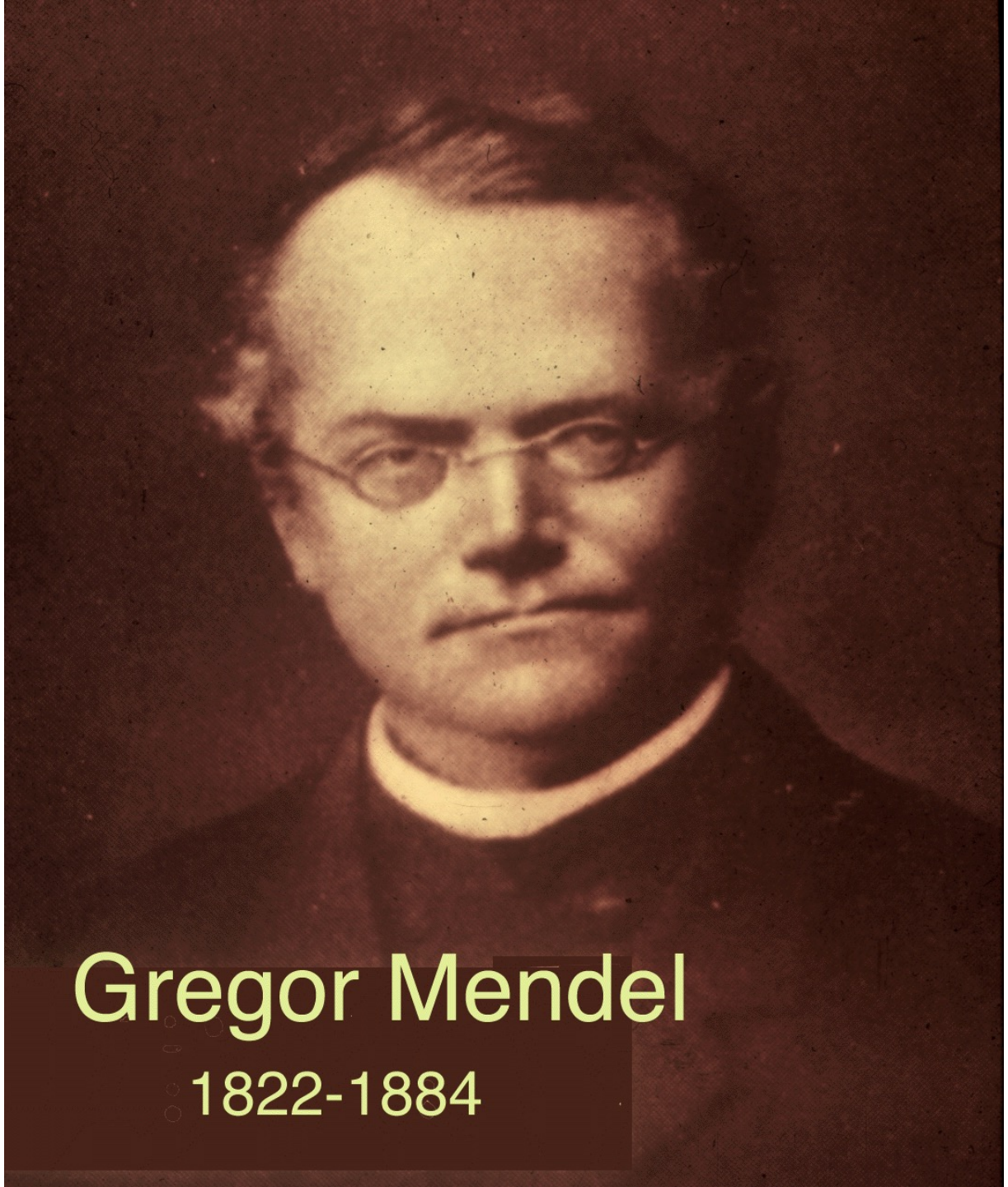
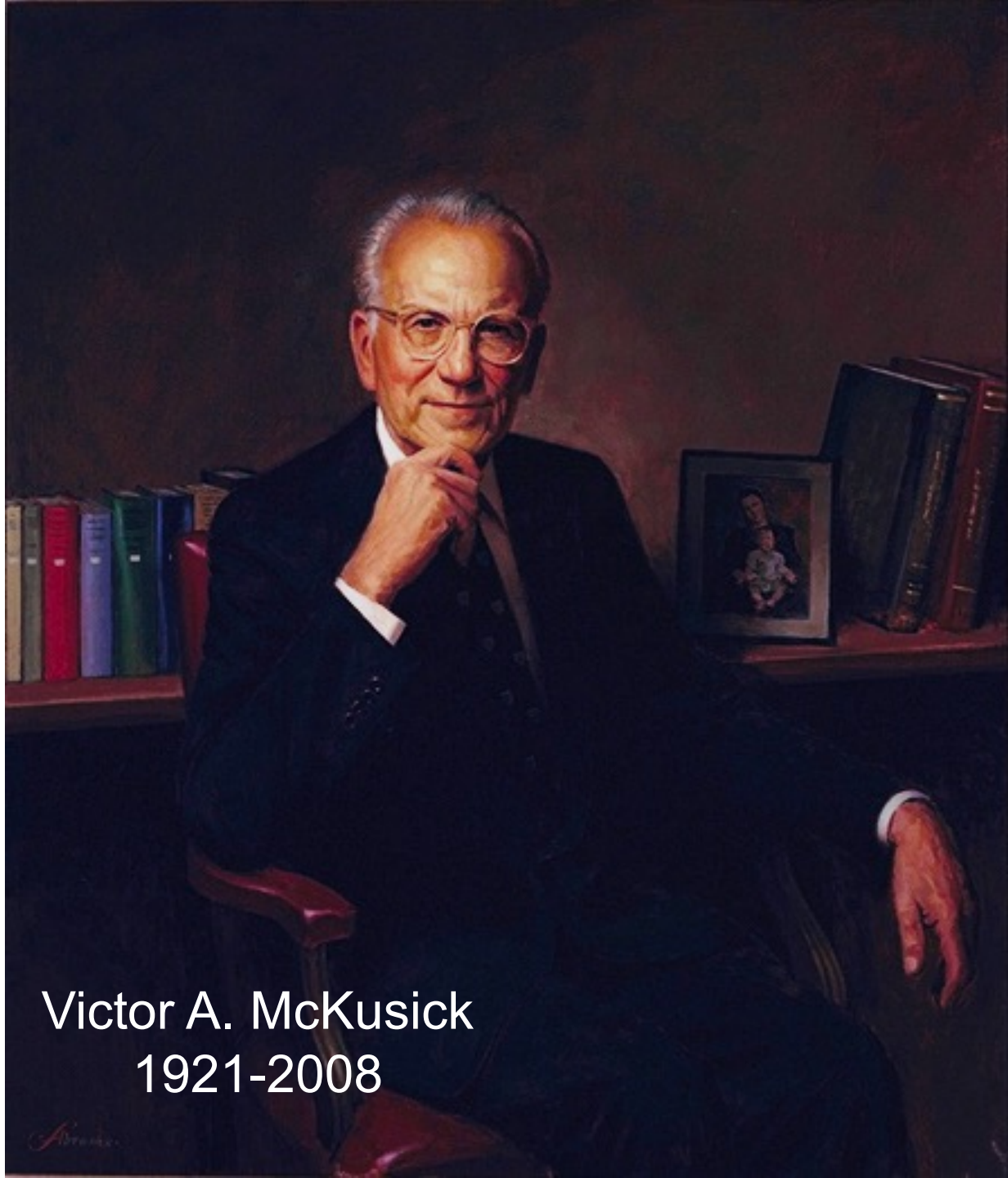
Phenotyping patients to characterize disorders and establish disease genes: Lessons from my 30 years at OMIM

Ada Hamosh, MD, MPH

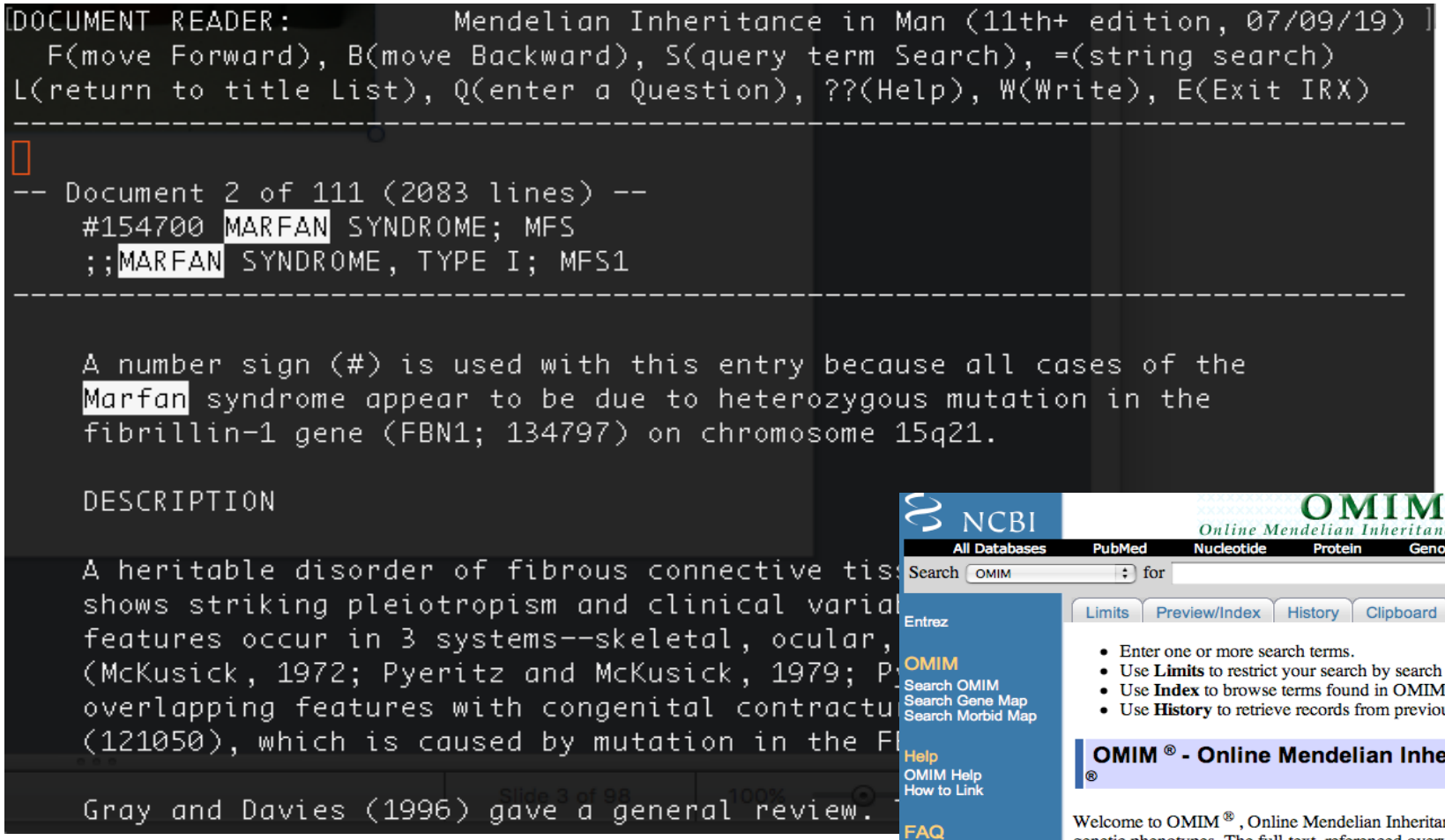
Dr. Frank V. Sutland Professor of Genetics

Department of Genetic Medicine, Johns Hopkins

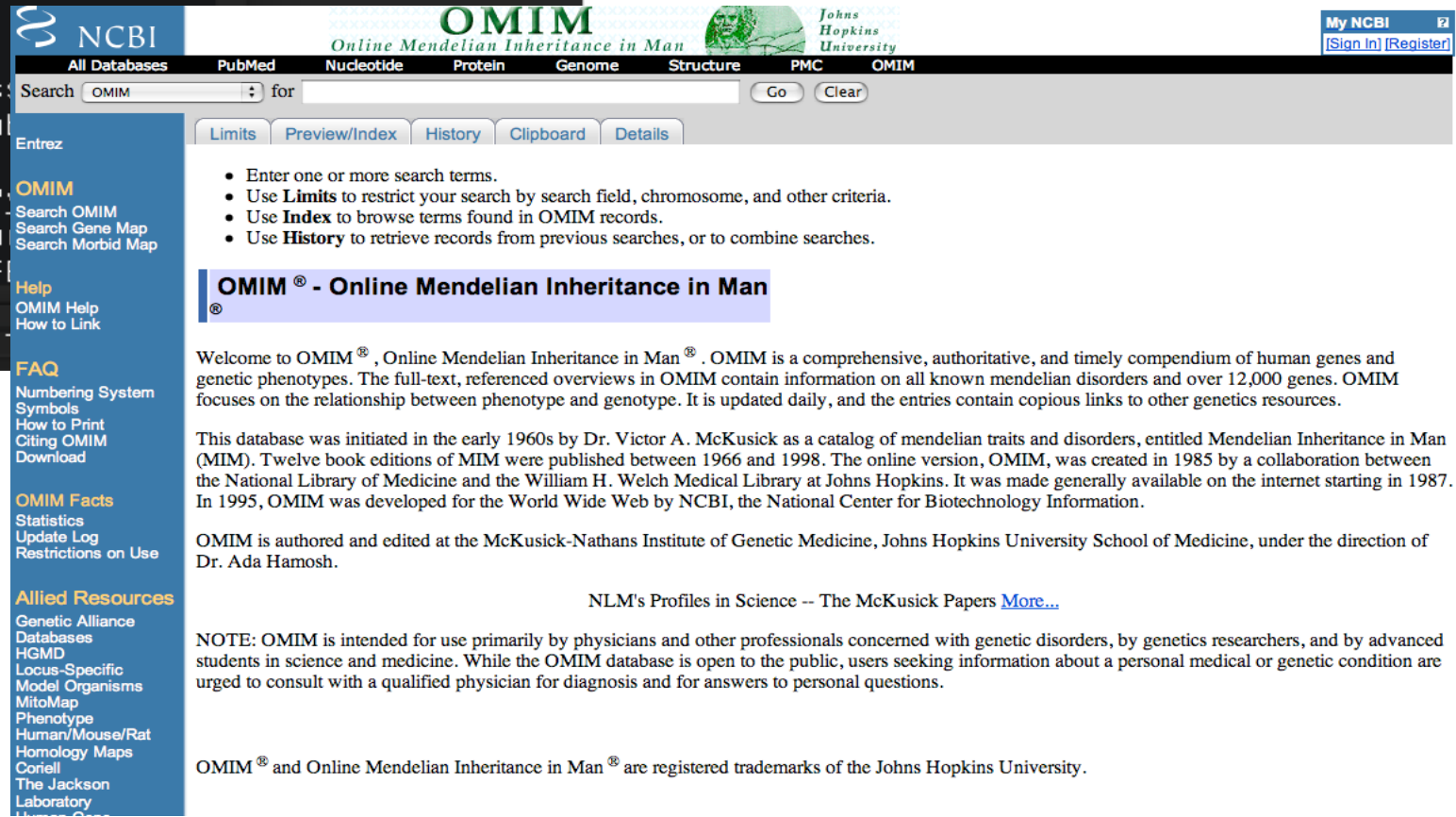

Gregor Mendel
1822-1884


Victor A. McKusick
1921-2008

Mendelian Inheritance in Man
from *A Catalog of Autosomal Dominant, Autosomal Recessive and X-linked Disorders*
to *A Catalog of Human Genes and Genetic Disorders*
1966 (1st edition) – 1998 (12th edition)

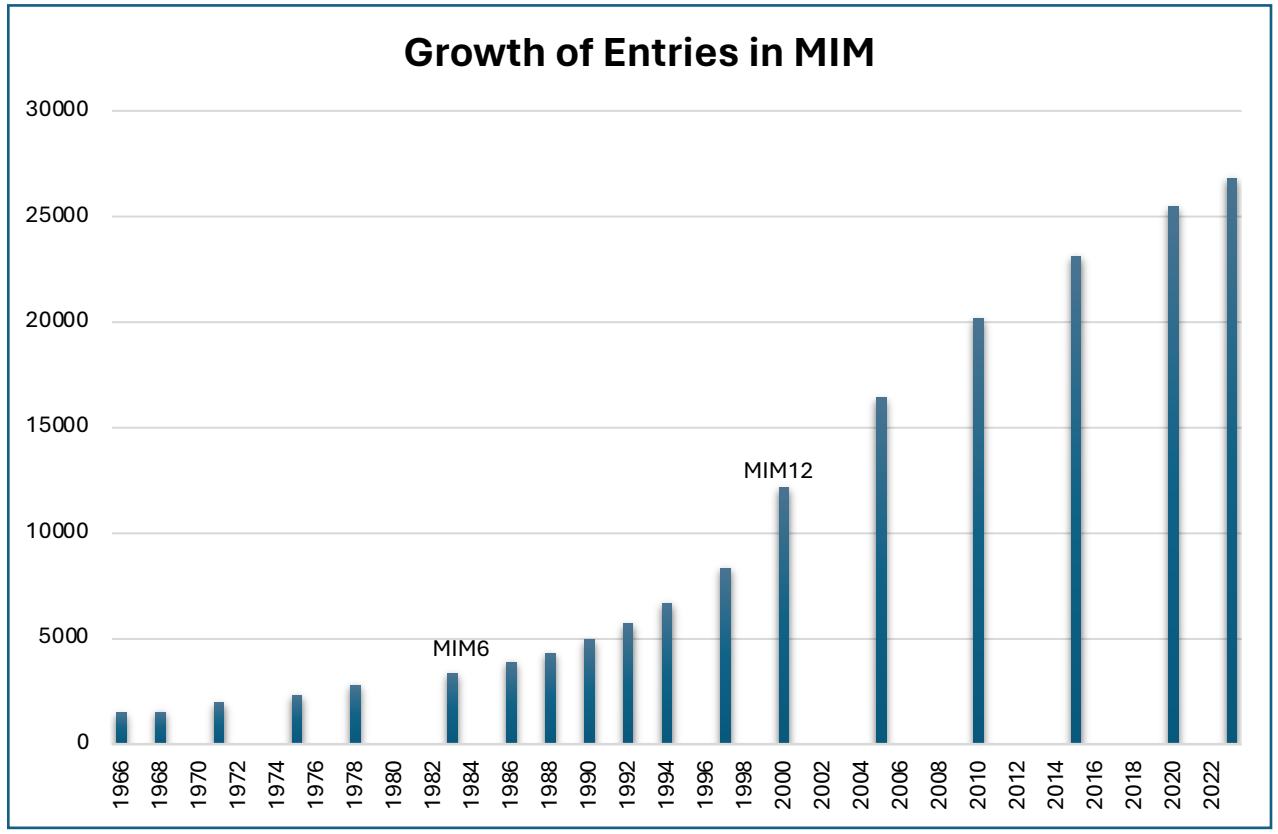


MIM was part of an Information Retrieval Experiment (IRx) project developed at the NLM. It supported full text retrieval using natural language. In 1987, MIM went online and became OMIM. It was made available on the internet from the Welch Medical Library.



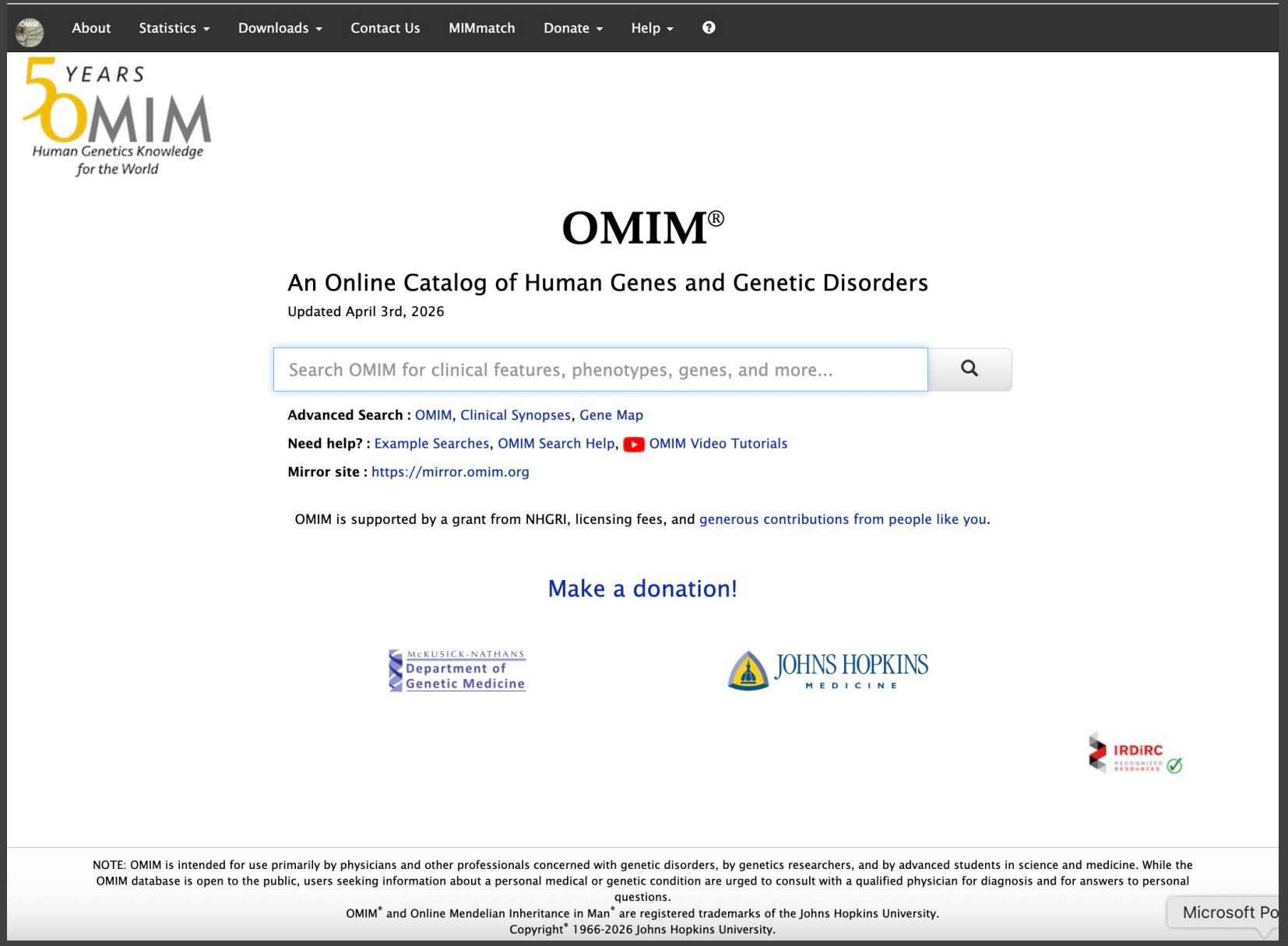
In 1995, OMIM was moved to the world wide web by NCBI and was incorporated into their Entrez suite of databases. It remained there until OMIM.org debuted in January 2011.

History of MIM/OMIM



- 1966 - MIM1 had 1486 entries, no genes
- 1983 - MIM6, when genes were added
- 1987 - OMIM becomes available by dial-up
- 1995 – NCBI adapts OMIM for the World Wide Web
- 1998 -MIM12, the last published with 8355 entries, majority genes
- 2011 – New home is OMIM.org, where searching is optimized
- Today 28,147 entries and adding ~250 new phenotypes per year

OMIM.org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An Online Catalog of Human Genes and Genetic Disorders
Updated April 3rd, 2026
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NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions.
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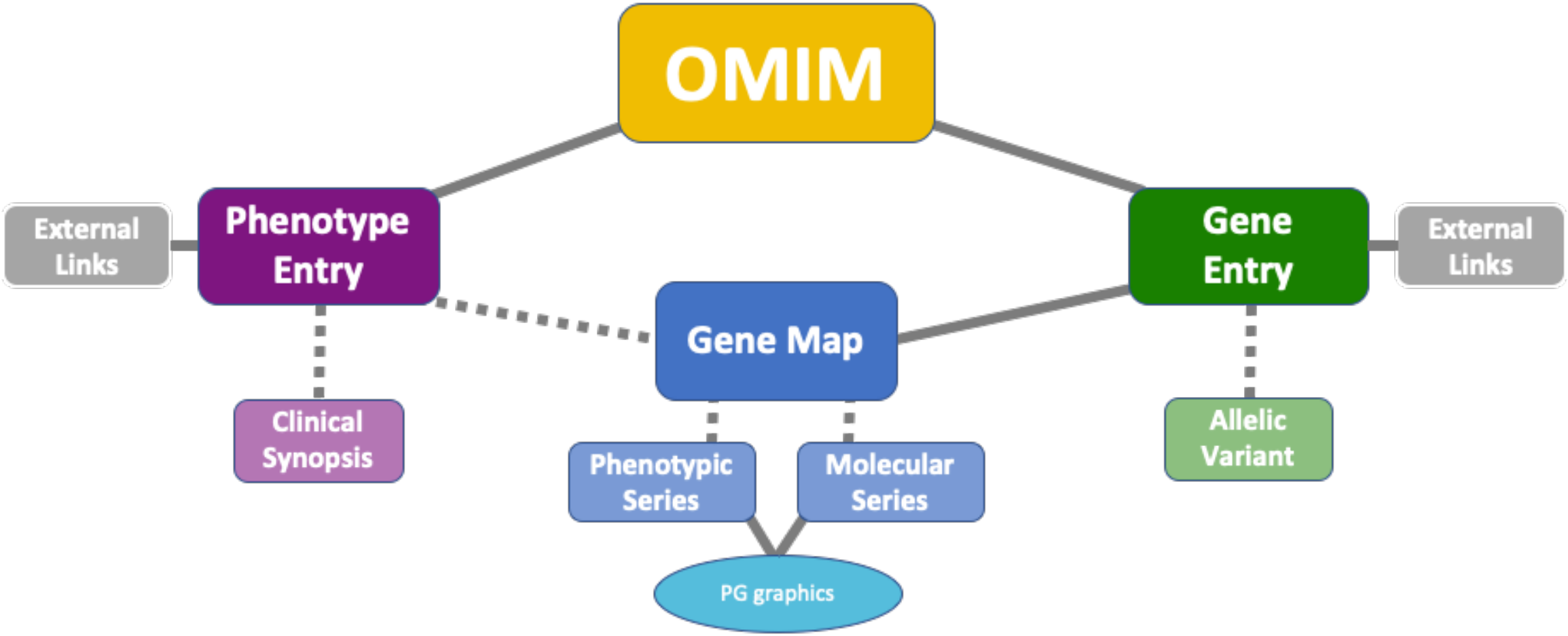
Microsoft Po

OMIM Information Framework



*Each gene or phenotype entry is assigned a unique 6-digit number (MIM number) that is stable.

OMIM Entries

- Each entry has a unique, stable MIM number (MIM numbers are used heavily in the biomedical literature and as crosslinks within other data resources.)
- Primary titles and other aliases and symbols
- Rich, full text descriptions of genes and genetic phenotypes/disorders in structured formats (e.g., gene structure, function, animal model, variation or clinical features, pathogenesis, molecular genetics, clinical synopsis)
- Expert curation and predictable semantic structure
- Cited to peer-reviewed biomedical literature

OMIM Staff

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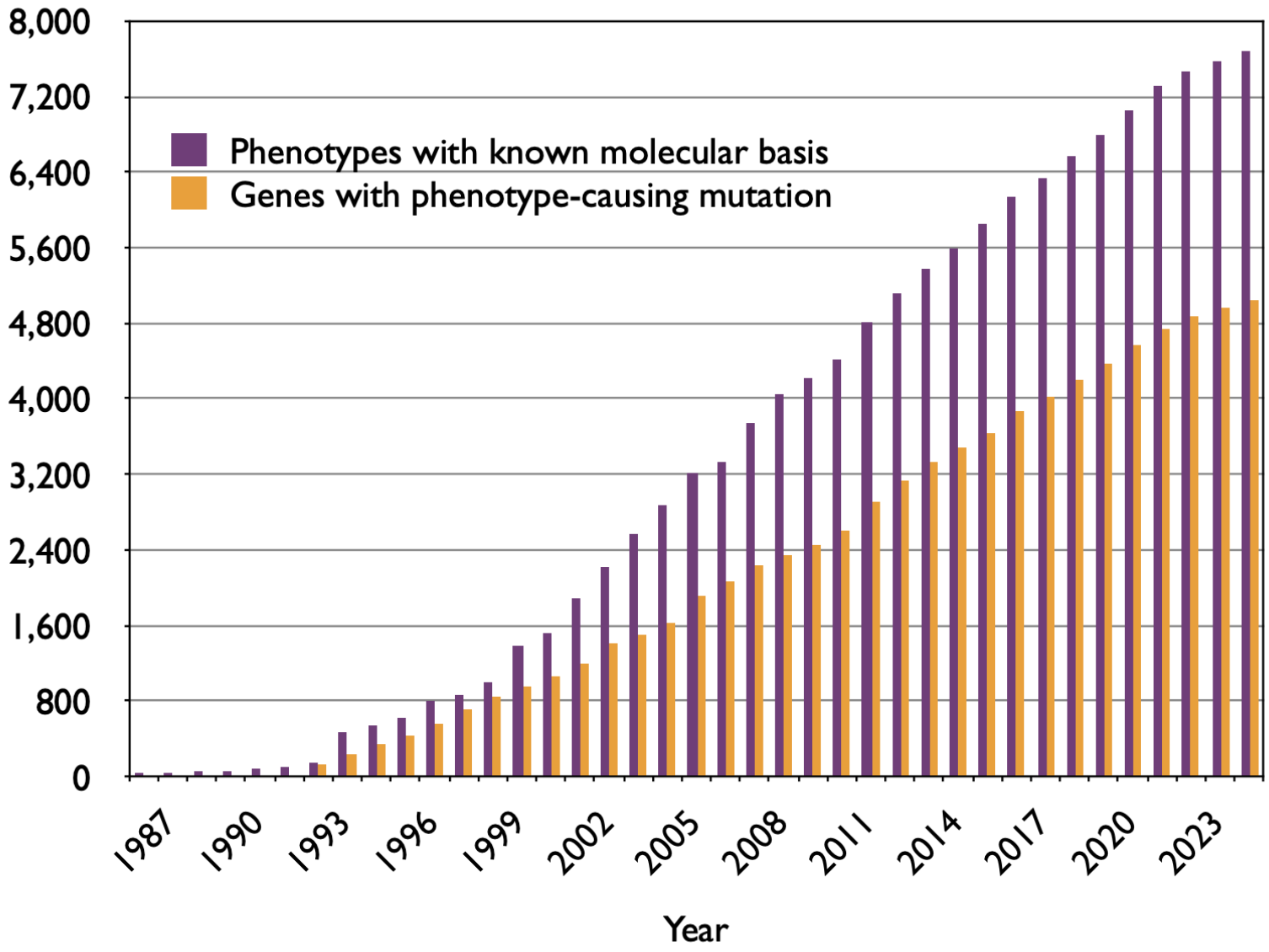
Growth of Gene-Phenotype Relationships

1 January 2026

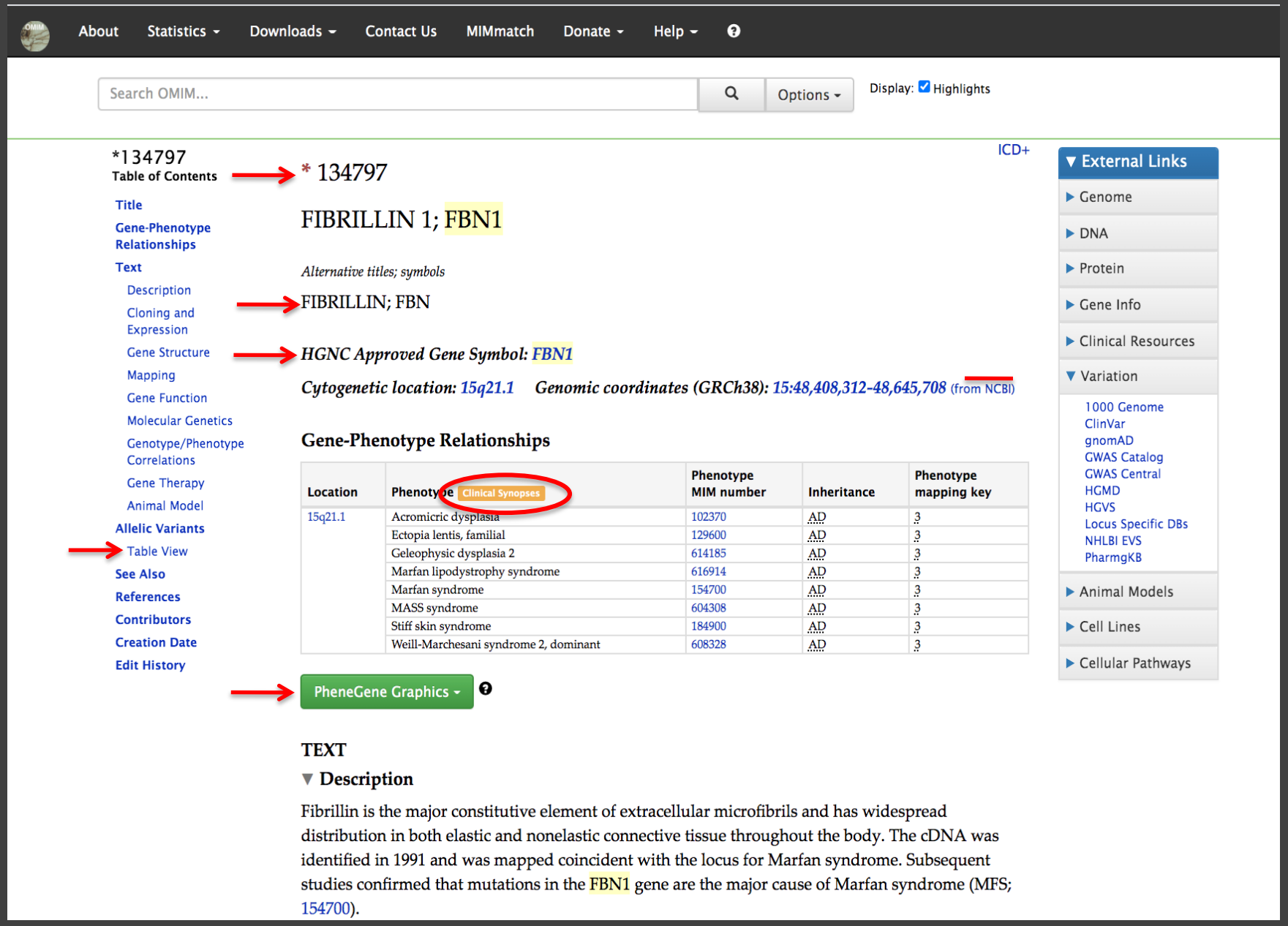


Source: OMIM®

OMIM Genes

- Over 17,800 entries
  - protein coding genes
  - microRNAs
  - long noncoding RNAs
  - locus control regions
  - and more
- Over 5,428 entries have allelic variants
- Over 36,000 allelic variants in OMIM

Gene Entry



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*134797
Table of Contents

Title
Gene-Phenotype Relationships
Text
Description
Cloning and Expression
Gene Structure
Mapping
Gene Function
Molecular Genetics
Genotype/Phenotype Correlations
Gene Therapy
Animal Model
Allelic Variants
Table View
See Also
References
Contributors
Creation Date
Edit History

ICD+

* 134797

FIBRILLIN 1; FBN1

Alternative titles; symbols

FIBRILLIN; FBN

HGNC Approved Gene Symbol: FBN1

Cytogenetic location: 15q21.1 Genomic coordinates (GRCh38): 15:48,408,312-48,645,708 (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
15q21.1	Acromicric dysplasia	102370	AD	3
	Ectopia lentis, familial	129600	AD	3
	Geleophysic dysplasia 2	614185	AD	3
	Marfan lipodystrophy syndrome	616914	AD	3
	Marfan syndrome	154700	AD	3
	MASS syndrome	604308	AD	3
	Stiff skin syndrome	184900	AD	3
	Weill-Marchesani syndrome 2, dominant	608328	AD	3

PheneGene Graphics

TEXT

Description

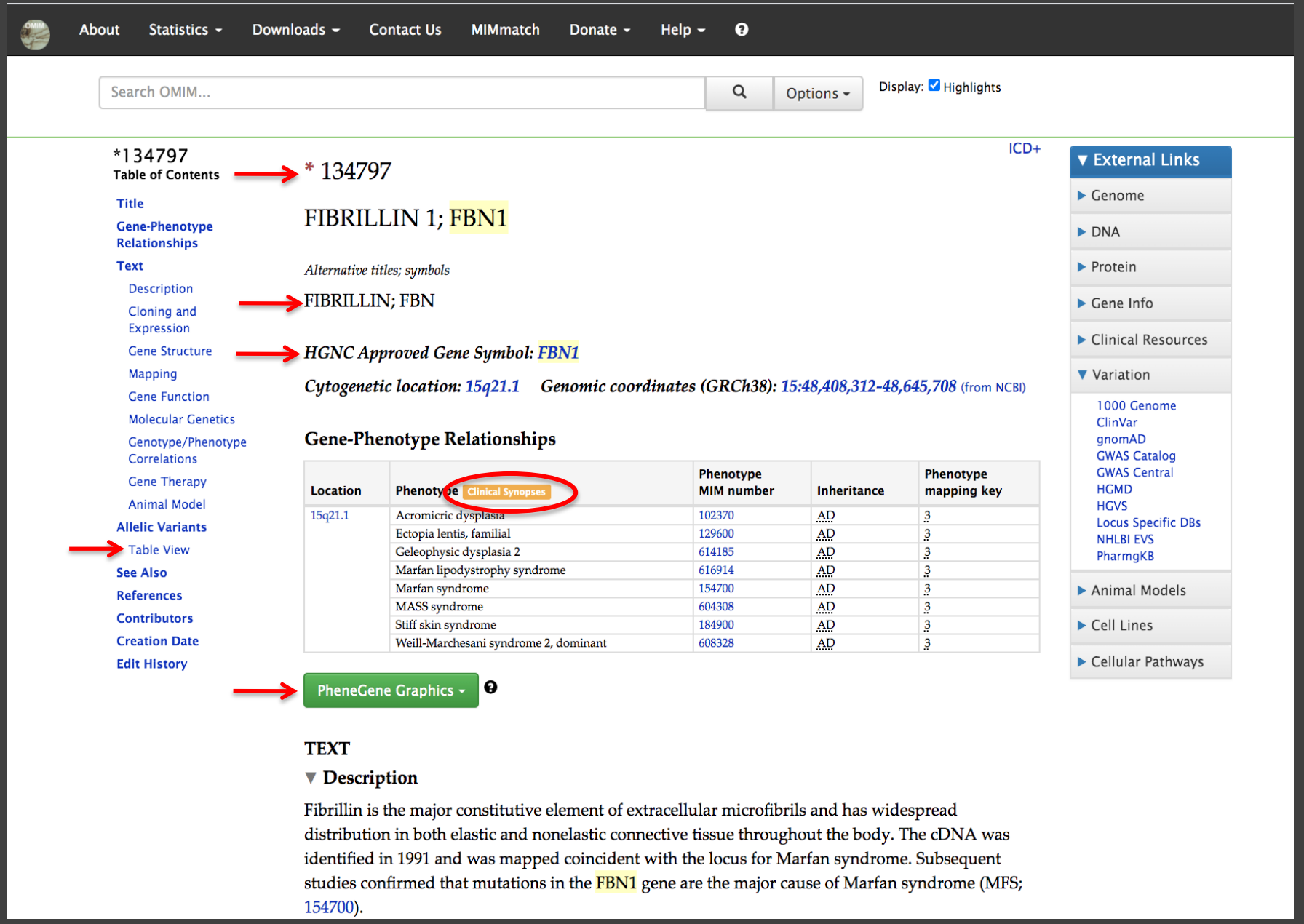
Fibrillin is the major constitutive element of extracellular microfibrils and has widespread distribution in both elastic and nonelastic connective tissue throughout the body. The cDNA was identified in 1991 and was mapped coincident with the locus for Marfan syndrome. Subsequent studies confirmed that mutations in the FBN1 gene are the major cause of Marfan syndrome (MFS; 154700).

External Links
Genome
DNA
Protein
Gene Info
Clinical Resources
Variation
1000 Genome
ClinVar
gnomAD
GWAS Catalog
GWAS Central
HGMD
HGVS
Locus Specific DBs
NHLBI EVS
PharmgKB
Animal Models
Cell Lines
Cellular Pathways

Gene Related Phenotypes Clinical Synopses Table

NUMBER	# 102370	# 129600	# 614185	# 616914	# 154700	# 604308	# 184900	# 608328
TITLE	ACROMICRIC DYSPLASIA; ACMICD	ECTOPIA LENTIS 1, ISOLATED, AUTOSOMAL DOMINANT; ECTOL1	GELEOPHYSIC DYSPLASIA 2; GPHYSD2	MARFANOID-PROGEROID-LIPODYSTROPHY SYNDROME; MFLS	MARFAN SYNDROME; MFS	MASS SYNDROME	STIFF SKIN SYNDROME; SSKS	WEILL-MARCHESANI SYNDROME 2; WMS2
GENE	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797
INHERITANCE (in 8/8)	- Autosomal dominant	- Autosomal dominant	- Autosomal dominant	- Autosomal dominant	- Autosomal dominant	- Autosomal dominant	- Autosomal dominant	- Autosomal dominant
GROWTH (in 7/8) ▼	*Height* - Short stature, severe		*Height* - Short stature	*Height* - Tall stature	*Height* - Mean length at birth 53 +/- 4.4 cm for males - Mean length at birth 52.5 +/- 3.5 cm for females - Mean adult height 191.3 +/- 9 cm for males - Mean adult height 175.4 +/- 8.2 cm for females - Disproportionate tall stature, upper to lower segment ratio less than 0.85 - Arm span to height > 1.05	*Height* - Tall stature	*Height* - Short stature, relative (in some patients)	*Height* - Short stature, proportionate - Adult male height 142-169 cm - Adult female height 130-157 cm
				Weight - Extremely low body mass index				
	Other - Pseudomuscular build			*Other* - Intrauterine growth retardation	*Other* - Puberty-associated peak in growth velocity is 2.4 years earlier for males and 2.2 years earlier for females			*Other* - Muscular build
HEAD & NECK (in 7/8) ▼				*Head* - Large head - Arrested hydrocephalus - Craniosynostosis	*Head* - Dolichocephaly			*Head* - Brachycephaly

Gene Entry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Help
Search OMIM...
Options
Display: Highlights
*134797
Table of Contents
Title
Gene-Phenotype Relationships
Text
Description
Cloning and Expression
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Mapping
Gene Function
Molecular Genetics
Genotype/Phenotype Correlations
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Cellular Pathways

Table View of the Allelic Variants

134797

Download As

FIBRILLIN 1; FBN1

Allelic Variants (70 Selected Examples) :

All ClinVar Variants

Number	Phenotype	Mutation	SNP	gnomAD	ClinVar
.0001	MARFAN SYNDROME, SEVERE CLASSIC	FBN1, ARG1137PRO	rs137854456	rs137854456	RCV000017883
.0002	MARFAN SYNDROME, MILD VARIABLE	FBN1, CYS2307SER	rs137854457	-	RCV000017884...
.0003	MARFAN SYNDROME	FBN1, 366-BP DEL	-	-	RCV000017885
.0004	MARFAN SYNDROME	FBN1, G8268A, TRP2756TER	rs267606796	-	RCV000017886
.0005	MARFAN SYNDROME	FBN1, CYS1249SER	rs137854458	-	RCV000017887
.0006	MARFAN SYNDROME	FBN1, CYS1663ARG	rs137854459	-	RCV000017888
.0007	MARFAN SYNDROME	FBN1, CYS2221SER	rs137854460	-	RCV000017889
.0008	MARFAN SYNDROME	FBN1, TYR2113TER, EX51DEL	rs267606797	rs267606797	RCV000701293...
.0009	MARFAN SYNDROME	FBN1, ASN2144SER	rs137854461	-	RCV001170530...
.0010	MARFAN SYNDROME	FBN1, ASN548ILE	rs137854462	-	RCV000017894
.0011	MARFAN SYNDROME	FBN1, ASP723ALA	rs137854463	-	RCV000017895
.0012	MASS SYNDROME	FBN1, 4-BP INS, NT5138	rs1131692049	-	RCV000017896
.0013	MARFAN SYNDROME	FBN1, 83-BP DEL	rs794728213	-	RCV000017897...
.0014	MARFAN SYNDROME	FBN1, IVS54DS, G-C, +1, 123-BP DEL	rs869025419	rs869025419	RCV000017898
.0015	ECTOPIA LENTIS 1, ISOLATED, AUTOSOMAL DOMINANT	FBN1, GLU2447LYS	rs137854464	rs137854464	RCV000844887...
.0016	MARFAN SYNDROME, NEONATAL	FBN1, CYS1074ARG	rs137854465	-	RCV000017900
.0017	MARFAN SYNDROME	FBN1, ARG2776TER	rs137854466	rs137854466	RCV000017901...

Full List of ClinVar Variants

ClinVar

9396 search results for **134797[MIM]**

Classification type
- Germline (9,376)
- Somatic (0)

Germline classification
- Conflicting classifications (700)
- Benign (284)
- Likely benign (2,076)
- Uncertain significance (2,707)
- Likely pathogenic (1,612)
- Pathogenic (2,591)

Types of conflicts
- P/LP vs LB/B (3)
- P/LP vs VUS (239)
- VUS vs LB/B (462)

Molecular consequence
- Frameshift (985)
- Missense (4,408)
- Nonsense (539)
- Splice site (405)

Search results

Display options ▾ Sort by Location ▾ Download ▾

Items: 1 to 100 of 9396

<< First < Prev Page 1 of 94 Next > Last >>

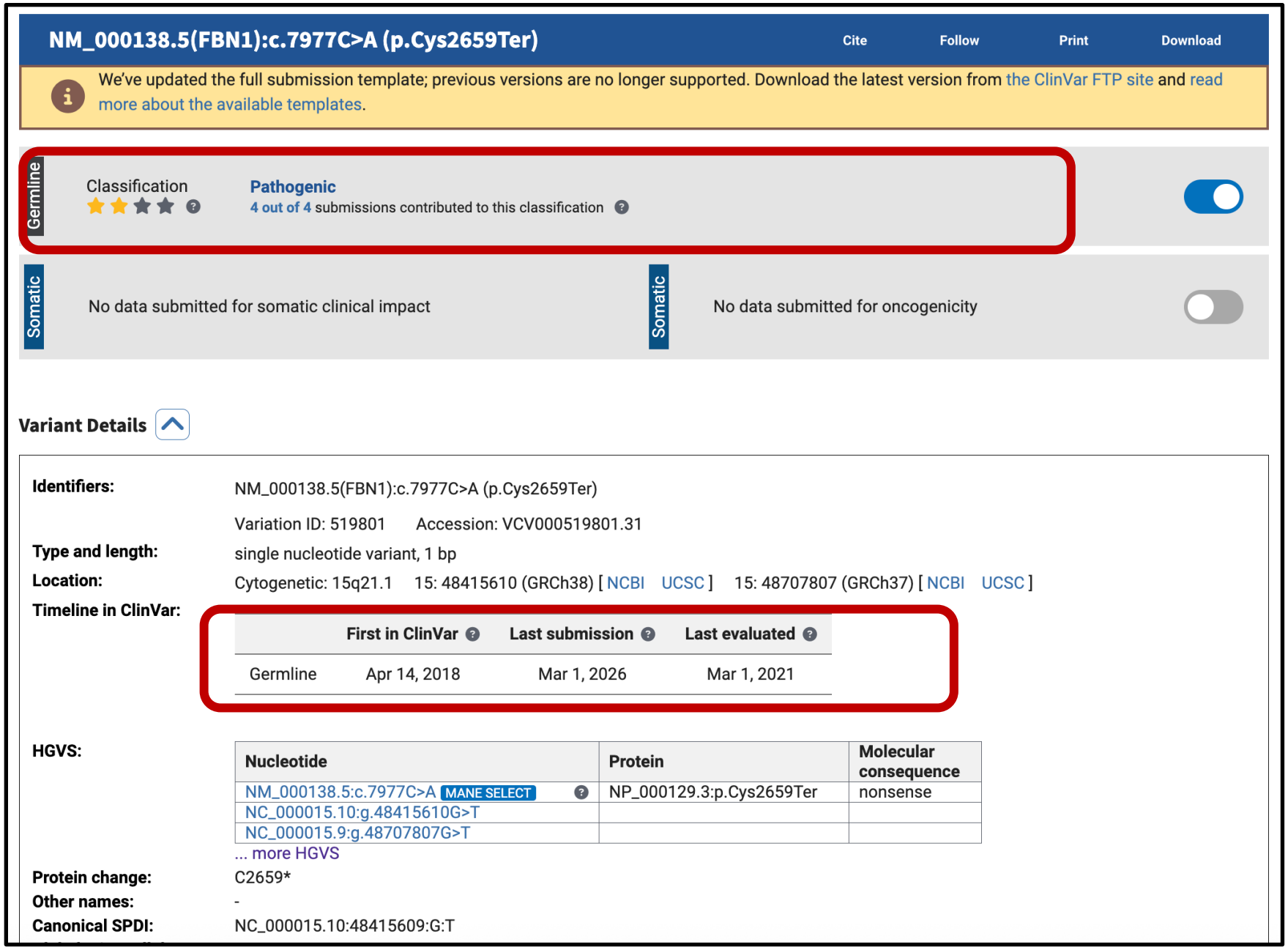
Variation	Gene (Protein Change)	Type (Consequence)	Condition	Classification, Review status
GRCh38/hg38 15q21.1-21.2(chr15:47460844-52494222)x1	GNB5, HDC +190 more	Copy number loss	See cases	G Pathogenic ★
NM_000138.5(FBN1):c.*2674T>A	FBN1	Single nucleotide variant (3 prime UTR variant)	Acromicric dysplasia +6 more	G Benign/Likely benign ★
NM_000138.5(FBN1):c.*2638T>C	FBN1	Single nucleotide variant (3 prime UTR variant)	Weill-Marchesani syndrome +5 more	G Uncertain significance ★
NM_000138.5(FBN1):c.*2592T>C	FBN1	Single nucleotide variant (3 prime UTR variant)	Stiff skin syndrome +5 more	G Uncertain significance ★
NM_000138.5(FBN1):c.*2556G>A	FBN1	Single nucleotide variant (3 prime UTR variant)	Weill-Marchesani syndrome +5 more	G Uncertain significance ★

ClinVar

- Database of reports of the relationships among human variants and phenotypes, with supporting evidence and history of the interpretations
- Interpretation of genetic variants changes over time, especially variants of uncertain significance

Use ClinVar to look up genetic variants.

ClinVar



NM_000138.5(FBN1):c.7977C>A (p.Cys2659Ter) Cite Follow Print Download

We've updated the full submission template; previous versions are no longer supported. Download the latest version from the ClinVar FTP site and read more about the available templates.

Germline

Classification ★★☆☆ ?

Pathogenic

4 out of 4 submissions contributed to this classification ?

Somatic

No data submitted for somatic clinical impact

Somatic

No data submitted for oncogenicity

Variant Details

Identifiers: NM_000138.5(FBN1):c.7977C>A (p.Cys2659Ter)

Variation ID: 519801 Accession: VCV000519801.31

Type and length: single nucleotide variant, 1 bp

Location: Cytogenetic: 15q21.1 15: 48415610 (GRCh38) [NCBI UCSC] 15: 48707807 (GRCh37) [NCBI UCSC]

Timeline in ClinVar:

	First in ClinVar	Last submission	Last evaluated
Germline	Apr 14, 2018	Mar 1, 2026	Mar 1, 2021

HGVS:

Nucleotide	Protein	Molecular consequence
NM_000138.5:c.7977C>A MANE SELECT	NP_000129.3:p.Cys2659Ter	nonsense
NC_000015.10:g.48415610G>T		
NC_000015.9:g.48707807G>T		

... more HGVS

Protein change: C2659*

Other names: -

Canonical SPDI: NC_000015.10:48415609:G:T

ClinVar

Submitter and date

Submissions - Germline

Classification (Last evaluated)	Review status (Assertion criteria)	Condition	Submitter	Collapse all rows
Pathogenic (Dec 04, 2017) C Contributing to aggregate classification	★☆☆☆ (Ambry Variant Classification Scheme 2023)	Familial thoracic aortic aneurysm and aortic dissection	Ambry Genetics Accession: SCV000738935.5 First in ClinVar: Apr 14, 2018 Last updated: May 01, 2024	

Publications:
PubMed: 19618372

Comment:
The p.C2659* pathogenic mutation (also known as c.7977C>A), located in coding exon 63 of the FBN1 gene, results from a C to A substitution at nucleotide position 7977. This changes the amino acid from a cysteine to a stop codon within coding exon 63. This alteration has been reported in an individual with some Marfan-like features (Magyar I et al. Hum. Mutat., 2009 Sep;30:1355-64). In addition to the clinical data presented in the literature, this alteration is expected to result in loss of function by premature protein truncation or nonsense-mediated mRNA decay. As such, this alteration is interpreted as a disease-causing mutation. (less)

Observation 1

Collection method: clinical testing
Allele origin: germline
Affected status: unknown

Details about variant interpretation and supporting evidence

Pathogenic (Mar 01, 2021) C Contributing to aggregate classification	★☆☆☆ (Submitter's publication)	Marfan syndrome	Centre of Medical Genetics, University of Antwerp Accession: SCV002025469.2 First in ClinVar: May 24, 2022 Last updated: Apr 13, 2025

Comment:
PM2, PVS1, PP4 (less)

Observation 1

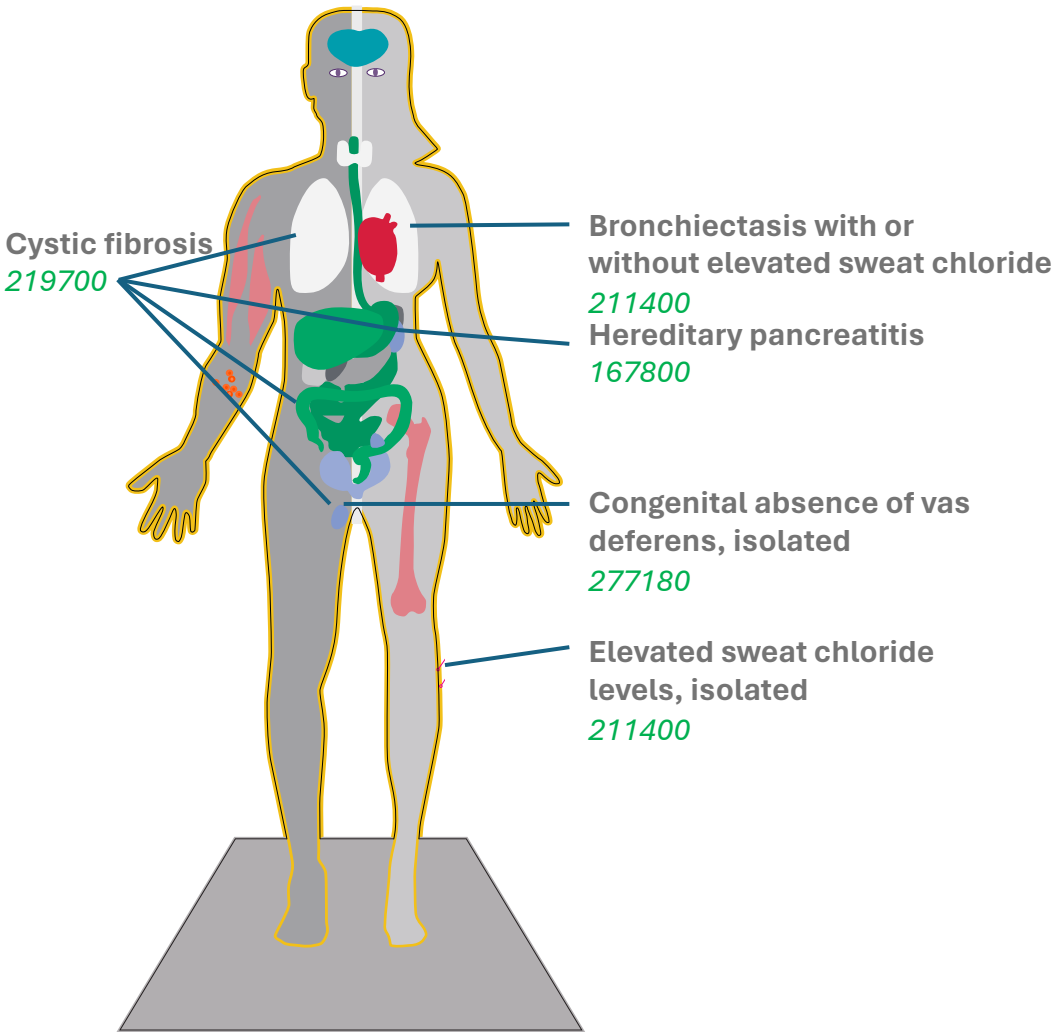
Collection method: research
Allele origin: unknown
Affected status: yes
Sex: male

Variant classification

Two Fundamental Principles in Genetics

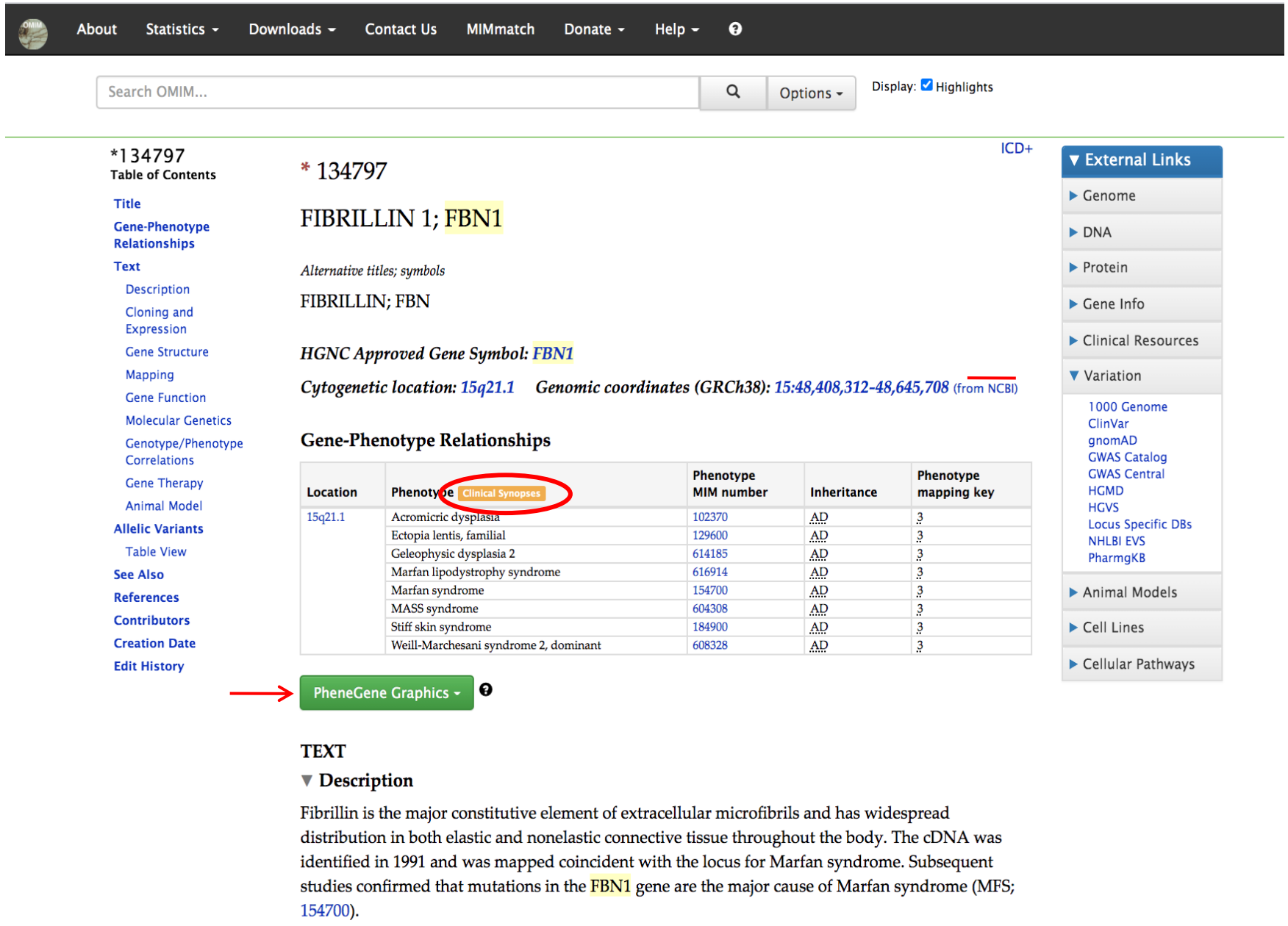
- Phenotypic Diversity at a locus
  - 30% of Disease Genes cause more than one phenotype (constellation of features recognizable as a disorder/disease/condition)
  - Sometimes these conditions have overlap, but many can be quite distinct
  - Often the differences are due to allelic burden, domain affect, or varying mutational mechanism
- Genetic Heterogeneity
  - Many similar or virtually identical diseases can be caused by pathogenic variants in different genes
  - OMIM has always separated these by molecular basis and numbered them
  - This is the basis of the phenotypic series

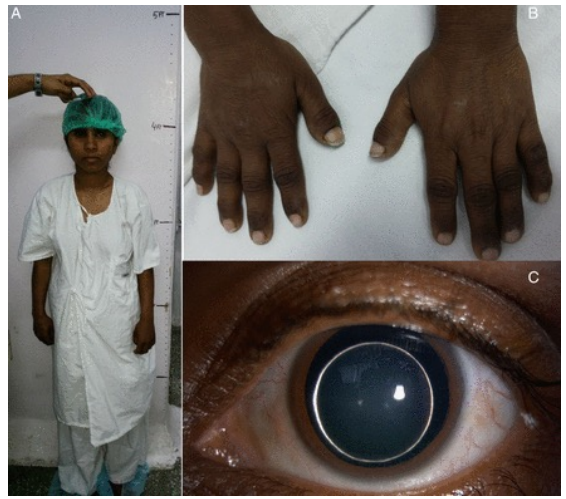
Phenotypic diversity at a locus

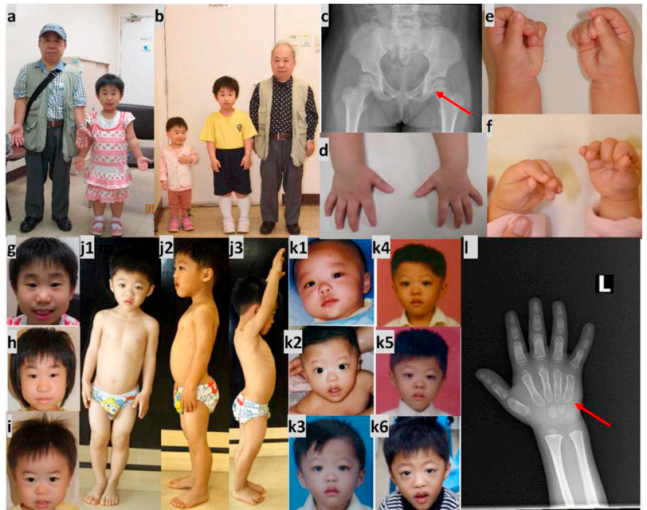


The **phenotypic diversity** caused by CFTR mutations is designated by distinct clinical names representing radically different prognoses and treatments.

FBN1 gene with 8 different AD disorders







NUMBER	# 102370 ▼	# 129600 ▼	# 614185 ▼	# 616914 ▼	# 154700 ▼	# 604308 ▼	# 184900 ▼	# 608328 ▼
TITLE	ACROMICRIC DYSPLASIA; ACMICD	ECTOPIA LENTIS 1, ISOLATED, AUTOSOMAL DOMINANT; ECTOL1	GELEOPHYSIC DYSPLASIA 2; GPHYSD2	MARFANOID-PROGEROID-LIPODYSTROPHY SYNDROME; MFLS	MARFAN SYNDROME; MFS	MASS SYNDROME	STIFF SKIN SYNDROME; SSKS	WEILL-MARCHESANI SYNDROME 2; WMS2
GENE	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797	*FBN1* - 134797
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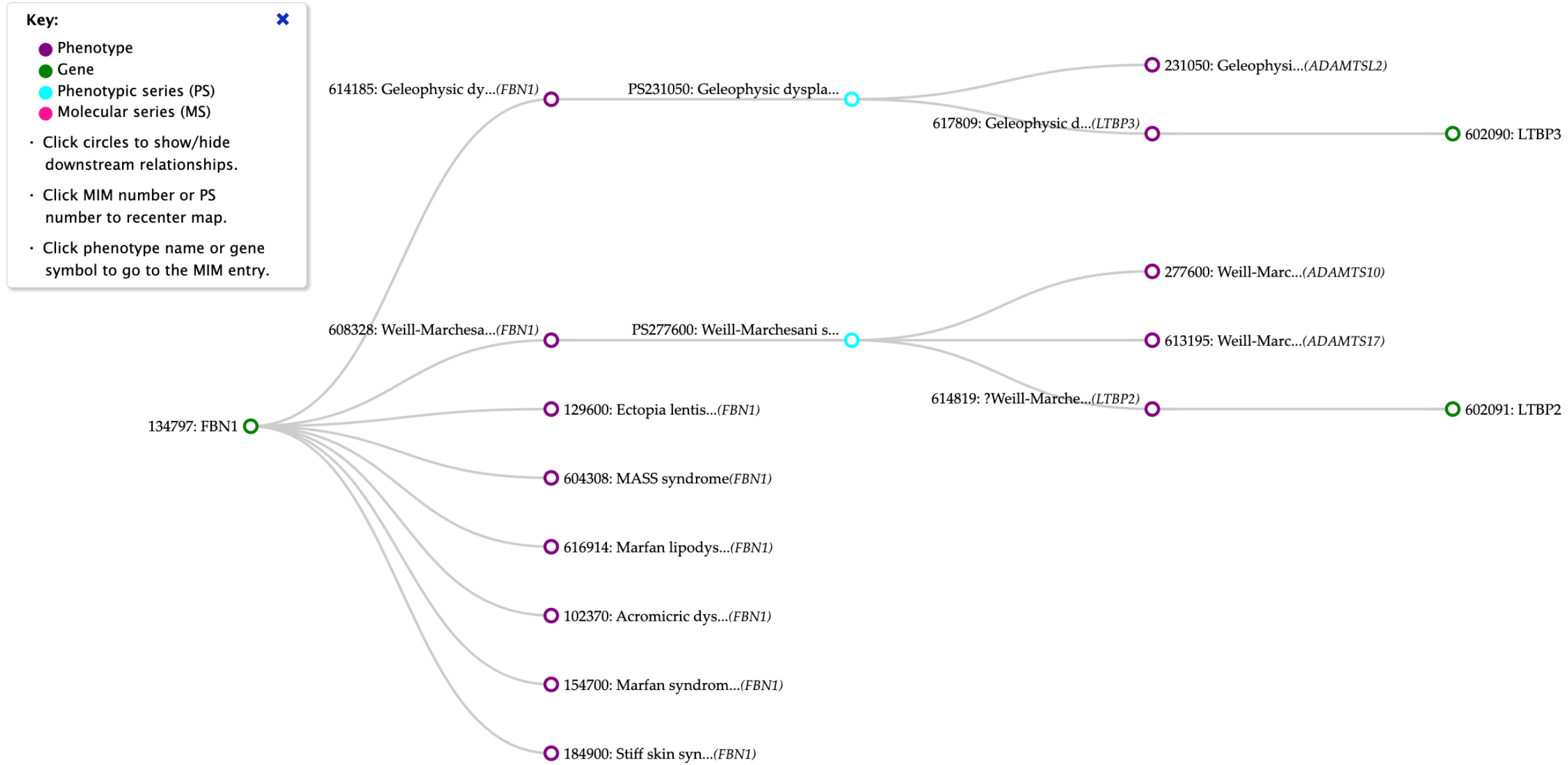
GROWTH (in 7/8) ▼	*Height* - Short stature, severe		*Height* - Short stature	*Height* - Tall stature	*Height* - Mean length at birth 53 +/- 4.4 cm for males - Mean length at birth 52.5 +/- 3.5 cm for females - Mean adult height 191.3 +/- 9 cm for males - Mean adult height 175.4 +/- 8.2 cm for females - Disproportionate tall stature, upper to lower segment ratio less than 0.85 - Arm span to height > 1.05	*Height* - Tall stature	*Height* - Short stature, relative (in some patients)	*Height* - Short stature, proportionate - Adult male height 142-169 cm - Adult female height 130-157 cm
				Weight - Extremely low body mass index				
HEAD & NECK (in 7/8) ▼				*Head* - Large head - Arrested hydrocephalus - Craniosynostosis (rare)	*Head* - Dolichocephaly 👤			*Head* - Brachycephaly 👤
	Face - Round face - Long philtrum - Prominent philtrum - Mild facial anomalies		*Face* - 'Happy' face - Full cheeks - Long philtrum - Flat philtrum	*Face* - Progeroid appearance - Prominent forehead - Scaphocephaly (in some patients) - Retrognathia 👤	*Face* - Long, narrow face - Malar hypoplasia - Micrognathia 👤 - Retrognathia 👤			*Face* - Maxillary hypoplasia
	Eyes - Long eyelashes - Well-defined eyebrows	*Eyes* - Ectopia lentis, isolated (congenital lens dislocation)	*Eyes* - Hypertelorism	*Eyes* - Proptosis 👤 - Downslanting palpebral fissures - Severe myopia - Ectopia lentis (in some patients)	*Eyes* - Enophthalmos - Ectopia lentis - Myopia - Increased axial globe length - Corneal flatness - Retinal detachment - Iris hypoplasia - Early glaucoma - Early cataracts - Downslanting palpebral fissures - Trabeculodysgenesis, primary (in some patients) - Strabismus (in	*Eyes* - Myopia		*Eyes* - Severe myopia - Glaucoma (in 80% of patients) - Ectopia lentis (84%) - Blindness - Microspherophakia (small, spherical lens) (74%) - Shallow anterior chamber - Cataract (28%)

Phene-Gene Graphic from FBN1



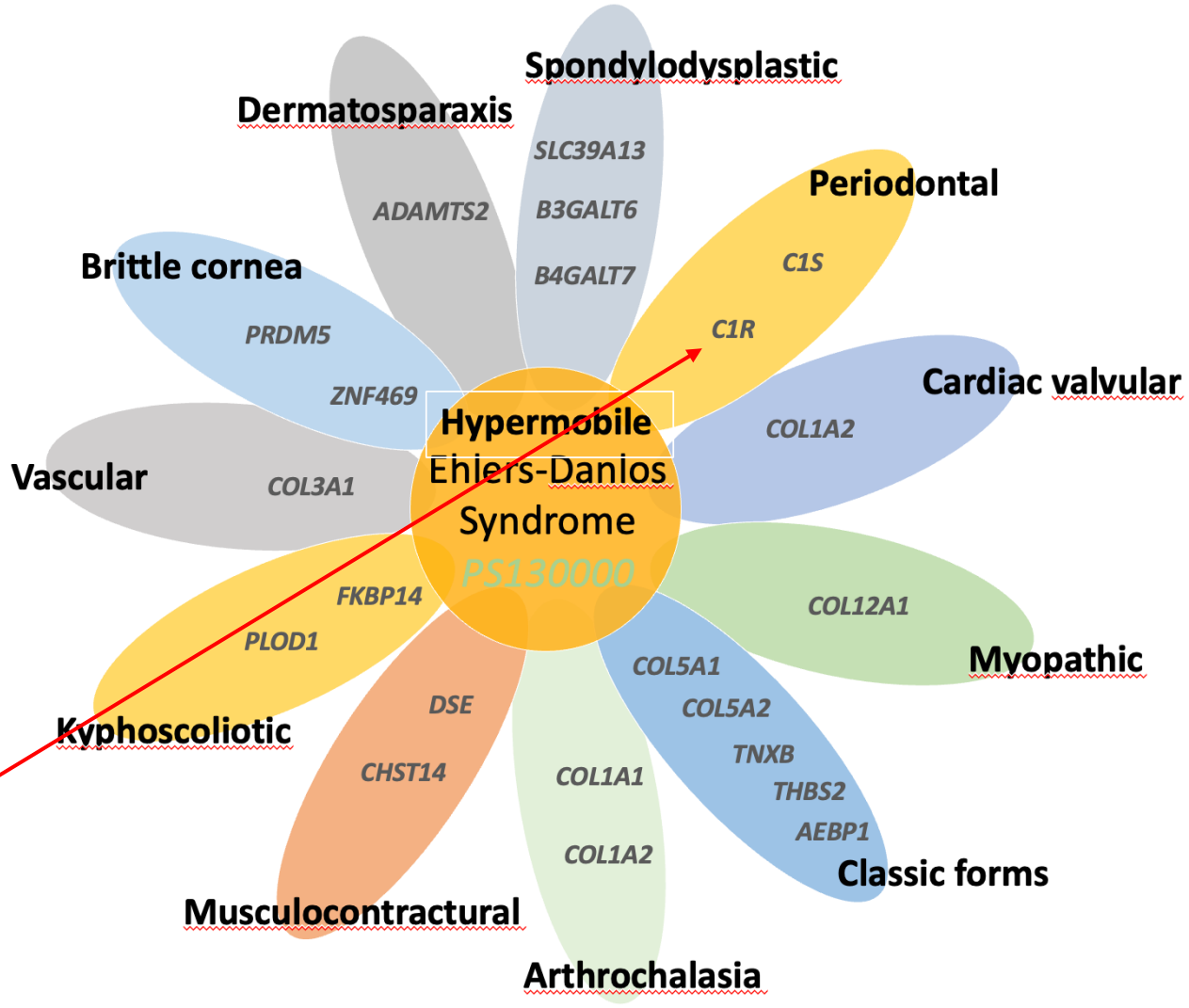
Genetic Heterogeneity

- When creating a new phenotype entry in OMIM
  - We look at the frequent (occurring in >50%) features in the cohort described. Does this resemble something that is already known, and is this part of a phenotypic series? If so, can it be the next number in the series
- Phenotypic Series
  - Currently 606 series, comprising 5,216 phenotypes
  - A phenotype may appear in more than one phenotypic series
  - These are hand curated and are updated as new members are added or when we create a new phenotypic series.

Ehlers-Danlos Phenotypic Series PS130000 with 23 entries

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number (Compare)	Gene/Locus	Gene/Locus MIM number
1p36.33	Ehlers-Danlos syndrome, spondylodysplastic type, 2	AR	3	615349	B3GALT6	615291
1p36.22	Ehlers-Danlos syndrome, kyphoscoliotic type, 1	AR	3	225400	PLOD1	153454
2q32.2	Ehlers-Danlos syndrome, vascular type	AD	3	130050	COL3A1	120180
2q32.2	Ehlers-Danlos syndrome, classic type, 2	AD	3	130010	COL5A2	120190
4q27	Brittle cornea syndrome 2	AR	3	614170	PRDM5	614161
5q35.3	Ehlers-Danlos syndrome, spondylodysplastic type, 1	AR	3	130070	B4GALT7	604327
5q35.3	Ehlers-Danlos syndrome, dermatosparaxis type	AR	3	225410	ADAMTS2	604539
6p21.33-p21.32	Ehlers-Danlos syndrome, classic-like, 1	AR	3	606408	TNXB	600985
6q13-q14.1	Bethlem myopathy 2	AD	3	616471	COL12A1	120320
6q22.1	Ehlers-Danlos syndrome, musculocontractural type 2	AR	3	615539	DSE	605942
6q27	?Ehlers-Danlos syndrome, classic-like, 3	AD	3	620865	THBS2	188061
7p14.3	Ehlers-Danlos syndrome, kyphoscoliotic type, 2	AR	3	614557	FKBP14	614505
7p13	Ehlers-Danlos syndrome, classic-like, 2	AR	3	618000	AEBP1	602981
7q21.3	Ehlers-Danlos syndrome, cardiac valvular type	AR	3	225320	COL1A2	120160
7q21.3	Ehlers-Danlos syndrome, arthrochalasia type, 2	AD	3	617821	COL1A2	120160
9q34.3	Ehlers-Danlos syndrome, classic type, 1	AD	3	130000	COL5A1	120215
11p11.2	Ehlers-Danlos syndrome, spondylodysplastic type, 3	AR	3	612350	SLC39A13	608735
12p13.31	Ehlers-Danlos syndrome, periodontal type, 2	AD	3	617174	C1S	120580
12p13.31	Ehlers-Danlos syndrome, periodontal type, 1	AD	3	130080	C1R	613785
15q15.1	Ehlers-Danlos syndrome, musculocontractural type 1	AR	3	601776	CHST14	608429
16q24.2	Brittle cornea syndrome 1	AR	3	229200	ZNF469	612078
17q21.33	Ehlers-Danlos syndrome, arthrochalasia type, 1	AD	3	130060	COL1A1	120150
Not Mapped	Ehlers-Danlos syndrome, hypermobility type	AD		130020	EDSHMB	130020

View corresponding clinical synopses as a table



Phene-Gene Graphics

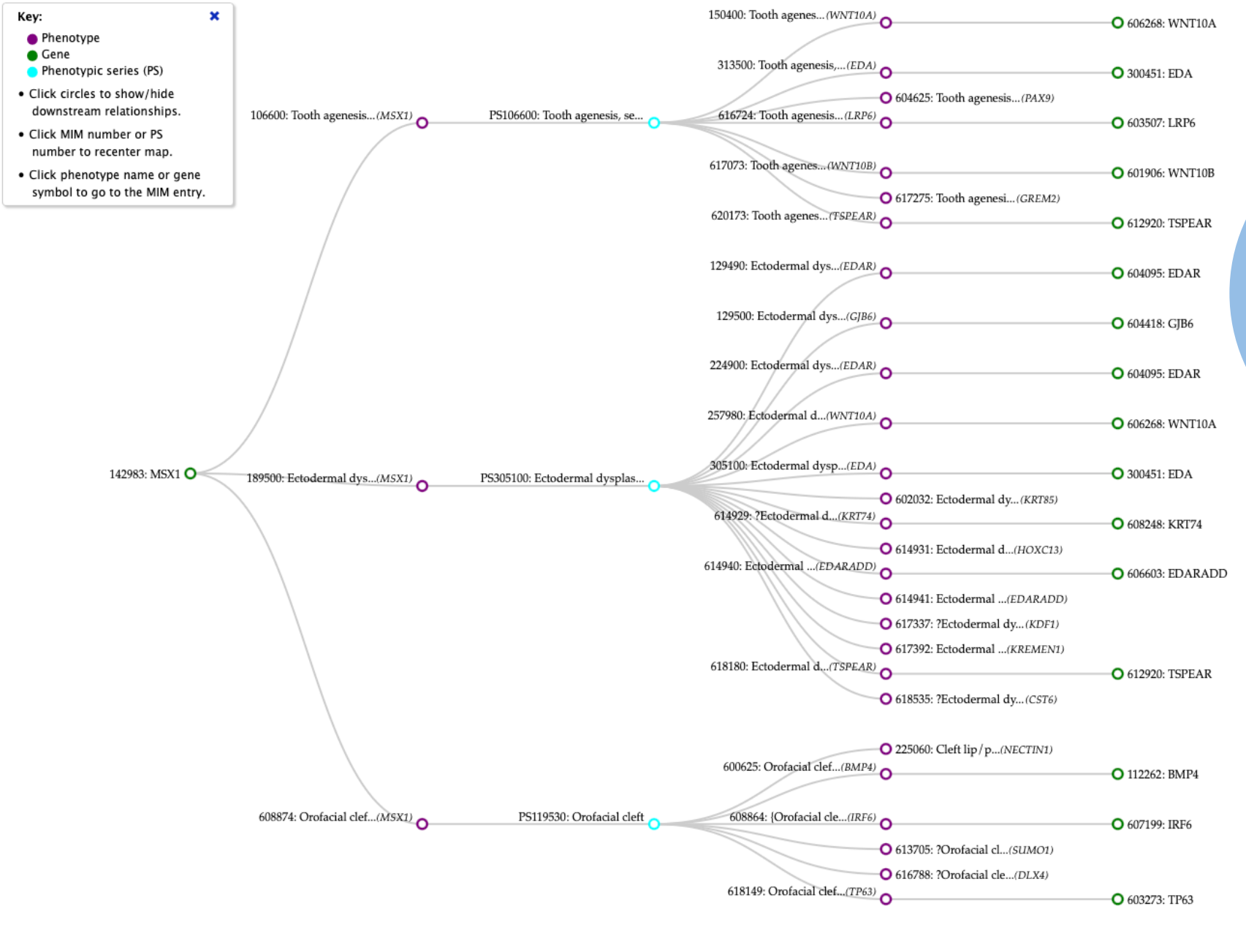
Created on the fly from the data in OMIM at that moment

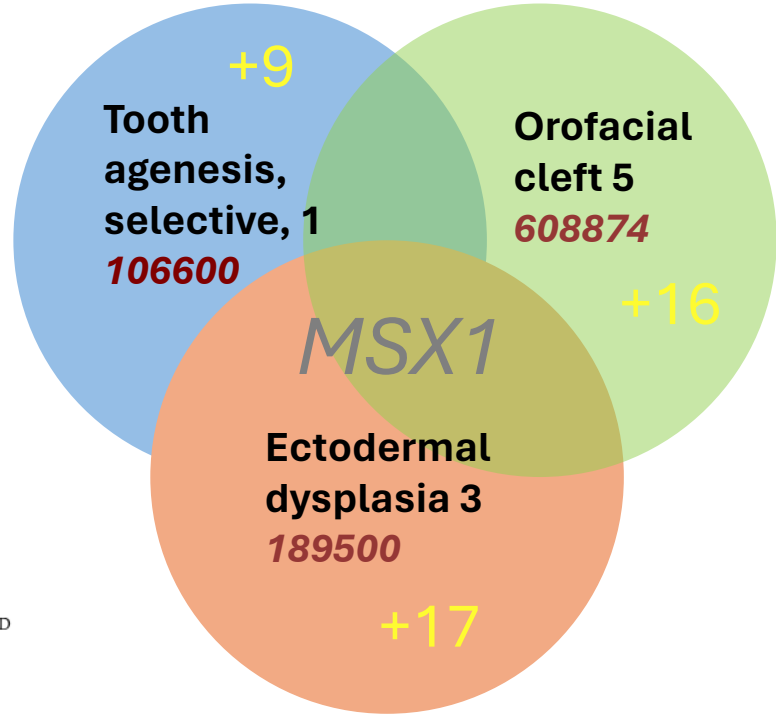
Based on the gene map, phenotypic series and molecular series

Adjustable to see what you want to see

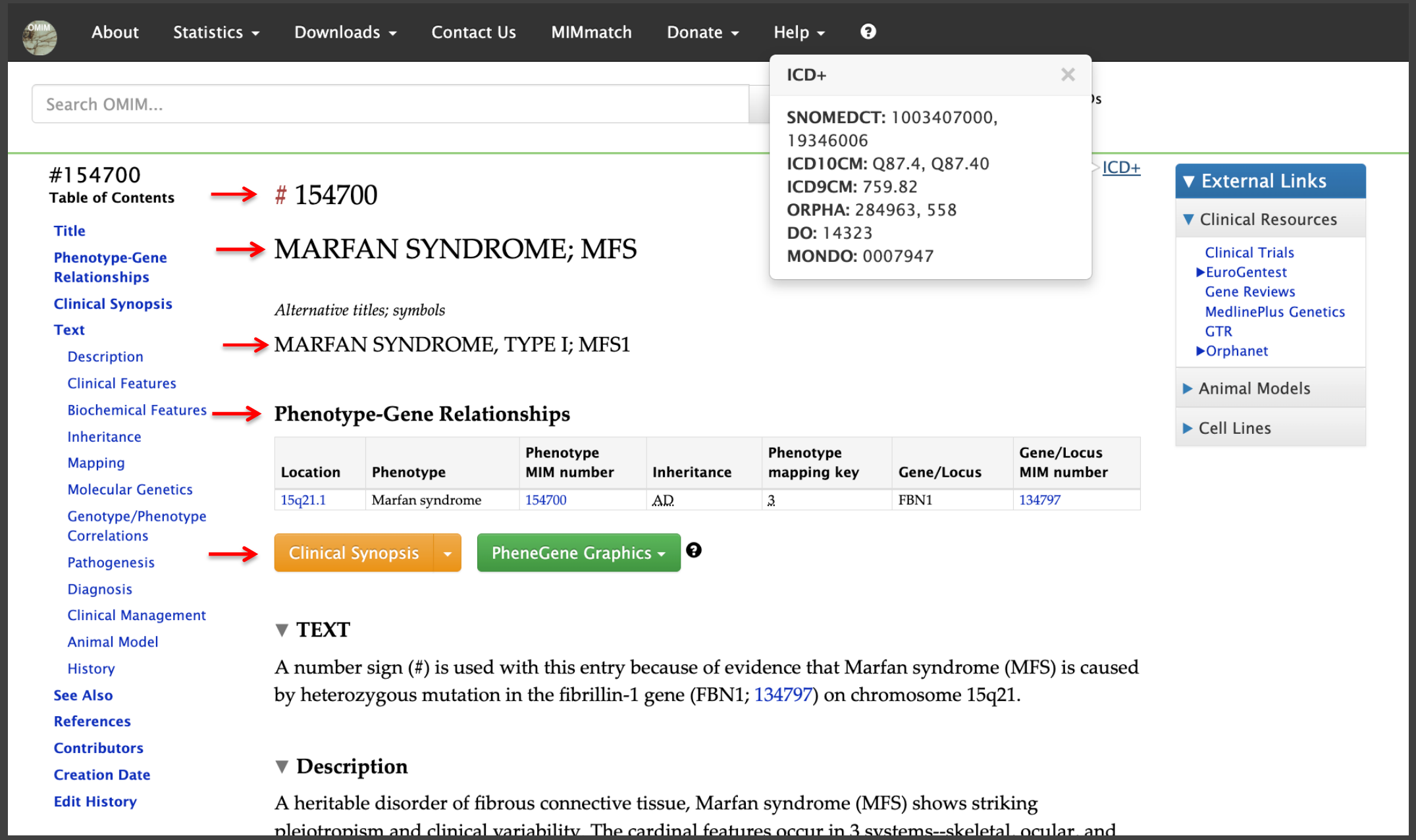
A tool for new insights into relationships

Graphical representation of phenotype/gene relationship(s) associated with this entry. Phenotypic Series (when available) are displayed with the relevant genes and subsequent phenotypes to a depth of 4 nodes. A quick reference overview and guide (PDF). **No hierarchy is implied.** Feedback





Phenotype Entry



Clinical Synopsis

#154700
Table of Contents

MIM Entry

ICD+

154700

MARFAN SYNDROME; MFS

INHERITANCE

- Autosomal dominant

GROWTH

Height

- Mean length at birth 53 +/- 4.4 cm for males
- Mean length at birth 52.5 +/- 3.5 cm for females
- Mean adult height 191.3 +/- 9 cm for males
- Mean adult height 175.4 +/- 8.2 cm for females
- Disproportionate tall stature, upper to lower segment ratio less than 0.85
- Arm span to height > 1.05

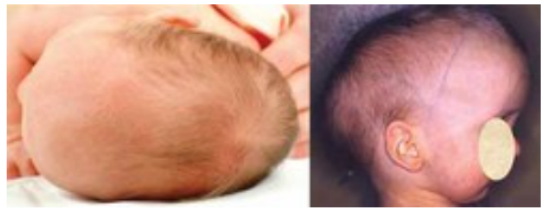
Other

- Puberty-associated r males and 2.2 years earlier for females

HEAD & NECK

Head

- Dolichocephaly



Further Information: Elements of Morphology

Face

- Long, narrow face
- Malar hypoplasia
- Micrognathia
- Retrognathia

Eyes

Clinical synopsis feature IDs

#154700
Table of Contents
MIM Entry

ICD+

154700

MARFAN SYNDROME; MFS

INHERITANCE

- Autosomal dominant [SNOMEDCT: 263681008, 771269000] [UMLS: C0443147, C1867440 HPO: HP:0000006] [HPO: HP:0000006]

GROWTH

Height

- Mean length at birth 53 +/- 4.4 cm for males [UMLS: C1835109]
- Mean length at birth 52.5 +/- 3.5 cm for females [UMLS: C1835110]
- Mean adult height 191.3 +/- 9 cm for males [UMLS: C1835111]
- Mean adult height 175.4 +/- 8.2 cm for females [UMLS: C1835112]
- Disproportionate tall stature, upper to lower segment ratio less than 0.85 [UMLS: C1835113]
- Arm span to height > 1.05 [UMLS: C1835114]

Other

- Puberty-associated peak in growth velocity is 2.4 years earlier for males and 2.2 years earlier for females [UMLS: C1835115]

HEAD & NECK

Head

- Dolichocephaly [SNOMEDCT: 72239002] [ICD10CM: Q67.2] [UMLS: C0221358 HPO: HP:0000268] [HPO: HP:0000268]

Face

- Long, narrow face [UMLS: C1865567]
- Malar hypoplasia [UMLS: C1858085 HPO: HP:0000272] [HPO: HP:0000272]
- Micrognathia [SNOMEDCT: 32958008] [ICD10CM: M26.04] [ICD9CM: 524.04] [UMLS:

▼ External Links

▼ Clinical Resources

Clinical Trials
▶EuroGentest
Gene Reviews
MedlinePlus
Genetics
GTR
GARD
▶Orphanet
POSSUM

Phenotype Entry

#608328
Table of Contents

Title
Phenotype-Gene Relationships
Clinical Synopsis
Phenotypic Series
Text
Description
Clinical Features
Inheritance
Mapping
Molecular Genetics
References
Contributors
Creation Date
Edit History

608328

WEILL-MARCHESANI SYNDROME 2; WMS2

Alternative titles; symbols

WEILL-MARCHESANI SYNDROME, AUTOSOMAL DOMINANT
SPHEROPHAKIA-BRACHYMORPHIA SYNDROME
MESODERMAL DYSMORPHODYSTROPHY, CONGENITAL
GLAUCOMA-LENS ECTOPIA-MICROSPHEROPHAKIA-STIFFNESS-SHORTNESS SYNDROME; GEMSS

ICD+

ICD+
ORPHA: 2084, 3449
DO: 0061274
MONDO: 0012013

Clinical Trials
▶EuroGentest
Gene Reviews
Genetic Alliance
MedlinePlus Genetics
GTR
▶Orphanet
▶ Animal Models

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
15q21.1	Weill-Marchesani syndrome 2, dominant	608328	AD	3	FBN1	134797

Clinical Synopsis | Phenotypic Series | PheneGene Graphics

▼ TEXT

A number sign (#) is used with this entry because Weill-Marchesani syndrome-2 (WMS2) is caused by heterozygous mutation in the FBN1 gene (134797) on chromosome 15q21.

Weill-Marchesani syndrome-2 is allelic to geleophysic dysplasia-2 (614185) and acromicric dysplasia (102370), the skeletal and joint features of which overlap with WMS, as well as Marfan syndrome (154700).

Phenotype Entry

Phenotypic Series - PS277600

Weill-Marchesani syndrome - PS277600 - 4 Entries

Location	Phenotype	Inheritance	Phenotype mapping
14q24.3	?Weill-Marchesani syndrome 3, recessive	AR	3
15q21.1	Weill-Marchesani syndrome 2, dominant	AD	3
15q26.3	Weill-Marchesani 4 syndrome, recessive	AR	3
19p13.2	Weill-Marchesani syndrome 1, recessive	AR	3

PheneGene Graphics

Phenotype Mapping Key

1 - The disorder is placed on the map due to its association with a gene, but the u
2 - The disorder was placed on the map by statistical methods
3 - The molecular basis of the disorder is known
4 - A contiguous gene duplication or deletion syndrome in which multiple genes a

Download As

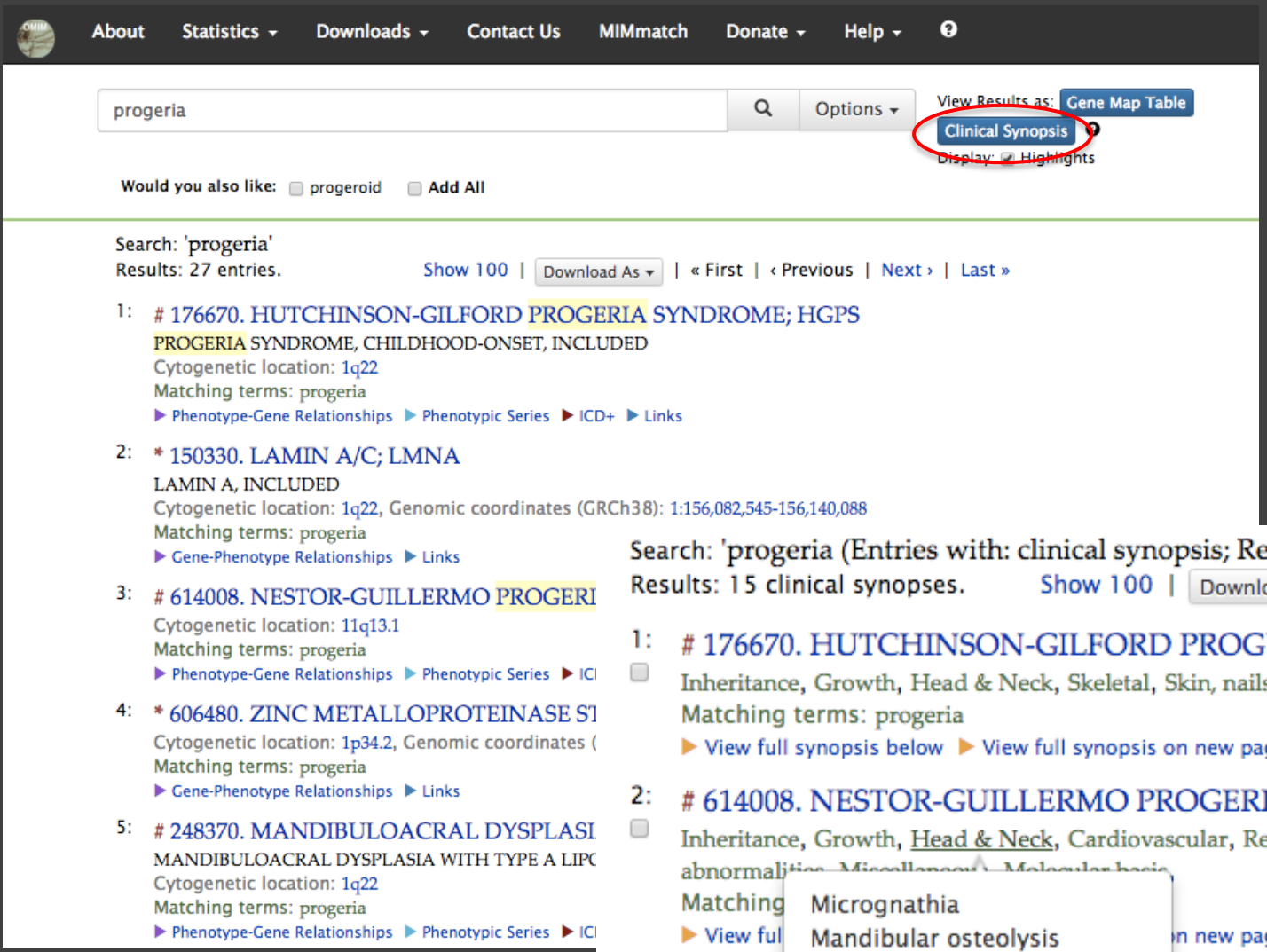
Phenotypic Series

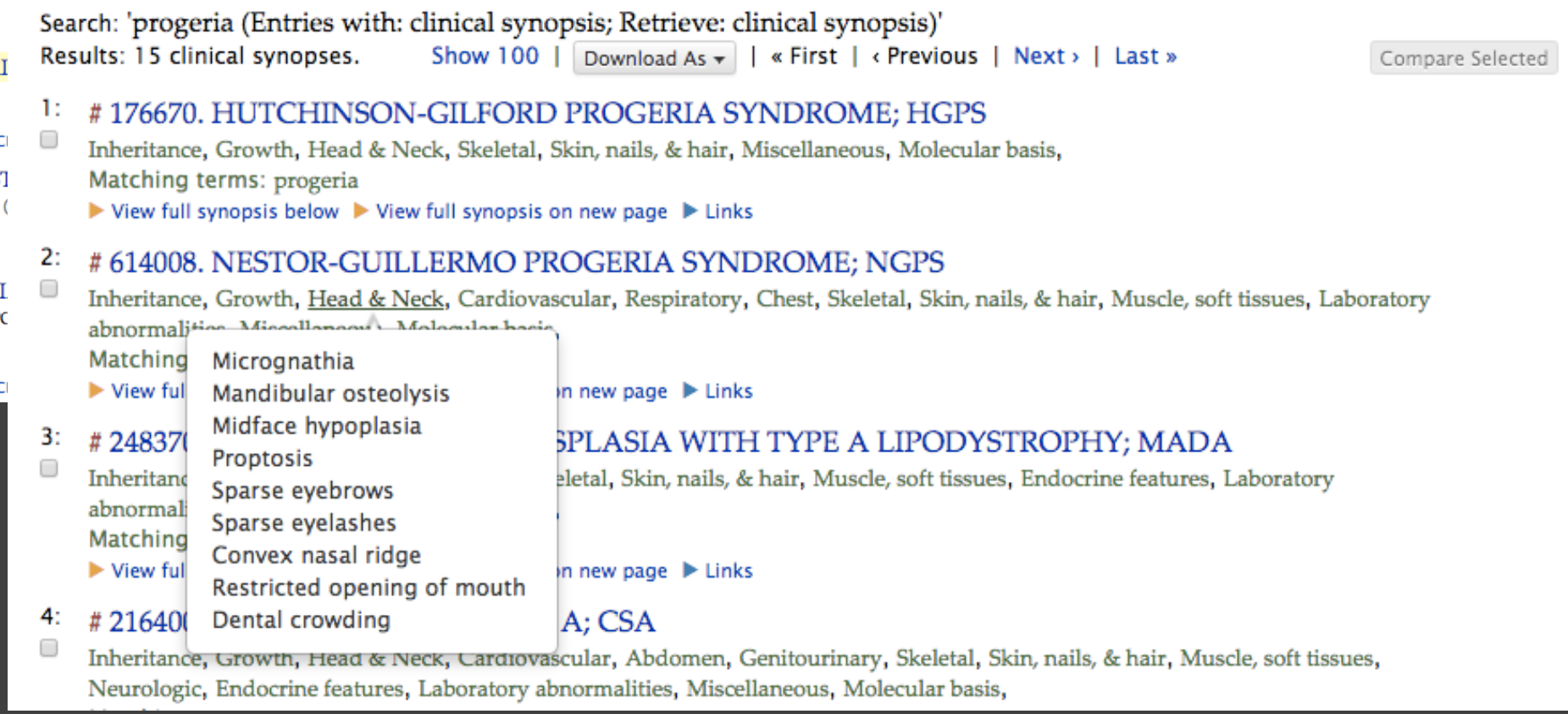
Weill-Marchesani syndrome - PS277600

NUMBER	# 614819	# 608328	# 613195	# 277600
TITLE	WEILL-MARCHESANI SYNDROME 3; WMS3	WEILL-MARCHESANI SYNDROME 2; WMS2	WEILL-MARCHESANI SYNDROME 4; WMS4	WEILL-MARCHESANI SYNDROME 1; WMS1
GENE	*LTBP2* - 602091	*FBN1* - 134797	*ADAMTS17* - 607511	*ADAMTS10* - 608990
INHERITANCE (in 4/4)	- Autosomal recessive	- Autosomal dominant	- Autosomal recessive	- Autosomal recessive
GROWTH (in 4/4)	*Height* - Short stature	*Height* - Short stature, proportionate - Adult male height 142-169 cm - Adult female height 130-157 cm	*Height* - Short stature	*Height* - Short stature, proportionate - Adult male height 142-169 cm - Adult female height 130-157 cm
		Other - Muscular build		*Other* - Muscular build
HEAD & NECK (in 4/4)		*Head* - Brachycephaly		*Head* - Brachycephaly
		Face - Maxillary hypoplasia		*Face* - Maxillary hypoplasia
	Eyes - Ectopia lentis - Myopia - Increased intraocular pressure - Shallow anterior chamber - Microspherophakia	*Eyes* - Severe myopia - Glaucoma (in 80% of patients) - Ectopia lentis (84%) - Blindness - Microspherophakia (small, spherical lens) (74%) - Shallow anterior chamber - Cataract (28%)	*Eyes* - Lenticular myopia - Ectopia lentis - Iridodonesis - Phacodonesis - Shallow anterior chambers - Narrow angles - Peripheral anterior synechiae - Elevated intraocular pressure - Glaucoma - Spherophakia	*Eyes* - Severe myopia - Glaucoma (75%) - Ectopia lentis (64%) - Blindness - Microspherophakia (small, spherical lens) (94%) - Shallow anterior chamber - Cataract (21%)
		Nose - Depressed nasal bridge		*Nose* - Depressed nasal bridge
		Mouth - Narrow palate		*Mouth* - Narrow palate
		Teeth - Malformed teeth - Malaligned teeth		*Teeth* - Malformed teeth - Malaligned teeth
CARDIOVASCULAR (in 3/4)	*Heart* - Pulmonary valve stenosis - Aortic valve stenosis	*Heart* - Cardiac anomalies (13%) - Mitral valve insufficiency - Aortic valve stenosis - Pulmonary valve stenosis - Ductus arteriosus - Ventricular septal defect		*Heart* - Cardiac anomalies (39%) - Mitral valve insufficiency - Aortic valve stenosis - Pulmonary valve stenosis - Ductus arteriosus - Ventricular septal defect
CHEST in 2/4)		*Ribs Sternum Clavicles & Scapulae* - Wide ribs		*Ribs Sternum Clavicles & Scapulae* - Wide ribs
SKELETAL (in 4/4)	- Joint stiffness	- Joint stiffness (hands, shoulder, elbows, knees, and ankles) - Joint limitations		- Joint stiffness (hands, shoulder, elbows, knees, and ankles) - Joint limitations
		Skull		*Skull*

OMIM Clinical Synopses

Clinical synopsis Quick View format





Mouse over anatomical subhead to see features

Search: 'progeria (Entries with: clinical synopsis; Retrieve: clinical synopsis)'

Results: 15 clinical synopses. Show 100 | Download As | « First | ‹ Previous | Next › | Last »

Compare Selected

1: # 176670. HUTCHINSON-GILFORD PROGERIA SYNDROME; HGPS

Inheritance, Growth, Head & Neck, Skeletal, Skin, nails, & hair, Miscellaneous, Molecular basis,

Matching terms: progeria

▶ View full synopsis below ▶ View full synopsis on new page ▶ Links

2: x # 614008. NESTOR-GUILLERMO PROGERIA SYNDROME; NGPS

Inheritance, Growth, Head & Neck, Cardiovascular, Respiratory, Chest, Skeletal, Skin, nails, & hair, Muscle, soft tissues, Laboratory abnormalities, Miscellaneous, Molecular basis,

Matching terms: progeria

▶ View full synopsis below ▶ View full synopsis

3: x # 248370. MANDIBULOACRAL DY

Inheritance, Growth, Head & Neck, Chest, Sk abnormalities, Miscellaneous, Molecular basis

Matching terms: progeria

▶ View full synopsis below ▶ View full synopsis

4: # 216400. COCKAYNE SYNDROME

Inheritance, Growth, Head & Neck, Cardiova Neurologic, Endocrine features, Laboratory al

Matching terms: progeria

▶ View full synopsis below ▶ View full synopsis

	# 614008	# 248370
NUMBER		
TITLE	NESTOR-GUILLERMO PROGERIA SYNDROME; NGPS	MANDIBULOACRAL DYSPLASIA WITH TYPE A LIPODYSTROPHY; MADA
INHERITANCE	- Autosomal recessive	- Autosomal recessive
GROWTH ▼	*Height* - Short stature	
	Other - Failure to thrive	*Other* - Growth retardation, postnatal
HEAD & NECK ▼	*Face* - Micrognathia - Mandibular osteolysis - Midface hypoplasia	*Face* - Mandibular hypoplasia - Bird-like facies - Normal or increased facial adipose tissue - Full cheeks
	Eyes - Proptosis - Sparse eyebrows - Sparse eyelashes	*Eyes* - Prominent eyes
	Nose - Convex nasal ridge	*Nose* - Pinched nose - Pointed nose - Beak nose
	Mouth - Restricted opening of mouth	*Mouth* - High-arched palate - Absence of tongue papillae
	Teeth - Dental crowding	*Teeth* - Dental overcrowding - Loss of teeth

Clinical synopsis Side-by-Side format

OMIM Phenotypes

Single gene mendelian disorders (e.g, cystic fibrosis, sickle cell disease, achondroplasia)
Phenotypic traits (e.g., hair and eye color, PTC tasting)
Susceptibility to drug reaction (e.g., malignant hyperthermia, warfarin sensitivity)
Altered susceptibility or reaction to infection (e.g., herpes simplex encephalitis, progression of HIV infection to AIDS)
Germline susceptibility to cancer (e.g., BRCA1/2 and breast/ovarian cancer)
Recurrent deletion and duplication syndromes (17p11.2 deletion and duplication syndromes)

Challenges in Defining a Phenotype

- Changes in diagnostic modalities
- Changes in diagnostic criteria
- Differences in medical care and medical intervention
- Cultural considerations
- Medical subspeciality bias
- Ascertainment of the phenotype at different stages of development
- Phenotypic diversity at a locus (e.g., Lamin A)
- Genetic heterogeneity

Amberger et al. *Hum Mutat* **32**:564, 2011

OMIM Allelic Variants

- >36,000 allelic variants cataloged in OMIM
- Allelic variants are in the gene entries
- Select examples include
    - first mutation to be discovered
    - high population frequency
    - distinctive phenotype
    - historic significance
    - unusual mechanism of mutation
    - unusual pathogenetic mechanism
    - distinctive inheritance

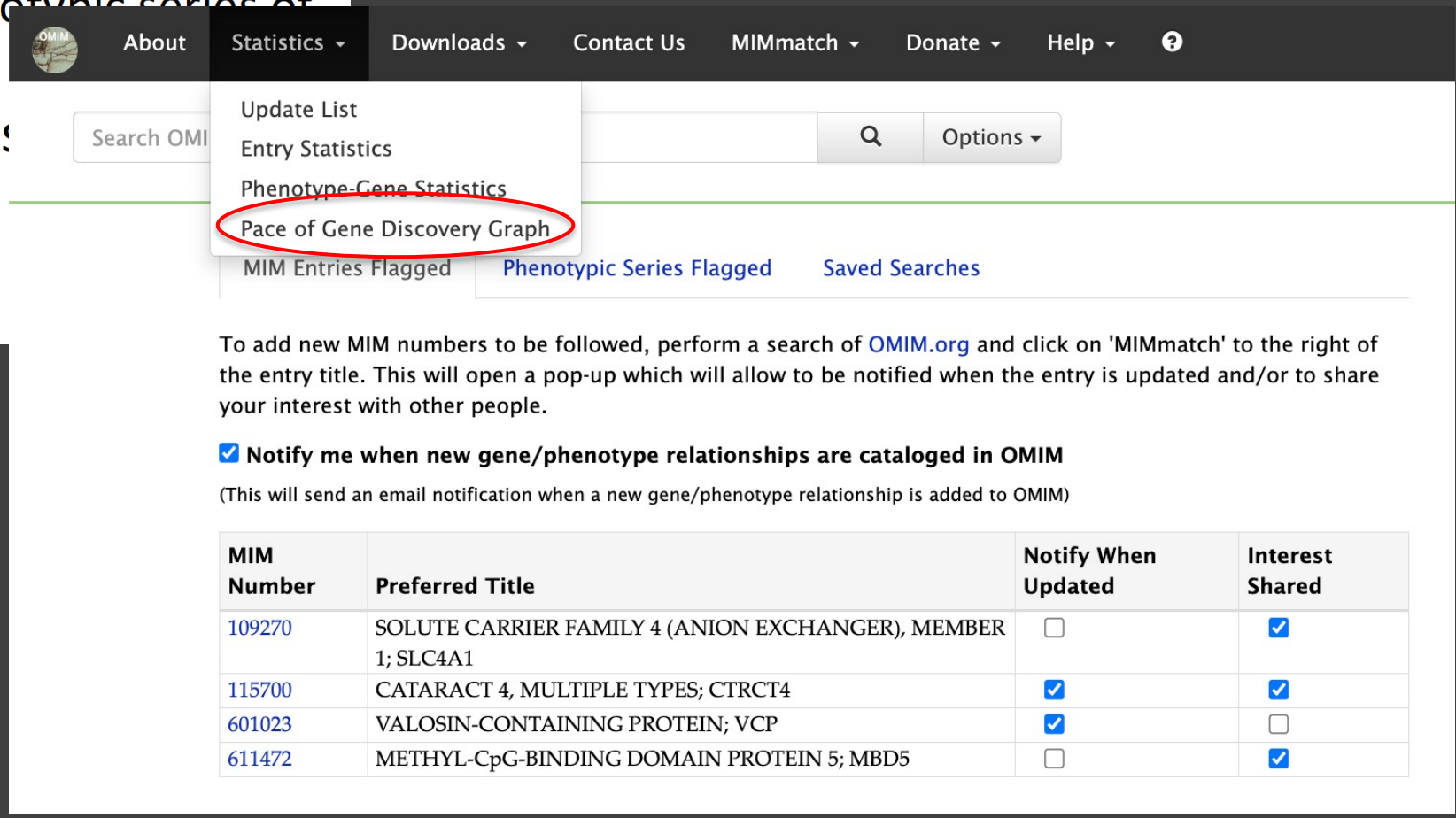
Available at: http://omim.org/help/faq#1.4

Inheritance and Allelic Variation

- OMIM catalogues select variants
- Extensive topical links to many variant resources, including population- and disease-based
- Inheritance resides with the phenotype
- Note that de novo variants will be classified by the inheritance of the disorder / allelic requirement

MIMmatch

- Create an account
- Receive e-mail confirmation
- Log in and set preferences
  - To receive e-mails about new gene-phenotype relationships or updates to phenotypic series of interest
- To follow a gene or phenotype s
  and select that gene
- To save your searches

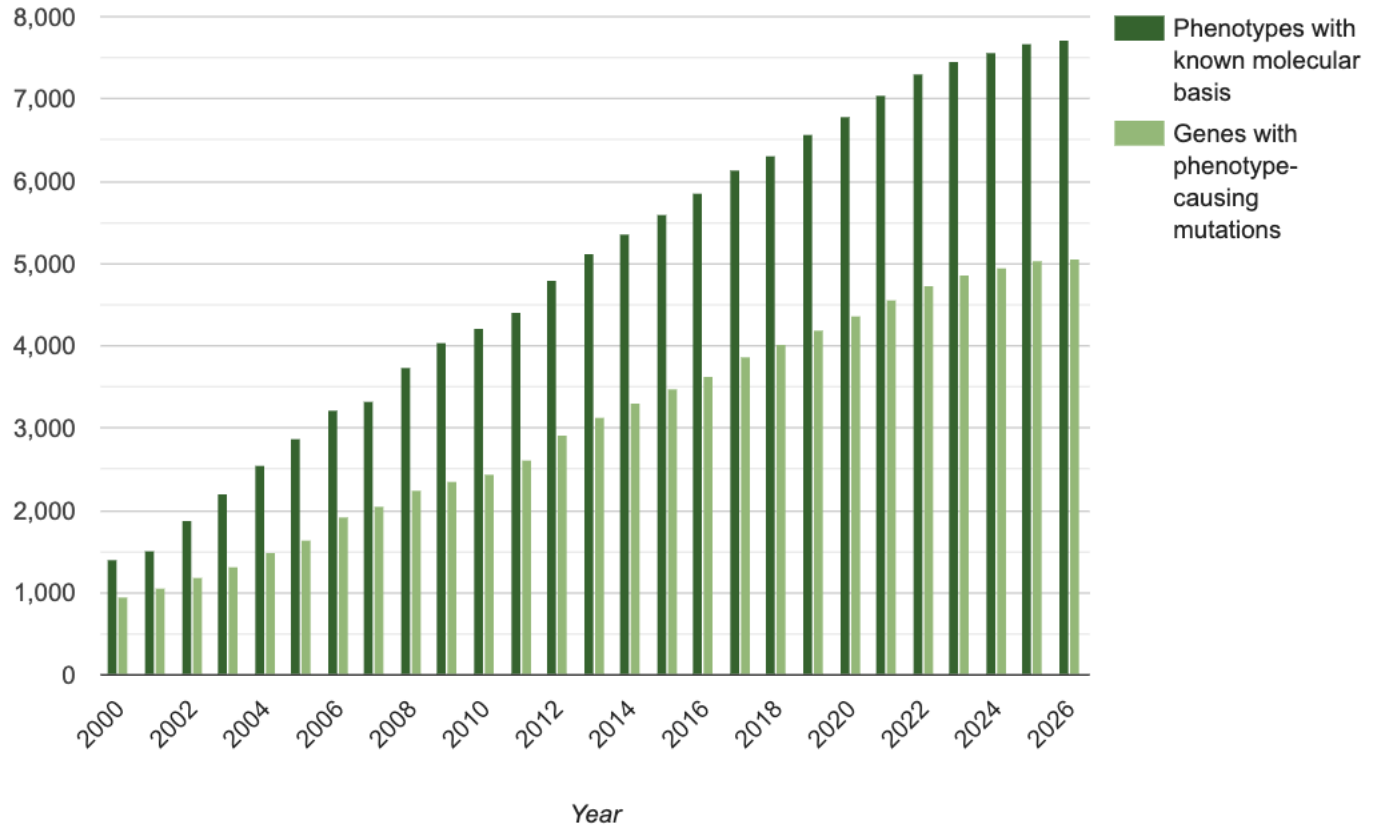


MIMmatch

Updated daily

OMIM Pace of Gene Discovery Graph

Growth of Gene-Phenotype Relationship (Updated April 3rd, 2026) :



MIMmatch

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Search OMIM... | Options

MIM Entries Flagged | Phenotypic Series Flagged | Molecular Series Flagged | Saved Searches | Custom Phene / Gene Lists

To add new MIM numbers to be followed, perform a search of OMIM.org and click on 'MIMmatch' to the right of the entry title. This will open a pop-up which will allow to be notified when the entry is updated and/or to share your interest with other people.

☑ **Notify me when new gene/phenotype relationships are cataloged in OMIM**

(This will send an email notification when a new gene/phenotype relationship is added to OMIM)

MIM Number	Preferred Title	Notify When Updated	Interest Shared
109270	SOLUTE CARRIER FAMILY 4 (ANION EXCHANGER), MEMBER 1; SLC4A1	☐	☑
115700	CATARACT 4, MULTIPLE TYPES; CTRCT4	☑	☑
601023	VALOSIN-CONTAINING PROTEIN; VCP		
611472	METHYL-CpG-BINDING DOMAIN PROTEIN 5; MBD5		

606 Phenotypic Series comprising
5216 disorders

MIM Entries Flagged | Phenotypic Series Flagged | Molecular Series Flagged | Saved Searches | Custom Phene / Gene Lists

A Phenotypic Series is a tabular view of genetic heterogeneity of similar phenotypes across the genome. The link is available under the Phenotype-Gene mini-table in many phenotype entries. A list of disorders with a phenotypic series is available here.

☐ **Notify me when phenotypic series are added to OMIM**

(This will send an email notification when a new phenotypic series is added to OMIM)

Phenotypic Series Title	Phenotypic Series Number	Notify me of new/removed entries within this series ☐	Notify me of updates to any entry within this series ☐
Abdominal obesity-metabolic syndrome	PS605552	☐	☐
Achondrogenesis	PS200600	☐	☐
Acne inversa	PS142690	☐	☐
Acrodysostosis	PS101800	☐	☐
Acromesomelic dysplasia	PS602875	☐	☐
Adams-Oliver syndrome	PS100300	☐	☐
Advanced sleep phase syndrome	PS604348	☐	☐

Molecular Series

- Tabular list of phenotypes brought together by a shared mechanism, etiology or pathology
- Current 16 Molecular Series, with 347 members

Molecular Series Title	Molecular Series Number
Alanine tract expansion disorders	MS142959
Aminoacyl-tRNA synthetase disorders	MS601065
Disorders of epigenetic machinery - eraser genes (Harris et al. 2023 PMID:36952035)	MS605314
Disorders of epigenetic machinery - reader genes (Harris et al. 2023 PMID:36952035)	MS607358
Disorders of epigenetic machinery - remodeler genes (Harris et al. 2023 PMID:36952035)	MS300032
Disorders of epigenetic machinery - writer genes (Harris et al. 2023 PMID:36952035)	MS607999
Disorders of Fe-S biogenesis	MS611911
Disorders of imprinting	MS601623
Disorders of the citric acid cycle	MS118950
Glycosylphosphatidylinositol biosynthesis defect disorders	MS610243
Morbid genomic regulatory sequences	MS620738
Nonprotein coding morbid genes	MS157660
Positional effects of structural variation	MS186550
Repeat expansion disorders	MS613004
Telomere disorders	MS602322
Urea cycle disorders	MS608310

Location	Gene/Locus	Gene/Locus MIM number	Gene Name	Phenotype	Phenotype MIM number	Compare	Inheritance
2q14.2	RNU4ATAC	601428	RNA, U4ATAC small nuclear	Lowry-Wood syndrome	226960	☐	AR
				Microcephalic osteodysplastic primordial dwarfism, type I	210710	☐	AR
				Roifman syndrome	616651	☐	AR
3q26.2	TERC	602322	Telomerase RNA component	Dyskeratosis congenita, autosomal dominant 1	127550	☐	AD
				Pulmonary fibrosis and/or bone marrow failure syndrome, telomere-related, 2	614743	☐	AD
7q32.2	MIR96	611606	Micro RNA 96	Deafness, autosomal dominant 50	613074	☐	AD
9p13.3	RMRP	157660	Mitochondrial RNA-processing endoribonuclease	Anauxetic dysplasia 1	607095	☐	AR
				Cartilage-hair hypoplasia	250250	☐	AR
				Metaphyseal dysplasia without hypotrichosis	250460	☐	AR
9q21.12	MIR204	610942	Micro RNA 204	Retinal dystrophy and iris coloboma with or without cataract	616722	☐	AD
9q34.11	MIR2861	613405	Micro RNA 2861	[Bone mineral density QTL 15]	613418	☐	AD, AR
10q22.3	NUTM2B-AS1	618639	NUTM2B antisense RNA 1	?Oculopharyngeal myopathy with leukoencephalopathy 1	618637	☐	AD
11p15.5	KCNQ1OT1	604115	KCNQ1-opposite strand/antisense transcript 1	Beckwith-Wiedemann syndrome	130650	☐	AD
11q12.3	RNU2-2	621238	RNA, U2 small nuclear 2	Developmental and epileptic encephalopathy 119	621304	☐	AD
12p13.31	RNU7-1	617876	RNA, U7 small nuclear 1	Aicardi-Goutieres syndrome 9	619487	☐	AR
12q24.23	RNU4-2	620823	RNA, U4 small nuclear 2	ReNU syndrome	620851	☐	AD
13q14.13	SNORA31	619378	Small nucleolar RNA, H/ACA box, 31	{Encephalopathy, acute, infection-induced (herpes-specific), susceptibility to, 10}	619396	☐	AD
13q21.33	ATXN8OS	603680	Ataxin 8 opposite strand	{Parkinson disease, susceptibility to}	168600	☐	AD, Mu
				Spinocerebellar ataxia 8	608768	☐	AD
15q22.31	RNU5B-1	621090	RNA, U5B small nuclear 1	Neurodevelopmental disorder with seizures and joint laxity	621302	☐	AD
15q25.1	MIR184	613146	Micro RNA 184	EDICT syndrome	614303	☐	AD
15q26.1	CHASERR	620993	CHD2-adjacent suppressive regulatory RNA	Neurodevelopmental disorder with dysmorphic facies, absent speech and ambulation, and brain abnormalities	621012	☐	AD
16q22.1	MIR140	611894	Micro RNA 140	Spondyloepiphyseal dysplasia, Nishimura type	618618	☐	AD
17p13.1	SNORD118	616663	Small nucleolar RNA, C/D box, 118	Leukoencephalopathy, brain calcifications, and cysts	614561	☐	AR
19q13.32	TRU-TCA1-1	165060	tRNA selenocysteine (anticodon TCA) 1-1	Thyroid hormone metabolism, abnormal, 3	620198	☐	AR
20q13.32	GNASAS1	610540	GNAS antisense RNA 1	Pseudohypoparathyroidism Ib	603233	☐	AD
22q13.2	RNU12	620204	RNA, U12 small nuclear	?Spinocerebellar ataxia, autosomal recessive 33	620208	☐	AR
				CDAGS syndrome	603116	☐	AR

View corresponding clinical synopses as a table

Nonprotein Coding Morbid Genes

- 21 genes causing 28 conditions
- Inheritance
  - 11 autosomal recessive
  - 16 autosomal dominant
  - 1 both
- Growth:
  - 17 no effect on growth
  - 1 overgrowth
  - 10 short stature
- 17/28 neurological involvement
  - DD, ID, ataxia, seizures, brain anomalies
- Remarkably broad phenotypic spectrum

Repeat expansion and alanine tract expansion disorders

Repeat expansion disorders - MS613004 - 48 Entries

View corresponding clinical synopses as a table

Location	Gene/Locus	Gene/Locus MIM number	Gene Name	Phenotype	Phenotype MIM number (Compare)	Inheritance
1p32.2-p32.1	DAB1	603448	DAB adaptor protein 1	Spinocerebellar ataxia 37	615945	AD
1p21.3	ABCD3	170995	ATP-binding cassette, subfamily D, member 3 (peroxisomal membrane protein 1, 70kD)	Oculopharyngodistal myopathy 5	621446	AD
1q21.2	NOTCH2NLC	618025	NOTCH2 N-terminal-like protein C	Neuronal intranuclear inclusion disease	603472	AD
				Oculopharyngodistal myopathy 3	619473	AD
				Tremor, hereditary essential, 6	618866	AD
1q22	NAXE	608862	NAD(P)HX epimerase	Encephalopathy, progressive, early-onset, with brain edema and/or leukoencephalopathy	617186	AR
2q11.2	STARD7	616712	START domain-containing protein 4	Epilepsy, familial adult myoclonic, 2	607876	AD
2q32.2	GLS	138280	Glutaminase	Global developmental delay, progressive ataxia, and elevated glutamine	618412	AR
3p14.1	ATXN7	607640	Ataxin 7	Spinocerebellar ataxia 7	164500	AD
3q21.3	CNBP	116955	CCHC-type zinc finger nucleic acid-binding protein	Myotonic dystrophy 2	602668	AD
3q27.1	YEATS2	613373	YEATS domain-containing protein 2	?Epilepsy, myoclonic, familial adult, 4	615127	AD
4p16.3	HTT	613004	Huntingtin	Huntington disease	143100	AD
4p14	RFC1	102579	Replication factor C1, 145kD (activator 1, 145kD)	Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome	614575	AR

Alanine tract expansion disorders are often static congenital anomalies that are not progressive

Repeat expansion disorders are predominantly neurological or neuromuscular progressive disorders

Alanine tract expansion disorders – MS142959 – 8 Entries

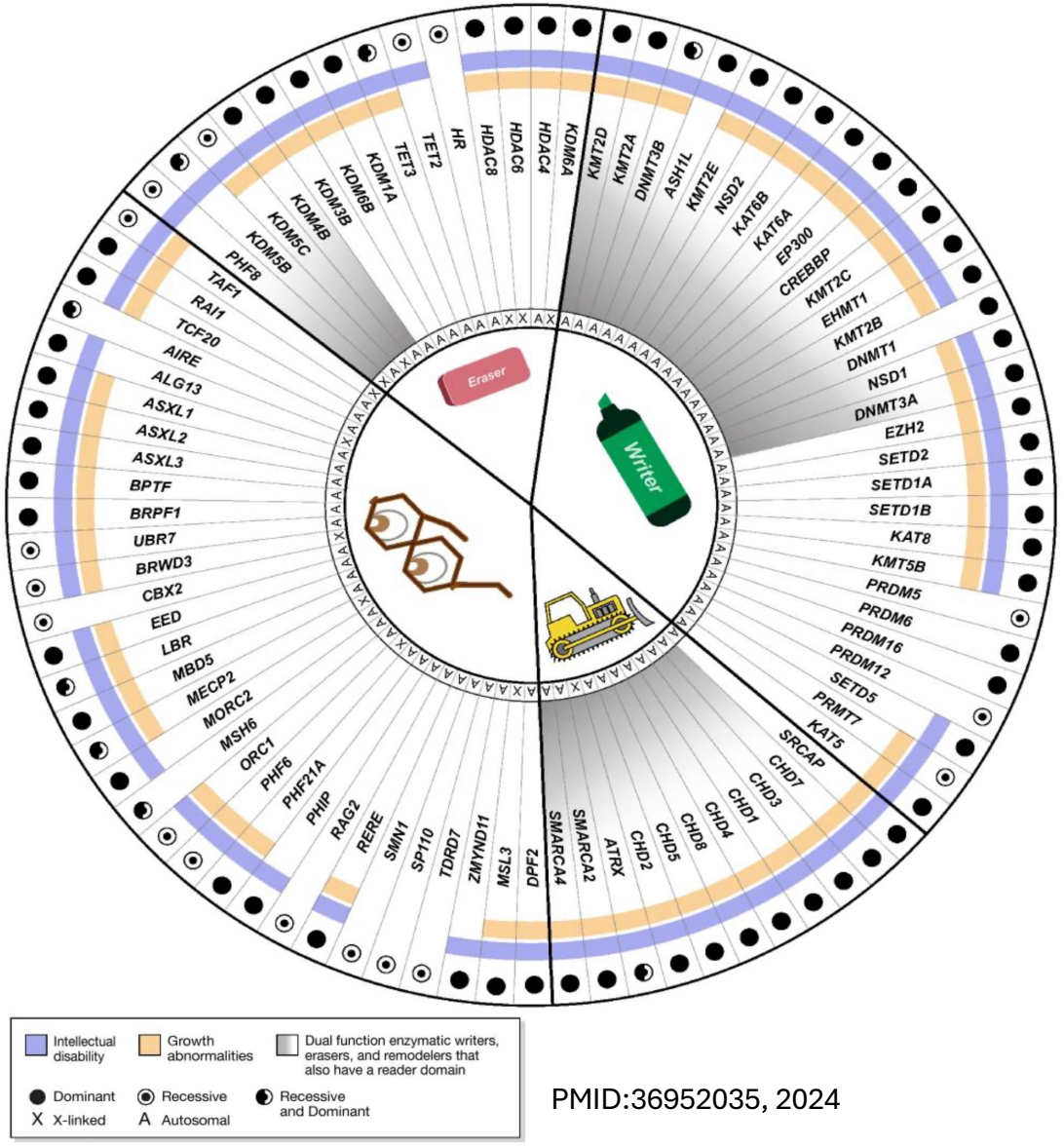
View corresponding clinical synopses as a table

Location	Gene/Locus	Gene/Locus MIM number	Gene Name	Phenotype	Phenotype MIM number (Compare)	Inheritance
2q31.1	HOXD13	142989	Homeobox D13	Synpolydactyly 1	186000	AD
3q22.3	FOXL2	605597	Forkhead transcription factor FOXL2	Blepharophimosis, epicanthus inversus, and ptosis, type 1	110100	AD, AR
				Blepharophimosis, epicanthus inversus, and ptosis, type 2	110100	AD, AR
4p13	PHOX2B	603851	Paired mesoderm homeobox 2B	Central hypoventilation syndrome, congenital, 1, with or without Hirschsprung disease	209880	AD
6p21.1	RUNX2	600211	Runt-related transcription factor 2	Cleidocranial dysplasia	119600	AD
				Cleidocranial dysplasia, forme fruste, dental anomalies only	119600	AD
				Cleidocranial dysplasia, forme fruste, with brachydactyly	119600	AD
7p15.2	HOXA13	142959	Homeobox A13	Hand-foot-genital syndrome	140000	AD
13q32.3	ZIC2	603073	ZIC family, member 2	Holoprosencephaly 5	609637	AD
Xp21.3	ARX	300382	Aristaless-related homeobox, X-linked	Intellectual developmental disorder, X-linked 29	300419	XLR
				Developmental and epileptic encephalopathy 1	308350	XLR
				Partington syndrome	309510	XLR
Xq27.1	SOX3	313430	SRY (sex determining region Y)-box 3	Intellectual developmental disorder, X-linked, with isolated growth hormone deficiency	300123	
				Panhypopituitarism, X-linked	312000	XL

Disorders of Epigenetic Machinery

- The correct amount of histone methylation and acetylation is essential for normal growth and development. Of note, *de novo* pathogenic variants in either a writer or an eraser gene can result in types of Kabuki syndrome.

- Each component of the epigenetic machinery: reader, writers, erasers, and remodelers has its own molecular series.



PMID:36952035, 2024

Disorders may sit in multiple series

#620938
Table of Contents

- Title
- Phenotype-Gene Relationships
- Clinical Synopsis
- Molecular Series
- Phenotypic Series
- Text
  - Description
  - Clinical Features
  - Inheritance
  - Molecular Genetics
- References

620938

SPASTIC PARAPLEGIA 93, AUTOSOMAL RECESSIVE; SPG93

▼ External Links
▼ Clinical Resources
Clinical Trials

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
2p13.3	Spastic paraplegia 93, autosomal recessive	620938	AR	3	NFU1	608100

Clinical Synopsis | Phenotypic Series | Molecular Series | PheneGene Graphics

(#) is used with this entry because of evidence that autosomal re
SPG93) is caused by homozygous or compound heterozygous m
n chromosome 2p13.

essive spastic paraplegia-93 (SPG93) is characterized by a spectru
x hereditary spastic paraplegia phenotypes associated with a lor
levelopmental delay with severe hypotonia on the other (summ

henotypic description and a discussion of genetic heterogeneity
c paraplegia, see 270800.

Spastic paraplegia - PS303350 - 86 Entries

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
1p36.13	Spastic paraplegia 78, autosomal recessive	AR	3	617225	ATP13A2	610513
1p34.1	Spastic paraplegia 83, autosomal recessive	AR	3	619027	HPDL	618994
1p31.1-p21.1	Spastic paraplegia 29, autosomal dominant	AD	2	609727	SPG29	609727
1p13.3	?Spastic paraplegia 63, autosomal recessive	AR	3	615686	AMPD2	102771
1p13.2	Spastic paraplegia 47, autosomal recessive	AR	3	614066	AP4B1	607245
1q32.1	Spastic paraplegia 23, autosomal recessive	AR	3	270750	DSTYK	612666
1q42.13	?Spastic paraplegia 44, autosomal recessive	AR	3	613206	GJC2	608803
1q42.13	?Spastic paraplegia 74, autosomal recessive	AR	3	616451	IBA57	615316
2p23.3	Spastic paraplegia 81, autosomal recessive	AR	3	618768	SELENOI	607915
2p22.3	Spastic paraplegia 4, autosomal dominant	AD	3	182601	SPAST	604277
2p13.3	Spastic paraplegia 93, autosomal recessive	AR	3	620938	NFU1	608100
2p11.2	Spastic paraplegia 31, autosomal dominant	AD	3	610250	REEP1	609139
2q33.1	Spastic paraplegia 13, autosomal dominant	AD	3	605280	HSPD1	118190
2q37.3	Spastic paraplegia 30, autosomal dominant	AD	3	610357	KIF1A	601255
2q37.3	Spastic paraplegia 30, autosomal recessive	AR	3	620607	KIF1A	601255
3q12.2	?Spastic paraplegia 57, autosomal recessive	AR	3	615658	TFG	602498
3q25.31	Spastic paraplegia 42, autosomal dominant	AD	3	612539	SLC33A1	603690
3q27-q28	Spastic paraplegia 14, autosomal recessive	AR	2	605229	SPG14	605229
4p16-p15	Spastic paraplegia 38, autosomal dominant	AD	2	612335	SPG38	612335
4p13	Spastic paraplegia 79A, autosomal dominant	AD	3	620221	UCHL1	191342
4p13	Spastic paraplegia 79B, autosomal recessive	AR	3	615491	UCHL1	191342
4q25	Spastic paraplegia 56, autosomal recessive	AR	3	615030	CYP2U1	610670
5q31.2	Spastic paraplegia 72A, autosomal dominant	AD	3	615625	REEP2	609347

Disorders of Fe-S biogenesis - MS611911 - 11 Entries

Location	Gene/Locus	Gene/Locus MIM number	Gene Name	Phenotype	Phenotype MIM number	Inheritance
1q42.13	IBA57	615316	Iron-sulfur cluster assembly factor IBA57	?Spastic paraplegia 74, autosomal recessive	616451	AR
				Multiple mitochondrial dysfunctions syndrome 3	615330	AR
2p13.3	NFU1	608100	NFU1 iron-sulfur cluster scaffold	Multiple mitochondrial dysfunctions syndrome 1	605711	AR
				Spastic paraplegia 93, autosomal recessive	620938	AR
2p13.1	BOLA3	613183	bolA family member 3	Multiple mitochondrial dysfunctions syndrome 2 with hyperglycinemia	614299	AR
6p25.1	LYRM4	613311	LYR motif-containing protein 4	?Combined oxidative phosphorylation deficiency 19	615595	AR
9q21.11	FXN	606829	Frataxin	Friedreich ataxia	229300	AR
				Friedreich ataxia with retained reflexes	229300	AR
12q23.3	ISCU	611911	Iron-sulfur cluster assembly enzyme	Myopathy with lactic acidosis, hereditary	255125	AR
14q12	NUBPL	613621	Nucleotide-binding protein-like protein	Mitochondrial complex I deficiency, nuclear type 21	618242	AR
14q32.13	GLRX5	609588	Glutaredoxin 5	Anemia, sideroblastic, 3, pyridoxine-refractory	616860	AR
				Spasticity, childhood-onset, with hyperglycinemia	616859	AR
19p13.2	FDX2	614585	Ferredoxin 2	Mitochondrial myopathy, episodic, with optic atrophy and reversible leukoencephalopathy	251900	AR
20q11.22	NFS1	603485	NFS1 cysteine desulfurase 1	Combined oxidative phosphorylation deficiency 52	619386	AR
Xq13.3	ABCB7	300135	ATP-binding cassette-7	Anemia, sideroblastic, with ataxia	301310	XL

Morbid Genomic Regulatory Sequences Molecular Series

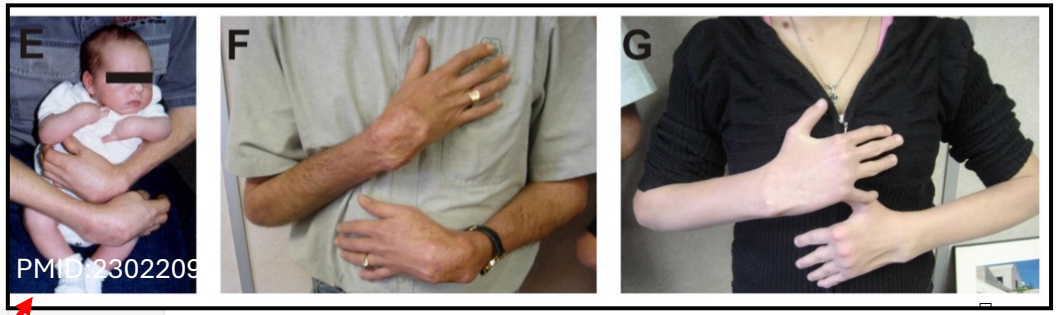
- These are genomic elements (enhancers, repressors, etc)
- They do not create an RNA or code for protein
- Their disruption or dislocation creates a recognizable phenotype
- 10 members of the series, thus far

View corresponding clinical synopses as a table

Gene/Locus	Gene/Locus MIM number	Gene Name	Phenotype	Phenotype MIM number (Compare)	Inheritance
MCM6	601806	Minichromosome maintenance complex component 6	Lactase persistence/nonpersistence	223100	AD
NHEJ1	611290	Nonhomologous end-joining factor 1	Microphthalmia/coloboma 13	620968	AR
ZRS	620738	ZPA regulatory sequence	Polydactyly, preaxial II	174500	AD
			Tibia, hypoplasia or aplasia of, with polydactyly	188740	AD, AR
			Triphalangeal thumb	174500	AD
CTSB	116810	Cathepsin B (regulatory element, cis-acting, enhancer upstream of CTSB, included)	Keratolytic winter erythema	148370	AD
CCDC26	613040	CCDC26 long non-coding RNA	{Glioma susceptibility 7}	613032	
PTF1A	607194	Pancreas transcription factor 1, alpha subunit	Pancreatic agenesis 2	615935	AR
ATOH7	609875	Atonal, Drosophila, homolog of, 7	Persistent hyperplastic primary vitreous, autosomal recessive	221900	AR
ELP4	606985	Elongation protein 4, S. cerevisiae, homolog of	?Aniridia 2	617141	AD
SOX9	608160	SRY (sex-determining region Y)-box 9	46XX sex reversal 2	278850	AD
			46XY sex reversal 10	616425	AD
			Acampomelic campomelic dysplasia	114290	AD
			Campomelic dysplasia	114290	AD
			Campomelic dysplasia with autosomal sex reversal	114290	AD
BMP2	112261	Bone morphogenetic protein-2	Brachydactyly, type A2	112600	AD

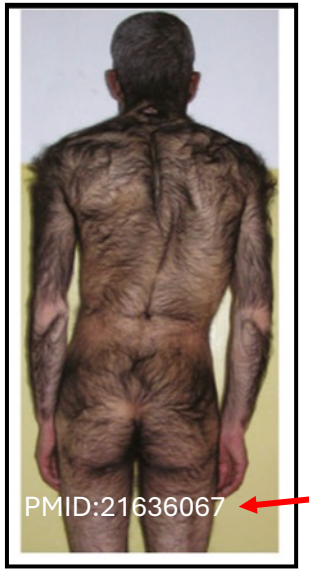
Positional effects of structural variation

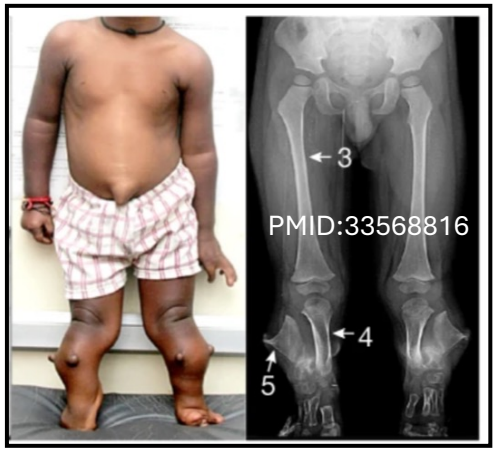
Structural variants are increasingly being associated with rare genetic diseases. Translocated enhancer elements and disruption of topologically associating domains are examples of this disease-causing molecular mechanism.

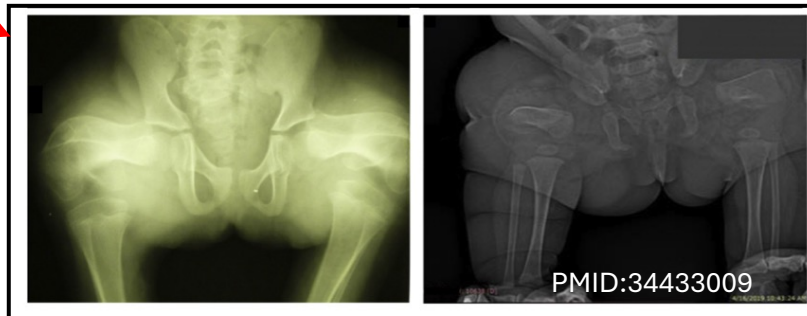


Location	Gene/Locus	Gene/Locus MIM number	Gene Name	Phenotype	Phenotype MIM number (Compare)	Inheritance
1q32	NYS7	614826	Nystagmus 7, congenital, autosomal dominant	Nystagmus 7, congenital, autosomal dominant	614826	AD
2q14	ENDOVESL	619217	ENDOVE syndrome, limb-only type	ENDOVE syndrome, limb-only type	619217	AR
5q23.2	ADLDAT	621061	Leukodystrophy, demyelinating, adult-onset, autosomal dominant, atypical	Leukodystrophy, demyelinating, adult-onset, autosomal dominant atypical	621061	AD
5q31.1	LBNBG	186550	Liebenberg syndrome	Liebenberg syndrome	186550	AD
10q24	HYPOFP	619545	Hypoplastic femurs and pelvis	Hypoplastic femurs and pelvis	619545	AD
15q21.2-q21.3	AEXS	139300	Aromatase excess syndrome	Aromatase excess syndrome	139300	AD
17q23.2	RP17	600852	Retinitis pigmentosa 17	Retinitis pigmentosa 17	600852	AD
20q11	OBHP	620195	Obesity and hypopigmentation	Obesity and hypopigmentation	620195	AD
Xq26	BZX	301845	Bazex-Dupre-Christol syndrome	Bazex-Dupre-Christol syndrome	301845	XLD
Xq27.1	HPT	307700	Hypoparathyroidism	Hypoparathyroidism, X-linked	307700	XL
Xq27.1	HTC2	307150	Hypertrichosis, congenital generalized	Hypertrichosis, congenital generalized	307150	XLD
Xq27	RDXGH	301149	Retinal dystrophy, X-linked, Gardner-Hardcastle type	Retinal dystrophy, X-linked, Gardner-Hardcastle type	301149	XLR

View corresponding clinical synopses as a table

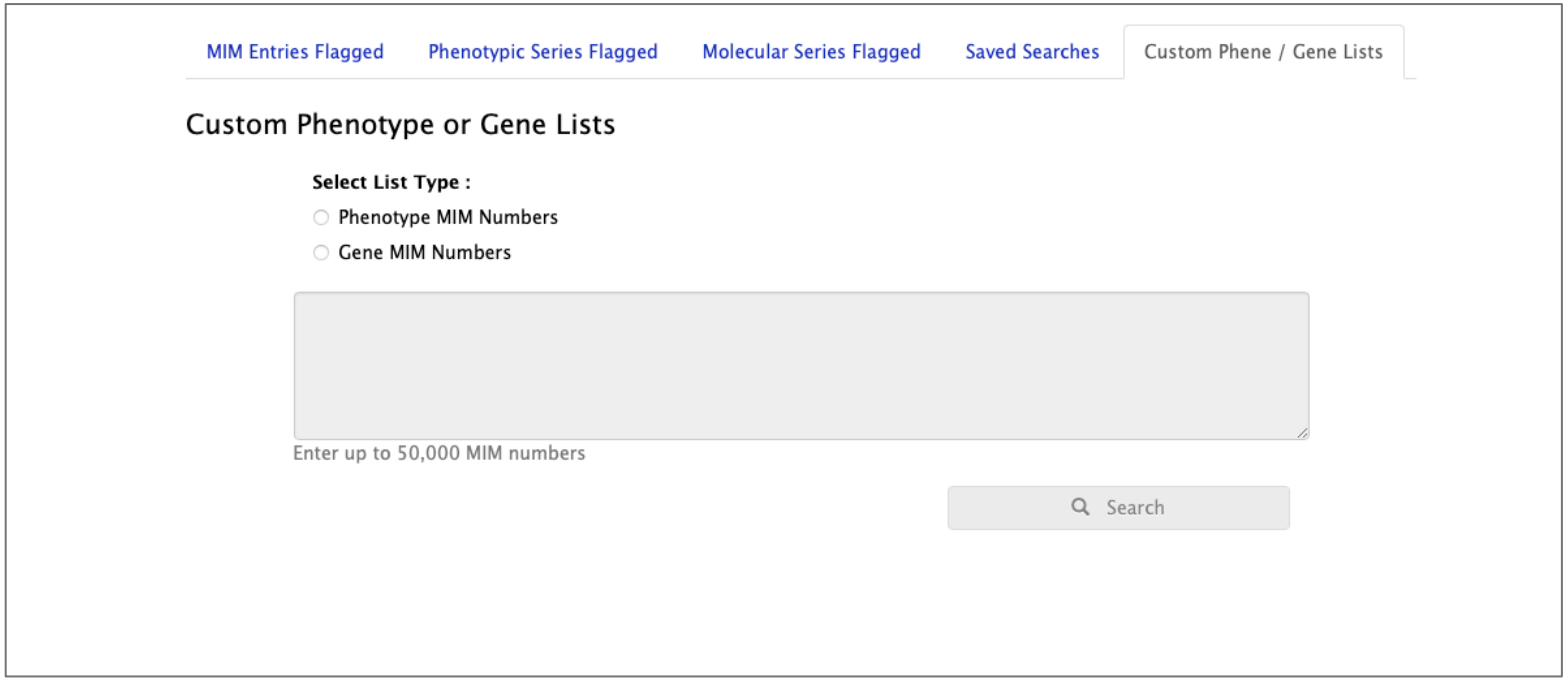






Custom Gene or Phenotype Lists

- MIMmatch users can create their own lists of genes or phenotypes



Custom Gene List

Input MIM#s:
602105
603382
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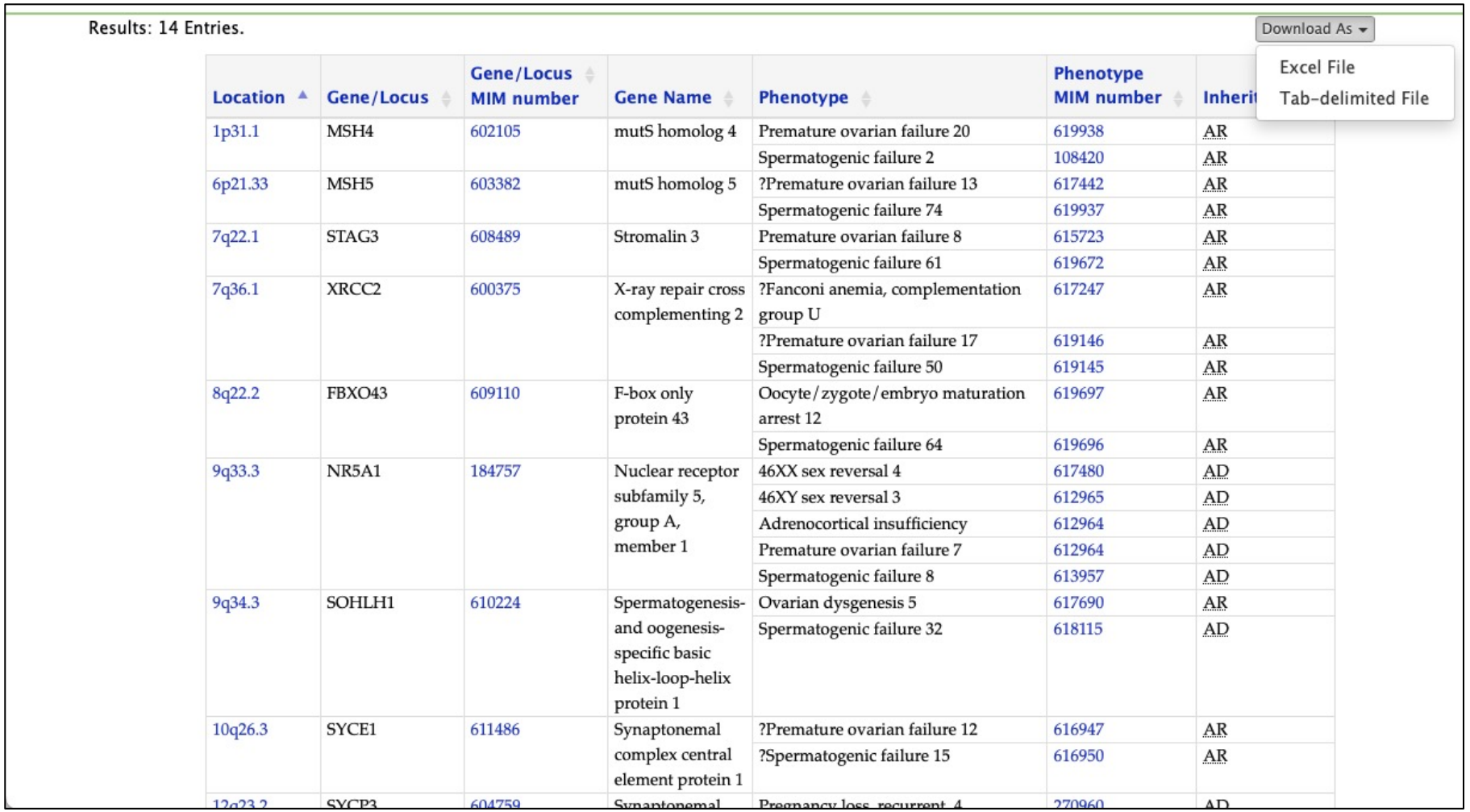
600375
609110
184757
610224
611486
604759
609644
617307
614535
618125
300247



Results: 14 Entries.

Download As
Excel File
Tab-delimited File

Location	Gene/Locus	Gene/Locus MIM number	Gene Name	Phenotype	Phenotype MIM number	Inheri
1p31.1	MSH4	602105	mutS homolog 4	Premature ovarian failure 20	619938	AR
				Spermatogenic failure 2	108420	AR
6p21.33	MSH5	603382	mutS homolog 5	?Premature ovarian failure 13	617442	AR
				Spermatogenic failure 74	619937	AR
7q22.1	STAG3	608489	Stromalin 3	Premature ovarian failure 8	615723	AR
				Spermatogenic failure 61	619672	AR
7q36.1	XRCC2	600375	X-ray repair cross complementing 2	?Fanconi anemia, complementation group U	617247	AR
				?Premature ovarian failure 17	619146	AR
				Spermatogenic failure 50	619145	AR
8q22.2	FBXO43	609110	F-box only protein 43	Oocyte/zygote/embryo maturation arrest 12	619697	AR
				Spermatogenic failure 64	619696	AR
9q33.3	NR5A1	184757	Nuclear receptor subfamily 5, group A, member 1	46XX sex reversal 4	617480	AD
				46XY sex reversal 3	612965	AD
				Adrenocortical insufficiency	612964	AD
				Premature ovarian failure 7	612964	AD
				Spermatogenic failure 8	613957	AD
9q34.3	SOHLH1	610224	Spermatogenesis- and oogenesis-specific basic helix-loop-helix protein 1	Ovarian dysgenesis 5	617690	AR
				Spermatogenic failure 32	618115	AD
10q26.3	SYCE1	611486	Synaptonemal complex central element protein 1	?Premature ovarian failure 12	616947	AR
				?Spermatogenic failure 15	616950	AR
12q23.2	SYCP3	604759	Synaptonemal	Pregnancy loss, recurrent, 4	270960	AD

Custom Phenotype List

Input MIM#s:
#614753
#616592
#618381
#117550
#130650
#312870
#612918
#615879
#277590
#613675
#615923
#616260
#616831
#617107
#618786

Results: 17 Entries.

Download As

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
2p23.3	Tatton-Brown-Rahman syndrome	AD	3	615879	DNMT3A	602769
3p21.31	Luscan-Lumish syndrome	AD	3	616831	SETD2	612778
3q26.32	CLOVE syndrome, somatic		3	612918	PIK3CA	171834
5q32	Kosaki overgrowth syndrome	AD	3	616592	PDGFRB	173410
5q35.3	Sotos syndrome	AD	3	117550	NSD1	606681
7q36.1	Weaver syndrome	AD	3	277590	EZH2	601573
9p13.3	Epiphyseal chondrodysplasia, Miura type	AD	3	615923	NPR2	108961
11p15.5	Beckwith-Wiedemann syndrome	AD	3	130650		616186
11p15.5	Beckwith-Wiedemann syndrome	AD	3	130650	KCNQ1OT1	604115
11p15.4	Beckwith-Wiedemann syndrome	AD	3	130650	CDKN1C	600856
11q13.1	Facial dysmorphism, hypertrichosis, epilepsy, intellectual/developmental delay, and gingival overgrowth syndrome	AD	3	618381	KCNK4	605720
11q13.1	Thauvin-Robinet-Faivre syndrome	AR	3	617107	FIBP	608296
17q11.2	Chromosome 17q11.2 deletion syndrome, 1.4Mb	AD	4	613675		613675
17q11.2	Imagawa-Matsumoto syndrome	AD	3	618786	SUZ12	606245
18q12.1	Tenorio syndrome	AD	3	616260	RNF125	610432
19p13.13	Malan syndrome	AD	3	614753	NFIX	164005
Xq26.2	Simpson-Golabi-Behmel syndrome, type 1	XLR	3	312870	GPC3	300037

OMIM Gene Map

OMIM Gene/Loci: 188 - 197 of 550 on Chromosome 15 (All Entries)

Show 100 | Download As | pter | « Towards pter | Towards qter » | qter

Phenotype Only Entries | All Entries

Location (from NCBI, GRCh38)	Gene/Locus	Gene/Locus name	Gene/Locus MIM number	Phenotype	Phenotype MIM number Compare	Inheritance	Pheno map key	Comments	Mouse symbol (from MGI)
15:48,120,990 15q21.1	SLC24A5, NCKX5, SHEP4, OCA6	Solute carrier family 24 (sodium/potassium/calcium exchanger), member 5	609802	[Skin/hair/eye pigmentation 4, fair/dark skin]	113750	AR	3		Slc24a5
				Albinism, oculocutaneous, type VI	113750	AR	3		
15:48,134,632 15q21.1	MYEF2, KIAA1341	Myelin expression factor 2	619395						Myef2, Myef2l
15:48,206,302 15q21.1	SLC12A1, NKCC2	Solute carrier family 12 (sodium/potassium/chloride transporters), member 1	600839	Bartter syndrome, type 1	601678	AR	3		Slc12a1
15:48,331,095 15q21.1	DUT, BMFDMS	dUTP pyrophosphatase	601266	Bone marrow failure and diabetes mellitus syndrome	620044	AR	3		Dut
15:48,408,313 15q21.1	FBN1, MFS1, WMS2, SSKS, GPHYSD2, ACMICD, ECTOL1, MFLS	Fibrillin-1	134797	Acromicric dysplasia	102370	AD	3		Fbn1
				Ectopia lentis, familial	129600	AD	3		
				Geleophysic dysplasia 2	614185	AD	3		
				Marfan lipodystrophy syndrome	616914	AD	3		
				Marfan syndrome	154700	AD	3		
				MASS syndrome	604308	AD	3		
				Stiff skin syndrome	184900	AD	3		
				Weill-Marchesani syndrome 2, dominant	608328	AD	3		
15:48,729,083 15q21.1	CEP152, KIAA0912, MCPH9, SCKL5	Centrosomal protein, 152kD	613529	Microcephaly 9, primary, autosomal recessive	614852	AR	3		Cep152

Challenges in identifying Novel Disease Genes and Diseases

- Finding patients with same phenotype and likely pathogenic variant(s) in the same gene
  - Interoperable detailed phenotypic features with longitudinal information
- Understanding the role of the wild-type protein or RNA in health
- Understanding the effect of the mutations on the protein or RNA
- Understanding how these cellular effects play out on an organ system and organismal level
- This will not all happen in one paper, but we still must show as much evidence as clearly as possible when making a claim of new disease gene identification

Approaches for Genomic Data Sharing

(a) Two-sided matchmaking

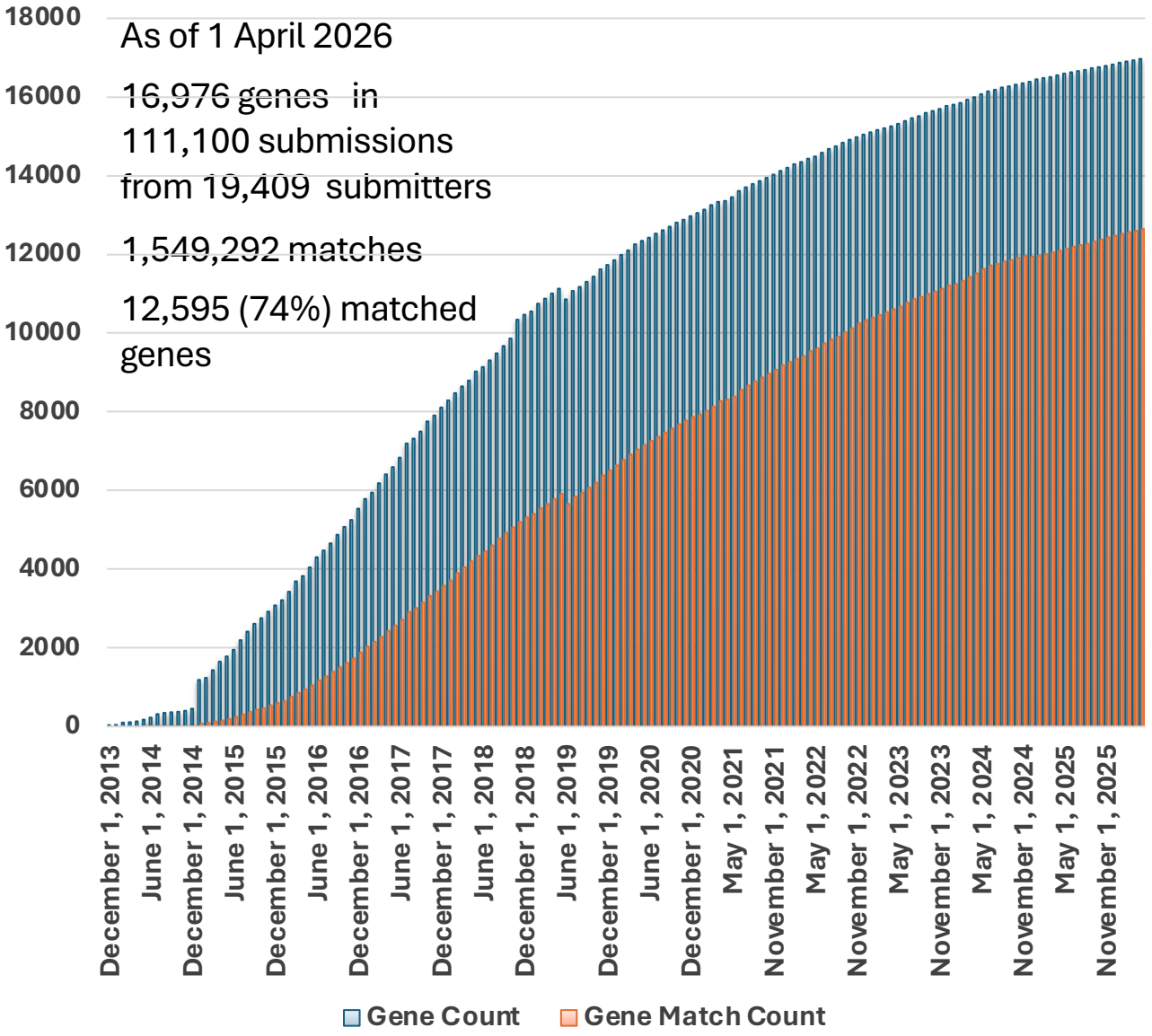
Current
(gene to gene matching)
Matchmaker Exchange

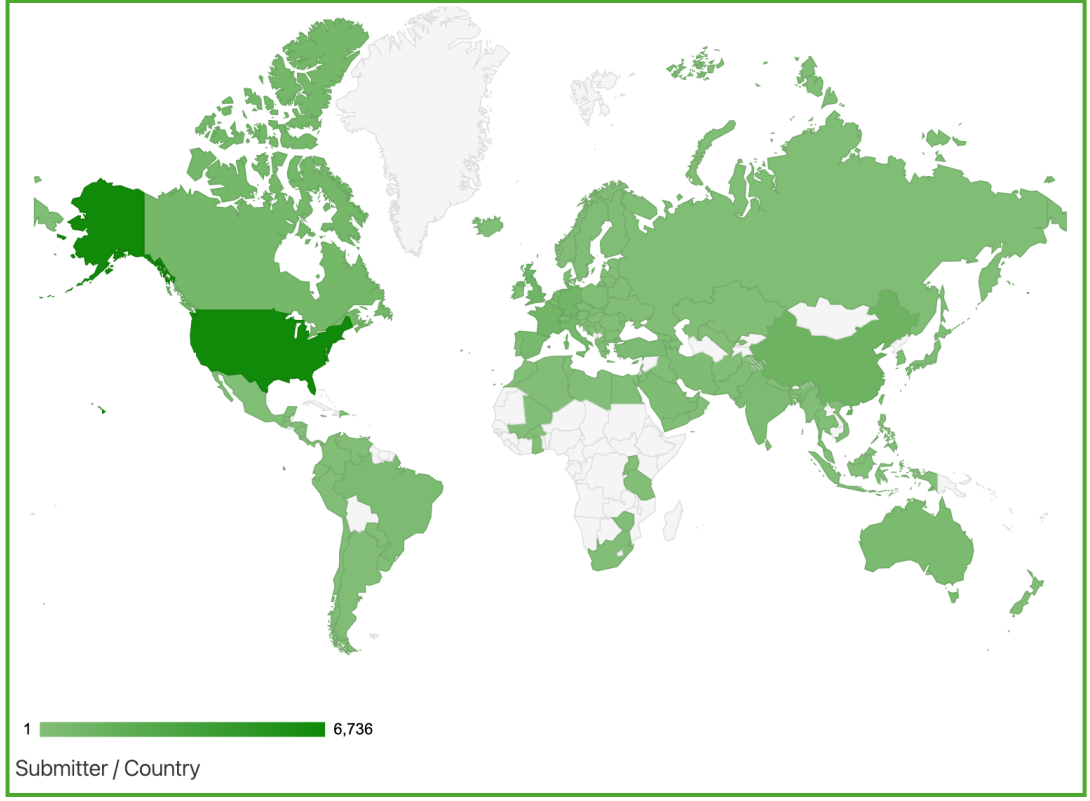
(b) One-sided matchmaking

Next step
(variant to genome matching)
Variant Level Matching

Boycott KM, Azzariti D, Hamosh A, Rehm HL. **Seven years since the launch of the Matchmaker Exchange.** Hum Mutat. 2022 43(6):659-667. PMID: 35537081

GeneMatcher





Submitters in 116 countries

GeneMatcher has been cited by >1095 papers, reporting >830 novel disease genes

https://genematcher.org

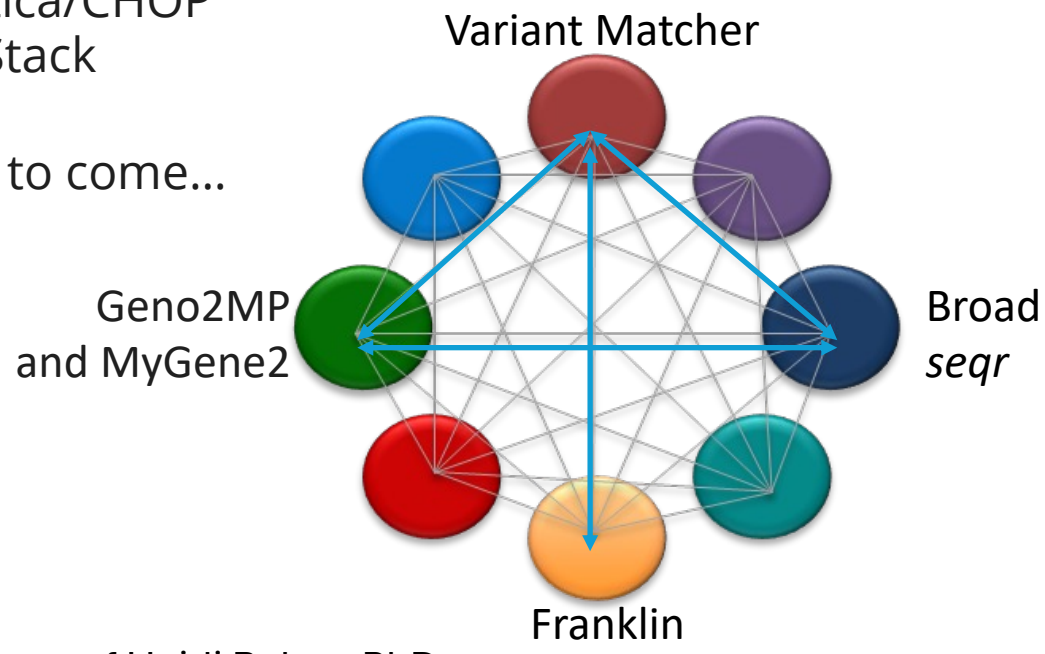
The Matchmaker Exchange

	Cases in MME	Unique Genes
DECIPHER (UK)	52,385	9,971
GeneMatcher (USA)	108,649	15,904
Broad *seqr* (USA)	1,735	1,715
Boston Children's Hospital *seqr* (USA)	28	33
MyGene2 (USA)	2,236	1,736
PatientMatcher (Sweden)	48	57
PhenomeCentral (Canada + UDNI)	12,332	3,628
RD-Connect GPAP (Europe)	8,726	795

https://www.matchmakerexchange.org

Building a federated variant-level matching (VLM) platform

Collaborating Databases
VariantMatcher – Johns Hopkins
Franklin by Genoox
Geno2MP and MyGene2 – University of Washington
seqr and AnVIL – Broad
RD-Connect – CNAG-CRG - Spain
seqr in Genomics4RD – Canada
Genomics England
Cavatica/CHOP
DNAStack
Elixir
More to come…



Global Alliance for Genomics & Health

Beacon v2 API

The Beacon API v2 represents a simple but powerful genomics API for federated data discovery and retrieval

- Three sites moved to automated authentication
- Current implementations display aggregate allele counts and provide a link to access phenotype

Next steps:
- Enable delivery of phenotype information directly through the API as an alternative to URL/login
- Expand sites supporting variant type queries

Slide courtesy of Heidi Rehm, PhD

Matching Requirements

- Higher Order HPO (e.g. abnormality of the skeleton) terms are fine to look for (or rule out) a match
- Gene
- Allelic Requirement
- Type of variant

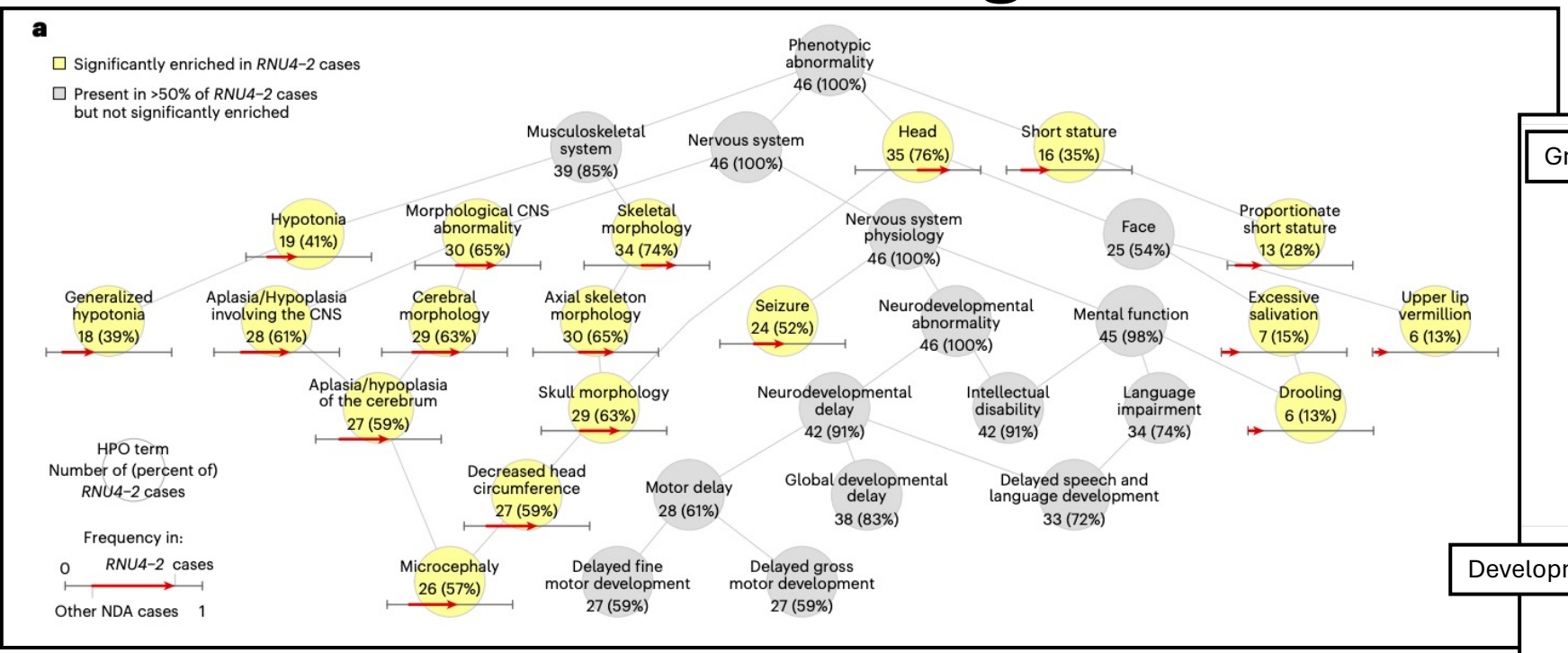
Publication (proof): Phenotypic Requirements

- Need interoperable information about features (shared and not) across the cohort
- Need detailed phenotypic information for each affected individual
- Need a vignette, describing each affected person's health trajectory, because being a very premature infant, or suffering severe infections or bleeds will alter the life course potentially independently of the genetic etiology
- Need photos and images so that the reader can independently assess the phenotype
- Each of these types of information is essential for establishing a legitimate gene-phenotype relationship

Specificity of Phenotypic Features*

- * a plus is limited information
  - e.g. seizures: what kind, what severity, what treatment
- Age of last assessment of the patient and age of diagnosis or onset of feature
- Presence (or absence) of pertinent features
- Not evaluated or Not Assessed or Not Determined needs to be listed; + is present, - is not present and looked for
- Evaluation of related features (e.g. skin and teeth, if talking about hair)

HPO terms are not enough



Greene et al., 2024, Nature Medicine, https://doi.org/10.1038/s41591-024-03085-5

Growth	IUGR	8 out of 45	18
	Short stature	37 out of 49	76
	Microcephaly	37 out of 48	77
	-congenital	19 out of 37	
	-acquired	9 out of 37	
	-not specified	9 out of 37	
Development	GDD	49 out of 49	100
	-severe	34 out of 49	
	-moderate	10 out of 49	
	-not specified	5 out of 49	
	Ambulatory (>5 years old)	30 out of 36	83
	-abnormal gait	7 out of 30	
	-not specified	23 out of 30	
	Speech abnormality	45 out of 48	94
	-non-verbal	35 out of 45	
	-few words	10 out of 45	

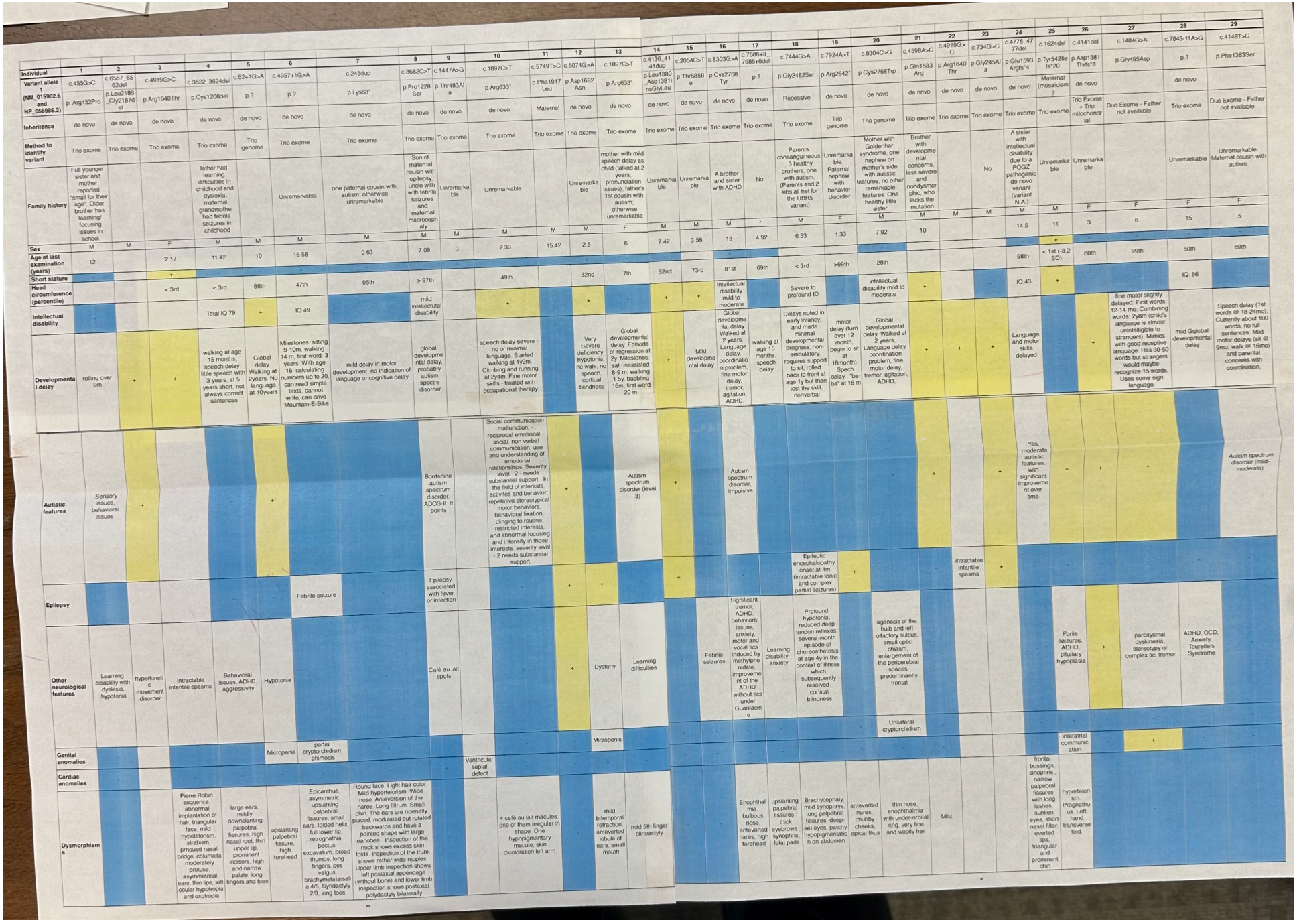
HPO numbers are not useful to humans,
please organize by organ system

Chen et al, 2024, Nature, https://doi.org/10.1038/s41586-024-07773-7

Supplemental Table of Phenotypic Features

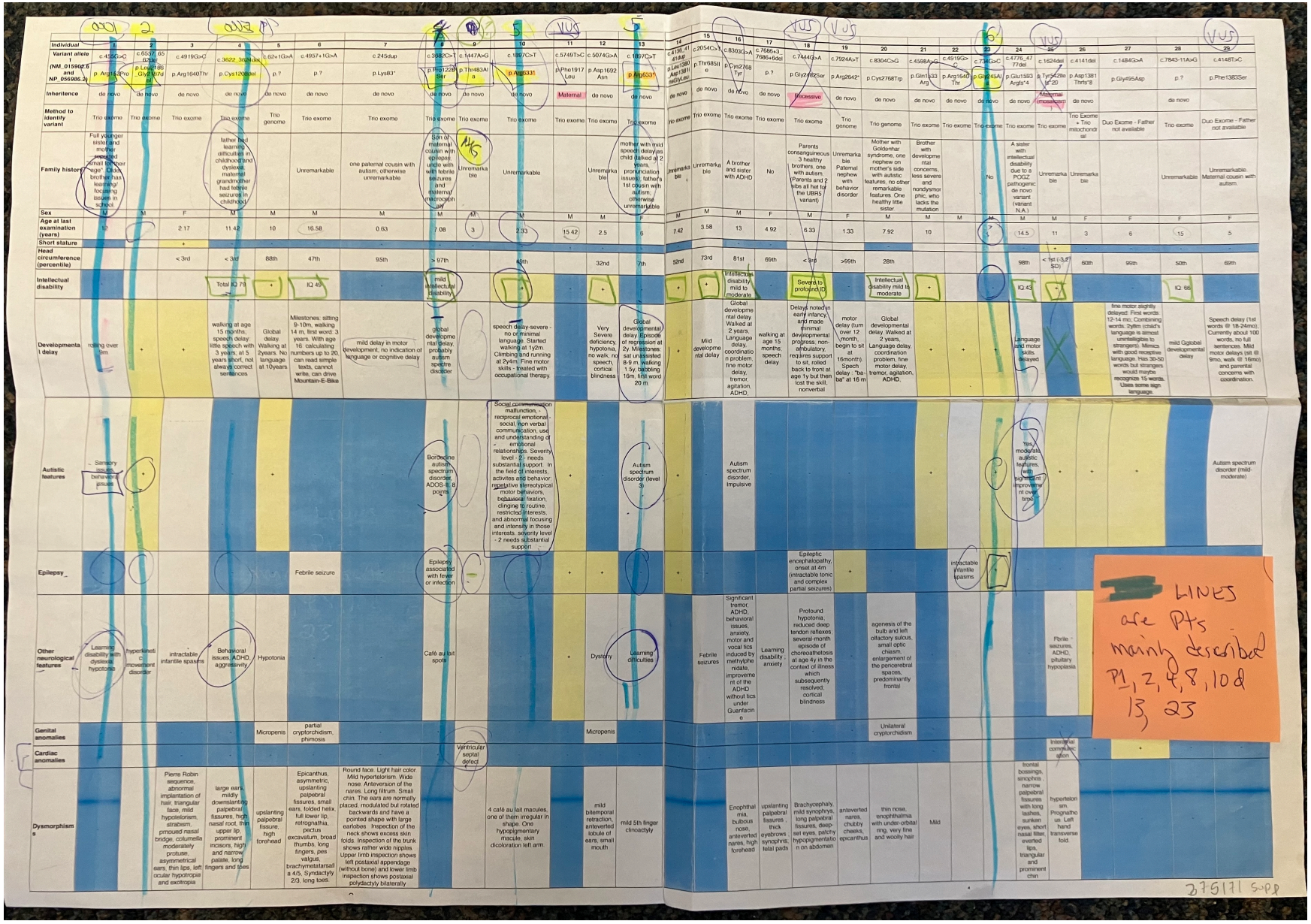
Individual	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Variant allele 1 (NM_0159 02.6 and NP_05698 6.2)	c.455G>C	c.6557_6562del	c.4919G>C	c.3622_3624del	c.62+1G>A	c.4957+1G>A	c.245dup	c.3682C>T	c.1447A>G	c.1897C>T	c.5749T>C	c.5074G>A	c.1897C>T	c.4136_4141dup	c.2054C>T	c.8303G>A	c.7886+3_7886+6del	c.7444G>A	c.7924A>T	c.8304C>G	c.4598A>G	c.4919G>C	c.734G>C	c.4776_4777del	c.1624del	c.4141del	c.1484G>A	c.7843-11A>G	c.4148T>C
	p.Arg152Pro	p.Leu2186_Gly2187del	p.Arg1640Thr	p.Cys1208del	p.?	p.?	p.Lys83*	p.Pro1228Ser	p.Thr483Ala	p.Arg633*	p.Phe1917Leu	p.Asp1692Asn	p.Arg633*	p.Leu1380_Asp1381insGlyLeu	p.Thr685Ile	p.Cys2768Tyr	p.?	p.Gly2482Ser	p.Arg2642*	p.Cys2768Trp	p.Gln1533Arg	p.Arg1640Thr	p.Gly245Ala	p.Glu1593Argfs*4	p.Tyr5421sfs*20	p.Asp1381Thrfs*8	p.Gly495Asp	p.?	p.Phe1383Ser
Inheritance	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	Maternal	de novo	de novo	de novo	de novo	de novo	de novo	Recessive	de novo	de novo	de novo	de novo	de novo	de novo	Maternal (mosaicism)	de novo		de novo	
Method to identify variant	Trio exome	Trio exome	Trio exome	Trio exome	Trio genome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	de novo	Trio exome	Trio exome	Trio exome	Trio exome	Trio genome	Trio genome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio Exome + Trio mitochondrial	Duo Exome - Father not available	Trio exome	Duo Exome - Father not available
Family history	Full younger sister and mother reported "small for their age". Older brother has learning/ focusing issues in school.			father had learning difficulties in childhood and dyslexia, maternal grandmother had febrile seizures in childhood		Unremarkable	one paternal cousin with autism, otherwise unremarkable	Son of maternal cousin with epilepsy, uncle with with febrile seizures and maternal macrocephaly	Unremarkable	Unremarkable		Unremarkable	mother with mild speech delay as child (talked at 2 years, pronunciation issues); father's 1st cousin with autism; otherwise unremarkable	Unremarkable	Unremarkable	A brother and sister with ADHD	No	Parents consanguineous. 3 healthy brothers, one with autism. (Parents and 2 sibs all het for the LBR5 variant)	Unremarkable. Paternal nephew with behavior disorder	Mother with Goldenhar syndrome, one nephew on mother's side with autistic features, no other remarkable features. One healthy	Brother with developmental concerns, less severe and nondysmorphic, who lacks the mutation		No	A sister with intellectual disability due to a PQGZ pathogenic de novo variant (variant N.A.)	Unremarkable	Unremarkable		Unremarkable	Unremarkable. Maternal cousin with autism.
Sex	M	M	F	M	M	M	M	M	M	M	M	M	F	M	M	M	F	M	F	M	M	M	M	M	M	F	F	F	F
Age at last examination (years)	12		2.17	11.42	10	16.58	0.63	7.08	3	2.33	15.42	2.5	6	7.42	3.58	13	4.92	6.33	1.33	7.92	10			14.5	11	3	6	15	5
Short stature	-		+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						-	+	-	-	-	-
Head circumference (percentile)			< 3rd	< 3rd	88th	47th	95th	> 97th		49th		32nd	7th	52nd	73rd	81st	69th	< 3rd	>99th	28th				98th	< 1st (-3.2 SD)	60th	99th	50th	69th
Intellectual disability	-			Total IQ 79	+	IQ 49	-	mild intellectual disability		+	-	+	-	+	+	Intellectual disability mild to moderate	-	Severe to profound ID	-	Intellectual disability mild to moderate	+		-	IQ:43	+	-	-	IQ: 66	-
Developmental delay	rolling over 9m	+	+	walking at age 15 months; speech delay: little speech with 3 years; at 5 years short, not always correct sentences	Global delay. Walking at 2years. No language at 10years	Milestones: sitting 9-10m, walking 14 m, first word: 3 years. With age 16: calculating numbers up to 20, can read simple texts, cannot write, can drive Mountain-E-Bike	mild delay in motor development; no indication of language or cognitive delay	global developmental delay, probably autism spectre disorder		speech delay- severe - no or minimal language. Started walking at 1y2m. Climbing and running at 2y4m. Fine motor skills - treated with occupational therapy	-	Very Severe deficiency hypotonia, no walk, no speech, cortical blindness	Global developmental delay. Episode of regression at 2y. Milestones sat unassisted 8-9 m, walking 1.5y, babbling 16m, first word 20 m	+	Mild developmental delay	Global developmental delay. Walked at 2 years. Language delay, coordination problem, fine motor delay, tremor, agitation, ADHD.	walking at age 15 months; speech delay	Delays noted in early infancy, and made minimal developmental progress; non-ambulatory, requires support to sit, rolled back to front at age 1y but then lost the skill, nonverbal	motor delay (turn over 12 month, begin to sit at 16month). Speech delay "baba" at 16 m	Global developmental delay. Walked at 2 years. Language delay, coordination problem, fine motor delay, tremor, agitation, ADHD.	+	+	+	Language and motor skills delayed	-	+	fine motor slightly delayed: First words: 12-14 mo; Combining words: 2y8m (child's language is almost unintelligible to strangers). Mimics with good receptive language. Has 30-50 words but strangers would maybe recognize 15 words. Uses some sign language.	mild Gglobal developmental delay	Speech delay (1st words @ 18-24mo); Currently about 100 words, no full sentences. Mild motor delays (sit @ 9mo, walk @ 16mo) and parental concerns with coordination.
Autistic features	Sensory issues, behavioral issues	+		-	+	-	-	Borderline autism spectrum disorder, ADOS-II: 8 points		Social communication malfunction, - reciprocal emotional - social, non verbal communication, use and understanding of emotional relationships. Severity level - 2 - needs substantial support. In the field of interests, activities and behavior: repetative stereotypic	+	-	Autism spectrum disorder (level 3)	+	-	Autism spectrum disorder, impulsive	-	-	-	-	+	+	Yes, moderate autistic features, with significant improvement over time	+	+	+	-	Autism: spectrum disorder (mild-moderate)
Epilepsy	-					Febrile seizure	-	Epilepsy associated with fever or infection			+	+	-	+			Epileptic encephalopathy. onset at 4m (intractable tonic and complex partial seizures)		+	-	intractable infantile spasms	+	-	-	-	-	-	-	-
Other neurological features	Learning disability with dyslexia, hypotonia	hyperkinetic movement disorder	intractable infantile spasms	Behavioral issues, ADHD, aggressivity	Hypotonia	-	-	Café au lait spots		-	+	Dystony	Learning difficulties	-	Febrile seizures	Significant tremor, ADHD, behavioral issues, anxiety, motor and vocal tics induced by methylphenidate, improvement of the ADHD without tics under Guanfacine	Learnng disability anxiety	Profound hypotonia, reduced deep tendon reflexes, several-month episode of choreoathetosis at age 4y in the context of illness which subsequently resolved, cortical blindness	-	agenesis of the bulb and left olfactory sulcus, small optic chiasm, enlargement of the pericerebral spaces, predominantly frontal				Fbrile seizures, ADHD, pituitary hypoplasia	+	paroxysmal dyskinesia, stereotypy or complex tic, tremor	ADHD, OCD, Anxiety, Tourette's Syndrome	
Genital anomalies	-			-	-	Micropenis	partial cryptorchidism, phimosis	-		-		Micropenis	-	-	-	-	-	-	-	Unilateral cryptorchidism	-	-	-	-	-	-	-	-	-
Cardiac anomalies	-			-	-	-	-	-	Ventricular septal defect	-		-	-	-	-	-	-	-	-	-	-	-	-	Interatrial communication	-	+	-	-	-
Dysmorphisms				Pierre Robin sequence, abnormal implantation of hair, triangular face, mild hypotelorism, strabism, peruoed nasal bridge, columella moderately protuse, asymmetrical ears, thin lips, left ocular hypotropia and exotropia	large ears, mildly downslanting palpebral fissures, high nasal root, thin upper lip, prominent incisors, high and narrow palate, long fingers and toes	upslanting palpebral fissure, high forehead	Epicanthus, asymmetric, upslanting palpebral fissures, small ears, folded helix, full lower lip, retrognathia, pectus excavatum, broad thumbs, long fingers, pes valgus, brachymetatarsalia 4/5, Syndactyly 2/3, long toes	Round face. Light hair color. Mild hypertelorism. Wide nose. Anteversion of the nares. Long filtrum. Small chin. The ears are normally placed, modulated but rotated backwards and have a pointed shape with large earlobes. Inspection of the neck shows excess		4 café au lait macules, one of them irregular in shape. One hypopigmentary macule, skin dicoloration left arm.		mild bitemporal retraction, anteverted lobule of ears, small mouth	mild 5th finger clinocatyly	-	Enophthalmia, bulbous nose, anteverted nares, high forehead	upslanting palpebral fisaures ; thick eyebrows ; synophris, fetal pads	Brachycephaly, mild synophrys, long palpebral fissures, deep-set eyes, patchy hypopigmentation on abdomen	antieverted nares, chubby cheeks, epicanthus	thin nose, enophthalmia with undercorbital ring, very fine and wooly hair	Mild		frontal bossings, sinophrys , narrow palpebral fissures with long lashes, sunken eyes, short nasal filter, everted lips, triangular and prominent chin		hypertelorism. Prognathous. Left hand transverse fold.				

What OMIM does to highlight
what is present (yellow) and what is absent (blue) to facilitate the work of the Science Writer



Individual	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Variant allele 1 (NM_015902.6 and NP_056986.2)	c.455G>C	c.6557_6562del	c.4919G>C	c.3622_3624del	c.62+1G>A	c.4957+1G>A	c.245dup	c.3682C>T	c.1447A>G	c.1897C>T	c.5749T>C	c.5074G>A	c.1897C>T	c.4136_4141dup	c.2054C>T	c.8303G>A	c.7686+3_7686+6del	c.7444G>A	c.7924A>T	c.8304C>G	c.4598A>G	c.4919G>C	c.734G>C	c.4776_4777del	c.1624del	c.4141del	c.1484G>A	c.7843-11A>G	c.4148T>C
	p. Arg152Pro	p.Leu2186_Gly2187del	p.Arg1640Thr	p.Cys1208del	p.?	p.?	p.Lys83*	p.Pro1228Ser	p.Thr483Ala	p.Arg633*	p.Phe1917Leu	p.Asp1692Asn	p.Arg633*	p.Leu1380_Asp1381insGlyLeu	p.Thr685Ile	p.Cys2768Tyr	p.?	p.Gly2482Ser	p.Arg2642*	p.Cys2768Trp	p.Gln1533Arg	p.Arg1640Thr	p.Gly245Ala	p.Glu1593Argfs*4	p.Tyr5421Iefs*20	p.Asp1381Thrfs*8	p.Gly495Asp	p.?	p.Phe1383Ser
Inheritence	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	de novo	Maternal	de novo	de novo	de novo	de novo	de novo	de novo	Recessive	de novo	de novo	de novo	Trio genome	Trio genome	de novo	Maternal (mosaicism)	de novo		de novo	
Method to identify variant	Trio exome	Trio exome	Trio exome	Trio exome	Trio genome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio genome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome	Trio exome + Trio mitochondrial	Duo Exome - Father not available	Trio exome	Duo Exome - Father not available
Family history	Full younger sister and mother reported "small for their age". Older brother has learning/ focusing issues in school		father had learning difficulties in childhood and dyslexia; maternal grandmother had febrile seizures in childhood		Unremarkable	one paternal cousin with autism; otherwise unremarkable	Son of maternal cousin with epilepsy, uncle with with febrile seizures and maternal macrocephaly	Unremarkable		Unremarkable		Unremarkable	mother with mild speech delay as child (talked at 2 years, pronunciation issues), father's 1st cousin with autism; otherwise unremarkable	Unremarkable	Unremarkable	A brother and sister with ADHD	No	Parents consanguineous 3 healthy brothers, one with autism. (Parents and 2 sibs all het for the UBR5 variant)	Unremarkable. Paternal nephew with behavior disorder	Mother with Goldenhar syndrome, one nephew on mother's side with autistic features, no other remarkable features. One healthy little sister	Brother with developmental concerns, less severe and nondysmorphic; who lacks the mutation			A sister with intellectual disability due to a POGZ pathogenic de novo variant (variant N.A.)	Unremarkable	Unremarkable		Unremarkable	Unremarkable. Maternal cousin with autism.
Sex	M	M	F	M	M	M	M	M	M	M	M	M	F	M	M	M	F	M	F	M	M	M	M	M	M	F	F	F	F
Age at last examination (years)	12		2.17	11.42	10	16.58	0.63	7.08	3	2.33	15.42	2.5	6	7.42	3.58	13	4.92	6.33	1.33	7.92	10			14.5	11	3	6	15	5
Short stature			+																					+				
Head circumference (percentile)			< 3rd	< 3rd	88th	47th	95th	> 97th		49th		32nd	7th	52nd	73rd	81st	69th	< 3rd	>99th	28th				98th	< 1st (-3.2 SD)	60th	99th	50th	69th
Intellectual disability				Total IQ 79	+	IQ 49		mild intellectual disability		+		+		+	+	Intellectual disability mild to moderate		Severe to profound ID		Intellectual disability mild to moderate	+			IQ 43	+			IQ 66	
Developmental delay	rolling over 9m	+	+	walking at age 15 months, speech delay little speech with 3 years, at 5 years short, not always correct sentences	Global delay Walking at 2years. No language at 10years	Milestones: sitting 9-10m, walking 14 m, first word 3 years. With age 16: calculating numbers up to 20, can read simple texts, cannot write, can drive Mountain-E-Bike	mild delay in motor development, no indication of language or cognitive delay	global developmental delay, probably autism spectre disorder		speech delay-severe - no or minimal language. Started walking at 1y2m. Climbing and running at 2y4m. Fine motor skills - treated with occupational therapy		Very Severe deficiency, hypotonia, no walk, no speech, cortical blindness	Global developmental delay. Episode of regression at 2y. Milestones: sat unassisted 8-9 m, walking 1.5y, babbling 16m, first word 20 m.	+	Mild developmental delay	Global developmental delay Walked at 2 years, Language delay, coordination problem, fine motor delay, tremor, agitation, ADHD.	walking at age 15 months, speech delay	Delays noted in early infancy, and made minimal developmental progress; non-ambulatory, requires support to sit, rolled back to front at age 1y but then lost the skill, nonverbal	motor delay (turn over 12 month, begin to sit at 16month) Spech delay "baba" at 18 m	Global developmental delay. Walked at 2 years, Language delay, coordination problem, fine motor delay, tremor, agitation, ADHD.	+	+	+	Language and motor skills delayed		+	fine motor slightly delayed: First words: 12-14 mo; Combining words: 2y8m (child's language is almost unintelligible to strangers). Mimics with good receptive language. Has 30-50 words but strangers would maybe recognize 15 words. Uses some sign language.	mild Gglobal developmental delay	Speech delay (1st words @ 18-24mo); Currently about 100 words, no full sentences. Mild motor delays (sit @ 9mo, walk @ 16mo) and parental concerns with coordination.
Autistic features	Sensory issues, behavioral issues	+			+			Borderline autism spectrum disorder, ADOS-II: 8 points		Social communication malfunction, - reciprocal emotional - social, non verbal communication, use and understanding of emotional relationships. Severity level - 2 - needs substantial support. In the field of interests, activities and behavior: repetative stereotypical motor behaviors, behavioral fixation, clinging to routine, restricted interests, and abnormal focusing and intensity in those interests. severity level - 2 needs substantial support.	+		Autism spectrum disorder (level 3)	+		Autism spectrum disorder: impulsive				+		+	Yes, moderate autistic features, with significant improvement over time	+	+	+		Autism spectrum disorder (mild-moderate)
Epilepsy						Febrile seizure		Epilepsy associated with fever or infection				+	+	+				Epileptic encephalopathy onset at 4m (intractable tonic and complex partial seizures)	+			intractable infantile spasms	+						
Other neurological features	Learning disability with dyslexia, hypotonia	hyperkinetic movement disorder	intractable infantile spasms	Behavioral issues, ADHD, aggressivity	Hypotonia		Café au lait spots				+	Dystony	Learning difficulties		Febrile seizures	Significant tremor, ADHD, behavioral issues, anxiety, motor and vocal tics induced by methylphenidate, improvement of the ADHD without tics under Guanfacine	Learning disability ; anxiety	Profound hypotonia, reduced deep tendon reflexes, several-month episode of choreoathetosis at age 4y in the context of illness which subsequently resolved, cortical blindness		agenesis of the bulb and left olfactory sulcus, small optic chiasm, enlargement of the pericerebral spaces, predominantly frontal					Febrile seizures, ADHD, pituitary hypoplasia	+	paroxysmal dyskinesia, stereotypy or complex tic, tremor	ADHD, OCD, Anxiety, Tourette's Syndrome	
Genital anomalies						Micropenis	partial cryptorchidism, phimosis						Micropenis							Unilateral cryptorchidism					Interatrial communication		+	
Cardiac anomalies									Ventricular septal defect																				
Dysmorphisms				Pierre Robin sequence, abnormal implantation of hair, triangular face, mild hypotelorism, strabism, prnoued nasal bridge, columella moderately protuse, asymmetrical ears, thin lips, left ocular hypotropia and exotropia	large ears, mildly downslanting palpebral fissures, high nasal root, thin upper lip, prominent incisors, high and narrow palate, long fingers and toes	upslanting palpebral fissure, high forehead	Epicanthus, asymmetric, upslanting palpebral fissures, small ears, folded helix, full lower lip, retrognathia, pectus excavatum, broad thumbs, long fingers, pes valgus, brachymetatarsalsia 4/5, Syndactyly 2/3, long toes	Round face. Light hair color. Mild hypertelorism. Wide nose. Anteversion of the nares. Long filtrum. Small chin. The ears are normally placed, modulated but rotated backwards and have a pointed shape with large earlobes. Inspection of the neck shows excess skin folds. Inspection of the trunk shows rather wide nipples. Upper limb inspection shows left postaxial appendage (without bone) and lower limb inspection shows postaxial polydactyly bilaterally.		4 café au lait macules, one of them irregular in shape. One hypopigmentary macule, skin dicoloration left arm.		mild bitemporal retraction, anteverted lobule of ears, small mouth	mild 5th finger clinoactyly		Enophthalmia, bulbous nose, anteverted nares, high forehead	upslanting palpebral fissures, thick eyebrows, synophris, fetal pads	Brachycephaly, mild synophrys, long palpebral fissures, deep-set eyes, patchy hypopigmentation on abdomen	anteverted nares, chubby cheeks, epicanthus	thin nose, enophthalmia with under-orbital ring, very fine and woolly hair	Mild		frontal bossings, sinophris, narrow palpebral fissures with long lashes, sunken eyes, short nasal filter, everted lips, triangular and prominent chin	hyperteliorism. Prognathous. Left hand transverse fold.		

What the Science Writer does to select which variants and patients to describe and include



This table is on the floor. There is no way to assess this information on a computer screen.

Publication (proof): Variant Requirements

- Segregation: BOTH the presence of the variant in affected individuals and its absence in unaffected individuals (if complete penetrance is argued)
- Show a pedigree, including unaffected sibs
- De Novo is not enough
- Robust functional evidence is really helpful (essential if the phenotype is non-specific)
- In highly consanguineous families, please report homozygous variants in other genes

Need for Deep Phenotyping to Establish a Disease Gene

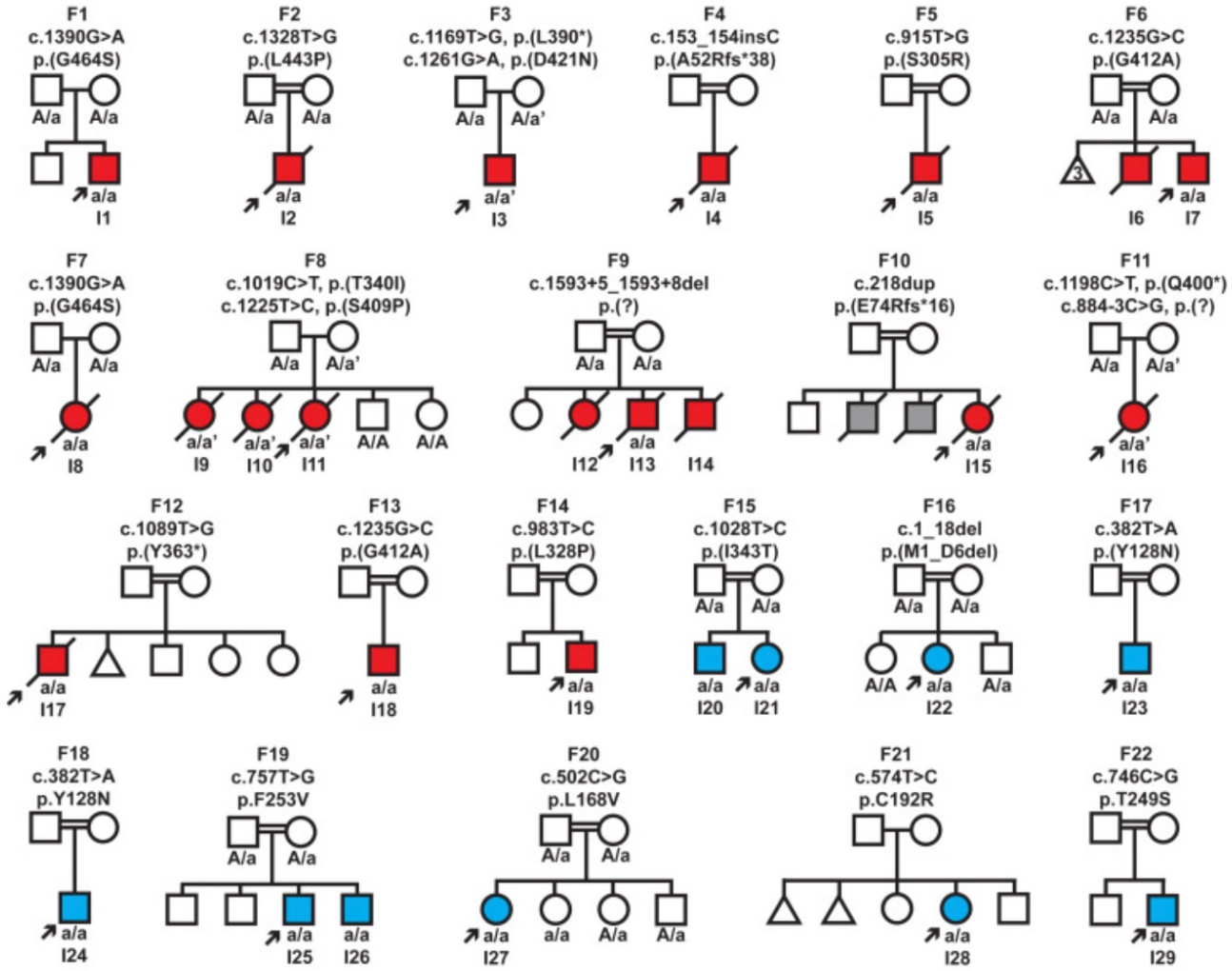
- Depends on the specificity and uniqueness of the phenotype

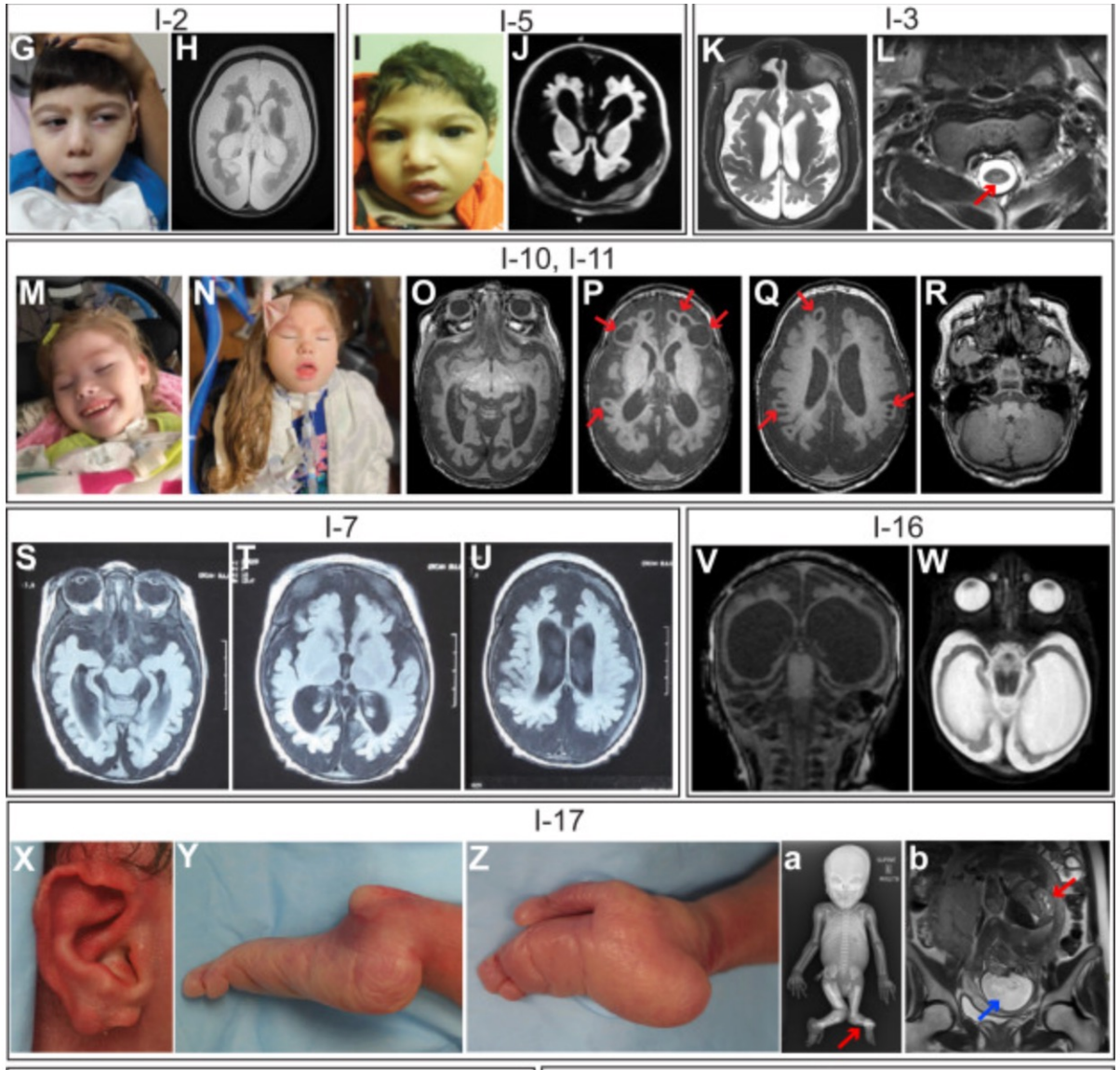
  - Easy: Specific and testable biochemical abnormality, or very specific single manifestation (e.g. lymphedema), or distinctive multiple congenital anomalies

  - Hard: non-specific and broad range neurodevelopmental disorder, or diffuse and non-specific multiple congenital anomalies

Calame et al, 2024 abstract (results): We ascertained 30 patients from 23 unrelated families with biallelic FLVCR1 variants and characterized a novel FLVCR1-related phenotype: severe developmental disorders with profound developmental delay, microcephaly (z-score -2.5 to -10.5), brain malformations, epilepsy, spasticity, and premature death. Brain malformations ranged from mild brain volume reduction to hydranencephaly. Severely affected patients share traits, including macrocytic anemia and skeletal malformations, with Flvcr1$^{-/-}$ mice and DBA. FLVCR1 variants significantly reduce choline and ethanolamine transport and/or disrupt mRNA splicing.

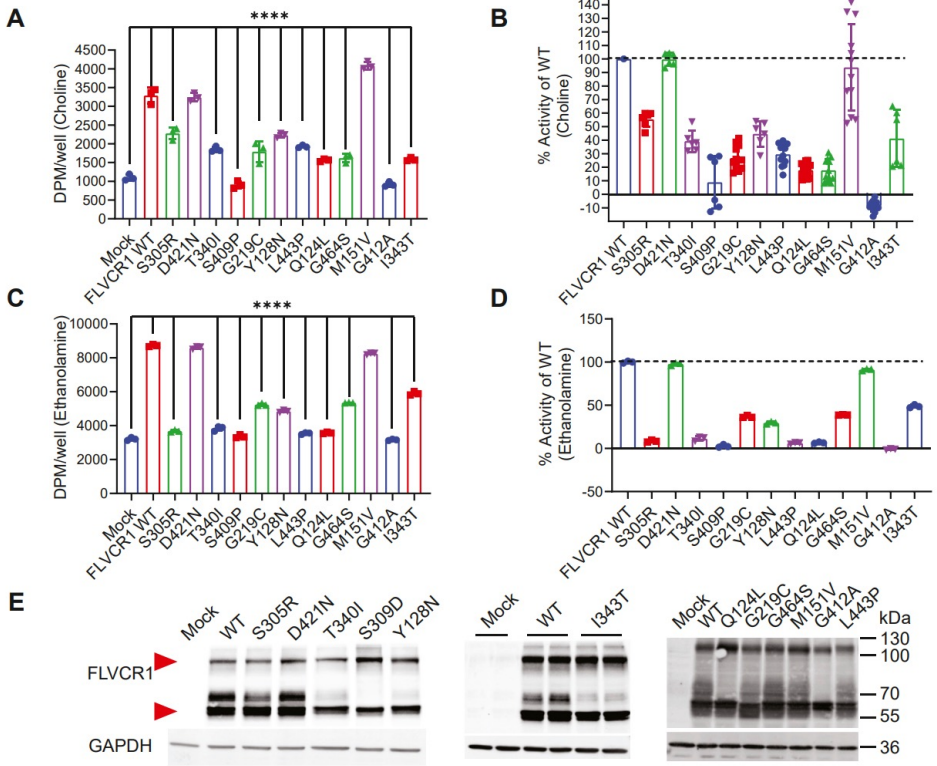
Calame et al. doi: 10.1016/j.gim.2024.101273. Epub 2024 Sep 19. PMID: 39306721.



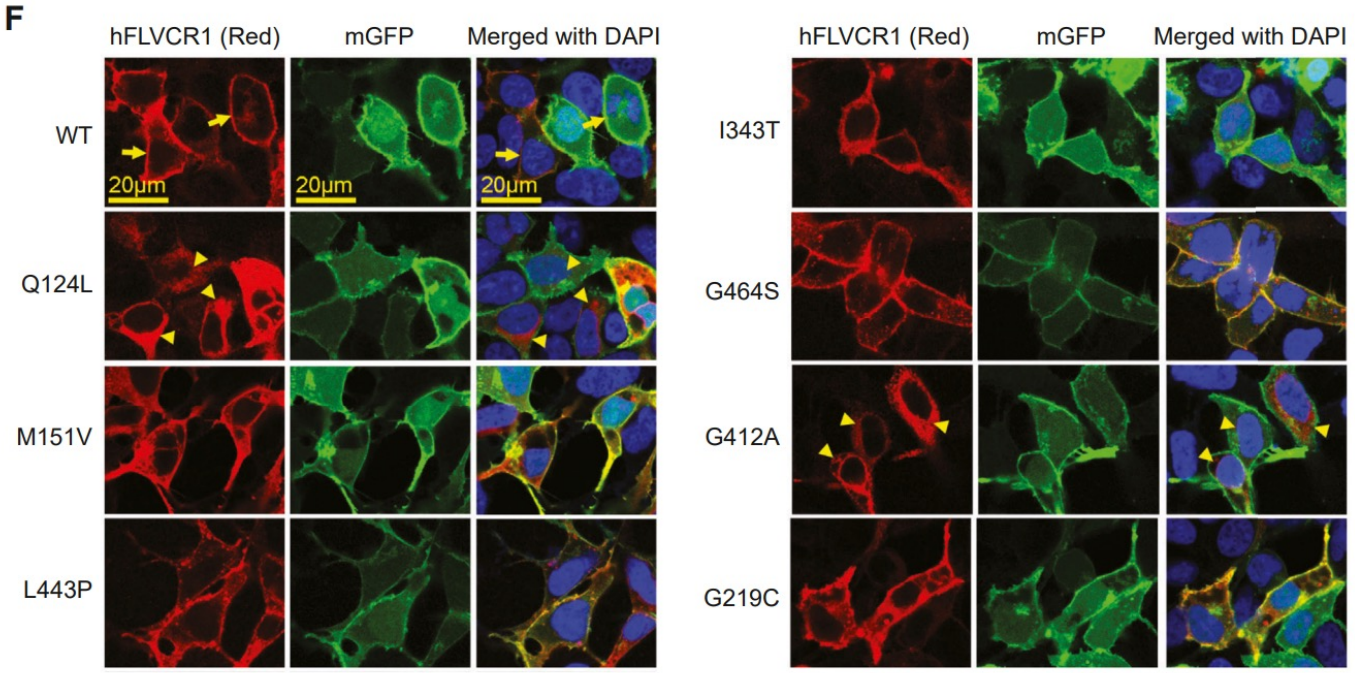


Red is severe NDD with microcephaly, absent speech and hypotonia; Blue is RP-neuropathy

Calame et al. doi: 10.1016/j.gim.2024.101273. Epub 2024 Sep 19. PMID: 39306721.



Beautiful, detailed, functional evidence



* 609144

FLVCR HEME TRANSPORTER 1; FLVCR1

Alternative titles; symbols

FELINE LEUKEMIA VIRUS SUBGROUP C RECEPTOR 1
FLVCR
SLC49A1

HGNC Approved Gene Symbol: FLVCR1

Cytogenetic location: 1q32.3 Genomic coordinates (G

Gene-Phenotype Relationships

Location	Phenotype	View
1q32.3	Neurodevelopmental disorder with microcephaly, absent speech, hypotonia	
	Retinopathy-sensory neuropathy syndrome	

NUMBER	# 621060	# 609033
TITLE	NEURODEVELOPMENTAL DISORDER WITH MICROCEPHALY, ABSENT SPEECH, AND HYPOTONIA; NEDMISH	RETINOPATHY-SENSORY NEUROPATHY SYNDROME; RETSNS
GENE	*FLVCR1* - 609144	*FLVCR1* - 609144
INHERITANCE (in 2/2)	- Autosomal recessive	- Autosomal recessive
HEAD & NECK (in 2/2)	*Head* - Small head circumference - Microcephaly	
	Eyes - Cortical visual impairment - Optic nerve atrophy - Retinitis pigmentosa	*Eyes* - Retinopathy - Ring scotoma (early) - Retinitis pigmentosa - Night blindness (infancy and early childhood) - Blindness by third decade - Fundus with peripheral 'bony spicules' - Optic atrophy - No light-evoked response seen on electroretinogram (ERG) - Cataracts (in some patients)
		Mouth - Oral ulcerations (in patients with pain insensitivity)
RESPIRATORY (in 1/2)	*Larynx* - Laryngomalacia	
ABDOMEN (in 1/2)		*Gastrointestinal* - Achalasia - Gastrointestinal dysmotility
GENITOURINARY (in 1/2)		*Bladder* - Urinary incontinence - Recurrent urinary tract infections
SKELETAL (in 2/2)	- Osteomyelitis	
	Spine - Scoliosis	*Spine* - Scoliosis
	Limbs - Limb malformations - Arthrogryposis	
	Hands - Digital malformations - Polydactyly	*Hands* - Camptodactyly - Finger ulceration (in patients with pain insensitivity) - Necrosis of the fingertips (in patients with pain insensitivity) - Acroosteolysis (in patients with pain insensitivity)
	Feet - Digital malformations	
SKIN, NAILS, & HAIR (in 1/2)		*Skin* - Skin ulceration (in patients with pain insensitivity)
		Nails - Nail dystrophy (in patients with pain insensitivity)
MUSCLE, SOFT TISSUES (in 1/2)		- Neurogenic muscle atrophy - Distal muscle weakness
NEUROLOGIC (in 2/2)	*Central Nervous System* - Global developmental delay, profound	*Central Nervous System* - Developmental delay (in some patients)

Phenotypic Expansion vs. New Disorder

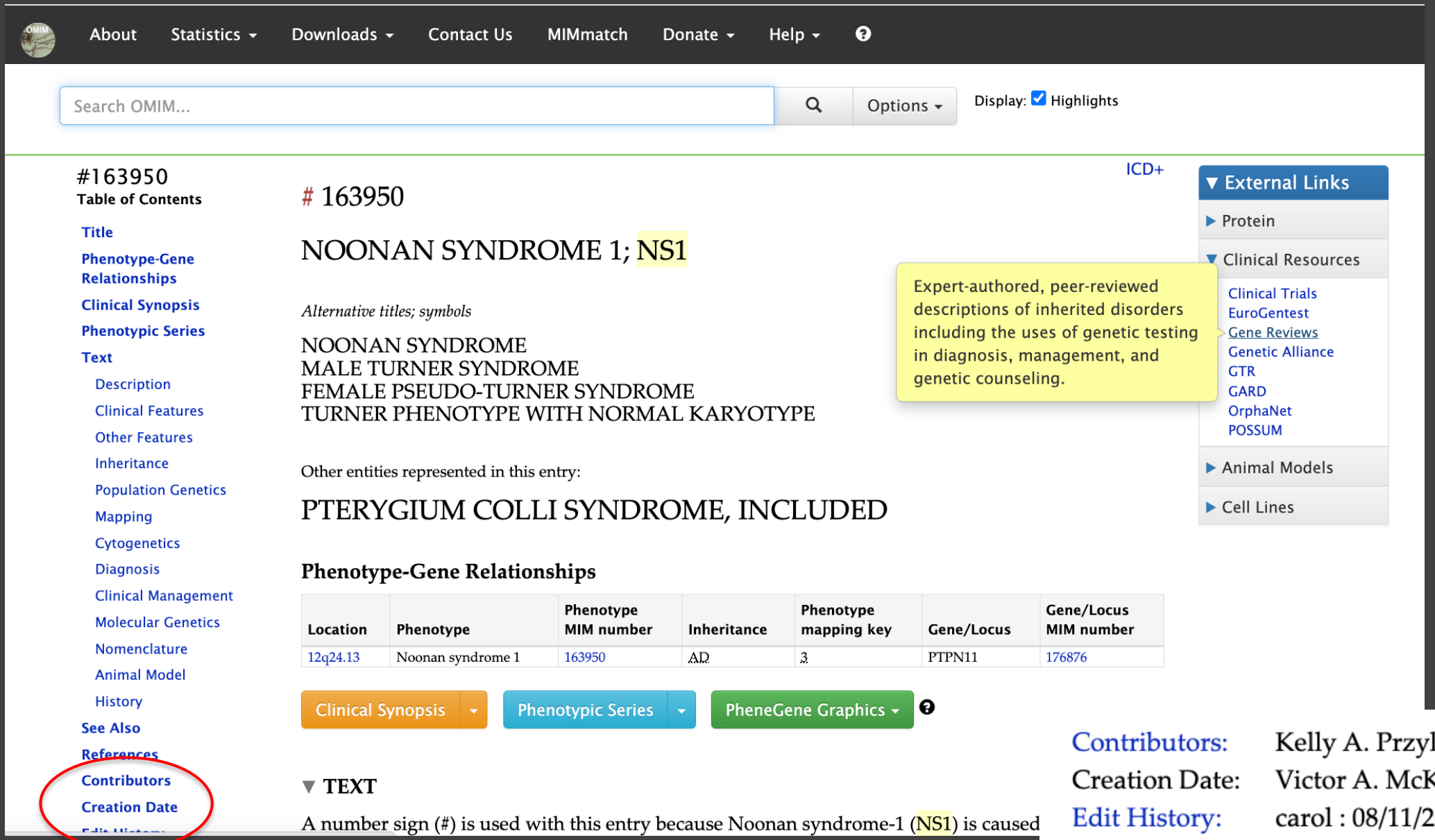
- New Disorder requires distinct features, and/or progression, and age of onset (not just more severe)
  - Or new mode of inheritance (allelic requirement)
  - Or mutational mechanism (e.g. dominant negative vs haploinsufficiency) with different consequences
- Phenotypic Expansion is expected as more affected individuals are identified

Conclusions to what is necessary to establish a new gene-phenotype relationship

- Please take the time to carefully phenotype the cohort of patients, working with clinicians
- For lists of features, give the numerator and the denominator and only give a percentage if you have the data on a majority of patients
- Include pictures of patients, features, and images (MRIs, xrays)
- Include vignettes describing the life course of affected individuals
- Perform the correct functional studies in cells or animal models

Other Useful Resources

Topical Links to Useful Resources



Contributors: Kelly A. Przylepa - updated : 07/06/2023
Creation Date: Victor A. McKusick : 4/28/1993
Edit History: carol : 08/11/2025

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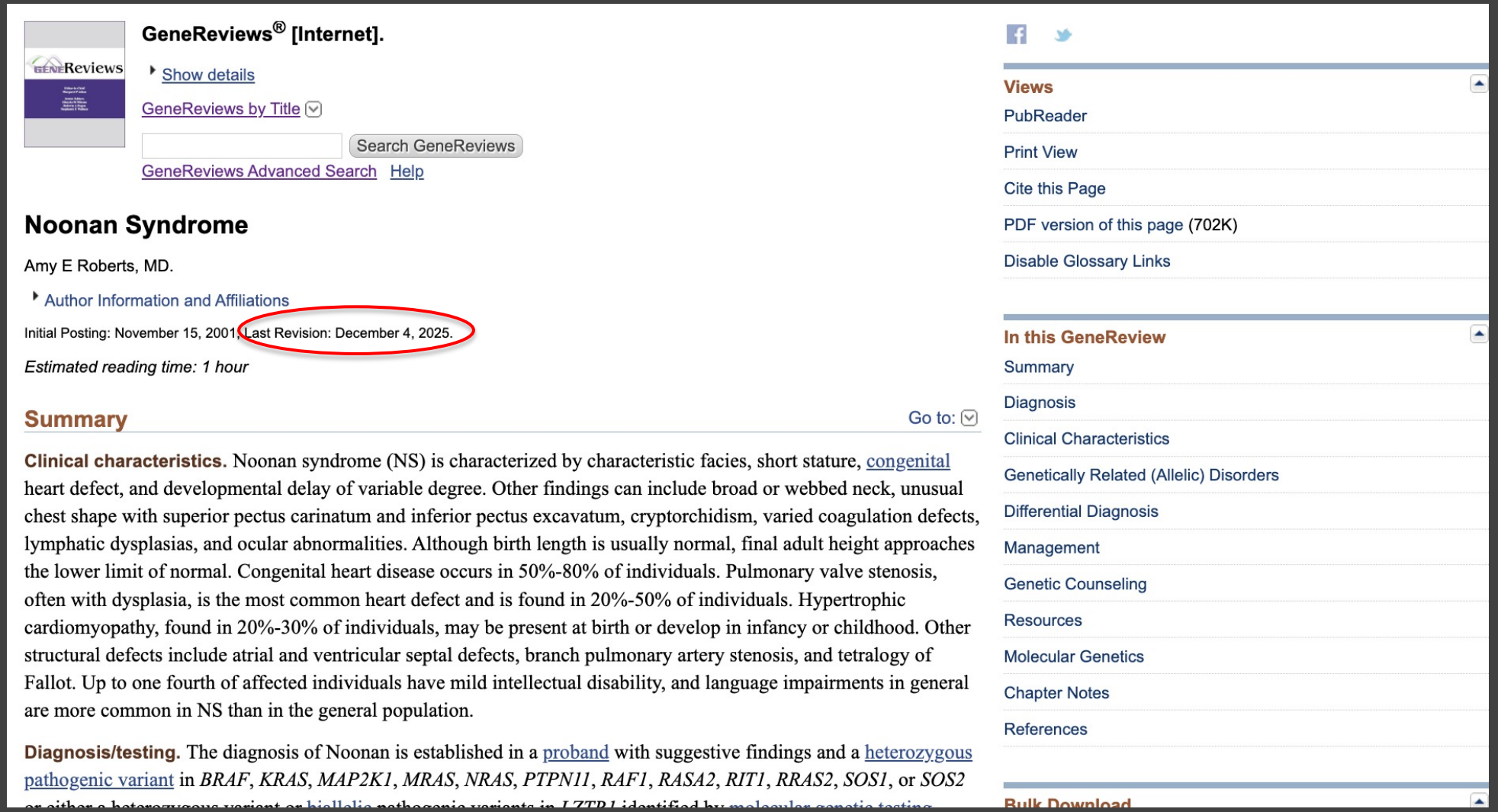

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Noonan Syndrome

Amy E Roberts, MD.

Author Information and Affiliations

Initial Posting: November 15, 2001; Last Revision: December 4, 2025.

Estimated reading time: 1 hour

Summary

Go to:

Clinical characteristics. Noonan syndrome (NS) is characterized by characteristic facies, short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one fourth of affected individuals have mild intellectual disability, and language impairments in general are more common in NS than in the general population.

Diagnosis/testing. The diagnosis of Noonan is established in a proband with suggestive findings and a heterozygous pathogenic variant in *BRAF*, *KRAS*, *MAP2K1*, *MRAS*, *NRAS*, *PTPN11*, *RAF1*, *RASA2*, *RIT1*, *RRAS2*, *SOS1*, or *SOS2*

Views

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In this GeneReview

Summary

Diagnosis

Clinical Characteristics

Genetically Related (Allelic) Disorders

Differential Diagnosis

Management

Genetic Counseling

Resources

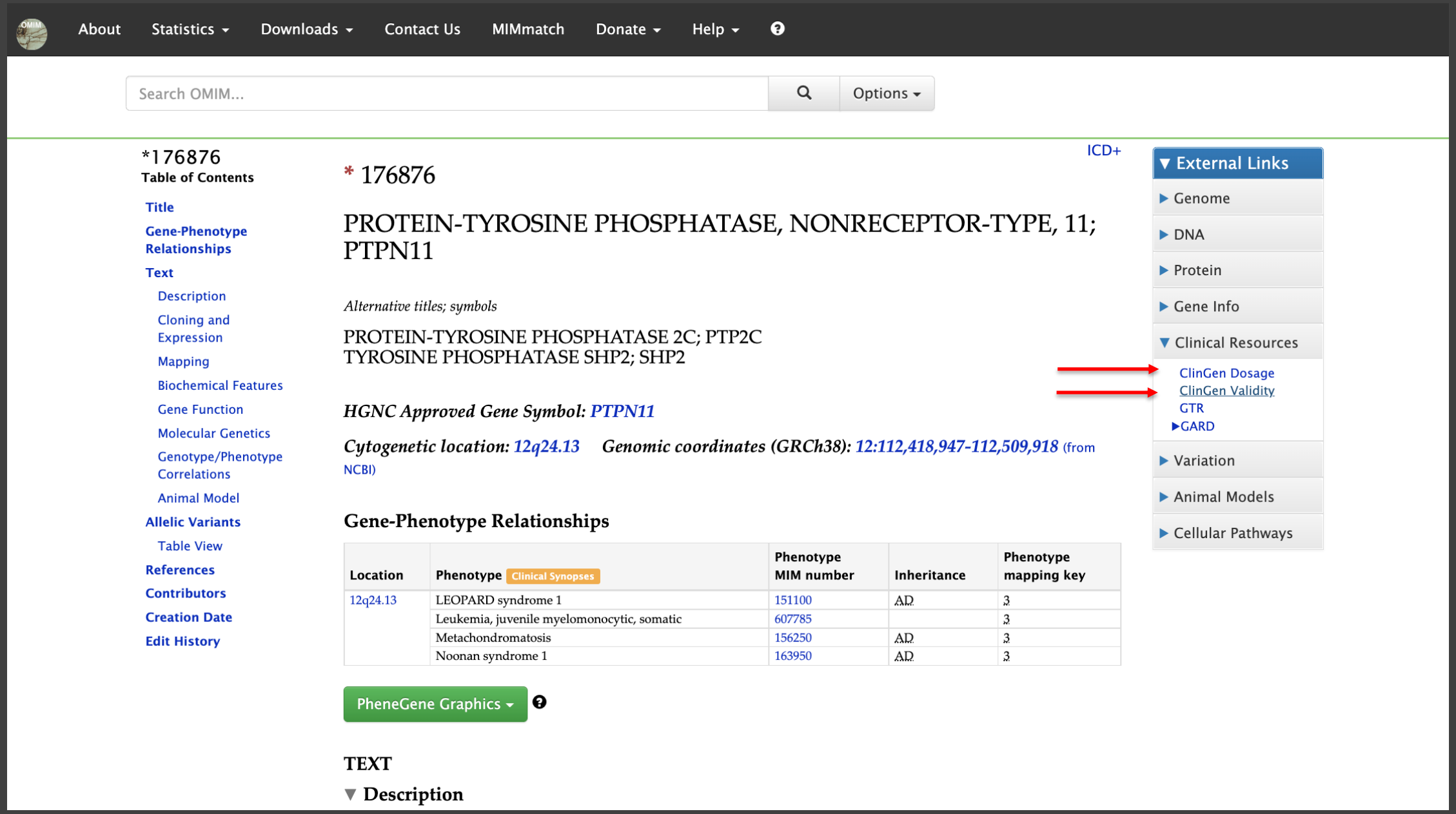
Molecular Genetics

Chapter Notes

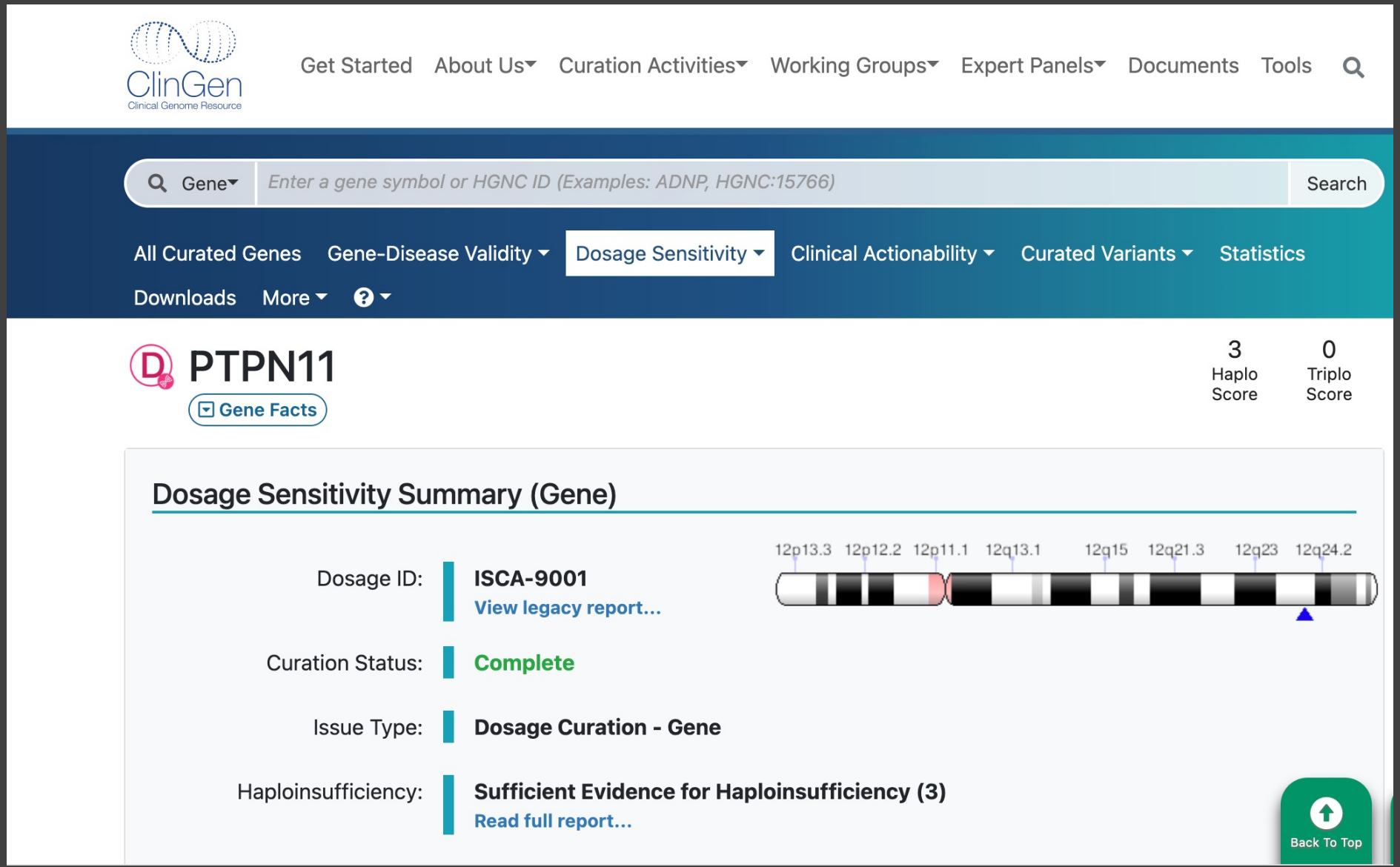
References

Bulk Download

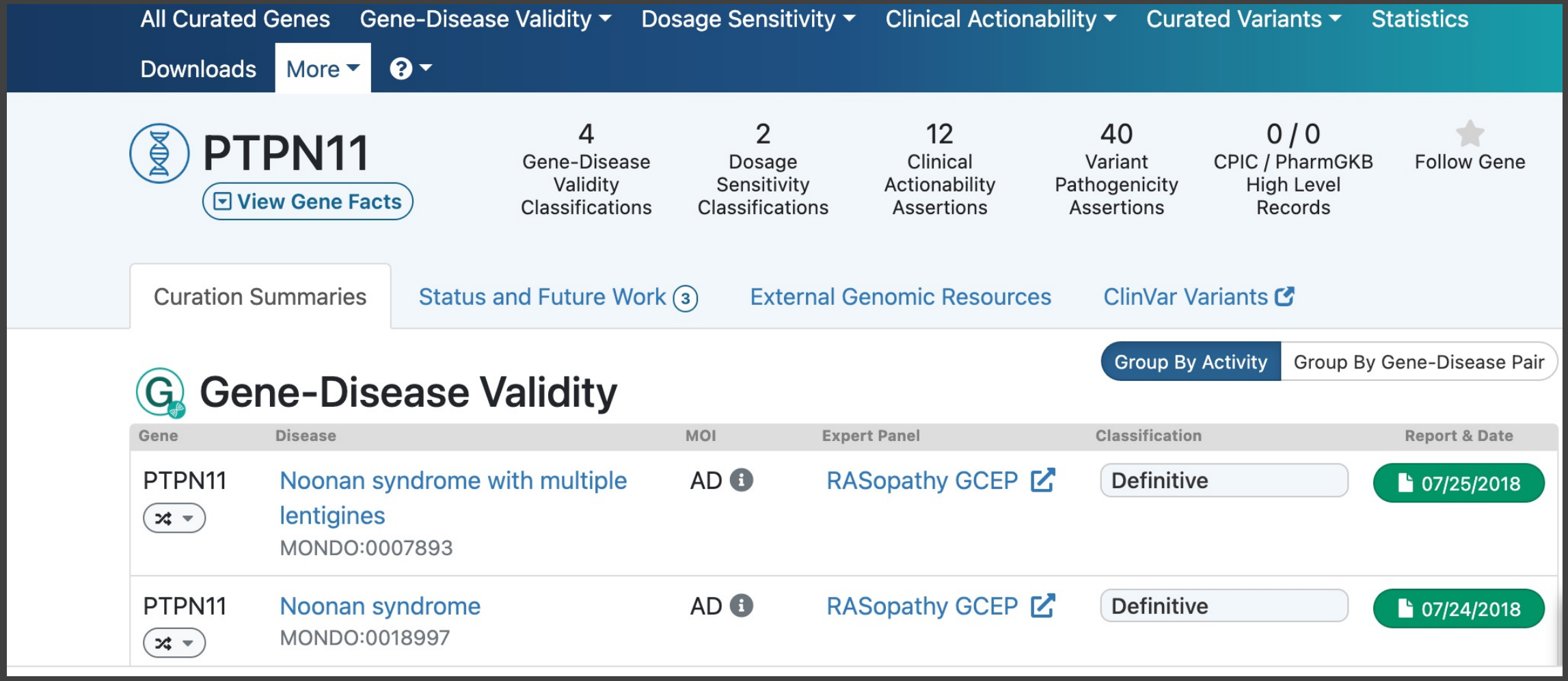
Topical Links to Useful Resources



ClinGen Dosage Sensitivity



ClinGen Gene-Disease Validity



ClinGen

- Resources on clinical relevance of genes and variants
  - Gene-disease validity
  - Variant curation
  - Dosage sensitivity
  - Clinical actionability

ClinGen
Clinical Genome Resource

Use ClinGen to find info about:

- Strength of the evidence of a gene-disease pair
- Dosage sensitivity of genes
- Clinical actionability for select genes and variants
- Information about select variants in some genes.

Genes

1 Genes with classifications based on your filters

fars2 | Filter by submitted disease... | Filter by Submitter

FARS2	5	6
HGNC:21062	Disease Equivalents	Submitters
1	2	1
3	0	0
2	0	0
		0

GenCC The Gene Curation Coalition

Genes | GenCC Members | Statistics | Download | FAQ | Contact | About | Stay Informed

FARS2

Return to list | Search genes... | Help

Gene Symbol:	FARS2 HGNC:21062
Locus Group:	Protein-Coding Gene
Locus Type:	Gene With Protein Product
Location:	6p25.1

By Classification | By Disease | By Submitter

Filters: Classifications 5 | Diseases 5 | MOI 1 | Submitters 6

Definitive classifications

Definitive	FARS2 HGNC:21062	metabolic disease MONDO:0005066	AR	03/08/2019 Evaluated 07/02/2025 Submitted	G2P	Public Report | Assertion Criteria | More Details

Strong classifications

Strong	FARS2 HGNC:21062	combined oxidative phosphorylation defect type 14 MONDO:0013986 Submitted as: OMIM:614946	AR	08/02/2023 Evaluated 11/30/2023 Submitted	Labcorp Genetics (formerly Invitae)	Assertion Criteria | More Details
Strong	FARS2 HGNC:21062	hereditary spastic paraplegia 77 MONDO:0014882 Submitted as: OMIM:617046	AR	12/15/2018 Evaluated 11/30/2023 Submitted	Labcorp Genetics (formerly Invitae)	Assertion Criteria | More Details
Strong	FARS2 HGNC:21062	mitochondrial oxidative phosphorylation disorder MONDO:0016387	AR	01/17/2025 Evaluated N/A	PanelApp Australia	Public Report | Assertion Criteria | More Details

GeneScout

https://genescout.omim.org

- A tool for looking at genomic regions
- Can also compare two individuals for what is or is not shared

genescout.omim.org

GeneScout Home About Help Contact Us

GeneScout is a tool to search genomic regions identified by chromosome microarray to show the genes and their associated phenotypes within the regions of interest. This can be used for deletion/duplications or for runs of homozygosity (ROH). ROH can be compared between individuals. Phenotypes and their associated gene(s) can then be sorted by inheritance or selected to show the specific clinical features side-by-side in OMIM. All results are provided in the assembly selected.

View the GeneScout video tutorial.

Primary coordinates (required), for example: chr1:112597961-114091606 - see search help for supported formats

Search Help Clear Search

Select genome assembly of input coordinates

GRCh37 (hg19) | GRCh38 (hg38)

Calculate CoI/CoR:

Add a second set of coordinates for comparison

Search

GeneScout Tutorial

10K views • 5 years ago

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M. All results are provided in the assembly selected.

1-

Select genome assembly of input coordinates

GRCh37 (hg19) | GRCh38 (hg38)

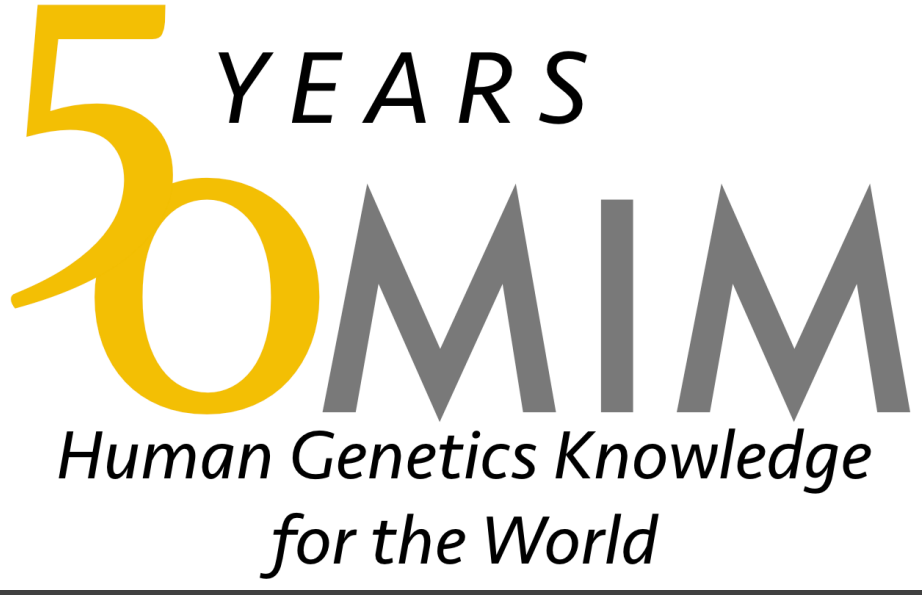
Calculate CoI/CoR:

Clear Search

Add a second set of coordinates for comparison

Show

Intersection | Subtraction



Contact Us link at OMIM.org

Ada Hamosh - ahamosh@jhmi.edu

Read, Research, Connect at OMIM.org