

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

Data sharing, phenotyping and solving unsolved cases

Aleš Maver



4th Variant Effect Prediction Training Course

29-31 May 2019

Moscow, Russia



I have found a novel variant. What now?

Legacy databases and literature



ClinVar



Use existing sources to get the most information on your variant

Share phenotypes in a standardized way



PHENOTIPS™



ClinVar



Geno2MP

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

Use match-making to identify similar patients



MyGene²



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





Qo. Does the voting work?

A. Yes

B. No

Voting link etc.ch/me6t

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<https://>

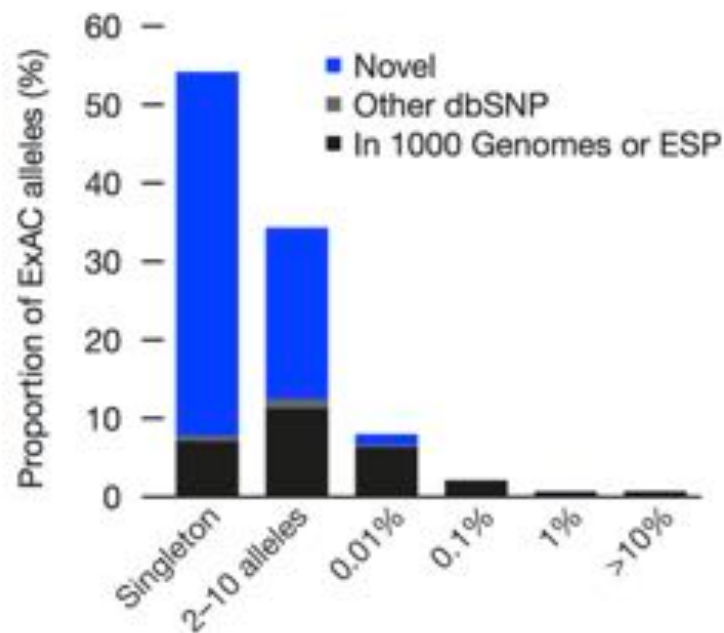
Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.

Genome sequencing constantly generates novel findings

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

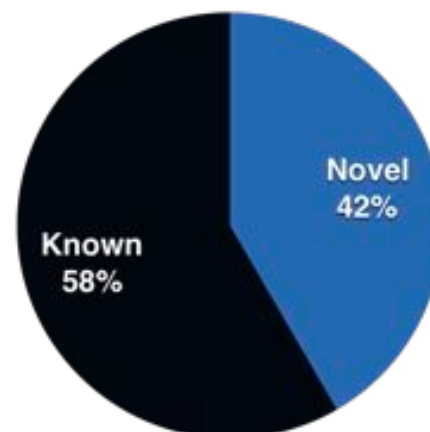
ExAC project

N=60.706



Reported clinically relevant variants in CMG database 2014-2016

(n=596 variants, in submission to ClinVar)



Variant interpretation



False negative



False positive

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

Mar 14, 2016 | [Tuma 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 Ravetto / 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."





**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)

The screenshot shows the LOVD3 Global Variome shared LOVD website for the TREX1 gene. The browser address bar shows 'databases.lovd.nl'. The page title is 'TREX1 gene homepage - Global Variome shared LOVD'. The LOVD3 logo is on the left, and the text 'Global Variome shared LOVD' and 'TREX1 (three prime repair exonuclease 1)' are in the center. The curator is 'Boukje de Vries'. The page has a navigation bar with links: Genes, Transcripts, Variants, Individuals, Diseases, Screenings, Submit, and Documentation. The main section is titled 'TREX1 gene homepage' and contains a 'General information' table.

General information	
Gene symbol	TREX1
Gene name	three prime repair exonuclease 1
Chromosome	3
Chromosomal band	p21.31
Imprinted	Unknown
Genomic reference	NG_009820.2
Transcript reference	NM_016381.4, NM_033629.3
Exon/Intron information	NM_016381.4 exon/intron table, NM_033629.3 exon/intron table
Associated with diseases	AGS-1, ID, SLE, Chilblain lupus, Vasculopathy, retinal, with cerebral leukodystrophy
Citation reference(s)	-
Refseq URL	Genomic reference sequence
Curators (1)	Boukje de Vries
Total number of public variants reported	102
Unique public DNA variants reported	73
Individuals with public variants	110
Hidden variants	0
Download all this gene's data	Download all data
Notes	Establishment of this gene variant database (LSDB) was supported by the Leiden University Medical Center (LUMC), Leiden, Nederland.
Date created	June 06, 2008
Date last updated	February 24, 2019
Version	TREX1:190224

Below the table is a section titled 'Graphical displays and utilities' with links for 'Graphs' and 'Reading frame checker'.

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

The screenshot shows the ClinVar website in a web browser. The browser's address bar displays `ncbi.nlm.nih.gov`. The page header includes the NCBI logo, navigation links for Resources and How To, and user options like `aleanctbi`, `My NCBI`, and `Sign Out`. The main header features the ClinVar logo, a search bar with the placeholder text "Search ClinVar for gene symbols, HGVS expressions, conditions, ar", and a "Search" button. Below the search bar is a "Help" link. A navigation menu contains links for Home, About, Access, Help, Submit, Statistics, and FTP. The main content area has a dark blue header with the ClinVar logo and a description: "ClinVar aggregates information about genomic variation and its relationship to human health." To the left of this header is a DNA sequence: `ACTGATGGTATGGGGCCAAGAGATATATCT
CAGGTACGGCTGTCATCACTTAGACCTCAC
CAGGGCTGGGCATAAAAGTCAGGGCAGAGC
CCATGGTGCATCTGACTCCTGAGGAGAAGT
GCAGGTTGGTATCAAGGTTACAAGACAGGT
GGCACTGACTCTCTCTGCCTATTGGTCTAT`. Below the main content area are three columns of links: "Using ClinVar" (About ClinVar, Data Dictionary, Downloads/FTP site, FAQ, Contact Us, RSS feed/What's new?, Factsheet), "Tools" (ACMG Recommendations for Reporting of Incidental Findings, ClinVar Submission Portal, Submissions, Variation Viewer, Clinical Remapping - Between assemblies and RefSeqGenes, RefSeqGene/LRG), and "Related Sites" (ClinGen, GeneReviews, GTR, MedGen, OMIM, Variation). At the bottom left, there is a "Submitter highlights" section.

ClinVar

ClinVar aggregates information about genomic variation and its relationship to human health.

Using ClinVar

- [About ClinVar](#)
- [Data Dictionary](#)
- [Downloads/FTP site](#)
- [FAQ](#)
- [Contact Us](#)
- [RSS feed/What's new?](#)
- [Factsheet](#)

Tools

- [ACMG Recommendations for Reporting of Incidental Findings](#)
- [ClinVar Submission Portal](#)
- [Submissions](#)
- [Variation Viewer](#)
- [Clinical Remapping - Between assemblies and RefSeqGenes](#)
- [RefSeqGene/LRG](#)

Related Sites

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- [MedGen](#)
- [OMIM](#)
- [Variation](#)

Submitter highlights

ACMG

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

Google “variant interpretation tool”

The screenshot shows a web browser window with the URL https://www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/. The page title is "Genetic Variant Interpretation Tool". On the left is a navigation menu with links: Home, Leadership, Administration, Program Members, Graduate Programs, Shared Resources, Membership, Implementation Projects, Seminars, For Healthcare Providers, and Contact Us. The main content area explains the tool's purpose: to aid in variant interpretation by classifying variants based on evidence categories from Richards et al. (2015). It includes a link to "Click here to group evidence by category". Below this are input fields for "Patient ID:" and "Variant ID:". A list of evidence categories is shown, with the first two highlighted by red boxes:

- ☐ PVS1 null variant (nonsense, frameshift, canonical ± 1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease
- ☐ PS1 Same amino acid change as a previously established pathogenic variant regardless of nucleotide change
- ☐ PS2 De novo (both maternity and paternity confirmed) in a patient with the disease and no family history
- ☐ PS3 Well-established in vitro or in vivo functional studies supportive of a damaging effect

On the right side, a disclaimer states: "Please note that the text of the variant evidence has been pulled directly from Richards, et al. Genet Med. 2015 May;17(5). This site does not claim authorship of any of the variant evidence descriptions. This tool is based on the published".

Varsome – for quick variant queries

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

The screenshot displays the Varsome website interface. At the top, there's a navigation bar with the Varsome logo, a search bar containing "NM_001355.4:c.553dup", and buttons for "Upload VCF", "Editions", "Community", "About", "Blog", and "AlsoView". Below the search bar, the variant "chr4-758811-C-T" is displayed. A sidebar on the right lists various resources: "Variant basic info", "Region browser", "ACMG classification", "Community contributions", "Publications", "Structural Variants", "Transcripts", "Frequencies", "Cancer databases", "Prediction scores", "Biocon network", and "Gene PCGF3". The main content area shows the variant details: Chromosome (chr4), Position (758811), REF Sequence (C), ALT Sequence (T), Variant type (SNV), Cytosine (488.3), HGVS (NM_001355.4:c.553dup), and Gene symbol (PCGF3). Below this, a "Region browser" section shows a genomic track with a red vertical line indicating the variant position. The track displays the reference sequence "GCTGGACATTTATCAACAGAGATCCTCCCAACGACCACACACTCAAGTTCCTTTCTCACTAGTTCAGATTCAG" and the variant sequence "GCTGGACATTTATCAACAGAGATCCTCCCAACGACCACACACTCAAGTTCCTTTCTCACTAGTTCAGATTCAG".

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Geno2MP

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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

Insert Web Page

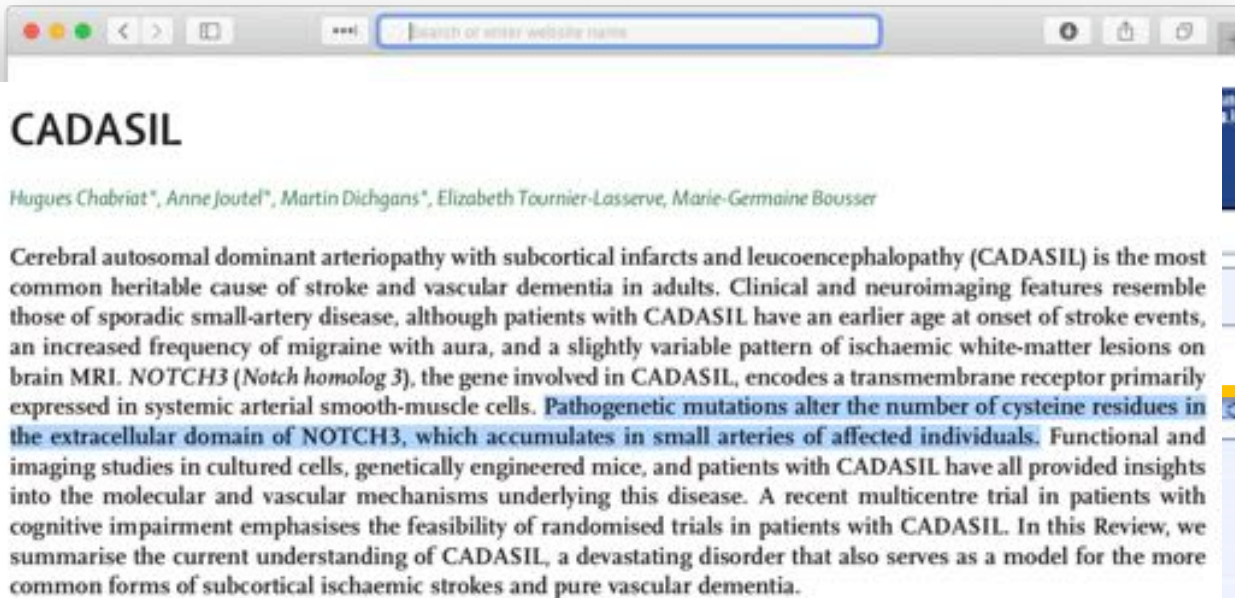
This app allows you to insert secure web pages starting with `https://` into the slide deck. Non-secure web pages are not supported for security reasons.

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.

Spectrum of pathogenic variation in the gene



Clinvar

101 missense variants with cysteine substitutions
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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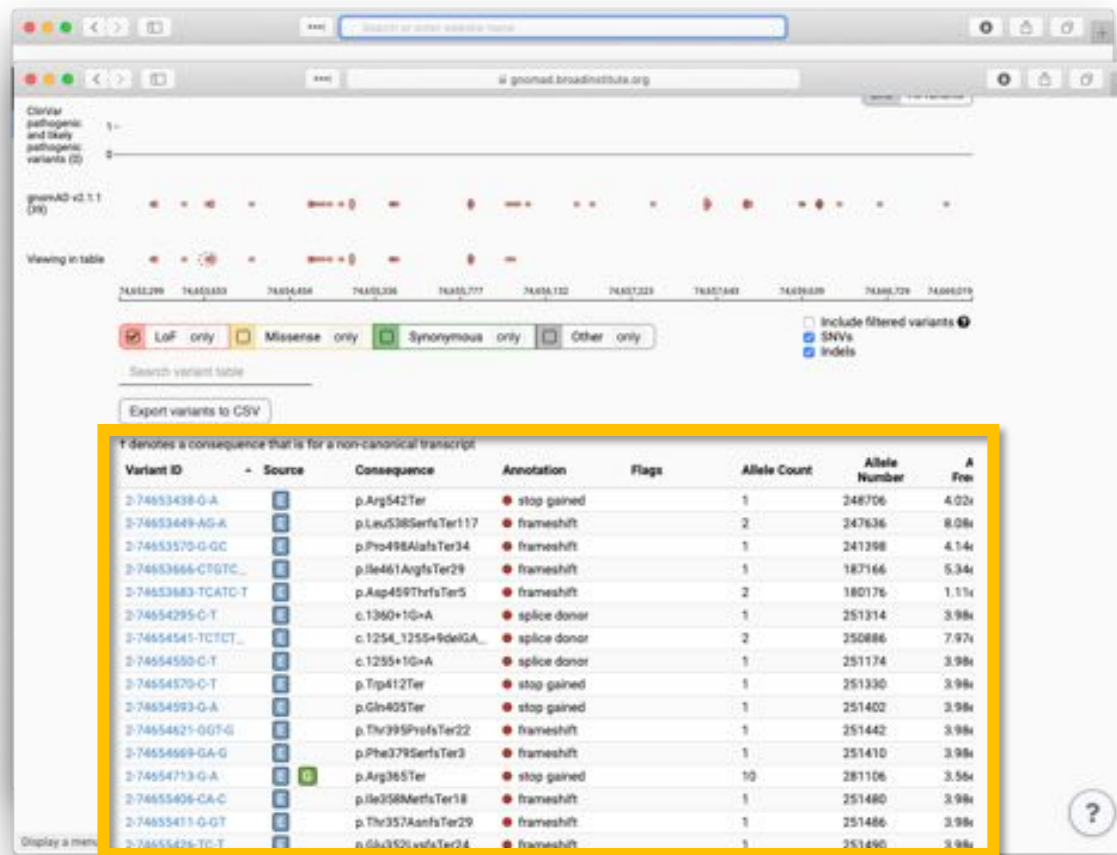
Please enter the URL below.

`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.

Free viewer online | Privacy & Cookies | Preview

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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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.

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Preview

Legacy mutation databases and old nomenclature



Table 1 • NYX mutations in families with complete CSNB

Family ^a	Origin	Mutation ^b	Codon change	Predicted effect on hydrophobic
290,745,835,Y1,Y2,Y3,PE ^c	USA	85-108del24nt ^d	RACPRACA29-36del	partial loss of N-terminal cysteine cluster
P03.345 (2) (ref. 13)	Netherlands	452C→T	P151L	missense, proline to leucine
650 (2)	Canada	464*465ins21nt	SWPRL155-158ins	expansion of LRR ^e
750 ^f (1),780 (1)	Canada/USA	951T→C	L184P	missense, leucine to proline
640 (2)	USA	619*620ins4	LJFDD7-206ins	expansion of LRR ^e
P520 (2)	Netherlands	638T→A	L213Q	missense, leucine to glutamine
580 (2)	Canada	647A→G	N216S	missense, asparagine to serine
550 (8)ref. 28, family 3)	Germany	695T→C	L232P	missense, leucine to proline
81 (3)	USA	780C→G	N264K	missense, asparagine to lysine
9080 (1)	USA	854T→C	L285P	missense, leucine to proline
82 (3)	USA	830T→C	F298S	missense, phenylalanine to serine
610, 620 (4,10)	China/Russia	1049G→A	W355X	protein truncation, loss of GPI anchoring

^aFamilies Y1, Y2, Y3, PE, P03, P05, P07, P11, P12, P13, P14, P15, P16, P17, P18, P19, P20, P21, P22, P23, P24, P25, P26, P27, P28, P29, P30, P31, P32, P33, P34, P35, P36, P37, P38, P39, P40, P41, P42, P43, P44, P45, P46, P47, P48, P49, P50, P51, P52, P53, P54, P55, P56, P57, P58, P59, P60, P61, P62, P63, P64, P65, P66, P67, P68, P69, P70, P71, P72, P73, P74, P75, P76, P77, P78, P79, P80, P81, P82, P83, P84, P85, P86, P87, P88, P89, P90, P91, P92, P93, P94, P95, P96, P97, P98, P99, P100, P101, P102, P103, P104, P105, P106, P107, P108, P109, P110, P111, P112, P113, P114, P115, P116, P117, P118, P119, P120, P121, P122, P123, P124, P125, P126, P127, P128, P129, P130, P131, P132, P133, P134, P135, P136, P137, P138, P139, P140, P141, P142, P143, P144, P145, P146, P147, P148, P149, P150, P151, P152, P153, P154, P155, P156, P157, P158, P159, P160, P161, P162, P163, P164, P165, P166, P167, P168, P169, P170, P171, P172, P173, P174, P175, P176, P177, P178, P179, P180, P181, P182, P183, P184, 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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 standardized way



I have found a novel variant. What now?

Legacy databases and literature



Use existing sources to get the most information on your variant

Share phenotypes in a standardized way



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

Use match-making to identify similar patients

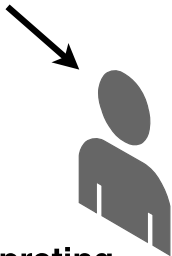


Genetic variant information sharing



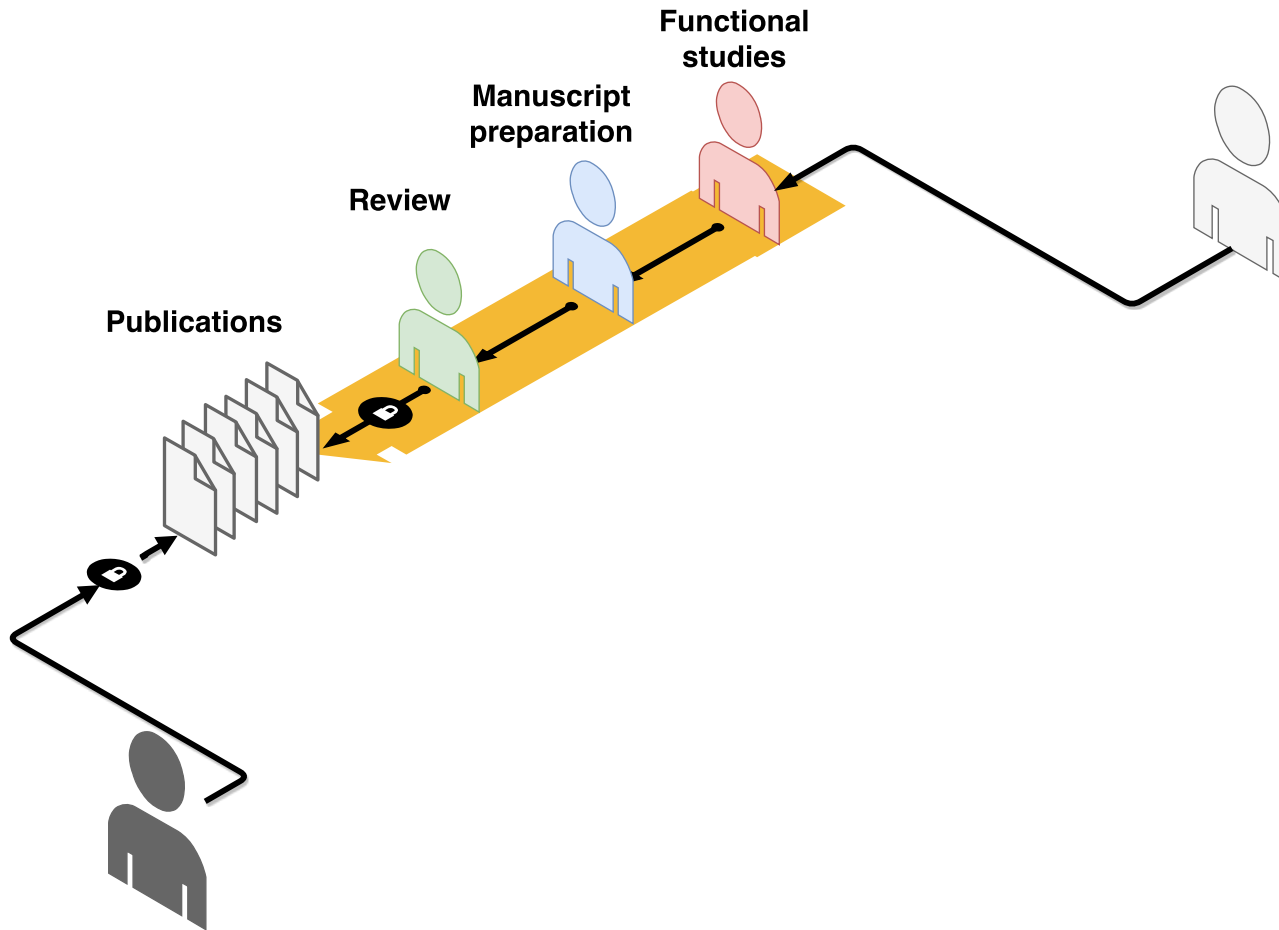
**Reporting the
variant**

You are here

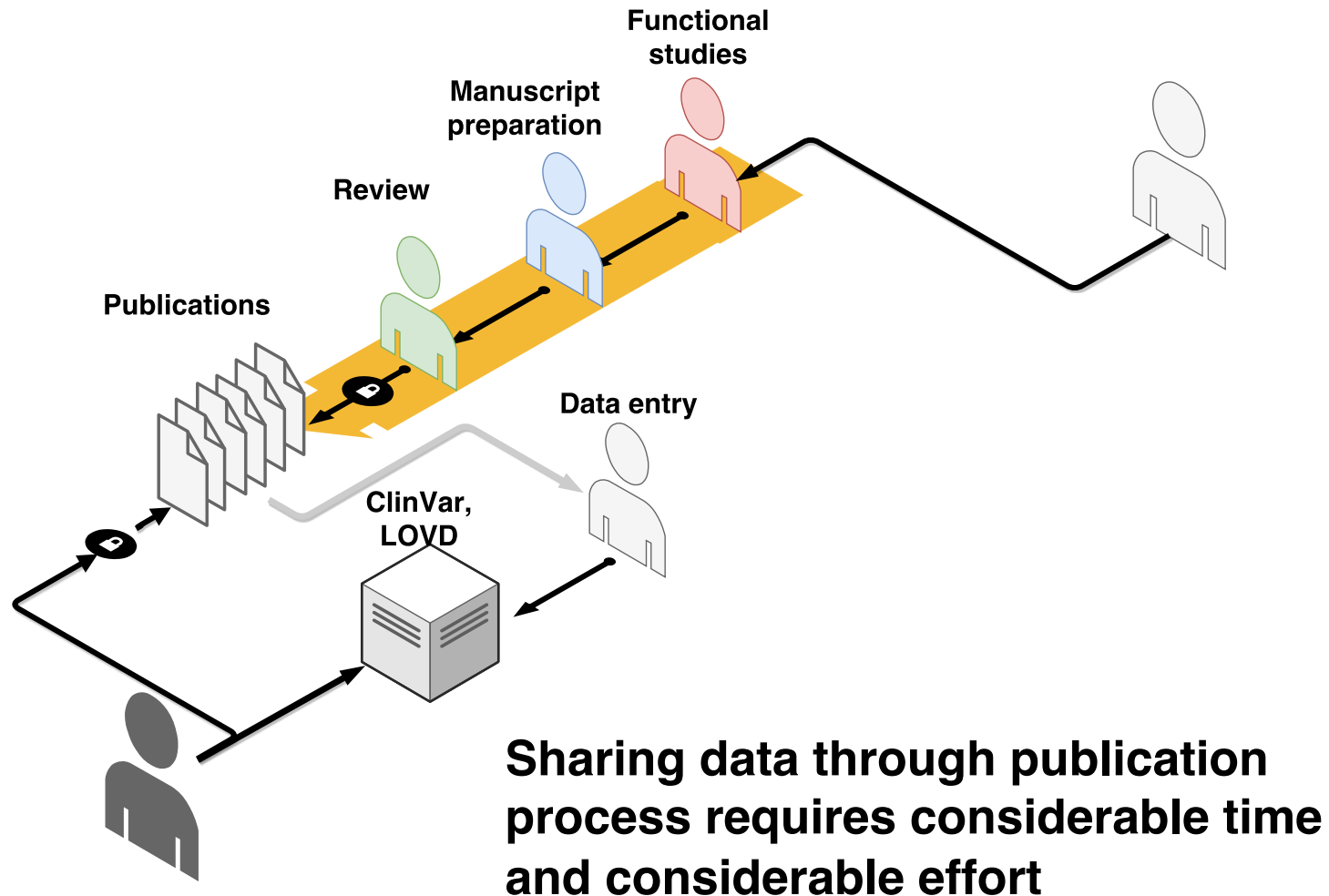


**Interpreting
exome/genome
sequencing
results**

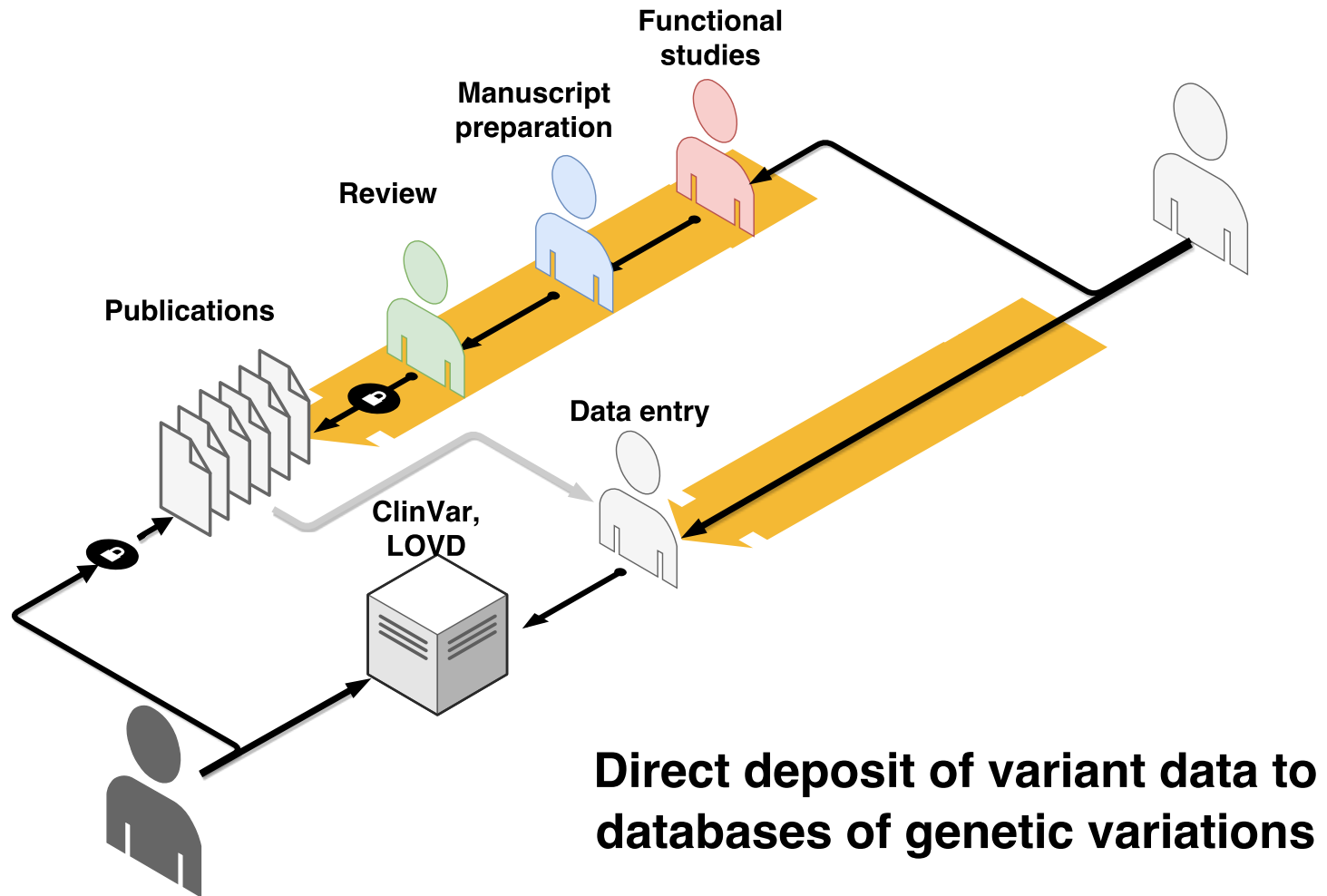
Genetic variant information sharing



Genetic variant information sharing

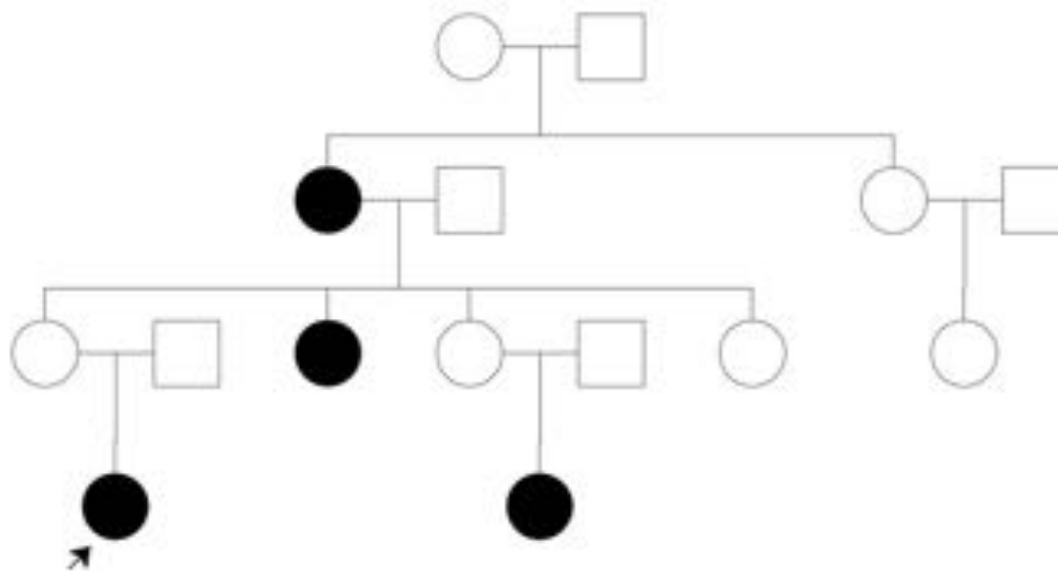


Genetic variant information sharing



Family with suspected mitochondrial disease

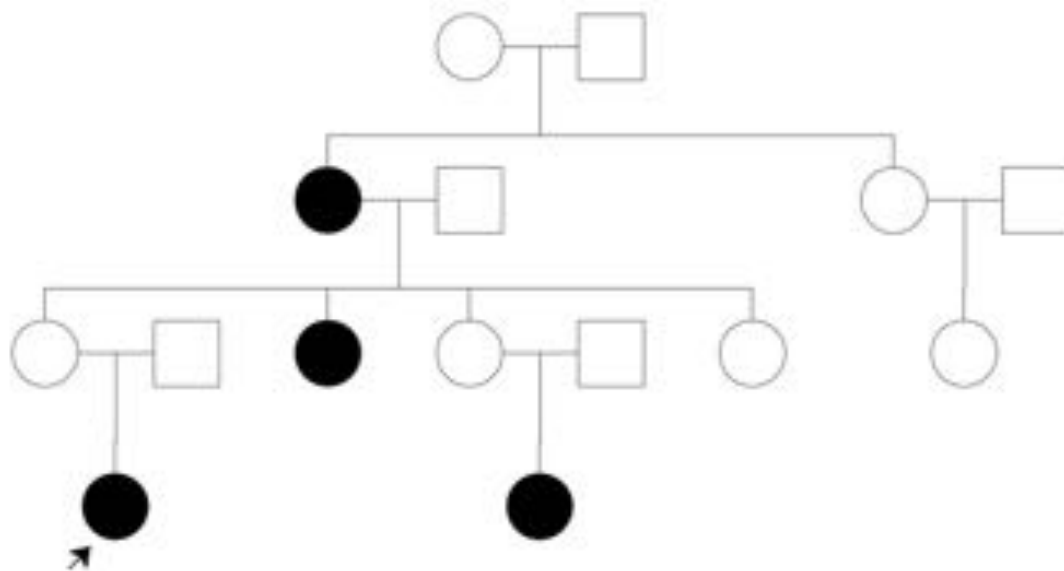
Apparent matrilineal inheritance of variable clinical presentation of seizures, renal disease and developmental delay



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

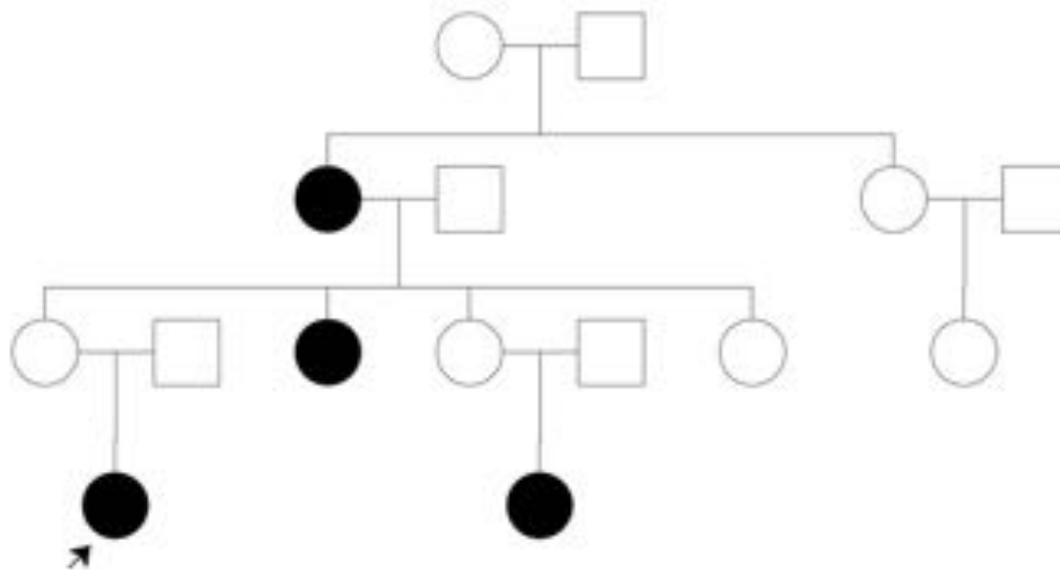
Family with suspected mitochondrial disease

Apparent matrilineal 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

There 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

Voting link etc.ch/me6t

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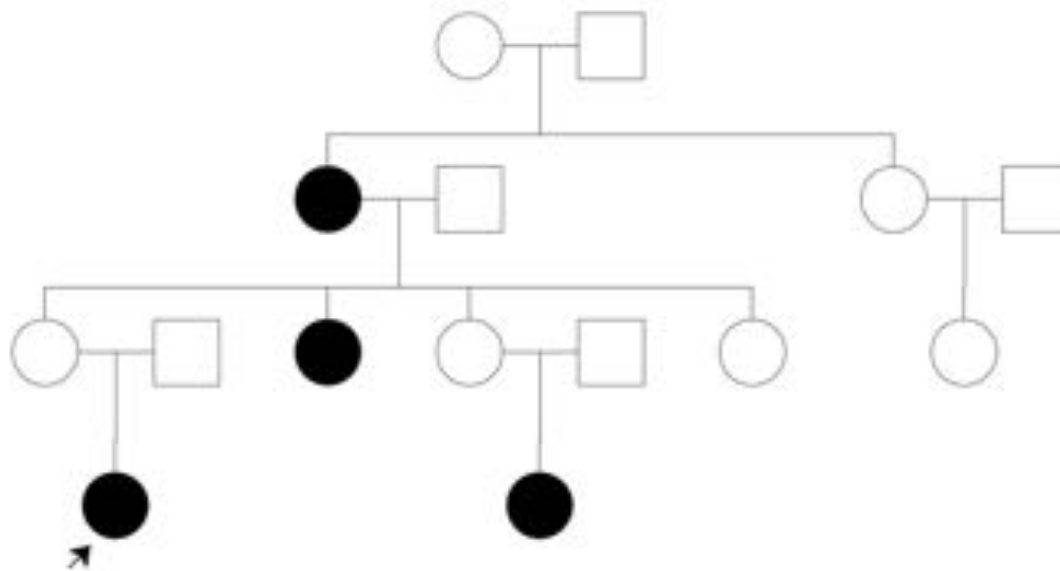
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https:// directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

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Preview



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

Paternal DNA sample not available for testing

There 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

Voting link etc.ch/me6t

Insert Web Page

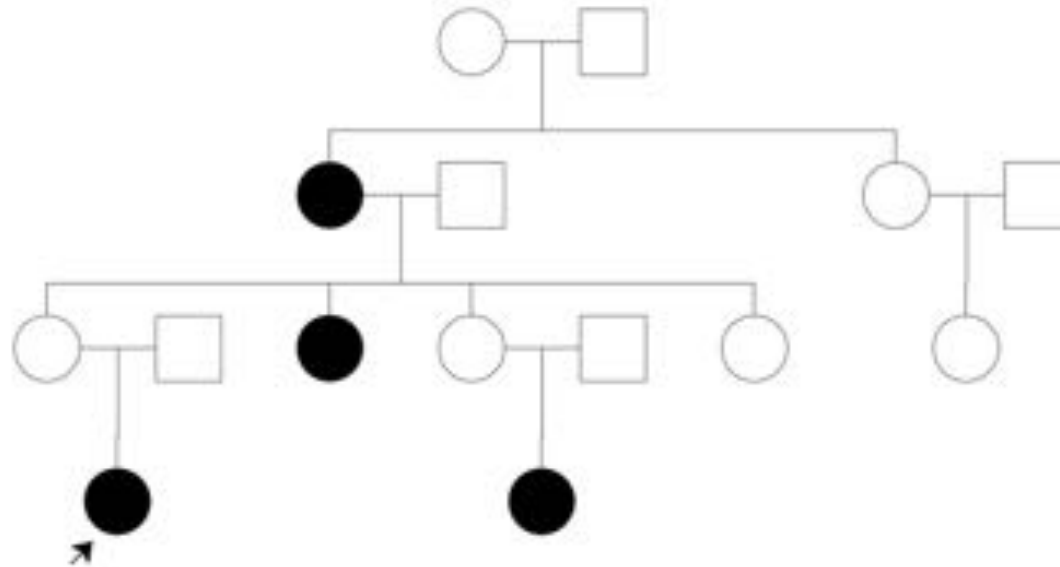
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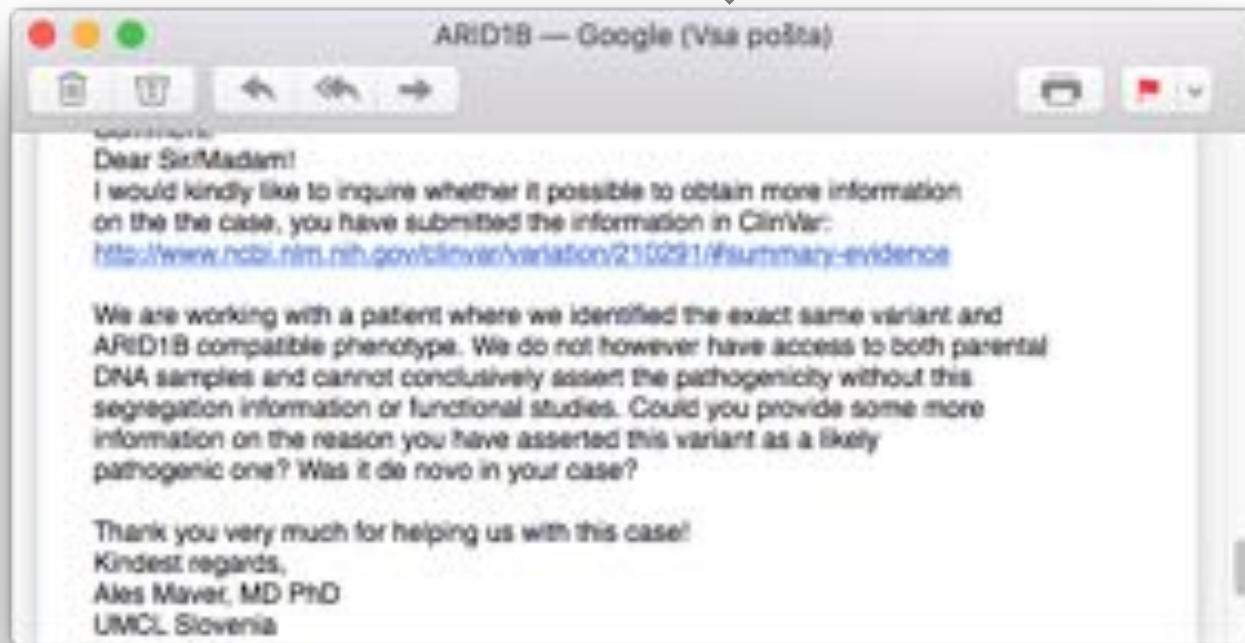
Synonymous p.Pro1370Pro
variant in **ARID1B** gene
Near intron-exon junction, rare and
possible effect on splicing

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 <ul style="list-style-type: none">ACMG Guidelines, 2015	Likely pathogenic (Dec 22, 2014)

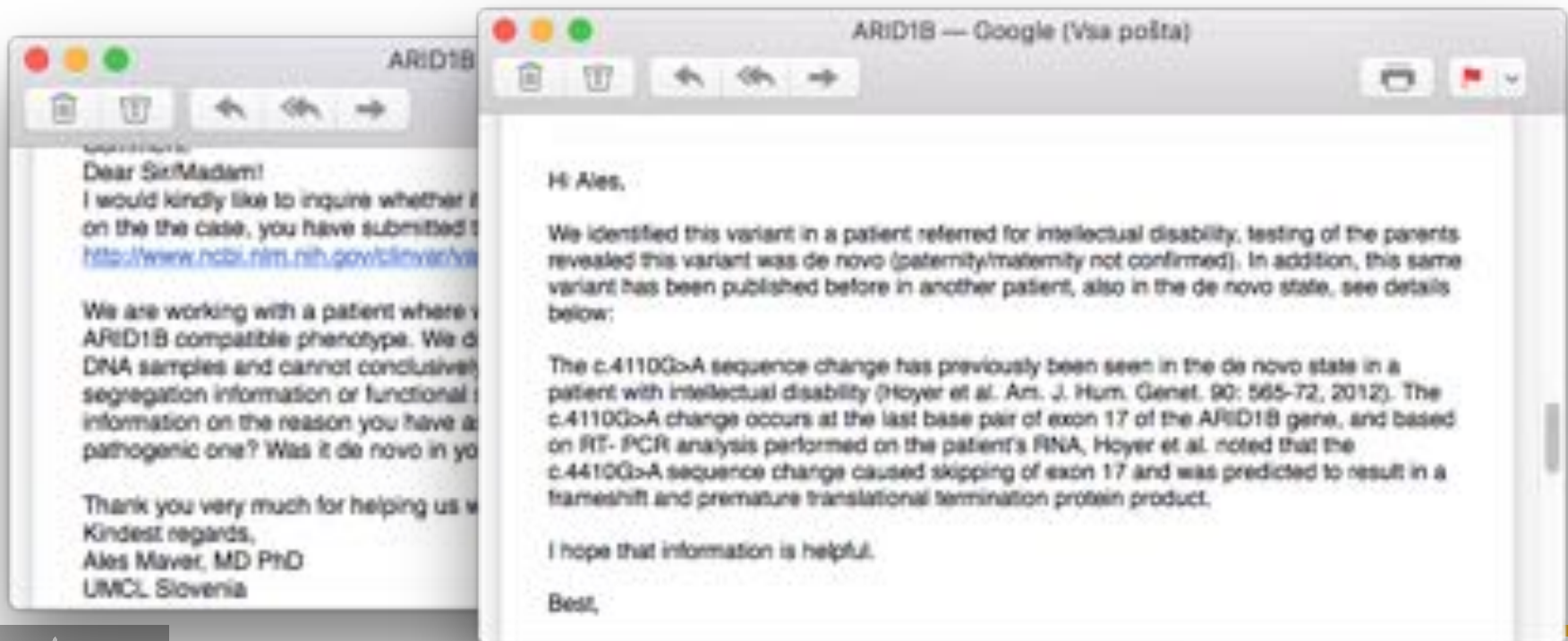
One report classifying it as a likely pathogenic variant in ClinVar

Submission Accession	Submitter	Review Status (Assertion method)	Clinical Significance (Last evaluated)
SCV000246523	Genetic Services Laboratory, University of Chicago	criteria provided, single submitter <ul style="list-style-type: none">ACMG Guidelines, 2015	Likely pathogenic (Dec 22, 2014)



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 <ul style="list-style-type: none">ACMG Guidelines, 2015	Likely pathogenic (Dec 22, 2014)



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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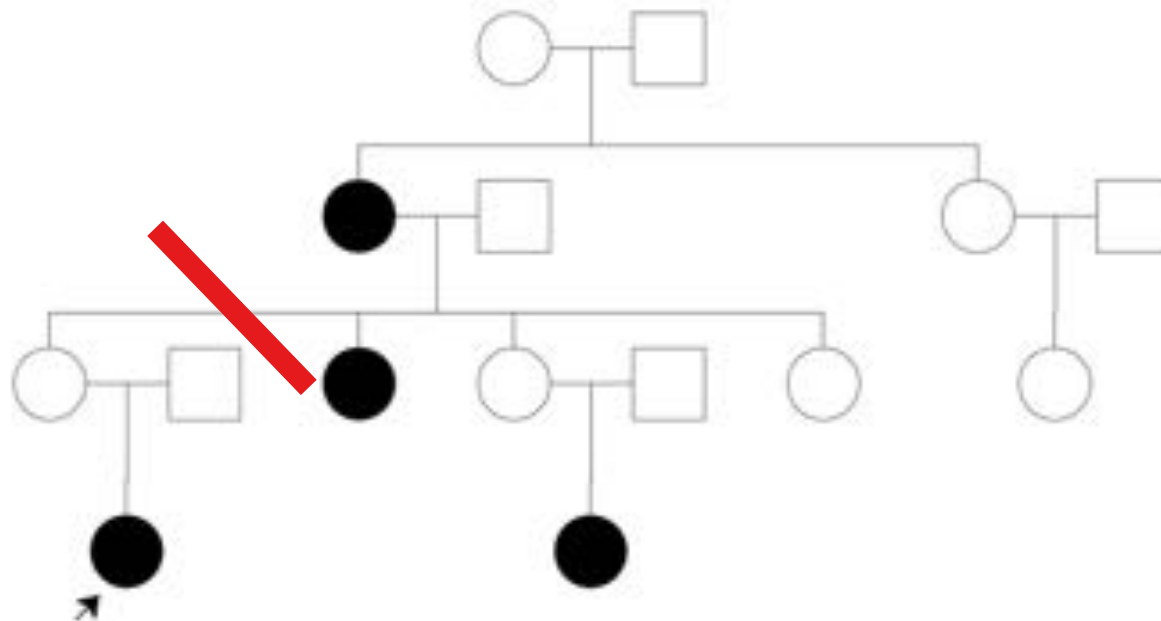
Please enter the URL below.

https:// directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

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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

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Please enter the URL below.

https:// directpoll.com/vr?XDbzPBd3bxYqg8ar52KsBWnhYXDzOZ7dQsWj8o8p

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The ClinVar entry

ncbi.nlm.nih.gov

HGVS:

- NG_031962.1:g.11023C>T
- NM_020745.3:c.985C>T
- NP_065796.1:p.Arg329Cys
- NC_000006.12:g.44307304G>A (GRCh38)
- NC_000006.11:g.44275041G>A (GRCh37)

Links:

- ClinGen: [CA3834454](#)
- dbSNP: [rs200187887](#)

NCBI 1000 Genomes Browser: [rs200187887](#)

Molecular consequence: NM_020745.3:c.985C>T: missense variant [Sequence Ontology [SO:0001583](#)]

Allele frequency:

- Exome Aggregation Consortium (ExAC) 0.00002
- NHLBI Exome Sequencing Project (ESP) Exome Variant Server 0.00008
- The Genome Aggregation Database (gnomAD), exomes 0.00002
- Trans-Omics for Precision Medicine (TOPMed) 0.00001

Assertion and evidence details [Go to](#) [-](#) [+](#)

Clinical assertions Summary evidence Supporting observations

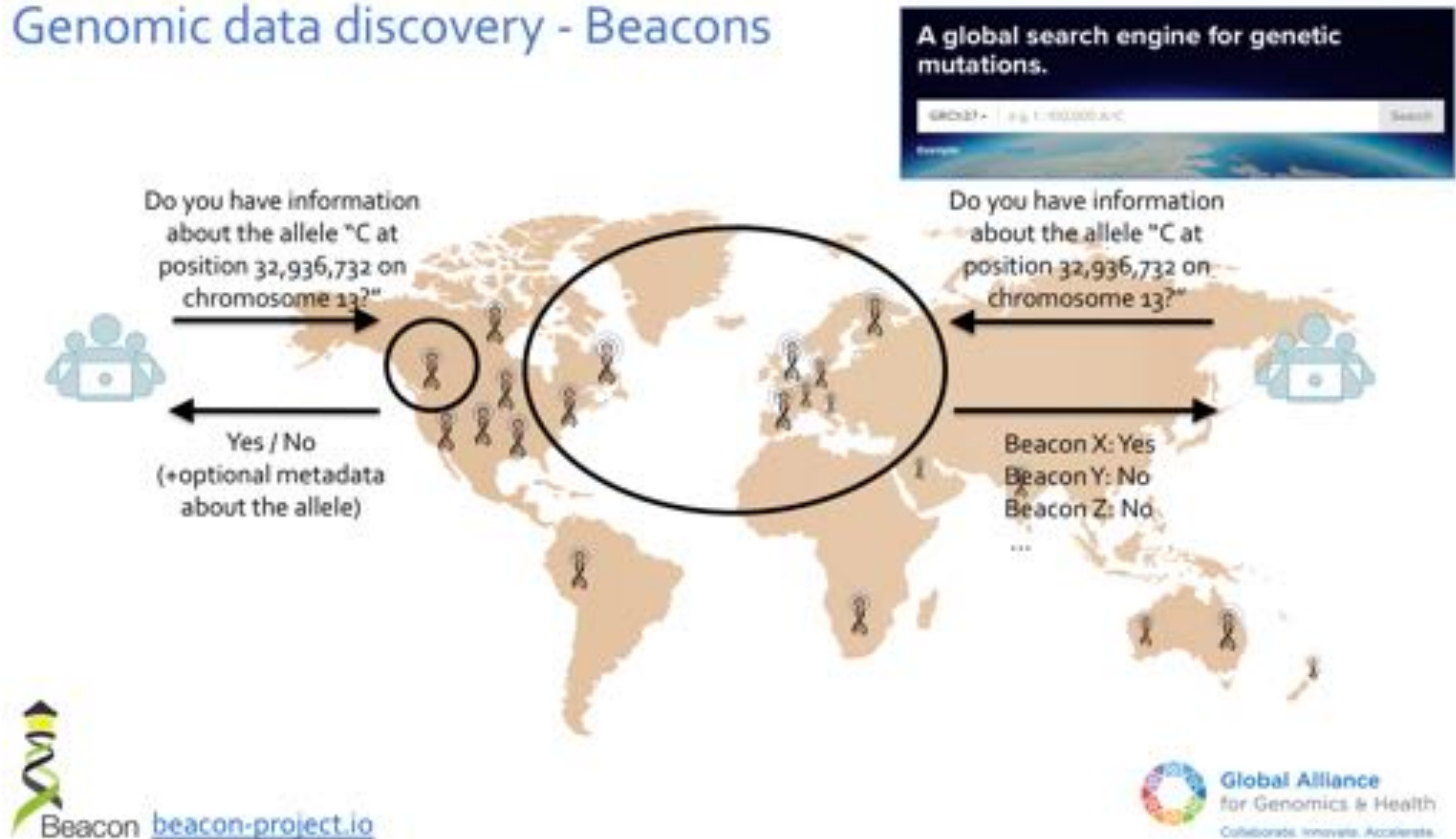
Germline

Filter

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Uncertain significance (Jun 14, 2016)	criteria provided, single submitter - ICSL Variant Classification 20161018	clinical testing	Combined oxidative phosphorylation deficiency [MedGen Orphanet OMIM]	germline		Illumina Clinical Services Laboratory/Illumina	SCV000463065.2
Likely pathogenic (Sep 8, 2017)	criteria provided, single submitter - Classification criteria August 2017	clinical testing	Combined oxidative phosphorylation deficiency 8 (Autosomal recessive inheritance) [MedGen Orphanet OMIM]	paternal		Institute of Human Genetics/Klinikum rechts der Isar	SCV000580133.1

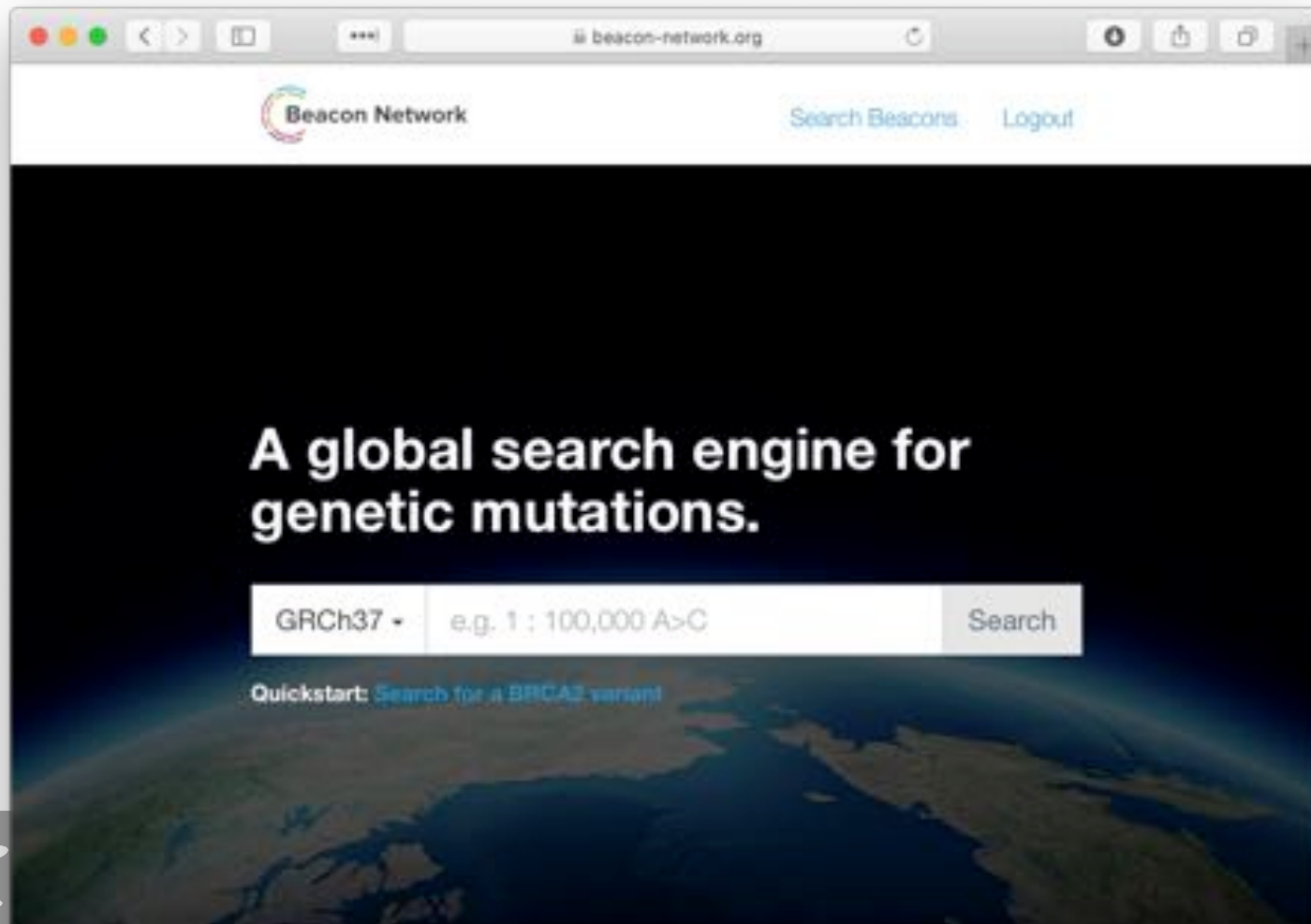
Beacon –etwork - a federated network for variant searches

Genomic data discovery - Beacons



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

Voting link [etc.ch/me6t](https://beacon-network.org/me6t)

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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.

Free viewer online | History & Settings Preview

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 Silveira,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

The screenshot shows the Geno2MP web application in a browser window. The address bar displays 'geno2mp.gs.washington.edu'. The header includes the University of Washington Center for Mendelian Genomics logo and navigation links: Home, About, Instructions, FAQ, and Usage. The main content area features two large buttons on the left: 'Click here to contribute data to Geno2MP' (blue) and 'HPO Browser' (green) with the subtext 'Need to find the HPO term for a clinical finding?'. To the right is a search bar with the placeholder 'Search for a gene, chromosomal position, region c' and an orange 'Search' button. Below the search bar, two radio buttons are visible: the first is selected and labeled 'Gene (MYH3); chromosome position of variant (17:10534960; dbSNP rsID (rs34393601)', and the second is labeled 'HPO term (oral cleft); HPO number (0000202)'. A section titled 'About the Genotype to Mendelian Phenotype (Geno2MP v2.0) Browser' follows, containing a paragraph about the tool's purpose and a paragraph about the current data (from ~10,547 individuals, updated January 2019). The bottom of the page mentions that the database is a collaborative, shared resource.

Click here to contribute data to Geno₂MP

HPO Browser
Need to find the HPO term for a clinical finding?

Geno₂MP

Search for a gene, chromosomal position, region c

Search

☒ Gene (MYH3); chromosome position of variant (17:10534960; dbSNP rsID (rs34393601)

☐ HPO term (oral cleft); HPO number (0000202)

About the Genotype to Mendelian Phenotype (Geno₂MP v2.0) Browser

Geno₂MP is a web-based query tool that searches a database of rare variants from exome sequencing data linked to phenotypic information from a wide variety of Mendelian gene discovery projects. Specifically, each rare genotype is linked to individual-level phenotypic profiles defined by human phenotype ontology (HPO) terms. Thus, it enables users to link "Genotypes to Mendelian Phenotypes" to facilitate new gene discovery efforts.

Currently, Geno₂MP contains data from ~10,547 individuals (updated January 2019), including both persons affected with a Mendelian condition and unaffected individuals who are relatives of persons with a Mendelian condition. Geno₂MP shows phenotypic profiles for affected individuals and, for unaffected individuals, the phenotypic profile of their affected relative(s). As with most genetic variation in humans, most of the variants in Geno₂MP are not causal for a Mendelian condition.

This database is a collaborative, shared resource for the human genetics community. In fact, the power of Geno₂MP will only grow as

Finding variants in Geno2MP

The screenshot shows the Geno2MP web application interface. The search bar contains "PCGF3" and the "Search" button is highlighted. Below the search bar, the results show the gene "PCGF3" with a description "polycomb group ring finger 3". The "Gene summary" section is visible, showing a table of variants. The table has columns for Chr/Pos, Alleles, rsID, HPO Profiles, # het, # hom, Gene, mRNA, Annotations, cDNA Change, Protein Change, ESP AC, ExAC AC, 1K Genome AC, and CADD Phred-scaled. The "HPO Profiles" column is highlighted with a yellow box.

Gene | PCGF3

Description: polycomb group ring finger 3
 Number of variants: 88
 UCSC Browser: 4,699,571-763,877
 GeneCards: PCGF3
 MalaCards: PCGF3
 OMIM: PCGF3
 ClinVar: PCGF3

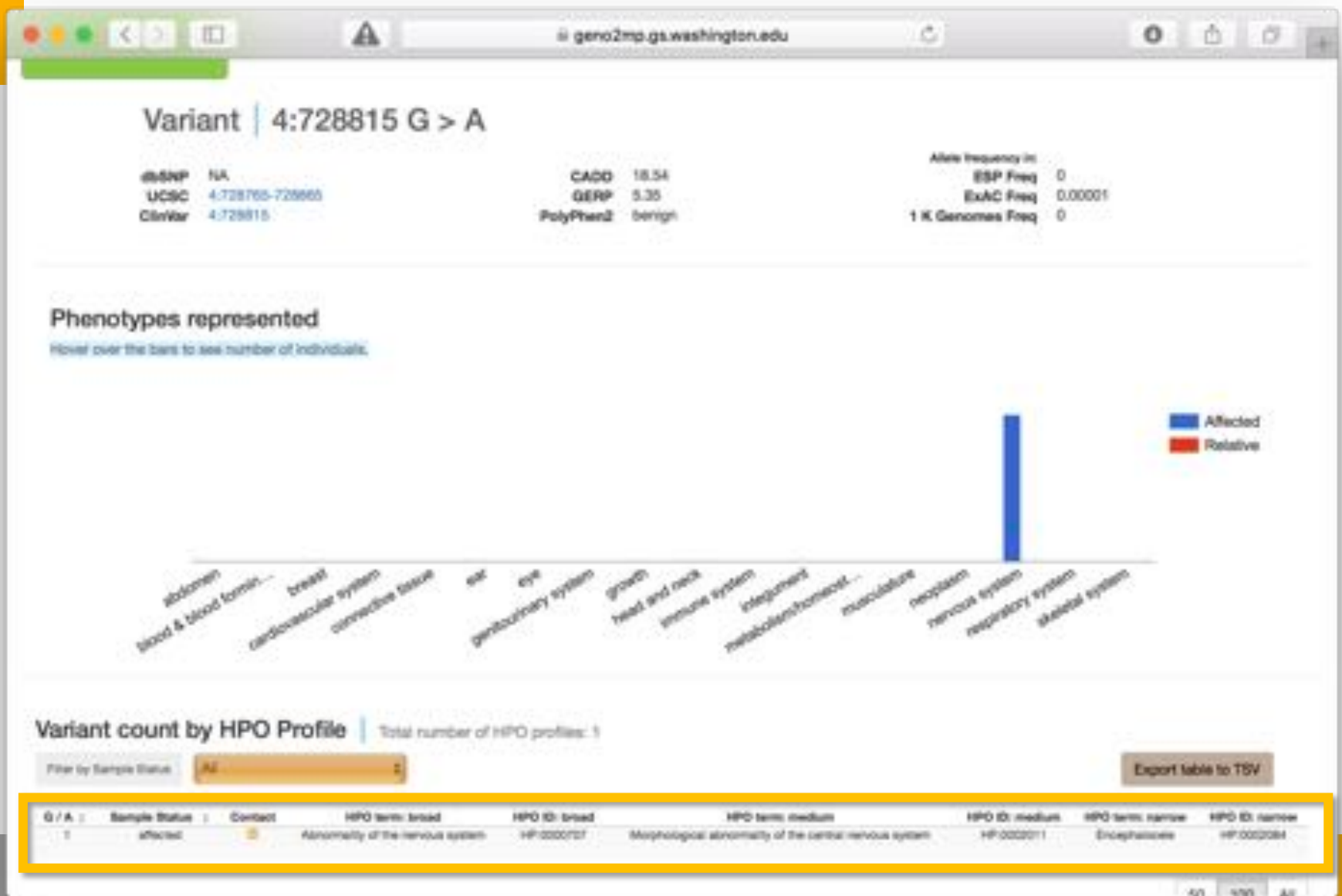
Gene summary

Filter by annotation category: Missense/Other Indel

Export table to TSV

Chr/Pos	Alleles	rsID	HPO Profiles	# het	# hom	Gene	mRNA	Annotations	cDNA Change	Protein Change	ESP AC	ExAC AC	1K Genome AC	CADD Phred-scaled
4:727522	G>A	rs200875455	1	1	0	PCGF3	NM_006315.4	missense	c.53G>A	p.(R18H)	0.000078	0.000016	0	25.3
4:728815	G>A	NA	1	1	0	PCGF3	NM_006315.4	missense-neu...	c.205G>A	p.(G69S)	0	0.00001	0	18.54
4:737262	C>T	NA	1	1	0	PCGF3	NM_006315.4	missense-neu...	c.263C>T	p.(A88V)	0	0	0	14.77
4:737321	A>C	rs201716638	2	2	0	PCGF3	NM_006315.4	missense	c.322A>C	p.(I108L)	0.000245	0.000014	0	12.75
4:737366	C>T	rs201626789	1	1	0	PCGF3	NM_006315.4	missense	c.367C>T	p.(R123W)	0.000408	0.000103	0.000458	24.1
4:738405	G>T	NA	1	1	0	PCGF3	NM_006315.4	missense	c.391G>T	p.(D131Y)	0	0	0	16.08

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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Please enter the URL below.

https:// directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

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Free viewer online | Privacy & Cookies

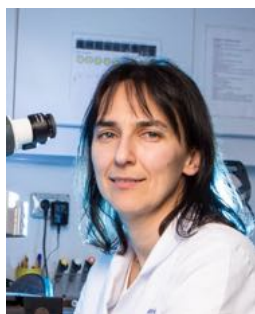
Preview



Matchmaking helps identify novel genes

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

REPORT

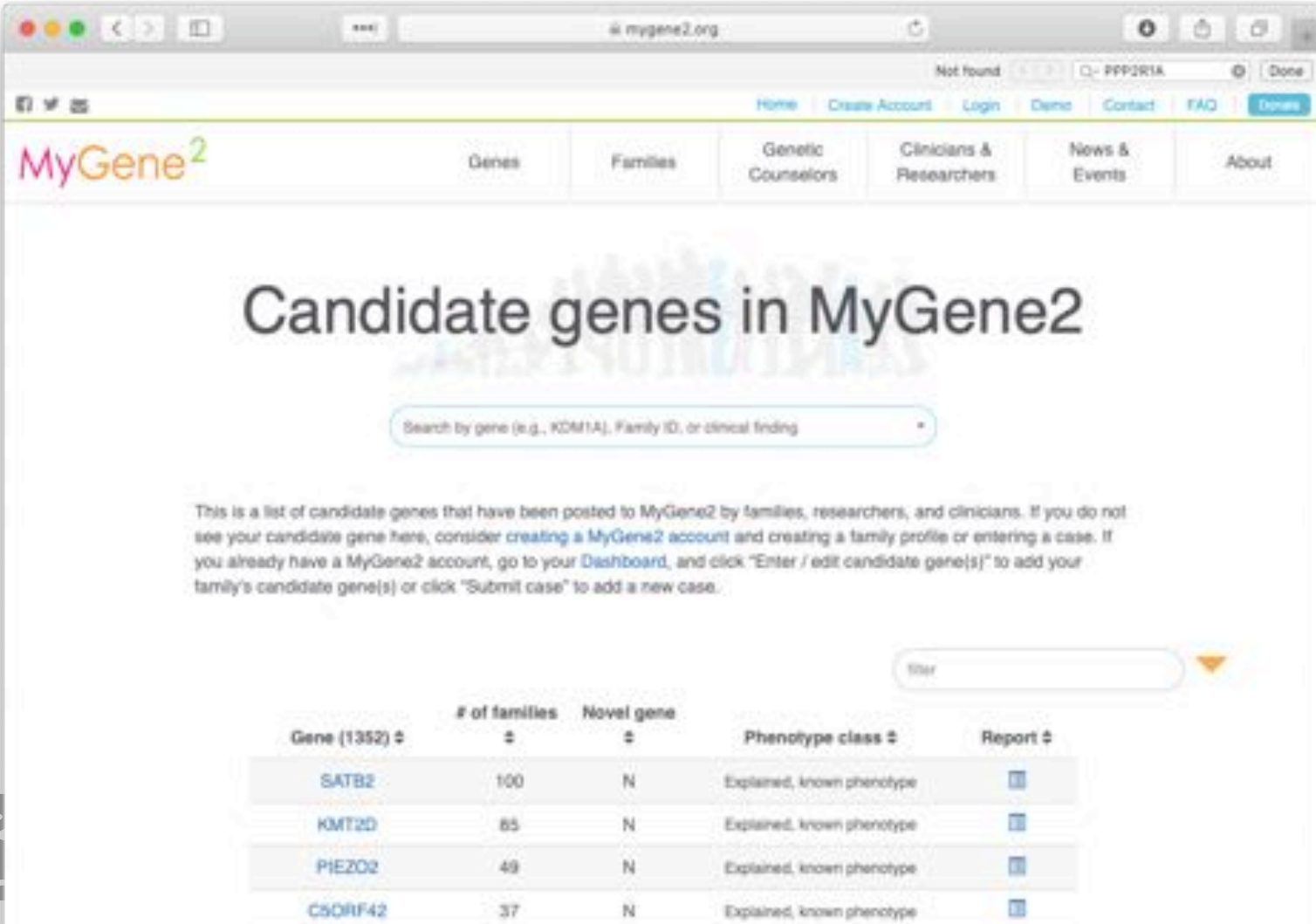


De Novo Mutations in *SLC25A24* Cause a Disorder Characterized by Early Aging, Bone Dysplasia, Characteristic Face, and Early Demise

Karin Witzl,^{1,*} Ales Maver,¹ Lidija Kovačić,² Paula Martinez-Valero,^{3,4,5} Laura Contreras,^{3,4,5} Jorgina Satrustegui,^{3,4,5} Marco Castori,⁶ Laurence Falvre,^{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. Hennekam¹³

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.

Find patient contributed information



The screenshot shows the MyGene2 website interface. At the top, there's a navigation bar with links: Home, Create Account, Login, Demo, Contact, FAQ, and Donate. Below this is a search bar with the text "Search by gene (e.g., KDM1A), Family ID, or clinical finding". The main heading is "Candidate genes in MyGene2". Below the heading, there's a paragraph explaining that this is a list of candidate genes posted to MyGene2 by families, researchers, and clinicians. It also provides instructions on how to create a MyGene2 account, create a family profile, or enter a case. At the bottom, there's a table with columns: Gene (1352) #, # of families, Novel gene, Phenotype class #, and Report #. The table lists four genes: SATB2, KMT2D, PIEZO2, and C5ORF42, each with its corresponding number of families, whether it's a novel gene, its phenotype class, and a report link.

Gene (1352) #	# of families	Novel gene	Phenotype class #	Report #
SATB2	100	N	Explained, known phenotype	Report
KMT2D	65	N	Explained, known phenotype	Report
PIEZO2	49	N	Explained, known phenotype	Report
C5ORF42	37	N	Explained, known phenotype	Report

Find patient contributed information

mygene2.org

Home Create Account Login Donate Contact FAQ

MyGene² Genes Families Genetic Counselors Clinicians & Researchers News & Events About

Variant(s): by gene

Search by gene (e.g., KCM1A), Family ID, or clinical finding *

Gene | SATB2

Description	SATB2 transcription 2
Number of families	106 (Show these families)
ORF	SATB2
GeneCards	SATB2
ClinVar	SATB2
MyGene2 Automated Match Report	Available

Filter results by:
Inheritance Model
- de novo
- autosomal recessive
- autosomal dominant
- X-linked
- other
Confidence in Pathogenicity
- benign
- likely benign
- uncertain significance
- suspected pathogenic
- likely pathogenic
- pathogenic

Candidate Variant ID	Ref. group	# Families	Inheritance	Chr Position	Alleles	Variant Type	Transcript	cDNA Change	Protein Change	Confidence in Pathogenicity
0142		1	de novo	chr2:200137108	G>	N/A	NM_001172509.1	c.200137108G>	p.(Glu175Ser)*1...	Likely pathogenic
0130		1	de novo	chr2:200137131	-C	N/A	NM_001172509.1	c.200137131C>	p.(Pro189Phe)*2...	Likely pathogenic
0141		1	de novo	chr2:200137189	AC>	N/A	NM_001172509.1	c.1492_1493AC>	p.(Thr506Ile)*1...	Likely pathogenic
0132		1	de novo	chr2:200137112	G>A	missense	NM_001172509.1	c.1964G>T	p.(Pro653Leu)	Likely pathogenic
0138		1	de novo	chr2:200137181	-T	N/A	NM_001172509.1	c.1965G>T	p.(Ser654Phe)*4...	Likely pathogenic
0143		1	de novo	chr2:200137238	GA	missense	NM_001172509.1	c.1905G>T	p.(Asp637Tyr)	Likely pathogenic
0009		1	unknown / other	chr2:200137380	G>A	stop_gained	NM_001172509.1	c.1758G>T	p.(Gln586*)	Likely pathogenic
0137		1	unknown / other	chr2:200137488	T>	N/A	NM_001172509.1	c.1728A>T	p.(Glu175Ser)*4...	Likely pathogenic
0136		1	unknown / other	chr2:200173688	G>	N/A	NM_001172509.1	c.1857G>C	p.(Asp603Ser)*7...	Likely pathogenic
0135		1	de novo	chr2:200173681	CTTC/TTT	N/A	NM_001172509.1	c.1858_1862CTTC/TTT	p.(Leu617Phe)*7...	Likely pathogenic

...and associated phenotypes

The screenshot shows the MyGene2.org website interface. The main heading is "Variant(s): by family". Below it is a search bar with the placeholder text "Search by gene (e.g., KCM1A), Family ID, or clinical finding". The candidate variant ID is 5142. The variant details are as follows:

Number of families	Gene	Chromosome	Position (hg19)	Allele	Transcript	cDNA change	Protein Change	Annotation	GERP	PolyPhen2(HumVar)	CAAD	ClinVar	Frequency in EVS	ExAC	1000 Genomes
1	SLIT3	10q2	201137108	G>A	NM_001172508.1	c.2026delG	p.(Gln170Serfs*18)	N/A	N/A	N/A	N/A	N/A	N/A (variant not seen in this database)	N/A (variant not seen in this database)	N/A (variant not seen in this database)

Search ClinVar for this variant

Filter results by:
Inheritance Model
- de novo
- autosomal recessive
- autosomal dominant
- X-linked
- other
Confidence in Pathogenicity
- benign
- likely benign
- uncertain significance
- suspected pathogenic
- likely pathogenic
- pathogenic

Family ID	Inheritance	Phenotype	Confidence in Pathogenicity
3447	de novo	Feeding difficulties in infancy (HP:0008672) Brain imaging abnormality (HP:0410803) Delayed speech and language development (HP:0000732) Abnormality of the dentition (HP:0000154) Delayed gross motor development (HP:0000134)	Likely pathogenic

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

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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.

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Preview

I have found a novel variant. What now?

Legacy databases and literature



Use existing sources to get the most information on your variant

Share phenotypes in a standardized way



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

Use match-making to identify similar patients



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 standardized way

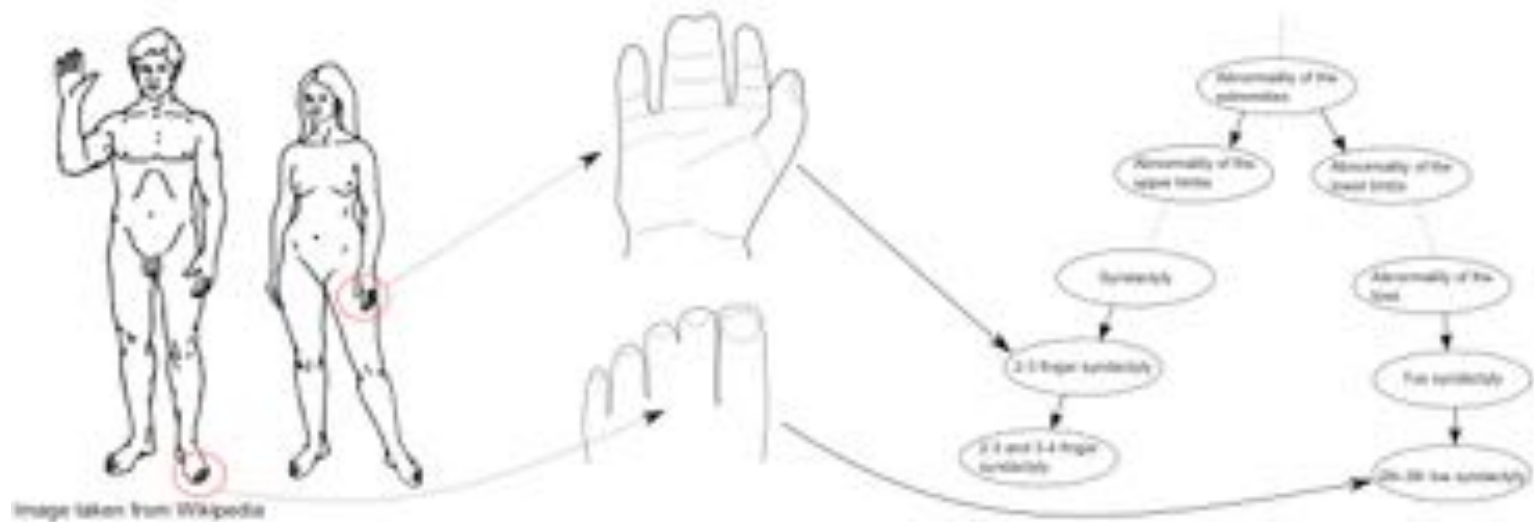


Use match-making to identify similar patients

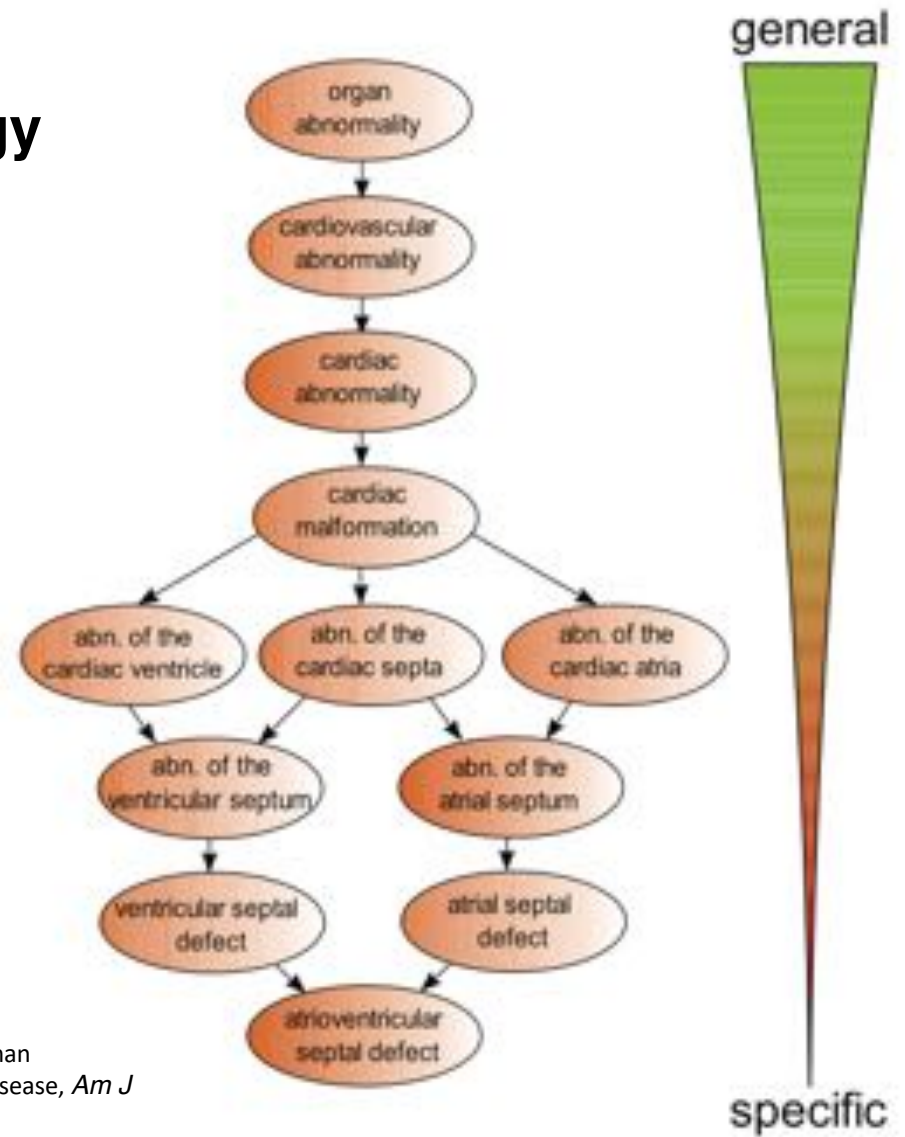


Human phenotype ontology

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



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

PHENO TIPS

Home > Data > P0000001 Create Browse Search

P0000001

Reported by Administrator on 2018/12/19 23:34 · Last modified on 2018/12/19 23:34 ✓ Save ✕ Cancel ✕ Delete Jump to... More actions

This record is owned by Administrator and is private. It is shared with no collaborators. [Modify permissions](#)

Patient information

Identifier: P0000001

Patient name:

Last name: Doe **First name:** John

Life status: Alive

Date of birth: 2004 01 10

Sex: ☒ Male ☐ Female ☐ Other ☐ Unknown

Indication for referral: Epileptic encephalopathy

Family history and pedigree

Phenotips enables streamlined collection of patients' phenotypes

The screenshot displays the Phenotips web application interface. The browser address bar shows "playground.phenotips.org". The page has a top navigation bar with "Save", "Cancel", "Delete", "Jump to...", and "More actions" buttons. The main content area is divided into sections: "Medical history", "Measurements", and "Clinical symptoms and physical findings". Below these, there is a checkbox for "This patient is clinically normal:" and a prompt to "Or select observed phenotypes:". A "Quick phenotype search:" box is present, followed by a "BROWSE CATEGORIES" list with expand/collapse controls. The right side shows a "CURRENT SELECTION" summary with a star rating and a "What's New?" link. Below this, there are lists of selected phenotypes under categories like "GROWTH PARAMETERS", "CUTANEOUS", "MUSCULOSKELETAL", and "NEUROLOGICAL", each with "ADD DETAILS" and "DELETE" buttons. At the bottom, there are buttons for "Display a menu", "SAVE AND VIEW SUMMARY", and "CANCEL CHANGES SINCE LAST SAVE".

Medical history

Measurements

Clinical symptoms and physical findings

☐ This patient is clinically normal:
Or select observed phenotypes: ?

Quick phenotype search:
Enter keywords and choose from the suggested ontology terms

BROWSE CATEGORIES EXPAND ALL COLLAPSE ALL

- ▶ GROWTH PARAMETERS
- ▶ CRANIOFACIAL
- ▶ EYE DEFECTS
- ▶ EAR DEFECTS
- ▶ CUTANEOUS
- ▶ CARDIOVASCULAR
- ▶ RESPIRATORY
- ▶ MUSCULOSKELETAL
- ▶ GASTROINTESTINAL
- ▶ GENITOURINARY
- ▶ BEHAVIOR, COGNITION AND DEVELOPMENT
- ▶ NEUROLOGICAL

CURRENT SELECTION

How informative is your phenotypic description: ★★★★★ [What's New?](#)

GROWTH PARAMETERS

Congenital microcephaly ADD DETAILS DELETE

CUTANEOUS

Synophrys ADD DETAILS DELETE

Hirsutism ADD DETAILS DELETE

Highly arched eyebrow ADD DETAILS DELETE

Long eyelashes ADD DETAILS DELETE

MUSCULOSKELETAL

2-3 toe syndactyly ADD DETAILS DELETE

Aplasia of the 5th finger ADD DETAILS DELETE

NEUROLOGICAL

Agenesis of corpus callosum ADD DETAILS DELETE

Display a menu SAVE AND VIEW SUMMARY CANCEL CHANGES SINCE LAST SAVE

Clinical information based on HPO profiles

The screenshot shows the 'playground.phenotips.org' web application. A yellow box highlights the 'Suggested Genes' section, which includes a 'HIDE' button and a list of terms: 'Microcephaly⁽⁷⁸⁰⁾', '2-3 toe syndactyly⁽³⁸¹⁾', and 'Hypercholesterolemia⁽³⁶¹⁾'. Below this, there is a 'DOWNLOAD' button and a checkbox for 'Exclude Tested Negative And Rejected Candidate Genes'. The main results section shows 'Results 1 - 10 out of 828 per page of 10'. It contains a table with two columns: 'Matching genes' and 'Associated phenotypes'. The table lists 10 genes: ARCN1, BCDR, CDC45, CEP55, COL4A3BP, DDX11, DHCR7, FGFR1, MEIS2, and MYCN. All associated phenotypes are '2-3 toe syndactyly; Microcephaly'. At the bottom, there are sections for 'Genotype information' and 'Diagnosis', each with a 'SHOW' button. The footer includes buttons for 'QUICK SAVE', 'SAVE AND VIEW SUMMARY', and 'CANCEL CHANGES SINCE LAST SAVE'.

Suggested Genes HIDE

Click on terms below (extracted from the phenotypic description) to disable or re-enable their contribution in the gene search results.

Microcephaly⁽⁷⁸⁰⁾ 2-3 toe syndactyly⁽³⁸¹⁾ Hypercholesterolemia⁽³⁶¹⁾

DOWNLOAD ? ☒ Exclude Tested Negative And Rejected Candidate Genes

Results 1 - 10 out of 828 per page of 10 Page 1 2 3 4 5 6 7 8 9 10 ... 83

Matching genes	Associated phenotypes
ARCN1 ?	2-3 toe syndactyly; Microcephaly
BCDR ?	2-3 toe syndactyly; Microcephaly
CDC45 ?	2-3 toe syndactyly; Microcephaly
CEP55 ?	2-3 toe syndactyly; Microcephaly
COL4A3BP ?	2-3 toe syndactyly; Microcephaly
DDX11 ?	2-3 toe syndactyly; Microcephaly
DHCR7 ?	2-3 toe syndactyly; Microcephaly
FGFR1 ?	2-3 toe syndactyly; Microcephaly
MEIS2 ?	2-3 toe syndactyly; Microcephaly
MYCN ?	2-3 toe syndactyly; Microcephaly

Results 1 - 10 out of 828 Page 1 2 3 4 5 6 7 8 9 10 ... 83

Genotype information SHOW

Diagnosis SHOW

QUICK SAVE **SAVE AND VIEW SUMMARY** **CANCEL CHANGES SINCE LAST SAVE**

Clinical information based on HPO profiles

playground.phenotips.org

Save Cancel Delete Jump to... More actions

Family history and pedigree [SHOW](#)

Medical history [SHOW](#)

Measurements [SHOW](#)

Clinical symptoms and physical findings [SHOW](#)

Suggested Genes [SHOW](#)

Genotype information [SHOW](#)

Diagnosis [HIDE](#)

Clinical diagnosis (ORDO)

Final diagnosis (OMIM)

▶ MATCHING DISORDERS IN OMIM

Additional comments:

☐ Case solved: ⓘ

Clinical information based on HPO profiles

The screenshot shows a web browser window at playground.phenotips.org. The page has a header with navigation buttons: Save, Cancel, Delete, Jump to..., and More actions. Below the header is a section titled "Diagnosis" with two input fields: "Clinical diagnosis (ORDO)" and "Final diagnosis (OMIM)". A yellow box highlights a section titled "MATCHING DISORDERS IN OMIM". Below this title is a paragraph explaining that the following terms are extracted from the phenotypic description and used automatically in searches. Below the paragraph are two tabs: "Generalized myoclonic seizures" and "Seizures". A list of disorders is displayed, each with a checkbox and a link to its OMIM entry. The disorders listed are:

- ☐ 410960 MYOCLONIC EPILEPSY, HARTUNG TYPE
- ☐ 310716 MYOCLONIC EPILEPSY, PROGRESSIVE
- ☐ 461236 MYOCLONIC EPILEPSY, JUVENILE, SUSCEPTIBILITY TO, 4
- ☐ 220205 DEAFNESS, CONGENITAL, AND FAMILIAL MYOCLONIC EPILEPSY
- ☐ 401618 EPILEPSY, IDIOPATHIC GENERALIZED, SUSCEPTIBILITY TO, 11
- ☐ 400848 MENTAL RETARDATION, X-LINKED 89
- ☐ 461240 EPILEPSY, IDIOPATHIC GENERALIZED, SUSCEPTIBILITY TO, 10
- ☐ 401621 MYOCLONIC EPILEPSY, FAMILIAL INFANTILE
- ☐ 400849 EPILEPSY, IDIOPATHIC GENERALIZED
- ☐ 401622 EPILEPSY, JUVENILE ABSENCE, SUSCEPTIBILITY TO, 1
- ☐ 400850 GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS, TYPE 2
- ☐ 421240 CARNOSINEMIA
- ☐ 423400 HYDROXYLYSINURIA
- ☐ 401623 EPILEPSY, JUVENILE ABSENCE, SUSCEPTIBILITY TO, 2

Try it: playground.phenotips.org

The screenshot shows a web browser window with the address bar displaying "playground.phenotips.org". The page features a header with the "PHENO TIPS" logo, a "Log-In" button, and a language selector set to "en". Below the header is a navigation bar with a "data" link, a "Create..." button (highlighted with a yellow box), a "Browse..." button, and a search bar. A prominent red banner across the middle of the page contains the following text: "This PhenoTips site is for demonstration/trial purposes only. Data entered here is public on the internet for everyone to see. Do not enter real patient data." Below the banner, the page is titled "PhenoTips Demo". On the left, under the heading "PHENOTIPS PLAYGROUND", there is a paragraph explaining the playground's purpose and a warning box stating: "Do not enter any private patient information in this demo database, as the data you enter may become available to all visitors of the playground. Do not rely on this demo database for any data storage, as all data is deleted periodically." On the right, under the heading "MY PATIENTS", there is a table of patient records. The table has columns for "Identifier", "Report name", and "Creation date". The first seven rows of the table are visible, showing identifiers from P0000001 to P0000007. The table also includes a "Results 1 - 25 out of 512" indicator and a "Page 1 2 3 4 5 6 7 8 9 10 ... 21" navigation bar.

PHENO TIPS

Log-In

Language: en

data Create... Browse... Search...

This PhenoTips site is for demonstration/trial purposes only. Data entered here is public on the internet for everyone to see.
Do not enter real patient data.

PhenoTips Demo

PHENOTIPS PLAYGROUND

The PhenoTips playground demonstrates the main features of the PhenoTips software as they are implemented in the latest stable snapshot. While the playground allows public access to the data (both read and write) for the visitor's convenience, real-world PhenoTips instances are always configured to be entirely password protected.

Do not enter any private patient information in this demo database, as the data you enter may become available to all visitors of the playground. Do not rely on this demo database for any data storage, as all data is deleted periodically.

For a quick tour of the PhenoTips functionalities, check out our

MY PATIENTS

Results 1 - 25 out of 512 per page of 25 1

Page 1 2 3 4 5 6 7 8 9 10 ... 21

Identifier	Report name	Creation date	
P0000001	123123	2019/03/11 16:08	
P0000002	03112019-case1	2019/03/11 16:32	
P0000003		2019/03/11 17:09	
P0000004		2019/03/11 18:02	
P0000006		2019/03/11 19:23	
P0000007	A2019	2019/03/11 19:38	
P0000008		2019/03/11 20:08	

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

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.

Free viewer online | Privacy & Cookies

Preview

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. Kleeftstra syndrome
5. Sotos syndrome

Voting link etc.ch/me6t

Insert Web Page

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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.

Free viewer online | Privacy & Cookies

Preview

Patient 2 - Diagnosis

CURRENT SELECTION

How informative is your phenotypic description: ★★★★★

GROWTH PARAMETERS

Macrocephaly ⓘ [ADD DETAILS](#)

Tall stature ⓘ [ADD DETAILS](#)

Overgrowth ⓘ [ADD DETAILS](#)

CRANIOFACIAL

Pointed chin ⓘ [ADD DETAILS](#)

Downslanted palpebral fissures ⓘ [ADD DETAILS](#)

Dolichocephaly ⓘ [ADD DETAILS](#)

Mandibular prognathia ⓘ [ADD DETAILS](#)

CARDIOVASCULAR

Atrial septal defect ⓘ [ADD DETAILS](#)

MUSCULOSKELETAL

Scoliosis ⓘ [ADD DETAILS](#)

BEHAVIOR, COGNITION AND DEVELOPMENT

Global developmental delay ⓘ [ADD DETAILS](#)

Top candidate diseases

- ☐ #317550 SOTOS SYNDROME 1 ⓘ
- ☐ #603331 NEUROFIBROMATOSIS-NOONAN SYNDROME ⓘ
- ☐ #614292 MENTAL RETARDATION, AUTOSOMAL RECESSIVE 15 ⓘ
- ☐ #300271 MENTAL RETARDATION, X-LINKED 72 ⓘ
- ☐ #614753 SOTOS SYNDROME 2 ⓘ
- ☐ #610883 POTOCKI-LUPSKI SYNDROME ⓘ
- ☐ #613615 CHROMOSOME 17q11.2 DELETION SYNDROME, 1.4-MB ⓘ
- ☐ #154700 MARFAN SYNDROME ⓘ
- ☐ #277580 WEAVER SYNDROME ⓘ
- ☐ #267000 PERLMAN SYNDROME ⓘ

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

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://](https://directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p) directpoll.com/r?XDbzPBd3ixYqg8ar52KsBWnhyXDsOZ7dQsWj8o8p

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

Free viewer online | Privacy & Cookies

Preview

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 standardized way



Use match-making to identify similar patients



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

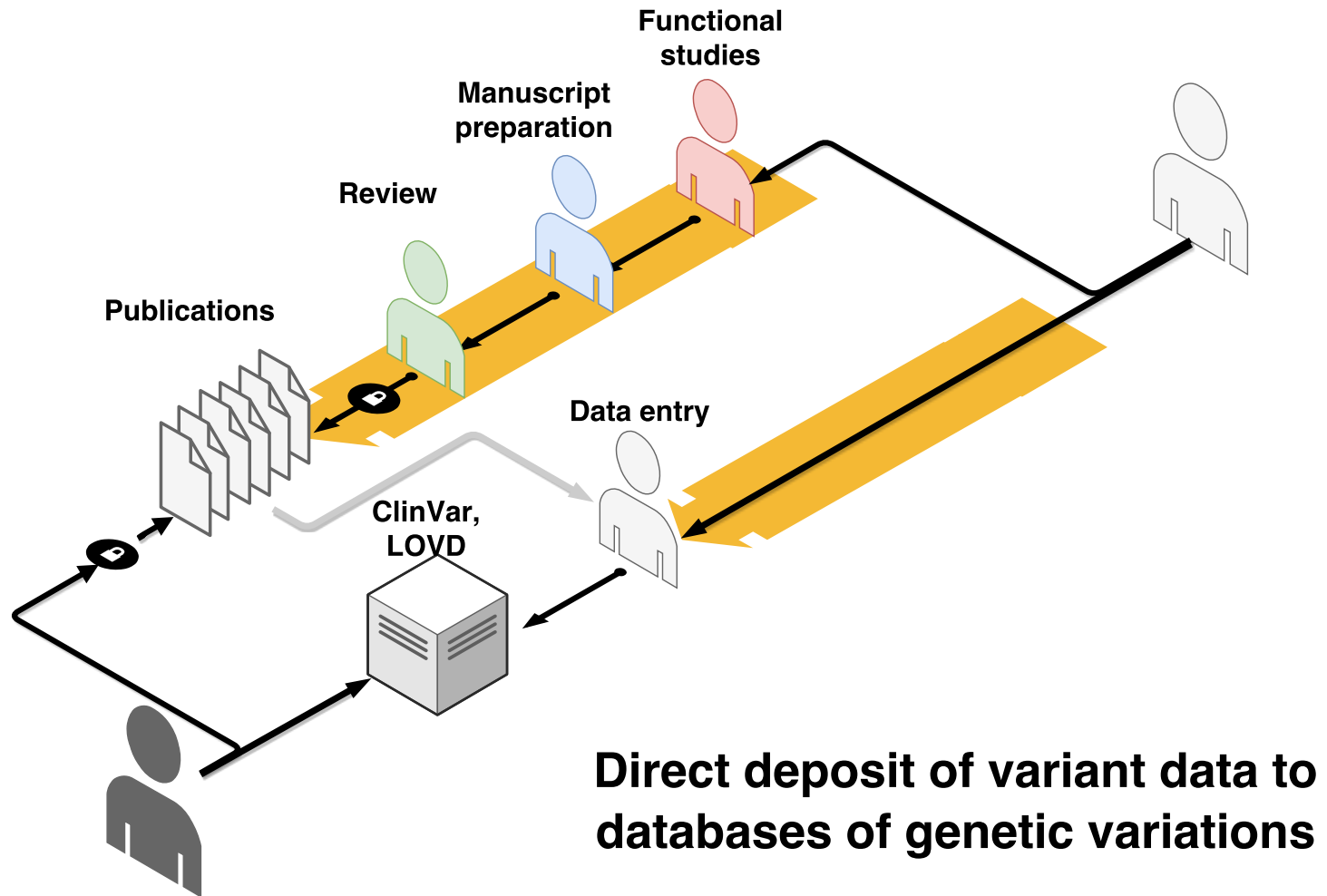
Share phenotypes in a standardized way

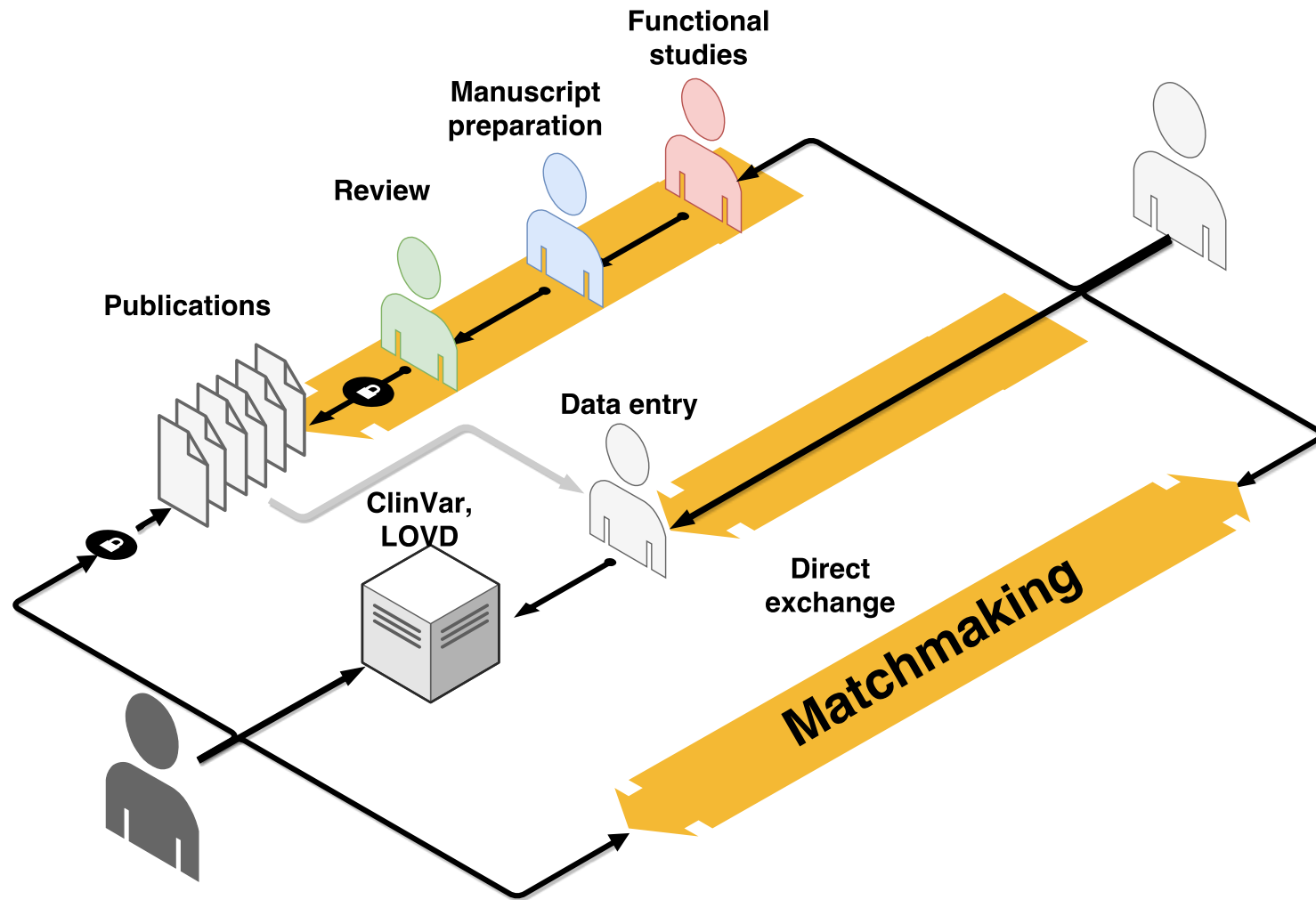


Use match-making to identify similar patients



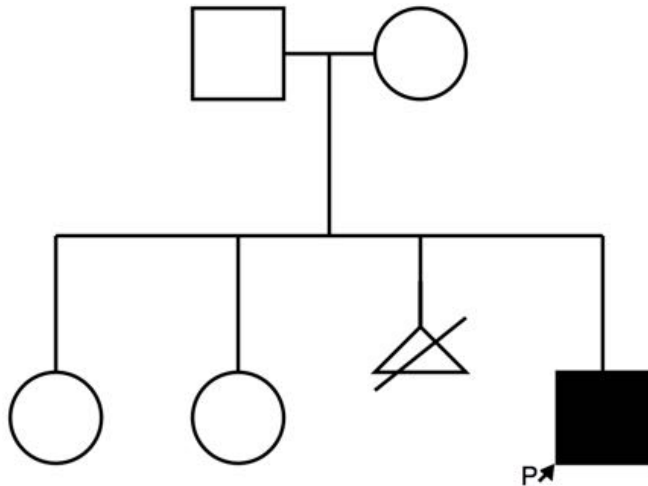
Genetic variant information sharing





Family with congenital arthrogryposis

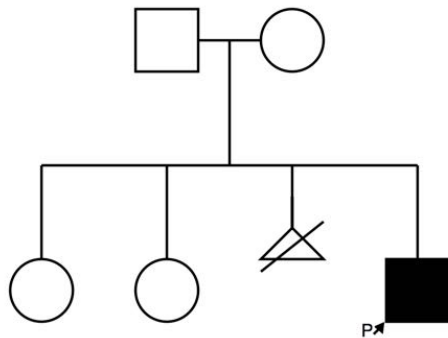
Family with a boy affected by congenital arthrogryposis multiplex, previous pregnancy was terminated due to similar symptoms



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

N-of-1

Patient #1
Clinical Geneticist #1



Patient #2
Clinical Geneticist #2



Phenotypic Data

Feature 1
Feature 2
Feature 3
Feature 4
Feature 5

Genotypic Data

Gene A
Gene B
Gene C
Gene D
Gene E
Gene F

Genomic Matchmaker

Genotypic Data

Gene D
Gene G
Gene H

Phenotypic Data

Feature 1
Feature 3
Feature 4
Feature 5
Feature 6

genomicsforall.org

Slide by Kym Boycott

<https://www.slideshare.net/raredisorders/kym-boycott-rare-disease-day-2016-conference>

Match-making



Match-making



Match-making



Match-making



Match-making



Match-making



Phenome Central

The screenshot shows a web browser window with the URL `phenomecentral.org`. The page header features the Phenome Central logo, navigation links like "About PhenomeCentral", and a user profile for "Ales Maver" with a "Log-out" button. A breadcrumb trail shows the path: `data > P0003531`. There are buttons for "Create...", "Browse...", and a search bar.

The main content area displays the patient ID **P0003531** in a dark box. Below it, a status bar indicates the record was "Reported by Ales Maver on 2017/02/08 18:23" and "Last modified on 2017/05/08 00:39". Action buttons include "Edit", "Delete", "Jump to...", and "More actions".

A summary line states: "This case is owned by you and is Q matchable. It is shared with no collaborators." An orange button labeled "Modify permissions" is on the right.

The section "Consents granted" contains the following text:

- I confirm that the data entered in this form corresponds to a real patient. (required)
- I confirm that consent has been obtained to share this patient's genetic sequencing data (e.g., a VCF file) on restricted access databases.
- I confirm that consent has been obtained to share this patient's medical and family history on restricted access databases.
- This patient is matchable through the MatchmakerExchange and you may receive occasional match notifications (unless you set the visibility to Private).

The "Patient information" section is expanded, showing:

- Identifier:** P00002
- Indication for referral:** Congenital contractures

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

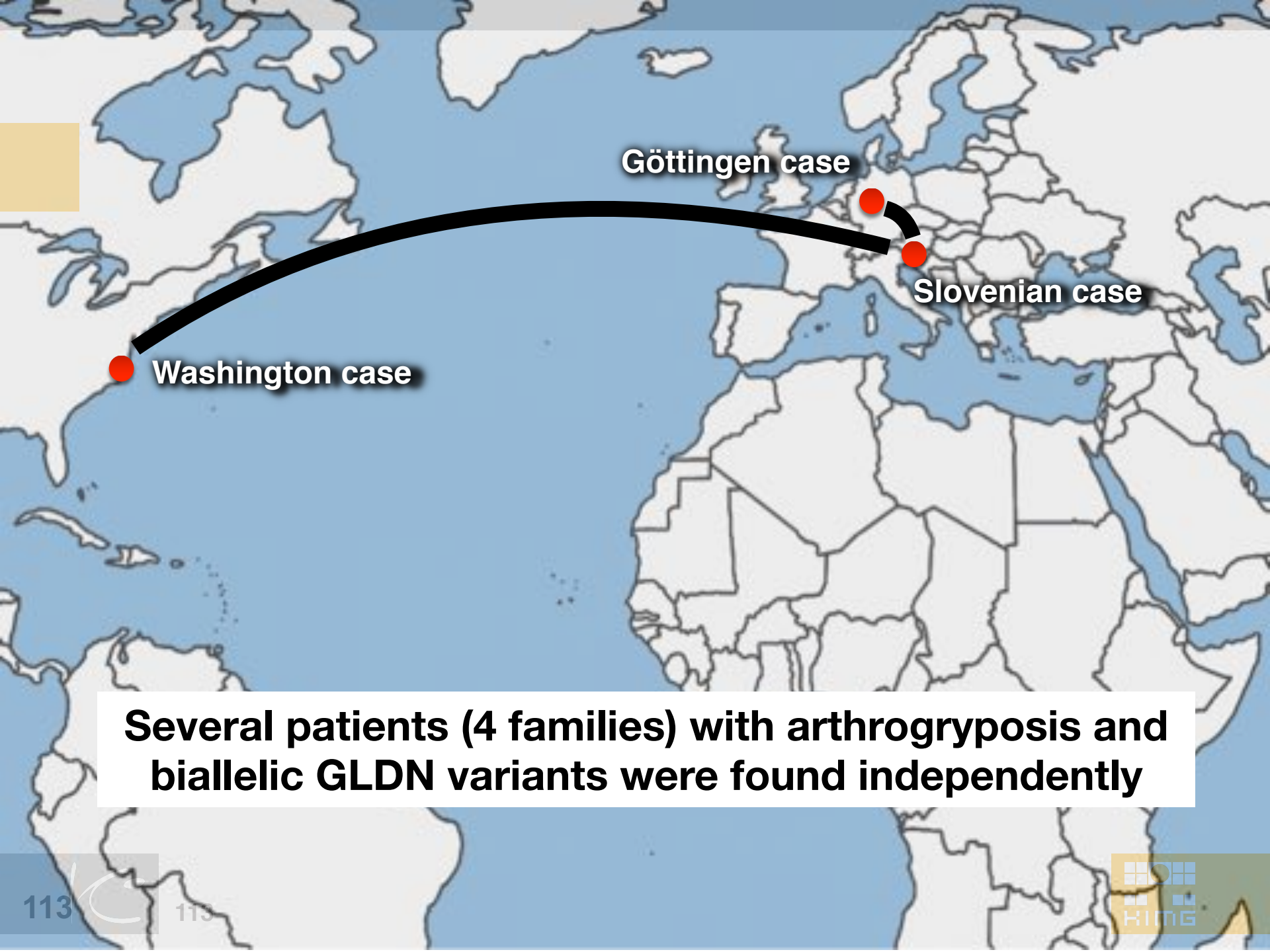
GENE	STATUS	STRATEGY	COMMENTS
1 GLDN ⓘ	Candidate	Sequencing	

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...



Göttingen case

Slovenian case

Washington case

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

Family with congenital arthrogryposis

REPORT

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

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

Jérôme
Marion
Ronald
Jérôme

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 Writzl⁷, Andreja Škofljanec⁸, Aleš Maver⁷, Francina Munell⁹, Stephan Ossowski^{4,10,11}, Mattia Bosio^{10,11}, Daniel J. Wegner¹, Marwan Shinawi¹, Dustin Baldridge¹, Bader Alhaddad⁵, Tim M. Strom^{5,6}, Dorothy K. Grange¹, Ekkehard Wilichowski², Robin Troxell¹², James Collins¹², Barbara B. Warner^{1,13}, Robert E. Schmidt¹⁴, Alan Pestronk¹⁴, F. Sessions Cole^{1,†}, and Robert Steinfeld^{2,†}

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

Try it yourself!

playground.phenomecentral.org

Login: MoscowVEP

Password: moscow

The screenshot shows a web browser window with the URL `playground.phenotips.org`. The page features a navigation bar with the PhenoTips logo, a 'Log-in' link, and a language selector. Below the navigation bar is a red warning banner that reads: "This PhenoTips site is for demonstration/trial purposes only. Data entered here is public on the internet for everyone to see. Do not enter real patient data." The main content area is titled "PhenoTips Demo" and contains two sections: "PHENOTIPS PLAYGROUND" and "MY PATIENTS". The "PHENOTIPS PLAYGROUND" section explains that the playground demonstrates the main features of the PhenoTips software and that data entered is public. The "MY PATIENTS" section displays a table of patient data with columns for Identifier, Report name, and Creation date. The table shows 6 patients, with the first one having the identifier P0000001 and the report name 123123. A warning icon and text are visible at the bottom left of the page.

PHENOTIPS PLAYGROUND

The PhenoTips playground demonstrates the main features of the [PhenoTips](#) software as they are implemented in the latest stable snapshot. While the playground allows public access to the data (both read and write) for the visitor's convenience, real-world PhenoTips instances are always configured to be entirely password protected.

MY PATIENTS

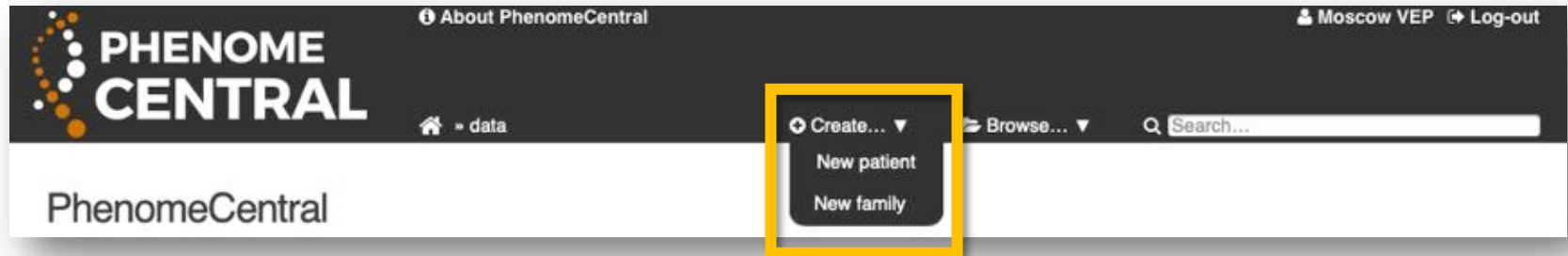
Results 1 - 25 out of 453 per page of 25

Page 1 2 3 4 5 6 7 8 9 10 ... 19

Identifier	Report name	Creation date	
Type to filter ...	Type to filter ...		
P0000001	123123	2019/03/11 16:08	
P0000002	03112019-case1	2019/03/11 16:32	
P0000003		2019/03/11 17:09	
P0000004		2019/03/11 18:02	
P0000006		2019/03/11 19:23	
P0000007		2019/03/11 19:23	

Do not enter any private patient information in this demo database, as the data you enter may become available to all visitors of the playground. Do not rely on this demo database for any data storage, as all data is deleted periodically.

Create a new patient



Grant matching consents

The image shows a form titled 'Consents granted'. It contains five checkboxes, all of which are checked:

- ☒ I confirm that the data entered in this form corresponds to a real patient. (required)
- ☒ I confirm that consent has been obtained to share this patient's genetic sequencing data (e.g., a VCF file) on restricted access databases.
- ☒ I confirm that consent has been obtained to share this patient's medical and family history on restricted access databases.
- ☒ I confirm that consent has been obtained to share this patient's medical images/photos on restricted access databases.
- ☒ This patient is matchable through the MatchmakerExchange and you may receive occasional match notifications (unless you set the visibility to Private).

At the bottom of the form, there is an orange button labeled 'I agree'.

Add phenotype data

The image shows a form titled 'Clinical symptoms and physical findings'. It has a 'HIDE' button in the top right corner. Below the title, there is a checkbox labeled 'This patient is clinically normal:' and a link 'Or select observed phenotypes:'. Below this, there is a search bar with a magnifying glass icon and the text 'Quick phenotype search: Enter keywords and choose from the suggested ontology terms'. Below the search bar, there is a section titled 'BROWSE CATEGORIES' with a link 'EXPAND ALL' and a link 'COLLAPSE ALL'. Below this, there is a list of categories, with 'GROWTH PARAMETERS' being the first one.

Add the genetic information

Genotype information HIDE

LIST OF GENES

GENE	STATUS	STRATEGY	COMMENTS
+ ADD GENE ?			

Click save and view summary at the bottom of page

[QUICK SAVE](#) [SAVE AND VIEW SUMMARY](#)

Find matches!

MATCHES IN PHENOMECENTRAL

Showing similar cases 1-10 out of 15 per page of 10

[REFRESH MATCHES](#)

Case ID	Diagnosis	Contact	Relevance	Phenotype and genotype similarity
P0000029	Undiagnosed	Moscow VEP <small>(this case belongs to you)</small>	71%	SHOW
P0000029	Rare genetic diseases	Alex Mayer	18%	SHOW
P0000005	SPINAL MUSCULAR ATROPHY, TYPE III	Mary Green	5%	SHOW
P0000026	Undiagnosed	Alex Mayer	3%	SHOW

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)

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.

Free viewer online | Privacy & Cookies

Preview

We have got a match!

Case ID	Diagnosis	Contact	Relevance	Phenotype and genotype similarity
P0000026	Undiagnosed	Alex Mayer	94%	<input type="checkbox"/> HIDE

THE CURRENT PATIENT (P0000030)	THE MATCHED PATIENT (P0000026)
AGE OF ONSET	
-	-
MODE OF INHERITANCE	
-	-
PHENOTYPE	
ABNORMALITY OF HEAD OR NECK	
Downslanted palpebral fissures	Downslanted palpebral fissures
Prominent forehead	Prominent forehead
Microcephaly	Microcephaly
Hypertelorism	Hypertelorism
Epicanthus	Epicanthus
Abnormal facial shape	
ABNORMALITY OF LIMBS	
Talipes calcaneovalgus	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	
DNKL1	

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

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)

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.

Free viewer online | Privacy & Cookies

Preview

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)

No gene match, partial phenotype overlap

Case ID	Diagnosis	Contact	Relevance	Phenotype and genotype similarity
P0000028	Rare genetic disease	Aleš Mayer	24%	HIDE
<div><div>THE CURRENT PATIENT (P0000031)</div><div>THE MATCHED PATIENT (P0000028)</div><div>AGE OF ONSET</div><div><div>-</div><div>Congenital onset</div></div><div>MODE OF INHERITANCE</div><div><div>-</div><div>Sporadic</div></div><div>PHENOTYPE</div><div>ABNORMALITY OF THE NERVOUS SYSTEM</div><div><div>Inability to walk Absent speech Central hypotonia Periventricular leukomalacia</div><div>Inability to walk Absent speech Abnormal brainstem MRI signal intensity</div></div><div>UNMATCHED</div><div><div></div><div>Generalized hypotonia</div></div><div>GENOTYPE</div><div>No genotype matches found</div></div>				

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.

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Preview

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

The image displays the PhenomeCentral website interface, which lists patient cases and their matches across various databases. The website shows a list of cases with columns for Remote Case ID, Diagnosis, Contact, Relevance, and Phenotype and genotype similarity. A circular inset diagram illustrates the global alliance network, centered around PhenomeCentral, with connections to various partner organizations.

Global Alliance Network Diagram:

- PhenomeCentral (Central Node)
- GeneMatcher
- DECIPHER
- matchbox
- BROAD INSTITUTE
- IRUD
- Japan Agency for Medical Research and Development
- Australian Genomics Health Alliance
- monarch INITIATIVE
- DBCLS
- MyGene2
- CARE for RARE
- RD Connect
- Johns Hopkins
- Baylor College of Medicine
- Sanger Institute
- DECIPHER

Website Interface Details:

- Search results for "Undiagnosed" cases.
- Case details for "46,XY SEX REVERSAL 3" and "ANDROGEN INSENSITIVITY SYNDROME".
- Match results for "DECIPHER" with a relevance of 50%.
- Buttons for "SHOW DISCLAIMER" and "REFRESH MATCHES".

Use data sharing platforms!

Legacy databases and literature



ClinVar



Use existing sources to get the most information on your variant

Share phenotypes in a standardized way



PHENOTIPS™



ClinVar



Geno2MP

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

Use match-making to identify similar patients



MyGene²



Thank you!

Prof. Borut Peterlin



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