

# Gene variant databases and the importance of data sharing

(using



as an example)

Variant Effect Prediction course, Avans Hogeschool, Breda

## Why is data sharing so important? (1)

- Patient with form of congenital muscular dystrophy
- Three candidate genes, 18 variants detected, no clear cause
- Homozygous for POMGNT1(NM\_017739.3):c.636C>T, but no expected protein change

## Why is data sharing so important? (1)

- Patient with form of congenital muscular dystrophy
- Three candidate genes, 18 variants detected, no clear cause
- Homozygous for POMGNT1(NM\_017739.3):c.636C>T, but no expected protein change
- In the ideal world...
  - Variant already reported online
  - Muscle biopsy, RNA analysis
  - c.636C>T causes skip of exon
  - Frameshift, truncated protein

## Why is data sharing so important? (1)

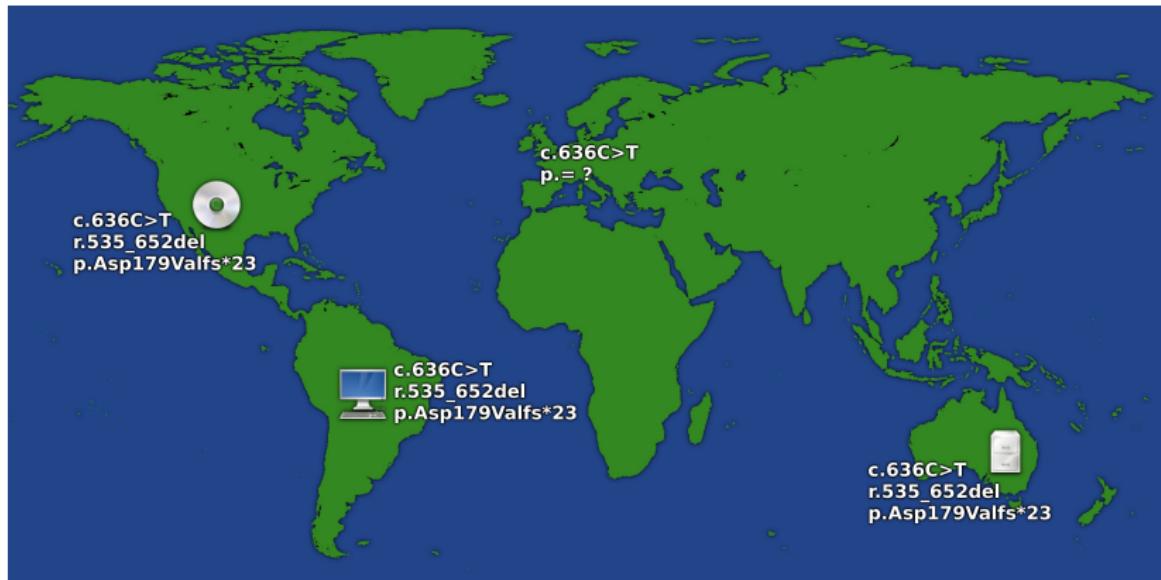
- Patient with form of congenital muscular dystrophy
- Three candidate genes, 18 variants detected, no clear cause
- Homozygous for POMGNT1(NM\_017739.3):c.636C>T, but no expected protein change
- In the ideal world...
  - Variant already reported online
  - Muscle biopsy, RNA analysis
  - c.636C>T causes skip of exon
  - Frameshift, truncated protein
- But in the real world...?



## Why is data sharing so important? (2)



## Why is data sharing so important? (2)



## DNA diagnostics is based on data sharing (1)

If there is no sharing, there is no diagnostics

- **VUS: Variant of Unsufficient Sharing**
- Sharing the relationship between variants and phenotypes
- Reported using standards to avoid confusion and errors
  - Variants: Human Genome Variation Society (HGVS)  
<http://varnomen.hgvs.org>
  - Phenotypes: Human Phenotype Ontology (HPO)  
<http://hpo.jax.org/>
- Data should be easily accessible and easily submitted
  - Requires online databases

## DNA diagnostics is based on data sharing (2)

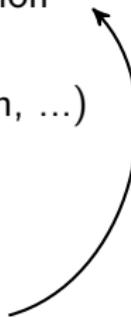
Positive feedback loop

- ① Analyze sample, identify variants
- ② Check external resources, draw initial conclusion
- ③ Perform additional experiments (RNA, protein, ...)
- ④ Plan to publish results
- ⑤ Share with colleagues ▷ submit to database

## DNA diagnostics is based on data sharing (2)

Positive feedback loop

- ① Analyze sample, identify variants
- ② Check external resources, draw initial conclusion
- ③ Perform additional experiments (RNA, protein, ...)
- ④ Plan to publish results
- ⑤ Share with colleagues ▷ submit to database



## Organizations promoting data sharing

- Human Variome Project (HVP)  
& Human Genome Variation Society (HGVS)
  - Promote collecting genome variation and establish standards
  - Database standards, variant nomenclature standards
- Global Alliance for Genomics and Health (GA4GH)
  - More recent initiative, similar goals
  - Very active (working groups, driver projects, beacon network)
- National Center for Biotechnology Information (NCBI)  
& European Bioinformatics Institute (EMBL-EBI)
  - Curate reference sequences and provide bioinformatic tools
  - Genome browsers, gene info resources, variant databases

## DNA variant databases (1)

Central databases (*inch deep, mile wide*)

- HGMD
  - First publication only, variants reported as pathogenic only
- OMIM
  - First report(s) & some interesting cases
- dbSNP (NCBI), EVA (EMBL-EBI)
  - All variants (originally mainly non pathogenic)
- ClinVar (NCBI)
  - Mainly clinical submissions, basic information only
- Many other databases and aggregators...
  - COSMIC, DBVar, Decipher, BRCA exchange, ...

## DNA variant databases (2)

Gene variant databases (LSDBs) (*inch wide, mile deep*)

### Locus Specific DataBase (LSDB) definition

A listing of sequence variants in a specific gene causing a Mendelian disorder or a change in phenotype, curated by an expert in that gene.

- All details per gene
- All variants, pathogenic as well as non-pathogenic
- Can contain detailed phenotype information
- Includes unpublished data, submitted directly to the database

## DNA variant databases (3)

Gene variant databases (LSDBs) - standards

- Use HGVS descriptions for the variant data
- Link to other relevant sources
  - OMIM, PubMed, genome browsers, ...
- Store all variants
  - All effects (pathogenic to benign)
  - All sources (published, unpublished, predicted)
- Detailed phenotype data possible
  - ... but often limited
- Variable formats, quality & update frequency
- Fragmented, not one central location for all genes

# Is there a database?

Try GENE.lovd.nl or GENE.variome.org, always a hit in LOVD and ClinVar!

**Locus Specific Database list**  
Based on various online resources and direct submissions of LSDBs

[LSDB list](#) | [Submit new LSDB](#) | [Log in](#)

### Locus Specific Mutation Databases

If you know of an LSDB, which is not included in this list, you can [submit it here](#).

Please select the first letter of the Gene:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Or, specify the HGNC Gene Symbol:  [Go to this gene »](#)

Supported by: 

**148859 databases**

148859 entries on 14886 pages. Showing entries 1 - 10.

Symbol	Database name	Curators	Software	Last updated
A-GAMMA3'E	ClinVar at NCBI <a href="https://www.ncbi.nlm.nih.gov/clinvar/?term=A-GAMMA3'E(gene)">https://www.ncbi.nlm.nih.gov/clinvar/?term=A-GAMMA3'E(gene)</a>		Other	2019-02-25
A1BG	BiPMed WES - HG19 Not curated, does not accept submissions <a href="http://bipmed.kpm.unicamp.br/wes_hg19/genes/A1BG">http://bipmed.kpm.unicamp.br/wes_hg19/genes/A1BG</a>	Admin BRAINN	LOVD 3.X	2019-01-14
A1BG	Global Variome shared LOVD <a href="https://databases.lovd.nl/shared/genes/A1BG">https://databases.lovd.nl/shared/genes/A1BG</a>	LOVD-team, but with Curator vacancy LUMC	LOVD 3.X	2017-09-01
A1BG	LOVD - Leiden Open Variation Database Not curated, does not accept submissions <a href="http://proteomics.bio21.unimelb.edu.au/lovd/genes/A1BG">http://proteomics.bio21.unimelb.edu.au/lovd/genes/A1BG</a>	Graham Taylor University of Melbourne	LOVD 3.X	2013-06-11
A1BG	ClinVar at NCBI <a href="https://www.ncbi.nlm.nih.gov/clinvar/?term=A1BG(gene)">https://www.ncbi.nlm.nih.gov/clinvar/?term=A1BG(gene)</a>		Other	2019-03-05
A1BG-AS1	BiPMed SNP Array - HG38 Not curated, does not accept submissions <a href="http://bipmed.kpm.unicamp.br/snparray_zib6/genes/A1BG-AS1">http://bipmed.kpm.unicamp.br/snparray_zib6/genes/A1BG-AS1</a>	Admin BRAINN	LOVD 3.X	2018-12-19
A1BG-AS1	ClinVar at NCBI <a href="https://www.ncbi.nlm.nih.gov/clinvar/?term=A1BG-AS1(gene)">https://www.ncbi.nlm.nih.gov/clinvar/?term=A1BG-AS1(gene)</a>		Other	2019-02-25
A1BG-AS1	Global Variome shared LOVD <a href="https://databases.lovd.nl/shared/genes/A1BG-AS1">https://databases.lovd.nl/shared/genes/A1BG-AS1</a>	LOVD-team, but with Curator vacancy LUMC	LOVD 3.X	Unknown
A1BG-AS1	LOVD - Leiden Open Variation Database Not curated, does not accept submissions <a href="http://proteomics.bio21.unimelb.edu.au/lovd/genes/A1BG-AS1">http://proteomics.bio21.unimelb.edu.au/lovd/genes/A1BG-AS1</a>	Graham Taylor University of Melbourne	LOVD 3.X	2013-06-11
A1BG-AS1	BiPMed SNP Array Not curated, does not accept submissions <a href="http://bipmed.kpm.unicamp.br/snparray/genes/A1BG-AS1">http://bipmed.kpm.unicamp.br/snparray/genes/A1BG-AS1</a>	Admin BRAINN	LOVD 3.X	2017-10-26

10 per page ▾ [First](#) [Prev](#) [1](#) [2](#) [3](#) [4](#) [5](#) [6](#) [7](#) [8](#) [9](#) [10](#) [11](#) ... [Next](#) [Last](#)

# What is LOVD?

LOVD is the software powering the largest network of curated gene variant databases in the world.

Main database:



## The LOVD software

Frequently Asked Questions (FAQ), documentation, download the software, see all installations, contact us...



Search all LOVDs for a variant

See all databases for a certain gene:

**GENE.LOVD.NL**

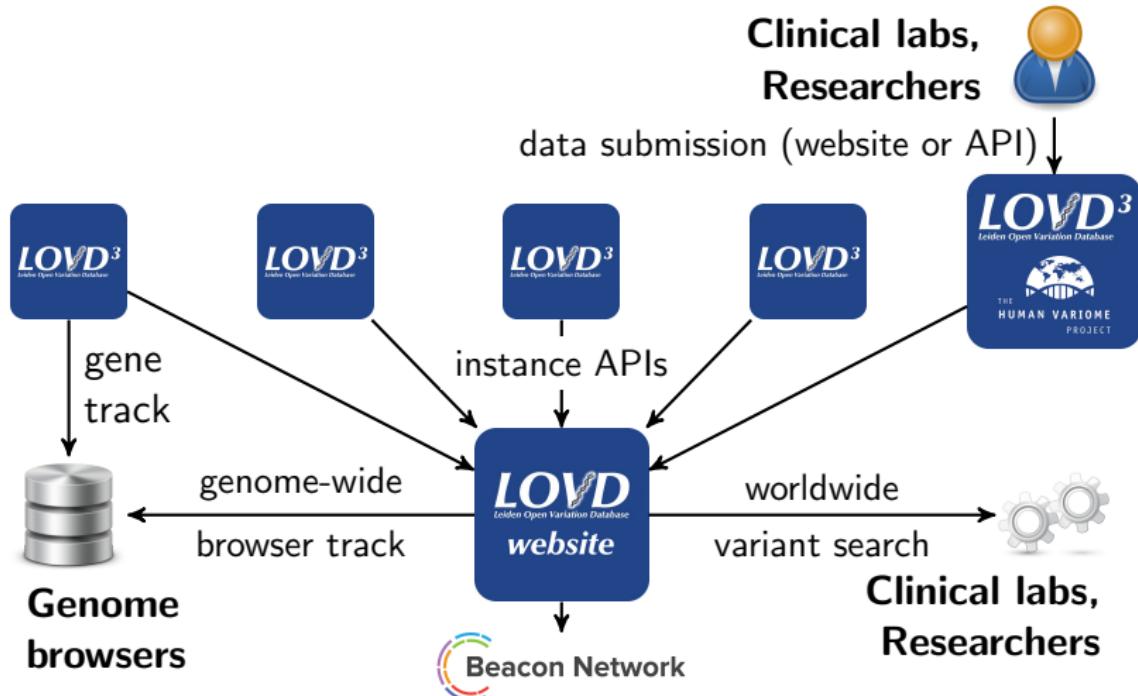
Examples: [DMD.lovd.nl](#), [BRCA1.lovd.nl](#).

See also our [full list of LSDBs](#), or the [list of registered LOVD installations](#).

LOVD is recommended by HVP and IRDIRC



# LOVD network overview



# Variant search across the LOVD network (1)

**LOVD**  
Leiden Open Variation Database

**LOVD v.3.0 - Leiden Open Variation Database**  
Online gene-centered collection and display of DNA variants

[Home](#) [News](#) [FAQ](#) [Documentation](#) [Download](#) [Contact](#) [Developers](#) [Vind ik leuk 762](#)

LOVD 3.0 LOVD 2.0 Public list of LOVD installations Search for a variant Our list of Locus Specific Databases

## Query all public LOVD installations

Query all public LOVD instances:

hg19 / GRCh37 ▾ chr15:g.40699840C>T

Examples: Precise: [chr15:g.40699840C>T](#), Range: [chr13:32936732-32936735](#).

LOVDs currently support only one genome build; if no results are found, you may want to repeat your query using a different genome build.  
LOVD contains for hg18 ~1K unique variants, hg19 ~2M unique variants, and hg38 ~1M.  
This service queries the variant's location, i.e. results of other variants on the same location will show as well. When searching using a ranged variant in HGVS format, only variants exactly matching that range will be returned. When searching using a range (2nd example above), all variants within that range will be returned (to a max of 50).

<b>IVD</b> <a href="http://databases.lovd.nl/whole_genome/">http://databases.lovd.nl/whole_genome/</a>	<b>NM_001159508.1:c.154-298C&gt;G</b>	(variant effect not shared) Variant location matches your query exactly
<b>IVD</b> <a href="https://databases.lovd.nl/shared/">https://databases.lovd.nl/shared/</a>	<b>NM_002225.3:c.157C&gt;T</b>	Affects function / Probably affects function Variant location matches your query exactly

Last modified 2017/11/29 20:16:44 CET

When using or discussing LOVD please refer to:  
Fokkema IF, Taschner PE, Schaafsma GC, Celli J, Laros JF, den Dunnen JT (2011). LOVD v.2.0: the next generation in gene variant databases. [Hum Mutat. 2011 May;32\(5\):557-63.](#)



LOVD has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 200754 - the GEN2PHEN project.  
©2004-2019 [Leiden University Medical Center](#), Netherlands  
Ivo F.A.C. Fokkema BSc., Prof. Johan T. den Dunnen PhD



# Variant search across the LOVD network (2)

**LOVD** *Leiden Open Variation Database*

**LOVD v.3.0 - Leiden Open Variation Database**  
Online gene-centered collection and display of DNA variants

[Home](#) [News](#) [FAQ](#) [Documentation](#) [Download](#) [Contact](#) [Developers](#) [Vind ik leuk 762](#)

LOVD 3.0 LOVD 2.0 Public list of LOVD installations Search for a variant Our list of Locus Specific Databases

## Query all public LOVD installations

Query all public LOVD instances:

hg19 / GRCh37 ▾ chr13:32936732-32936735 [Search](#)

Examples: Precise: [chr15:g.40699840C>T](#), Range: [chr13:32936732-32936735](#).

LOVDs currently support only one genome build; if no results are found, you may want to repeat your query using a different genome build.  
LOVD contains for hg18 ~1K unique variants, hg19 ~2M unique variants, and hg38 ~1M.

This service queries the variant's location, i.e. results of other variants on the same location will show as well. When searching using a ranged variant in HGVS format, only variants exactly matching that range will be returned. When searching using a range (2nd example above), all variants within that range will be returned (to a max of 50).

<b>BRCA2</b> <a href="https://databases.lovd.nl/shared/">https://databases.lovd.nl/shared/</a>	<b>NM_000059.3:c.7878_7881dup</b>	Affects function / Affects function <i>Variant location matches your query exactly</i>
<b>BRCA2</b> <a href="https://databases.lovd.nl/shared/">https://databases.lovd.nl/shared/</a>	<b>NM_000059.3:c.7878G&gt;A</b>	Affects function / Affects function <i>Variant is within range of your query</i>
<b>BRCA2</b> <a href="https://databases.lovd.nl/shared/">https://databases.lovd.nl/shared/</a>	<b>NM_000059.3:c.7878G&gt;C</b>	Effect unknown; Probably affects function; Affects function / Affects function <i>Variant is within range of your query</i>
<b>BRCA2</b> <a href="https://databases.lovd.nl/shared/">https://databases.lovd.nl/shared/</a>	<b>NM_000059.3:c.7879A&gt;T</b>	Effect unknown; Affects function / Affects function <i>Variant is within range of your query</i>

When using or discussing LOVD please refer to:  
Folkema IF, Taschner PE, Schaaftsma GC, Celli J, Laros JF, den Dunnen JT (2011). LOVD v.2.0: the next generation in gene variant databases. [Hum Mutat. 2011 May;32\(5\):557-63.](#)

Last modified 2017/11/29 20:16:44 CET

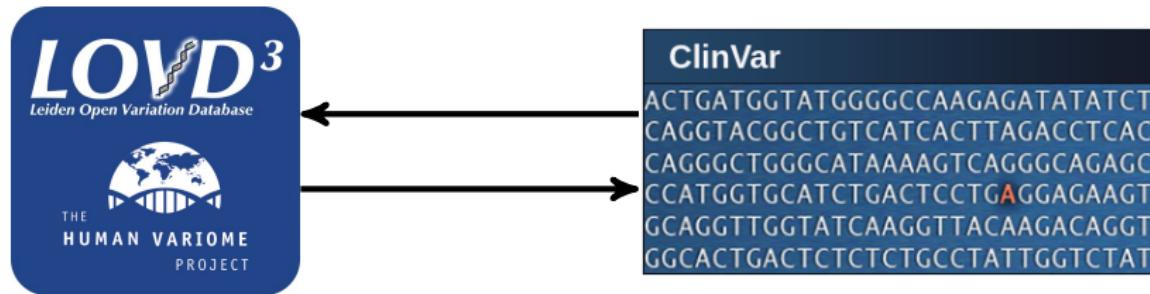


LOVD has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 200754 - the GEN2PHEN project.  
©2004-2019 [Leiden University Medical Center](#), Netherlands  
Ivo F.A.C. Folkema BSc., Prof. Johan I. den Dunnen PhD



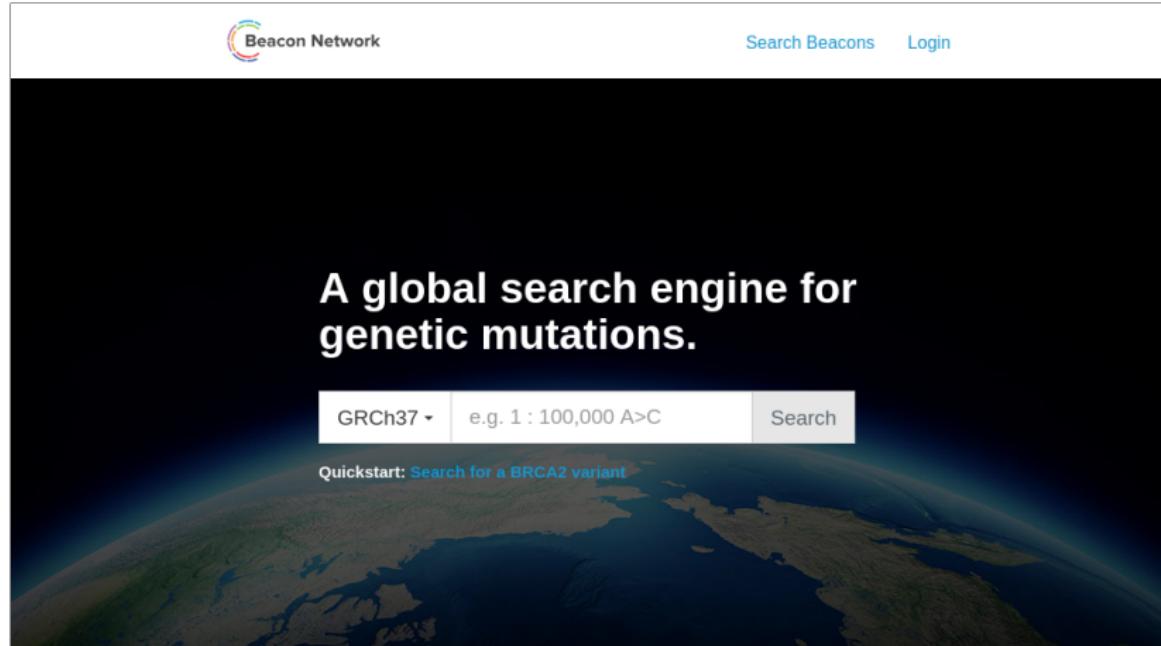
## Planned collaboration

- ▷ Exchange information between LOVD and ClinVar to find all data in either database



- ▷ Approach other databases to merge their data

# Global search for other databases



Returns just a yes/no!

# Global search for other databases

Beacon Network

Search Beacons    Login

Search all beacons for allele

GRCh37 ▾ 13 : 32936732 G > C Search

Response    All None  
 Found 10  
 Not Found 32  
 Not Applicable 25  


Access    All None  
 Controlled 0  
 Public 67

 BRCA Exchange Hosted by BRCA Exchange	<span>Found</span>
 HGMD Public Hosted by University of California, Santa Cruz	<span>Found</span>
 Leiden Open Variation Hosted by University of California, Santa Cruz	<span>Found</span>

Returns just a yes/no!

# Global search for other databases

Beacon Network

Search Beacons    Login

Search all beacons for allele

GRCh37 ▾ 13 : 32936732 G > C Search

Response	All	None
<input checked="" type="checkbox"/> Found	10	
<input type="checkbox"/> Not Found	32	
<input type="checkbox"/> Not Applicable	25	

Access All None

Controlled 0  
 Public 67

	BRCA Exchange	Found
	Hosted by BRCA Exchange	
	HGMD Public	Found
	Hosted by University of California, Santa Cruz	
	Leiden Open Variation	Found
	Hosted by University of California, Santa Cruz	

Returns just a yes/no!

Sometimes returns additional data, too.

## Variant Details

Variant Nomenclature		?	Clinical Significance (LOVD)		▲ ▼
Gene Symbol	BRCA2		▶ Submitter(s)	Peter Devilee (Leiden, NL)	Variant Effect: +/-.
Reference cDNA Sequence	NM 000059.3		▶ Submitter(s)	Åsa Ehlén (Orsay, FR)	Variant Effect: +?/.
HGVS Nucleotide	c.7878G>C		▶ Submitter(s)	Aleen D. Auerbach (New ...	Variant Effect: +/-.
HGVS Protein	p.(Trp2626Cys)		▶ Submitter(s)	Peter Devilee (Leiden, NL)	Variant Effect: +/-.
Abbreviated AA Change	W2626C		▶ Submitter(s)	ENIGMA consortium (Bri...	Variant Effect: +/-+
BIC Designation	8106G>C		▶ Submitter(s)	Arjen Mensenkamp (Nijm...	Variant Effect: +/-
Genome (GRCh38)	chr13:g.32362595:G>C		▶ Submitter(s)	Raphael Johannes Mors...	Variant Effect: +?/.
Genome (GRCh37)	chr13:g.32936732:G>C		▶ Submitter(s)	Johan den Dunnen (Rotter...	Variant Effect: +/-.
Genome (GRCh36)	chr13:g.31834732:G>C				
RNA (LOVD)	r.(?)		In Silico Prior Prediction (prior to considering other evidence)		▲ ▼
Beacons	<a href="https://beacon-network.org/#/search?chrom=13&amp;pos=32936732&amp;ref=G&amp;allele=C&amp;rs=GRCh37">https://beacon-network.org/#/search?chrom=13&amp;pos=32936732&amp;ref=G&amp;allele=C&amp;rs=GRCh37</a>		▼ In Silico Prior Probability of Pathogenicity 0.81		
			Credits: Computational algorithm and display derived from the <a href="#">HCI Breast Cancer Genes Prior Probabilities</a> website.		

## LOVD as an example

Gene variant database features,  
using LOVD as an example

# The LOVD menu



The screenshot shows the LOVD 3.0 interface. At the top left is the LOVD logo with 'Leiden Open Variation Database' below it. To its right is the Global Variome logo with 'HUMAN VARIOME PROJECT'. Next is the 'Global Variome shared LOVD' section with 'DMD (dystrophin)' and a magnifying glass icon. To the right is the 'LOVD is supported by: interactive biosoftware' logo. At the top right are links for 'LOVD v.3.0 Build 21c [ Current LOVD status ]', 'Register as submitter', and 'Log In'. Below the header is a navigation bar with tabs: Genes, Transcripts, Variants, Individuals, Diseases, Screenings, Submit, and Documentation. The 'Variants' tab is currently selected.

- Genes, Transcripts
- **Variants** (fields variable per gene)
  - Genomic variants, variants affecting genes.
  - Gene-specific: Unique variant view, all variants, full data view
- **Individuals**
  - View all individuals in the database
  - Gene-specific: All individuals with variants in selected gene
- **Diseases** (phenotype fields variable per disease)
  - All diseases in the database, all phenotype records
  - Gene-specific: All diseases related to selected gene
- **Screenings**
  - All screenings performed
  - Gene-specific: All screenings that checked the selected gene

# Detailed gene information page

**LOVD 3**  **Global Variome shared LOVD**  
**DMD (dystrophin)** 

Curator: Johan den Dunnen

LOVD is supported by:  
interactive  
biosoftware

LOVD v.3.0 Build 21c [ Current LOVD status ]  
Register as submitter | Log in

**Genes** **Transcripts** **Variants** **Individuals** **Diseases** **Screenings** **Submit** **Documentation**

## DMD gene homepage

---

### General information

Gene symbol	DMD
Gene name	dystrophin
Chromosome	X
Chromosomal band	p21.2
Imprinted	Unknown
Genomic reference	<a href="#">LRG_199</a>
Transcript reference	<a href="#">NM_004006.2</a>
Exon/intron information	<a href="#">NM_004006.2 exon/intron table</a>
Associated with diseases	<a href="#">BMD</a> , <a href="#">BMD/DMD</a> , <a href="#">CMD-3B</a> , <a href="#">DMD</a>
Citation reference(s)	-
RefSeq URL	<a href="#">Genomic reference sequence</a>
Curators (1)	Johan den Dunnen
Total number of public variants reported	<a href="#">16908</a>
Unique public DNA variants reported	<a href="#">5390</a>
Individuals with public variants	37614
Hidden variants	1300
Notes	When referring to this database please cite <a href="#">Aartsma-Rus et al. (2005)</a> , <a href="#">Muscle Nerve</a> , <a href="#">34</a> :135-144 and/or <a href="#">White SJ, den Dunnen JT (2006)</a> , <a href="#">Cytogenet Genome Res.</a> , <a href="#">115</a> : 240-246.
Date created	July 29, 1997
Date last updated	March 26, 2019
Version	DMD:190326

---

### Graphical displays and utilities

Graphs	Graphs displaying summary information of all variants in the database »
Reading frame checker	The Reading-frame checker generates a prediction of the effect of whole-exon changes. Active for: <a href="#">NM_004006.2</a> .
UCSC Genome Browser	Show variants in the UCSC Genome Browser ( <a href="#">full view</a> , <a href="#">compact view</a> )
Ensembl Genome Browser	Show variants in the Ensembl Genome Browser ( <a href="#">full view</a> , <a href="#">compact view</a> )
NCBI Sequence Viewer	Show distribution histogram of variants in the <a href="#">NCBI Sequence Viewer</a>

---

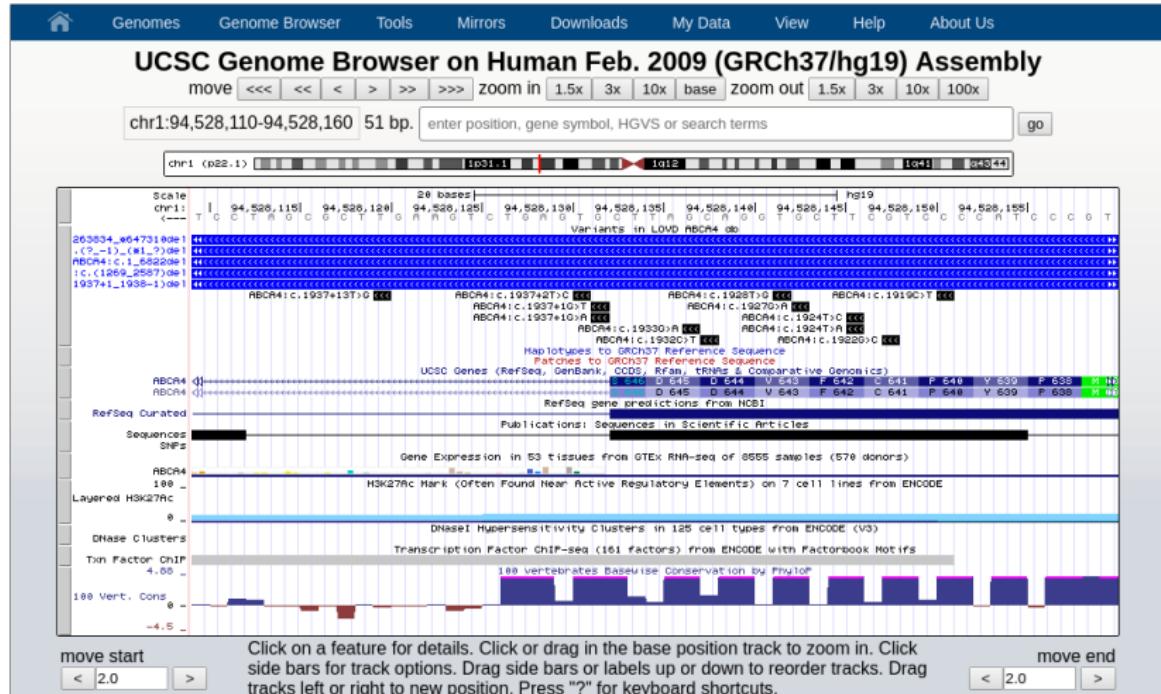
### Links to other resources

Homepage URL	<a href="https://www.LOVD.nl/DMD">https://www.LOVD.nl/DMD</a>
External URL	<a href="#">DOVE (DMD Open-access Variant Explorer)</a> <a href="#">the Lesden Muscular Dystrophy pages</a> <a href="#">Orphanet</a>
HGNC	2928
Entrez Gene	1756
PubMed articles	<a href="#">DMD</a>
OMIM - Gene	300372
OMIM - Diseases	<a href="#">BMD (dystrophy, muscular, Becker type (BMD))</a> <a href="#">CMD-3B (cardiomyopathy, dilated, type 3B (CMD-3B))</a> <a href="#">DMD (dystrophy, muscular, Duchenne type (DMD))</a>
HGMD	<a href="#">DMD</a>
GeneCards	<a href="#">DMD</a>
GeneTests	<a href="#">DMD</a>

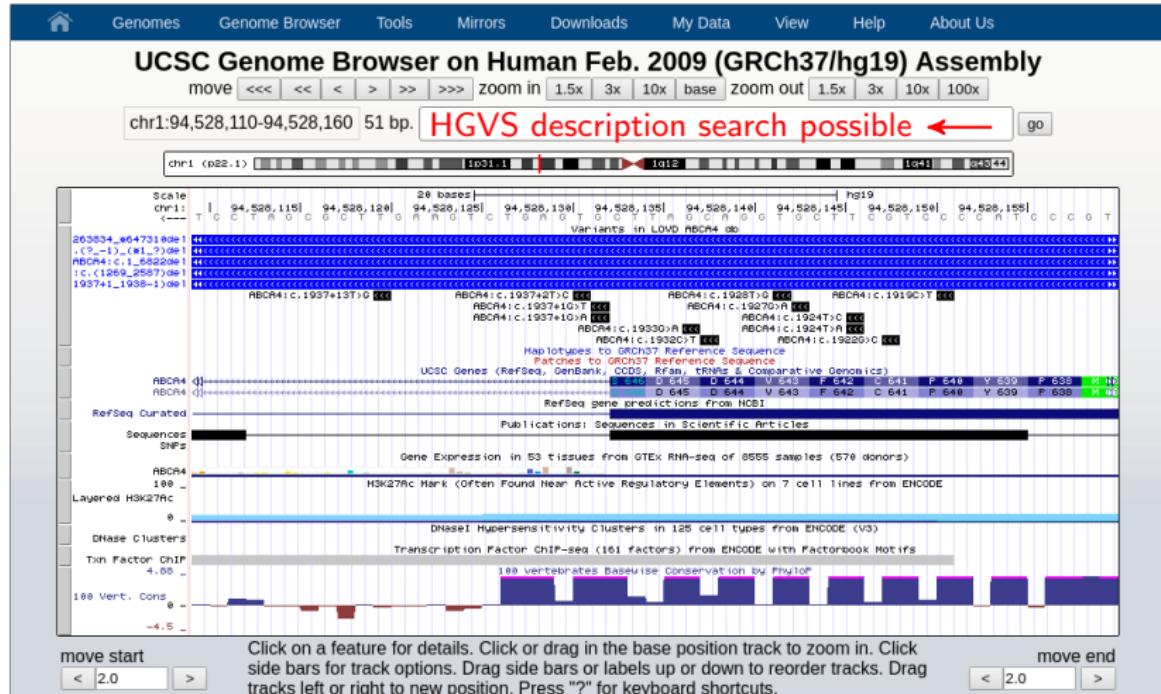
# Detailed gene information page

Graphical displays and utilities	
Graphs	Graphs displaying summary information of all variants in the database »
Reading frame checker	The Reading-frame checker generates a prediction of the effect of whole-exon changes. Active for: <a href="#">NM_004006.2</a> .
UCSC Genome Browser	Show variants in the UCSC Genome Browser ( <a href="#">full view</a> , <a href="#">compact view</a> )
Ensembl Genome Browser	Show variants in the Ensembl Genome Browser ( <a href="#">full view</a> , <a href="#">compact view</a> )
NCBI Sequence Viewer	Show distribution histogram of variants in the <a href="#">NCBI Sequence Viewer</a>
Links to other resources	
Homepage URL	<a href="https://www.LOVD.nl/DMD">https://www.LOVD.nl/DMD</a>
External URL	<a href="#">DOVE (DMD Open-access Variant Explorer)</a> <a href="#">the Leiden Muscular Dystrophy pages</a> <a href="#">Orphanet</a>
HGNC	<a href="#">2928</a>
Entrez Gene	<a href="#">1756</a>
PubMed articles	<a href="#">DMD</a>
OMIM - Gene	<a href="#">300377</a>
OMIM - Diseases	<a href="#">BMD (dystrophy, muscular, Becker type (BMD))</a> <a href="#">CMD-3B (cardiomyopathy, dilated, type 3B (CMD-3B))</a> <a href="#">DMD (dystrophy, muscular, Duchenne type (DMD))</a>
HGMD	<a href="#">DMD</a>
GeneCards	<a href="#">DMD</a>
GeneTests	<a href="#">DMD</a>

# Link to genome browsers, per gene and genome-wide



# Link to genome browsers, per gene and genome-wide



# One gene can contain multiple transcripts

Not all genes have only one relevant isoform

**LOVD<sup>3</sup>** | LOVD Open Variation Database | HUMAN VARIOME PROJECT | Curator: Nienke van der Stoep

**Global Variome shared LOVD**  
CDKN2A (cyclin-dependent kinase inhibitor 2A)

LOVD is supported by: interactive biosoftware

LOVD v.3.0 Build 21c [ Current LOVD status ] Welcome, Ivo F.A.C. Fokkema Your account | Log out

**Genes Transcripts Variants Individuals Diseases Screenings Submit Users Configuration Setup Documentation**

**Unique variants in gene CDKN2A**

The variants shown are described using the NM\_000077.4 transcript reference sequence.

NM\_000077.4  
NM\_058195.3

170 entries on 17 pages. Showing entries 1 - 10.  
10 per page ▾ Legend « First « Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

Effect	Reported	Exon	DNA change (cDNA)	RNA change	Protein	DNA change (genomic) (hg19)
?.	1	1b	c.-9G>A	r.(?)	p.(=)	g.21994339C>T
?.	1	1b	c.43T>C	r.(?)	p.(Cys15Arg)	g.21994288A>G
+/-, ?+?	3	-	c.193+1G>A	r.spl?	p.?	g.21994137C>T
??	1	-	c.194-3714G>A	r.(=)	p.(=)	g.21974921C>T
?	1	-	c.194-3653G>T	r.(=)	p.(=)	g.21974860C>A
??, J.	2	-	c.194-3652G>C	r.(=)	p.(=)	g.21974859C>G
??, J.	2	-	c.194-3644C>T	r.(=)	p.(=)	g.21974851G>A
?.	1	-	c.194-3611_194-3598dup	r.(=)	p.(=)	g.21974805_21974818dup
??	4	-	c.194-3611_194-3588del24	r.(=)	p.(=)	g.21974795_21974818del
??	2	-	c.194-3611_194-3588dup	r.(=)	p.(=)	g.21974795_21974818dup

10 per page ▾ Legend « First « Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

# Special variant records (1) - Classification record

- Consortia share classifications
- Dutch diagnostic laboratories

**LOVD<sup>3</sup>** Global Variome shared LOVD

LOVD is supported by: LOVD v.3.0 Build 21c [ Current LOVD status ]  
Interactive biosoftware Welcome, Ivo F.A.C. Fokkema  
Your account | Log out

Genes Transcripts Variants Individuals Diseases Screenings Submit Users Configuration Setup Documentation

### All variants affecting transcripts

114294 entries on 11430 pages. Showing entries 1 - 10.

Gene	Transcript	Chr	DNA change (genomic) (hg19)	DB-ID	Variant remarks	Origin
A2M	NM_000014.4	12	g.9258821A>G	A2M_000004	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2M	NM_000014.4	12	g.9268473A>C	A2M_000005	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2M	NM_000014.4	12	g.9248233T>C	A2M_000003	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2M	NM_000014.4	12	g.9232268T>C	A2M_000001	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2M	NM_000014.4	12	g.9243907G>A	A2M_000002	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2ML1	NM_144670.4	12	g.8995761A>G	A2ML1_000006	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2ML1	NM_144670.4	12	g.8990171A>G	A2ML1_000005	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2ML1	NM_144670.4	12	g.9006811G>A	A2ML1_000011	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2ML1	NM_144670.4	12	g.9013481G>A	A2ML1_000016	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record
A2ML1	NM_144670.4	12	g.9007381_9007382del	A2ML1_000012	VKGL data sharing initiative Nederland; correct HGVS to be checked	CLASSIFICATION record

10 per page ▾ Legend « First < Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

# Special variant records (2) - Summary record

- Summarizes all data supporting the variant's classification
- InSiGHT consortium, ENIGMA consortium

**LOVD<sup>3</sup>** Version 3.0 Build 21c | Current LOVD status  
The Human Variation Database |  Global Variome shared LOVD

LOVD is supported by: 

Welcome, Ivo F.A.C. Fokkema  
Your account | Log out

Genes Transcripts Variants Individuals Diseases Screenings Submit Users Configuration Setup Documentation

### All variants affecting transcripts

11499 entries on 1150 pages. Showing entries 1 - 10.

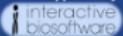
10 per page ▾ Legend « First ‹ Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

Gene	Transcript	Chr	DNA change (genomic) (hg19)	DB-ID	Variant remarks	Reference	Origin
ABCA4	NM_000350.2	1	g.94505622_94505623insNN	ABCA4_001010	variant significantly enriched in >3000 likely Caucasian STGD1 patients compared to the non-Finnish ExAC population	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94517255_94544233del	ABCA4_000000	variant significantly enriched in >3000 likely Caucasian STGD1 patients compared to the non-Finnish ExAC population	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94586599_94586601delinsGAC	ABCA4_000262	-	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94458793_94586601del	ABCA4_000862	-	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94546126G>C	ABCA4_000343	-	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94546124A>G	ABCA4_000342	-	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94578583_94578586del	ABCA4_000249	not statistically tested, classification unknown	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94546118A>C	ABCA4_000082	-	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94546115A>C	ABCA4_000341	variant significantly enriched in >3000 likely Caucasian STGD1 patients compared to the non-Finnish ExAC population	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record
ABCA4	NM_000350.2	1	g.94546111T>C	ABCA4_000340	-	PubMed: Cornelis 2017, Journal: Cornelis 2017	SUMMARY record

10 per page ▾ Legend « First ‹ Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

# Special variant records (3) - In-vitro record

- Reports results of functional effect assays
- ENIGMA consortium

**LOVD<sup>3</sup>**  **Global Variome shared LOVD**  LOVD is supported by: LOVD v.3.0 Build 21c | Current LOVD status | Welcome, Ivo F.A.C. Fokkema | Your account | Log out

Genes Transcripts Variants Individuals Diseases Screenings Submit Users Configuration Setup Documentation

### All variants affecting transcripts

6056 entries on 606 pages. Showing entries 1 - 10.

10 per page ▾ Legend « First ‹ Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

Gene	Transcript	Chr	DNA change (genomic) (hg19)	DB-ID	Variant remarks	Origin
ABCA4	NM_000350.2	1	g.94578524C>G	ABCA4_000068	expression cloning midigene splicing construct: 0.343 correctly spliced RNA	In vitro
ABCA4	NM_000350.2	1	g.94577135C>A	ABCA4_000241	expression cloning midigene splicing construct: no correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94576990T>G	ABCA4_000221	expression cloning midigene splicing construct: no correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94574275G>C	ABCA4_001025	expression cloning midigene splicing construct: no correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94564350C>A	ABCA4_000045	expression cloning midigene splicing construct: no correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94546283A>G	ABCA4_000356	expression cloning midigene splicing construct: 0.757 correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94545023A>T	ABCA4_000334	expression cloning midigene splicing construct: no correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94528120A>C	ABCA4_000976	expression cloning midigene splicing construct: 0.14 correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94522152C>G	ABCA4_000731	expression cloning midigene splicing construct: 0.479 correctly spliced RNA	In vitro (cloned)
ABCA4	NM_000350.2	1	g.94517254C>G	ABCA4_000034	expression cloning midigene splicing construct: 0.60 correctly spliced RNA	In vitro (cloned)

10 per page ▾ Legend « First ‹ Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

# Detailed phenotype information (HPO)

- HP:1234567 - Observed
- -HP:1234567 - Not observed
- ?HP:1234567 - Unknown

## Phenotype #0000073527

Individual ID	<a href="#">00095132 (Public)</a>
Associated disease	-
Phenotype details	Spasticity (HP:0001257), Dysarthria (HP:0001260), Chorea (HP:0002072), Myoclonus (HP:0001336), Ataxia (HP:0001251), Increased deep tendon reflexes (HP:0001347), Unknown Hoffmann's sign (?HP:0003487), Plantar reflex (HP:0002487), Motor deficit (HP:0002333), No amyotrophy (-HP:0003202), No fasciculations (-HP:0002380), Normal vibration sense at ankles (-HP:0006938), No objective sensory loss (-HP:0010835), No skeletal deformities (-HP:0000924), No sphincter disturbances (-HP:0002839), White matter abnormalities (HP:0002500), No spinal abnormalities (-HP:0002143), Delayed intellectual development (HP:0001263), Hypodontia (HP:0000668), Ptosis (HP:0000508)
Diagnosis/Initial	-
Inheritance	Familial, autosomal recessive
Diagnosis/Definite	-
Age/Examination	-
Age/Diagnosis	-
Age/Onset	04y
Phenotype/Onset	-
Protein	-
Owner name	<a href="#">Johan den Dunnen</a>
Phenotype data status	Public
Created by	<a href="#">Johan den Dunnen</a>
Date created	2016-09-22 12:41:04
Last edited by	<a href="#">Johan den Dunnen</a>
Date last edited	2017-01-06 14:42:37

# LOVD requires the use of the RNA column

RNA analysis is essential to prove the predicted effect is correct

**LOVD<sup>3</sup>** Leiden Open Variation Database   **Global Variome shared LOVD**   **DMD (dystrophin)**   Curator: Johan den Dunnen

LOVD is supported by: **interactive biosoftware**   LOVD v.3.0 Build 21c [ Current LOVD status ]   Welcome, Ivo F.A.C. Fokkema   Your account | Log out

**Genes** **Transcripts** **Variants** **Individuals** **Diseases** **Screenings** **Submit** **Users** **Configuration** **Setup** **Documentation**

**Full data view for gene DMD**

This database is one of the gene variant databases from the [Leiden Muscular Dystrophy pages](#).

The variants shown are described using the NM\_004006.2 transcript reference sequence.

240 entries on 24 pages. Showing entries 1 - 10.  
10 per page ▾ Legend « First < Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

Effect	Exon	DNA change (cDNA)	RNA change	Protein	DNA change (genomic)
+/-	1i	c.31+36947G>A	r.[=, 31_32ins31+36949_31+37097]	p.[=, Tyr11_Glu12Serins*45]	g.33192452C>T
+/-	1i	c.31+36947G>A	r.[=, 31_32ins31+36949_31+37097]	p.[=, Tyr11_Glu12Serins*45]	g.33192452C>T
+/-	1i	c.32-2A>T	r.32_93del	p.Tyr11Phefs*6	g.33038319T>A
+/-	2i	c.93+5590T>A	r.[93_94ins93+5592_93+5722, 93_94ins93+5592_93+563	p.[Lys21_Phe22ins44, Lys21_Phe22ins15fs*20]	g.33032666A>T
+/-	2i	c.93+5590T>A	r.93_94ins93+5592_93+5723	p.Lys31Phe32ins44	g.33032666A>T
+/-	2i	c.94-2A>G	r.(94_186del)?	p.fs	g.32867939T>C
+/-	2i	c.94-2A>T	r.94_186del	p.Phe32_Leu62del	g.32867939T>A
+/-	2i	c.94-2A>T	r.[=, 94_186del]	p.[=, Phe32_Leu62del]	g.32867939T>A
+/-	2i	c.94-1G>A	r.[=, 94_186del]	p.[=, Phe32_Leu62del]	g.32867938C>T
+/-	2i	c.94-1G>T	r.94_186del	p.Phe32_Leu62del	g.32867938C>A

10 per page ▾ Legend « First < Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next » Last »

# External views

(e.g. country nodes, mx.lovd.org)

**Nodo mexicano del Varioma Humano**  
Based on:  
**LOVD**  
Online Open Variation Database

[Home](#) [Variants in individuals from Mexico](#) [Variants by submitters from Mexico](#) [Registrarse](#) [Log in](#)

  
sharing data • reducing disease

**Proyecto del Varioma Humano**

El HVP es una Organización Internacional No Gubernamental que exhorta a reducir las enfermedades genéticas a través de compartir gratuitamente el conocimiento derivado del estudio de las variantes en el genoma humano.

HVP es auspiciado por la Organización para la Educación, la Ciencia y la Cultura de las Naciones Unidas (UNESCO) para asegurar y garantizar que la información de variantes genéticas y su efecto sobre la salud humana pueda captarse, ser curada, interpretada y compartida libre y abiertamente.

Para colectar las variantes genéticas de una población, un país o una región y revisar esta información para hacerla confiable para su uso en la práctica clínica, se requiere de un repositorio electrónico al cual se le ha denominado "nodo" y se compone de un conjunto de bases de datos de genes relevantes a estudiar para cada país, un comité científico/académico y reglas de operación.

Cada país es responsable de generar su nodo, enviar y resguardar la información de manera homogénea y accesible para que los profesionales de la salud la consulten y tomen decisiones médicas óptimas.

El nodo mexicano del varioma humano representa un esfuerzo para reunir los cambios en el ADN descubiertos en población mexicana y sus consecuencias para la detección y prevención de enfermedades, así como para el desarrollo de la medicina de precisión.

El nodo es un repositorio digital que posee medidas de seguridad e incluye distintas herramientas para el uso amigable de esta base de datos, pretende ser una contribución emanada de un grupo de entusiastas investigadores mexicanos alineándose al proyecto internacional.

# External views

(e.g. country nodes, mx.lovd.org)

**Nodo mexicano del Varioma Humano**  
Based on:  
**LOVD**  
variant Open Variation Database

Home Variants in individuals from Mexico Variants by submitters from Mexico Registrarse Log in

660 entries on 27 pages. Showing entries 1 - 25.  
25 per page ▾ Legend First Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next Last

Gene	Transcript	Effect	DNA change (cDNA)	RNA change	Protein	Function/GVS	Predict/CADD	Non_Public
ABCA4	NM_000350.2	+?.	c.5318C>T	r.(?)	p.(Ala1773Val)	-	-	-
ABCA4	NM_000350.2	+?.	c.634C>T	r.(?)	p.(Arg212Cys)	-	-	-
ABCA4	NM_000350.2	+?.	c.5318C>T	r.(?)	p.(Ala1773Val)	-	-	-
ABCA4	NM_000350.2	+?.	c.3396G>T	r.(?)	p.(Arg1120Leu)	-	-	-
ABCA4	NM_000350.2	+?.	c.4124C>T	r.(?)	p.(Arg1374Cys)	-	-	-
ABCA4	NM_000350.2	+?.	c.5318C>T	r.(?)	p.(Ala1773Val)	-	-	-
ABCA4	NM_000350.2	+?.	c.2453G>A	r.(?)	p.(Gly818Glu)	-	-	-
ABCA4	NM_000350.2	+?.	c.4249_4251del	r.(?)	p.(Phe1417del)	-	-	-
ABCA4	NM_000350.2	+?.	c.5318C>T	r.(?)	p.(Ala1773Val)	-	-	-
ABCA4	NM_000350.2	+?.	c.868C>T	r.(?)	p.(Arg290Trp)	-	-	-
ABCA4	NM_000350.2	+?.	c.1004_1013G>A	r.(?)	p.-	-	-	-
ABCA4	NM_000350.2	+?.	c.5318C>T	r.(?)	p.(Ala1773Val)	-	-	-
ABCA4	NM_000350.2	+?.	c.3041T>G	r.(?)	p.(Leu1014Asp)	-	-	-
ABCA4	NM_000350.2	+?.	c.52C>T	r.(?)	p.(Arg187Trp)	-	-	-
ABCA4	NM_000350.2	+?.	c.1804C>T	r.(?)	p.[Arg602Trp, Arg943Gln]	-	-	-
ABCA4	NM_000350.2	+?.	c.2453G>A	r.(?)	p.(Gly818Glu)	-	-	-
ABCA4	NM_000350.2	+?.	c.5324T>A	r.(?)	p.(Ile1775Asn)	-	-	-
ABCA4	NM_000350.2	+?.	c.5603C>T	r.(?)	p.(Asp1868Asn)	-	-	-
ABCA4	NM_000350.2	+?.	c.2650C>T	r.(?)	p.(Glu199P)	-	-	-
ABCA4	NM_000350.2	+?.	c.5335T>C	r.(?)	p.(Tyr1779His)	-	-	-
ABCA4	NM_000350.2	+?.	c.2453G>A	r.(?)	p.(Gly818Glu)	-	-	-
ABCA4	NM_000350.2	+?.	c.723A>T	r.(?)	p.(Glu241Asp)	-	-	-
ABCA4	NM_000350.2	+?.	c.5114G>A	r.(?)	p.(Arg1705Gln)	-	-	-
ABCA4	NM_000350.2	?.	c.71G>A	r.(?)	p.(Arg244His)	-	-	-
ABCA4	NM_000350.2	?.	c.4537dup	r.(?)	p.(Gln1515Profs*42)	-	-	-

25 per page ▾ Legend First Prev 1 2 3 4 5 6 7 8 9 10 11 ... Next Last

## LOVD URLs

- LOVD.nl/BRCA1
  - Reference LOVD for BRCA1
- BRCA1.LOVD.nl  
[BRCA1.variome.org](http://BRCA1.variome.org)
  - List of databases for BRCA1 (including non-LOVD)
- mx.LOVD.org   (mx = country code)
  - Country-specific view of the GV shared LOVD

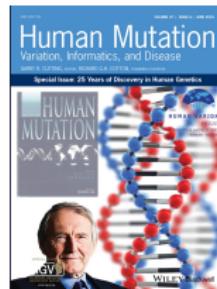
## How to improve data sharing?

Make variant submission mandatory!

- ... for clinical labs
  - As part of QC, to get accreditation
  - United States, Germany
- ... for publications
- ... for grants
- ...

## Mandatory to share data prior to publication

- Human Mutation
  - First to demand using HGVS nomenclature
  - First to demand database submission before accepting a paper for publication
- European Journal of Human Genetics
  - Demanding HGVS nomenclature & database submission
  - ... and checking every paper!  
(collaboration with LOVD)



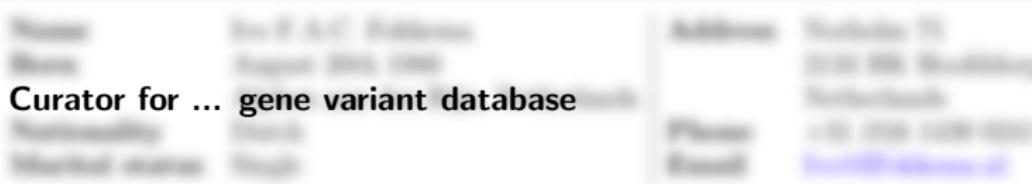
Adopt a gene!

---

## Curriculum Vitae

---

Curator for ... gene variant database



Many orphan genes,  
become a foster parent database curator!



Questions?

