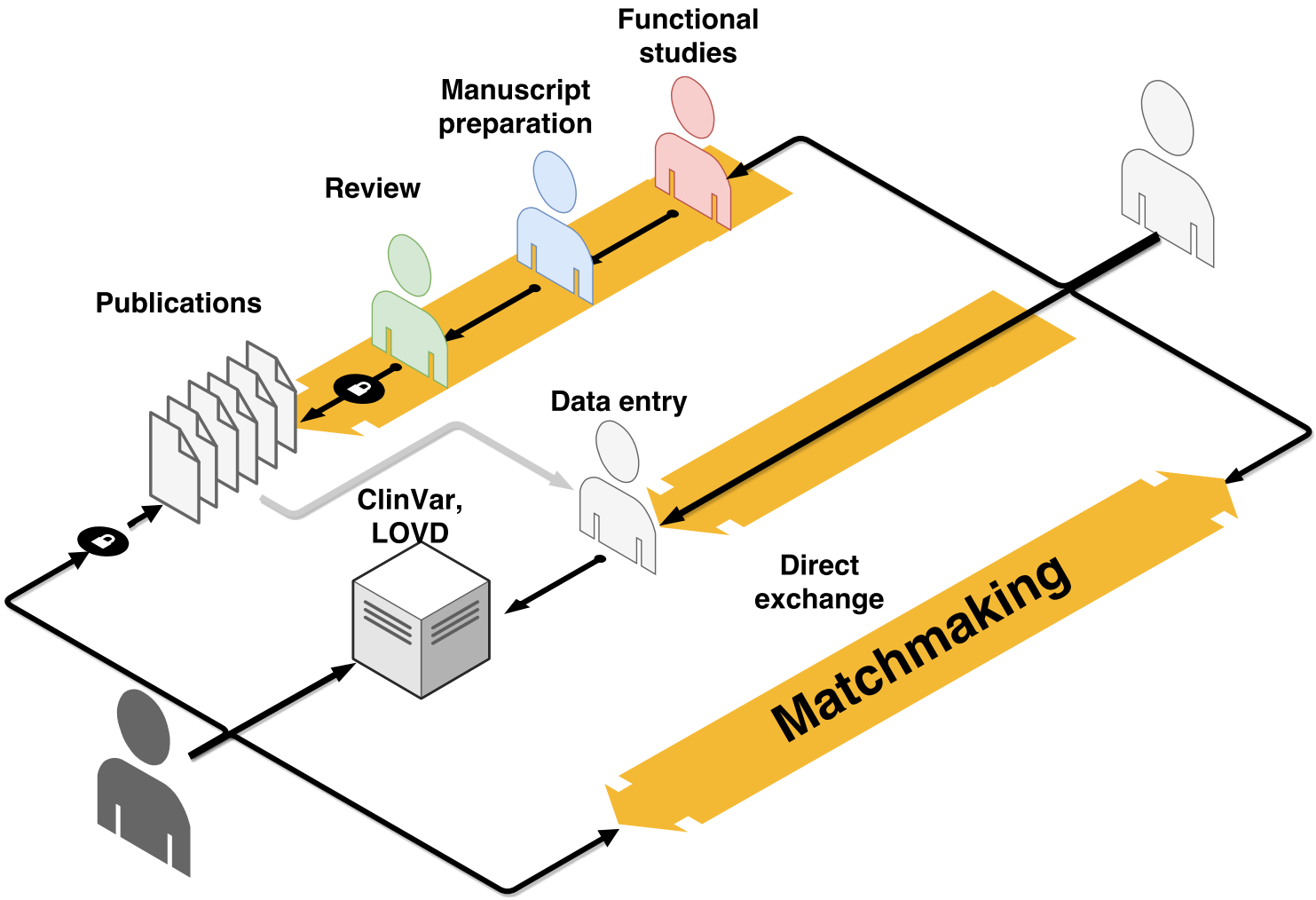
Genetic variant information sharing

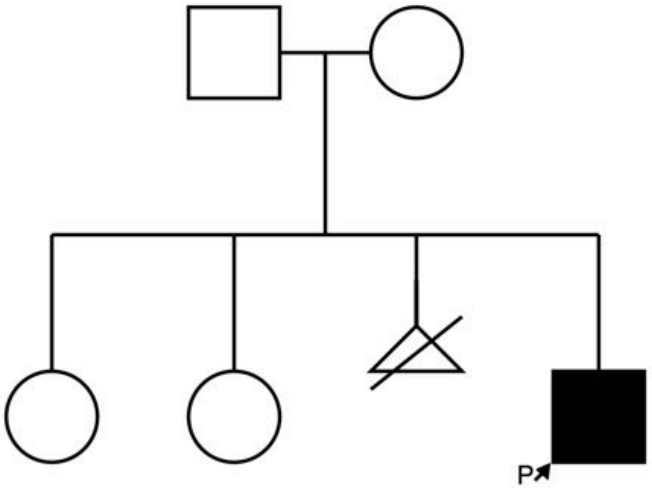


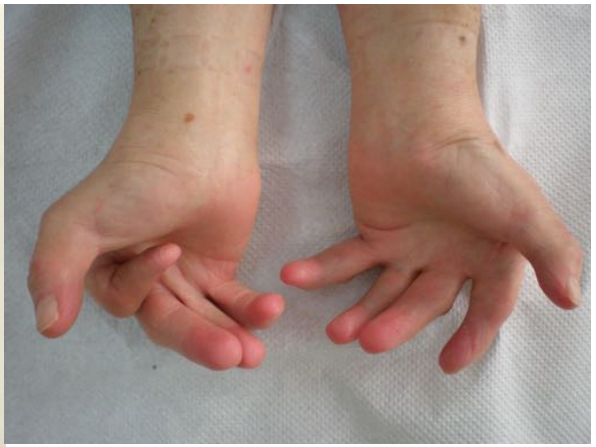
Direct deposit of variant data to databases of genetic variations


Functional studies
Manuscript preparation
Review
Publications
Data entry
ClinVar, LOVD
Direct exchange
Matchmaking

Family with congenital arthrogryposis

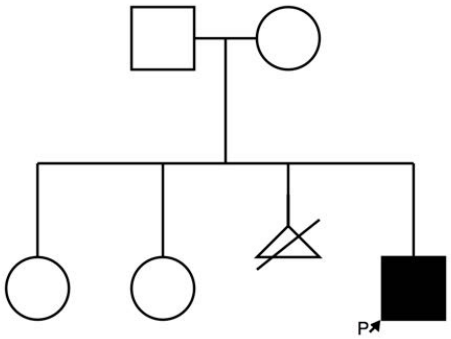
Family with a boy affected by congenital congenital arthrogryposis multiplex, previous pregnancy was terminated due to similar symptoms





Images:
http://www.patienthelp.org/diseases-conditions/arthrogryposis-multiplex-congenita.html

Family with congenital arthrogryposis

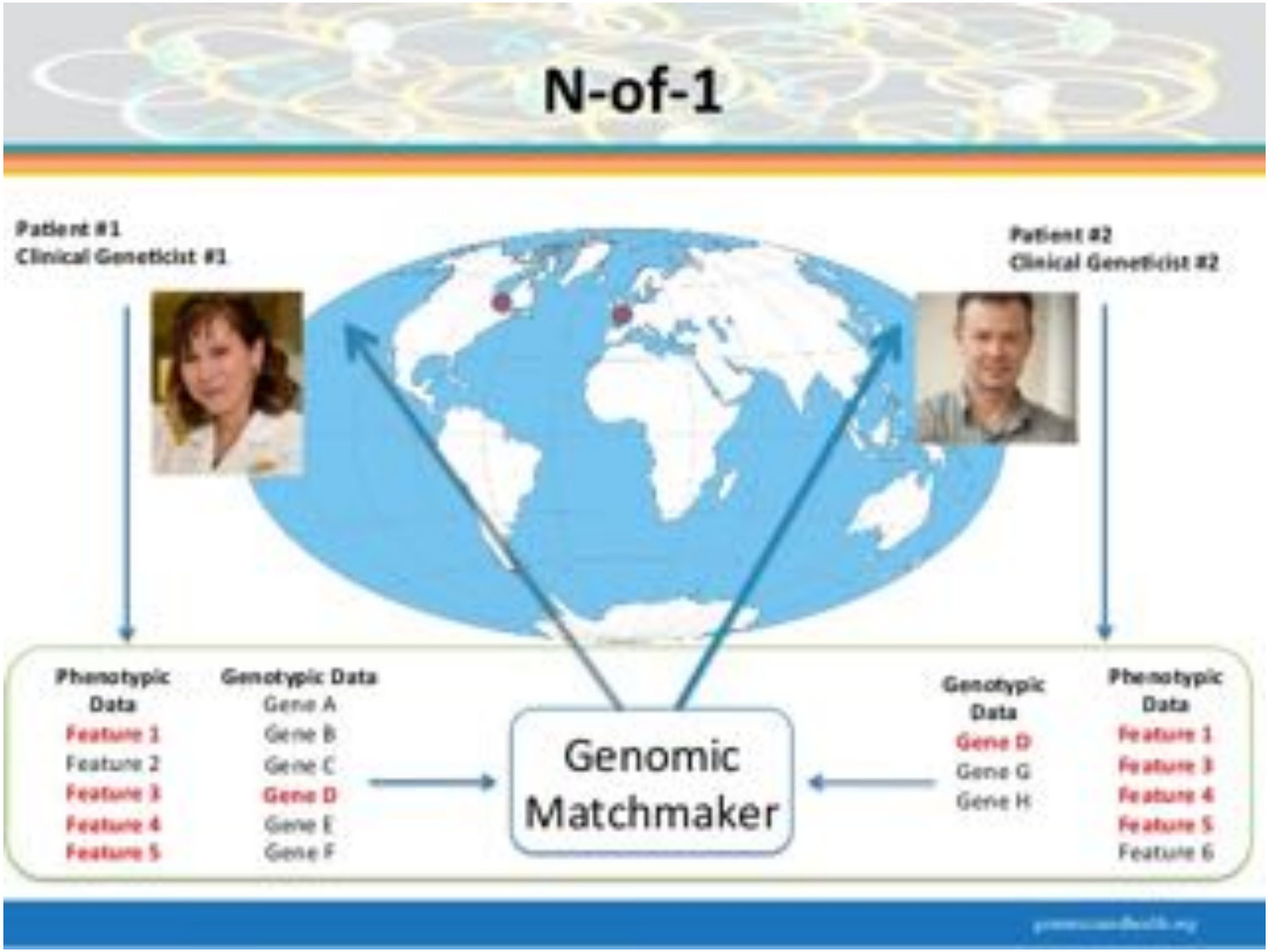


A 31Mb block of homozygosity on chromosome 15

www.homozygositymapper.org

A homozygous truncating variant in **gliomedin** gene in proband and fetus from previous pregnancy (*GLDN*)

Implicated in development of Ranvier nodes in peripheral nerves



Slide by Kym Boycott
https://www.slideshare.net/raredisorders/kym-boycott-rare-disease-day-2016-conference

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Match-making

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Global Alliance for Genomics & Health

Match-making

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Global Alliance for Genomics & Health

Match-making

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Match-making

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Phenome Central

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Clinical symptoms and physical findings

RESPIRATORY

Restrictive deficit on pulmonary function testing

MUSCULOSKELETAL

Flexion contracture

CONNECTIVE TISSUE

Congenital contracture
Congenital foot contraction deformities

Clinical symptoms and physical findings

RESPIRATORY

Restrictive deficit on pulmonary function testing

MUSCULOSKELETAL

Flexion contracture

CONNECTIVE TISSUE

Congenital contracture
Congenital foot contraction deformities

Genotype information

LIST OF GENES

	Gene	Status	Strategy	Comments
1	GLDN	Candidate	Sequencing	

Clinical symptoms and physical findings

RESPIRATORY

Restrictive deficit on pulmonary function testing

MUSCULOSKELETAL

Flexion contracture

CONNECTIVE TISSUE

Congenital contracture
Congenital foot contraction deformities

Genotype information

LIST OF GENES

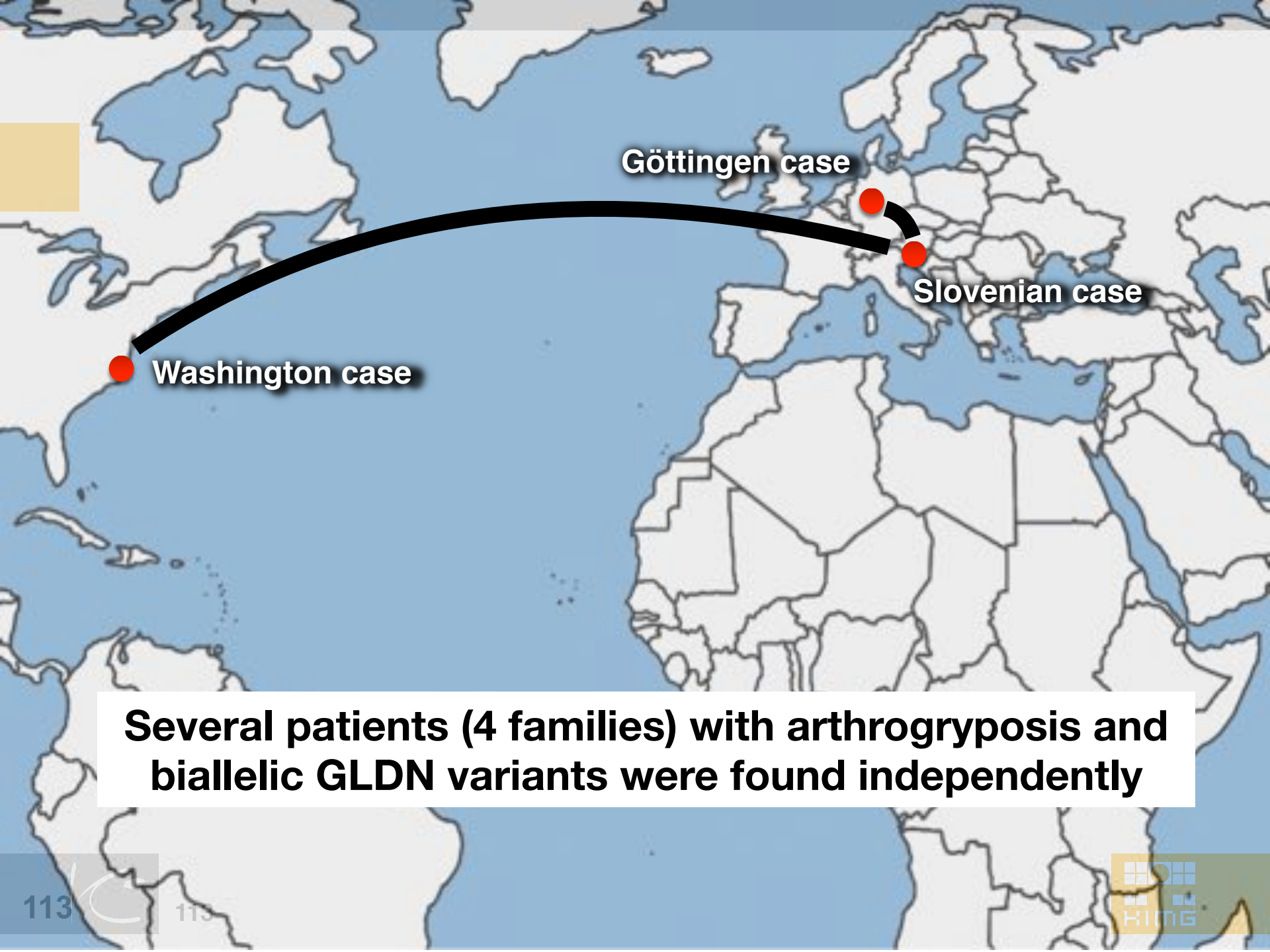
	Gene	Status	Strategy	Comments
1	GLDN	Candidate	Sequencing	

GeneMatcher

SHOW DISCLAIMER REFRESH MATCHES

Showing 4 similar cases

Remote Case ID	Potential diagnosis	Contact	Relevance	Details
6538	Undiagnosed	University of Goettingen	100%	SHOW PHENOTYPE AND GENOTYPE SIMILARITY...
7593	Undiagnosed	Washington University in St. Louis	100%	SHOW PHENOTYPE AND GENOTYPE SIMILARITY...



Several patients (4 families) with arthrogryposis and biallelic GLDN variants were found independently

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Family with congenital arthrogryposis

REPORT

Mutations in *GLDN*, Encoding Gliomedin,
a Critical Component of the Nodes of Ranvier
Ar

Published in final edited form as:
Hum Mutat. 2017 November ; 38(11): 1477–1484. doi:10.1002/humu.23297.

Jérô
Mar
Ron
Jérô

Survival among Children with "Lethal" Congenital Contracture Syndrome 11 Caused by Novel Mutations in the Gliomedin Gene (*GLDN*)

Jennifer A. Wambach[1,*], Georg M. Stettner[2,3,*], Tobias B. Haack[4,5,6], Karin Writzl[7], Andreja Škofljanec[8], Aleš Maver[7], Francina Munell[9], Stephan Ossowski[4,10,11], Mattia Bosio[10,11], Daniel J. Wegner[1], Marwan Shinawi[1], Dustin Baldridge[1], Bader Alhaddad[5], Tim M. Strom[5,6], Dorothy K. Grange[1], Ekkehard Wilichowski[2], Robin Troxell[12], James Collins[12], Barbara B. Warner[1,13], Robert E. Schmidt[14], Alan Pestronk[14], F. Sessions Cole[1,†], and Robert Steinfeld[2,†]

[1]Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri, USA [2]Department of Pediatric Neurology, University of Göttingen, Göttingen, Germany [3]Division of Pediatric Neurology, University Children's Hospital Zürich, Zürich, Switzerland [4]Institute of Medical Genetics and Applied

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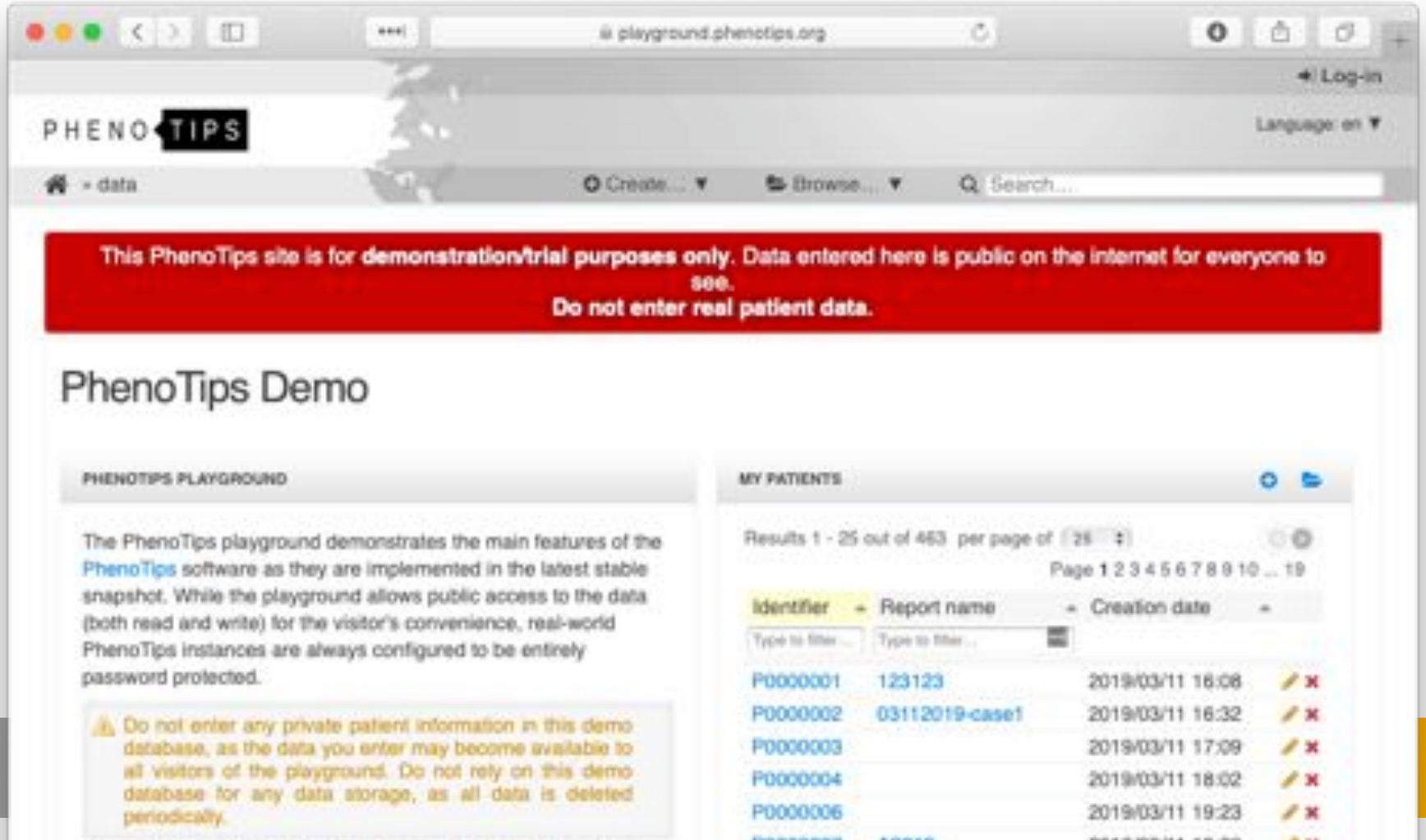
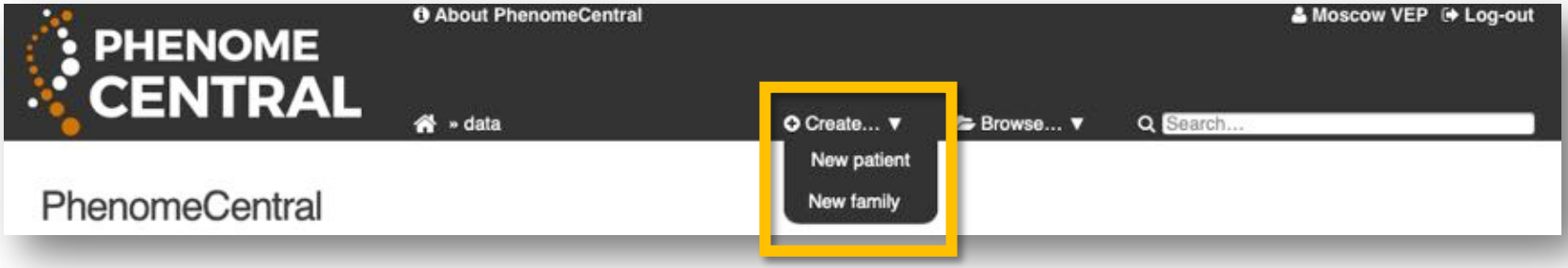
Try it yourself!

playground.phenomecentral.org
Login: MoscowVEP
Password: moscow

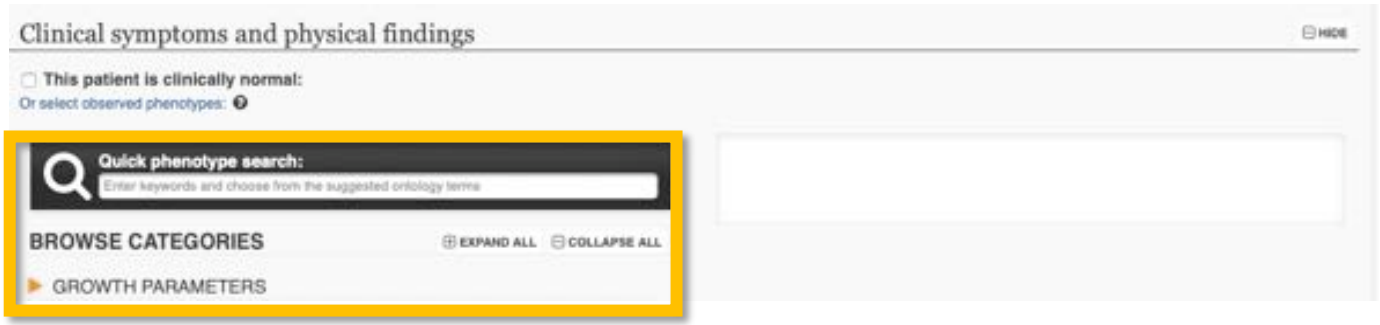


Create a new patient



Grant matching consents

Add phenotype data



Add the genetic information

Click save and view summary at the bottom of page

Find matches!

Check the features that match

Match-making case 1

- A 9-year old male was referred for whole exome sequencing for **global developmental delay**. He also has **dysplastic features** (hypertelorism, epicanthus, downslanting palpebral features, prominent forehead, microcephaly, low-set ears). He has **atrial septal defect** and **talipes calcaneovalgus**.
- You identified a novel variant in DMXL1 gene

  NM_001290321.1:c.7136-1G>C
- Neither this variant nor this gene have been reported in association with human disease
- Log in to the playground.phenomecentral.org website. Can you find a matching patient?

Q14 - Did you find a match?

- Yes, one patient having a candidate variant in the same gene and perfect phenotype match
- Yes, one patient having a candidate variant in the same gene and partial phenotype match
- No, I have only found patients with a similar phenotype but no gene match
- I have found no matches

Ignore the matches that belong to you (MoscowVEP)

Voting link etc.ch/me6t

Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https:// directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.

Voting link **etc.ch/me6t**

We have got a match!

Case ID	Diagnosis	Contact	Relevance	Phenotype and genotype similarity
P0000026	Undiagnosed	Aleš Maver	■■■■■ 94%	HIDE

THE CURRENT PATIENT (P0000030)	THE MATCHED PATIENT (P0000026)
AGE OF ONSET	
-	-
MODE OF INHERITANCE	
-	-
PHENOTYPE	
ABNORMALITY OF HEAD OR NECK	
Downslanted palpebral fissures Prominent forehead Microcephaly Hypertelorism Epicanthus Abnormal facial shape	Downslanted palpebral fissures Prominent forehead Microcephaly Hypertelorism Epicanthus
ABNORMALITY OF LIMBS	
Talipes calcaneovarus	Talipes calcaneovalgus
ABNORMALITY OF THE CARDIOVASCULAR SYSTEM	
Atrial septal defect	Atrial septal defect
ABNORMALITY OF THE NERVOUS SYSTEM	
Global developmental delay	Global developmental delay
GENOTYPE	
DMXL1	

Match-making case 2

- A 4-year old female was referred for whole exome sequencing for **Rett-like syndrome**, however, no pathogenic variants have been identified in MECP2 and genes associated with Rett-like conditions.
- She does not speak and her movements are characterized by stereotypical body rocking. She has strabismus. She also gas gastroesophageal reflux disease and has feeding difficulties.
- You identified a de novo variant in PCGF3 gene

NM_006315.4 c.640C>T

- Neither this variant nor this gene have been reported in association with human disease

Log in to the playground.phenomecentral.org website and submit this patients phenotype and the variant to PhenomeCentral. Can you find a matching patient?

A match!

Case ID	Diagnosis	Contact	Relevance	Phenotype and genotype similarity
P0000027	Rare neurologic disease	Aleš Maver	81%	HIDE

THE CURRENT PATIENT (P0000029)	THE MATCHED PATIENT (P0000027)
AGE OF ONSET	
-	-
MODE OF INHERITANCE	
-	-
PHENOTYPE	
ABNORMALITY OF THE DIGESTIVE SYSTEM	
Gastroesophageal reflux	Gastroesophageal reflux
ABNORMALITY OF THE EYE	
Strabismus	Congenital strabismus
ABNORMALITY OF THE NERVOUS SYSTEM	
Absent speech Stereotypy	Neurological speech impairment
GENOTYPE	
PCGF3	

Q15 - Did you find a match?

- Yes, one patient having a candidate variant in the same gene and perfect phenotype match
- Yes, one patient having a candidate variant in the same gene and partial phenotype match
- No, I have only found patients with a similar phenotype but no gene match
- I have found no matches

Ignore the matches that belong to you (MoscowVEP)

Voting link etc.ch/me6t

Insert Web Page

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https:// directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.

Voting link **etc.ch/me6t**

Match-making case 3

- A 8-year old boy was referred for whole exome sequencing for **severe hypotonia.**
- The patient has extreme central hypotonia, without neuropathic/myopathic features. He has absent speech, cannot walk, MRI shows periventricular leukomalacia.
- You identified a de novo missense variant in BCL10 gene

NM_003921.4:c.70T>G

- Neither this variant nor this gene have been reported in association with human disease

Log in to the playground.phenomecentral.org website and submit this patients phenotype and the variant to PhenomeCentral. Can you find a matching patient?

Q16 - Did you find a match?

- Yes, one patient having a candidate variant in the same gene and perfect phenotype match
- Yes, one patient having a candidate variant in the same gene and partial phenotype match
- No, I have only found patients with somewhat similar phenotype but no gene match
- I have found no matches

Ignore the matches that belong to you (MoscowVEP)

Voting link etc.ch/me6t

No gene match, partial phenotype overlap

Case ID	Diagnosis	Contact	Relevance	Phenotype and genotype similarity
P0000028	Rare genetic disease	Aleš Maver	24%	HIDE

THE CURRENT PATIENT (P0000031)	THE MATCHED PATIENT (P0000028)
AGE OF ONSET	
-	Congenital onset
MODE OF INHERITANCE	
-	Sporadic
PHENOTYPE	
ABNORMALITY OF THE NERVOUS SYSTEM	
Inability to walk Absent speech Central hypotonia Periventricular leukomalacia	Inability to walk Absent speech Abnormal brainstem MRI signal intensity
UNMATCHED	
	Generalized hypotonia
GENOTYPE	
No genotype matches found	

Insert Web Page

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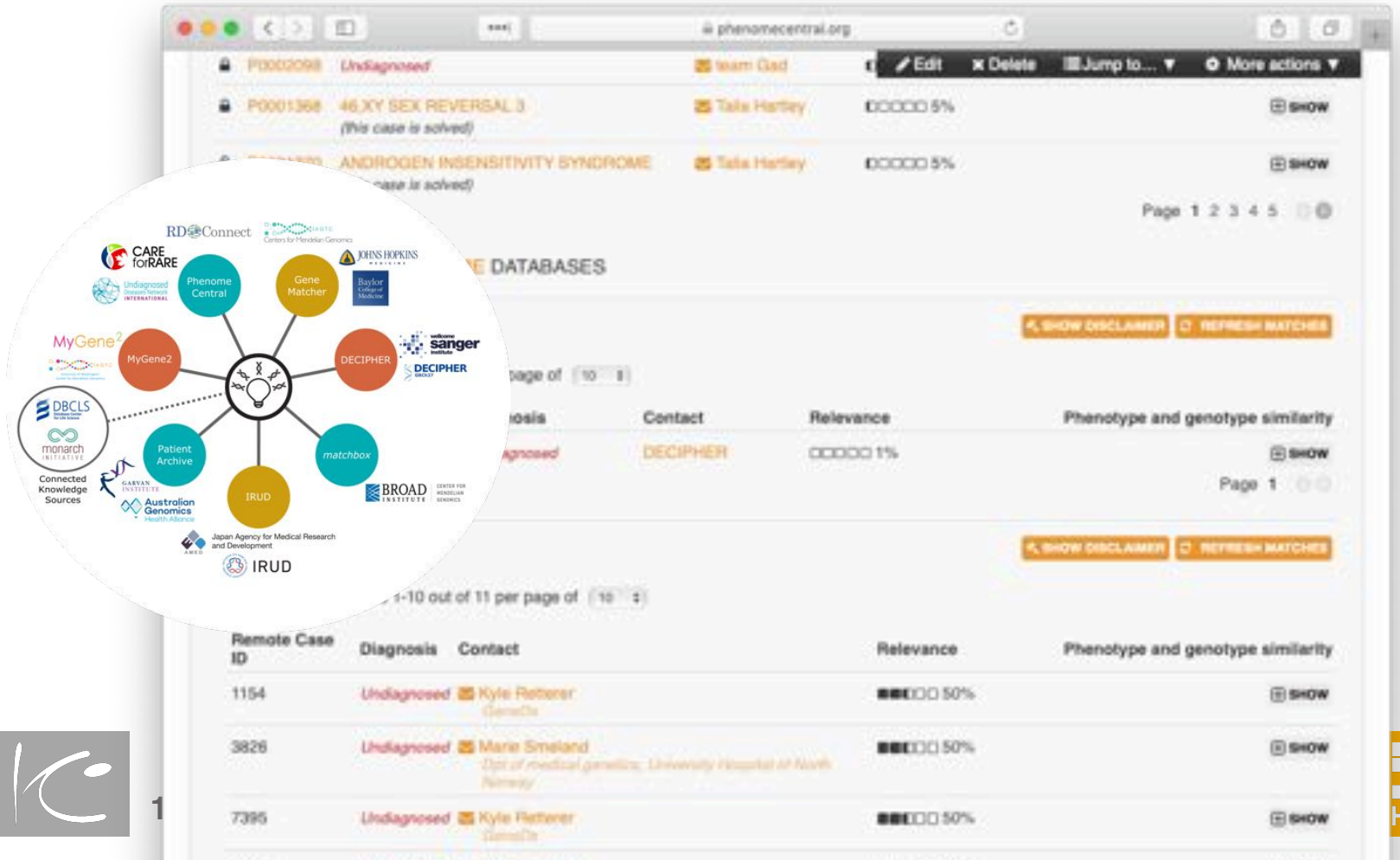
https:// directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.

Voting link **etc.ch/me6t**

The actual PhenomeCentral website allows actual patient matches across PhenomeCentral and multiple networks in the global alliance – make your account after this workshop

www.phenomecentral.org



Use data sharing platforms!

Legacy databases and literature

Use existing sources to get the most information on your variant

Get in touch with institutions to get more information about my variant of interest

Share phenotypes in a standarized way

Use match-making to identify similar patients

Thank you!

Prof. Borut Peterlin

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