GeneGrid: finding disease-causing variants in NGS data

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Basis

Genomic variants like SNPs or InDels are of major interest to biologists and clinicians

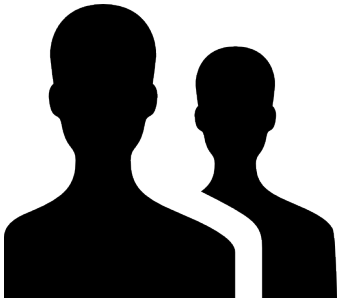
Identifying causal variants is crucial for the diagnostics of rare and common diseases

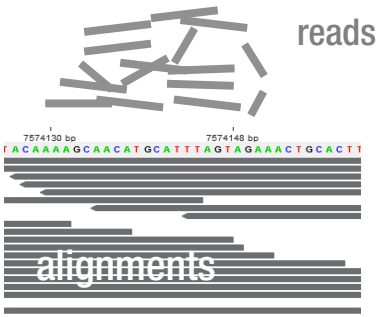
With NGS technology it is possible to detect millions of variants within an individual genome

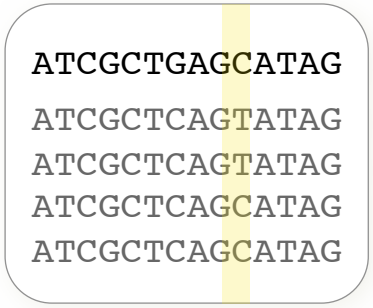
Which are the relevant ones?

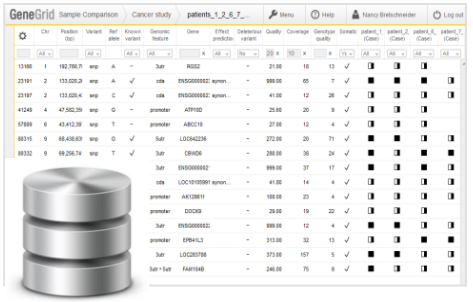
General workflow

Patient sampling → **Sequencing and alignment** → **Variant calling** → **Variant analysis in GeneGrid**









Sequencing library

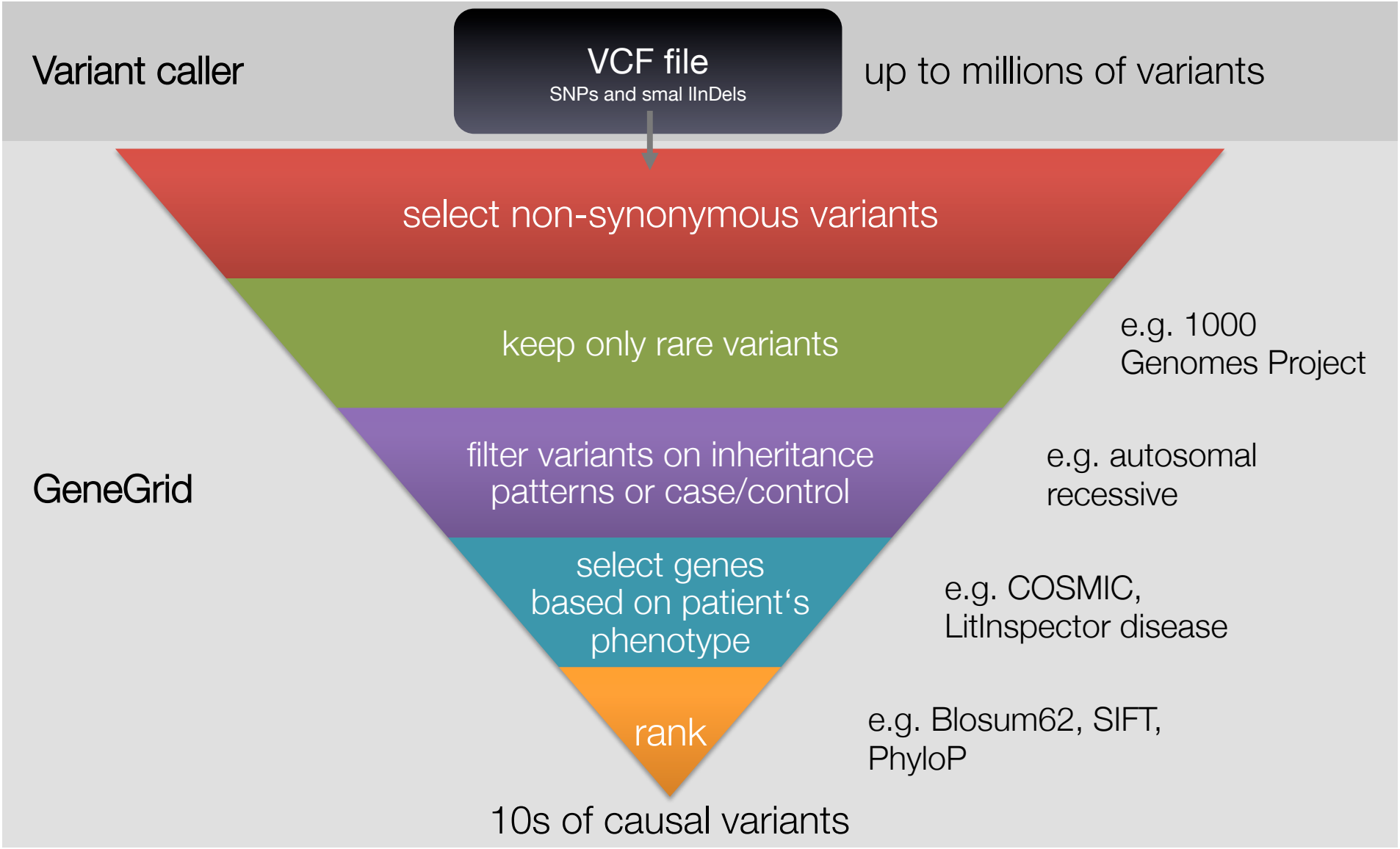
BAM file with read positions

VCF file with variant information

Short list of potentially interesting variants

"Icon by Daniel Bruce from Flaticon.com"

Finding the needle in the haystack



Selected GeneGrid filter fields

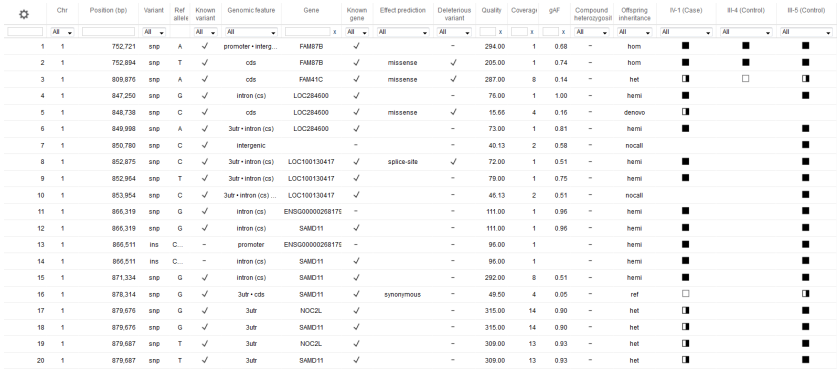
Field	Description
Known gene	Variant is in an annotated gene
Genotype quality	Variant confidence score; higher is better; max 999
gAF	Global minor allele frequency from 1000 Genomes Project; also separate for African, American, Asian, European; <0.01: rare
espMAF	Minor allele frequency from Exome Sequencing Project; also separate for African American, European American; <0.01: rare
exacAF	Alternative allele frequency from the Exome Aggregation Consortium (ExAC) project; <0.01: rare
BLOSUM	AA substitution score; <0: rare; >0: common
SIFT	Sorting Intolerant From Tolerant: predicts effect of AA substitution on protein function; <0.05: affects function
SIFT pred	Yes: damaging prediction based on SIFT score
PhyloP	DNA conservation score; >0: conserved
GERP	Genomic Evolutionary Rate Profiling; RS Score; >0: fewer substitutions than expected -> evolutionary constraint

Selected GeneGrid filter fields

Field	Description
SiPhy Pi, Omega	Overlap with evolutionary constrained elements (two parameter sets)
Literature diseases	Associated diseases based on gene co-citations
Literature tissues	Associated tissues based on gene co-citations
Somatic mutation tissues	Associated tissues; source: COSMIC
Clinical diseases	Associated clinical diseases; source: ClinVar and OMIM
Diagnostic tests	Number of diagnostic tests available for gene
Diagnostic diseases	Associated disease terms based on diagnostic gene tests (gene level)
Clinical significance	Summary of clinical significance based on ClinVar database (position level)
GO processes	Associated GO terms for the domain of cellular components
GO functions	Associated GO terms for the domain of molecular functions
GO components	Associated GO terms for the domain of biological processes

The Genomatix GeneGrid technology

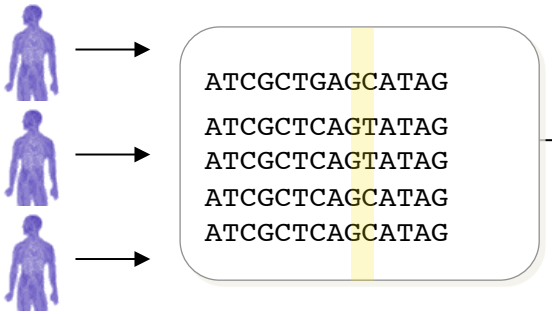
available online



	Chr	Position (bp)	Variant	Ref allele	Known variant	Genomic feature	Gene	Known gene	Effect prediction	Deleterious variant	Quality	Coverage	gAF	Compound heterozygosity	Offspring inheritance	IV-1 (Case)	III-4 (Control)	III-5 (Control)
1	1	752,721	snp	A	✓	promoter • interg...	FAM87B	✓		–	294.00	1	0.68	–	hom	■	■	■
2	1	752,894	snp	T	✓	cds	FAM87B	✓	missense	✓	205.00	1	0.74	–	hom	■	■	■
3	1	809,876	snp	A	✓	cds	FAM41C	✓	missense	✓	287.00	8	0.14	–	het	◨	□	◨
4	1	847,250	snp	G	✓	intron (cs)	LOC284600	✓		–	76.00	1	1.00	–	hemi	■		■
5	1	848,738	snp	C	✓	cds	LOC284600	✓	missense	✓	15.66	4	0.16	–	denovo	◨		
6	1	849,998	snp	A	✓	3utr • intron (cs)	LOC284600	✓		–	73.00	1	0.81	–	hemi	■		■
7	1	850,780	snp	C	✓	intergenic		–		–	40.13	2	0.58	–	nocall			■
8	1	852,875	snp	C	✓	3utr • intron (cs)	LOC100130417	✓	splice-site	✓	72.00	1	0.51	–	hemi	■		■
9	1	852,964	snp	T	✓	3utr • intron (cs)	LOC100130417	✓		–	79.00	1	0.75	–	hemi	■		■
10	1	853,954	snp	C	✓	3utr • intron (cs) ...	LOC100130417	✓		–	46.13	2	0.51	–	nocall			■
11	1	866,319	snp	G	✓	intron (cs)	ENSG0000026817E	–		–	111.00	1	0.96	–	hemi	■		■
12	1	866,319	snp	G	✓	intron (cs)	SAMD11	✓		–	111.00	1	0.96	–	hemi	■		■
13	1	866,511	ins	C...	–	promoter	ENSG0000026817E	–		–	96.00	1		–	hemi	■		■
14	1	866,511	ins	C...	–	intron (cs)	SAMD11	✓		–	96.00	1		–	hemi	■		■
15	1	871,334	snp	G	✓	intron (cs)	SAMD11	✓		–	292.00	8	0.51	–	hemi	■		■
16	1	878,314	snp	G	✓	3utr • cds	SAMD11	✓	synonymous	–	49.50	4	0.05	–	ref	□		◨
17	1	879,676	snp	G	✓	3utr	NOC2L	✓		–	315.00	14	0.90	–	het	◨		■
18	1	879,676	snp	G	✓	3utr	SAMD11	✓		–	315.00	14	0.90	–	het	◨		■
19	1	879,687	snp	T	✓	3utr	NOC2L	✓		–	309.00	13	0.93	–	het	◨		■
20	1	879,687	snp	T	✓	3utr	SAMD11	✓		–	309.00	13	0.93	–	het	◨		■

view, compare
filter, sort

Pre-knowledge database
annotations
disease & medical info



SNPs/InDels

import

annotate

GeneGrid database

Results &
Reports

Data sources

Internal sources

Variant annotation	Genomatix
Genome annotation	ElDorado
Text mining (PubMed)	LitInspector
Combined thesaurus (MeSH, NCIt, UMLS)	Genomatix Thesaurus
Pathways and networks	GePS

Data sources

External sources

Alleles and allele frequencies	dbSNP 1000 Genomes Project ESP6500 ExAC
Protein effect predictions	BLOSUM SIFT
Evolutionary conservation	PhyloP GERP 29 Mammals Project
Diagnostic annotation	GTR
Phenotype annotation	ClinVar COSMIC OMIM
Gene ontology	GO
Sequence variant description	HGVS
Regulatory regions	Ensembl Regulatory Build

GeneGrid example 1

Trio analysis

Leber congenital amaurosis (LCA)

Inherited eye disease

Onset at birth or in early childhood

Blindness or impaired vision with loss of central vision

Genetically heterogeneous

e.g. LCA1 caused by homozygous mutation in GUCY2D
LCA2: RPE65
LCA3: SPATA7
LCA4: AIPL1
etc. (18 types known)

Leber congenital amaurosis

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Nat Genet. 2012 September ; 44(9): 1040–1045. doi:10.1038/ng.2361.

NMNAT1 mutations cause Leber congenital amaurosis

Marni J Falk[1,2,22], **Qi Zhang**[3,4,22], **Eiko Nakamaru-Ogiso**[5], **Chitra Kannabiran**[6], **Zoe Fonseca-Kelly**[3,4], **Christina Chakarova**[7], **Isabelle Audo**[8,9,10,11], **Donna S Mackay**[7], **Christina Zeitz**[8,9,10], **Arundhati Dev Borman**[7,12], **Magdalena Staniszewska**[3,4], **Rachna Shukla**[6], **Lakshmi Palavalli**[6], **Saddek Mohand-Said**[8,9,10,11], **Naushin H Waseem**[7], **Subhadra Jalali**[6,13], **Juan C Perin**[14], **Emily Place**[1,3,4], **Julian Ostrovsky**[1], **Rui Xiao**[15], **Shomi S Bhattacharya**[7,16], **Mark Consugar**[3,4], **Andrew R Webster**[7,12], **José-Alain Sahel**[8,9,10,11,17,18], **Anthony T Moore**[7,12,19], **Eliot L Berson**[4], **Qin Liu**[3,4], **Xiaowu Gai**[20,21,23], and **Eric A. Pierce**[3,4,23]

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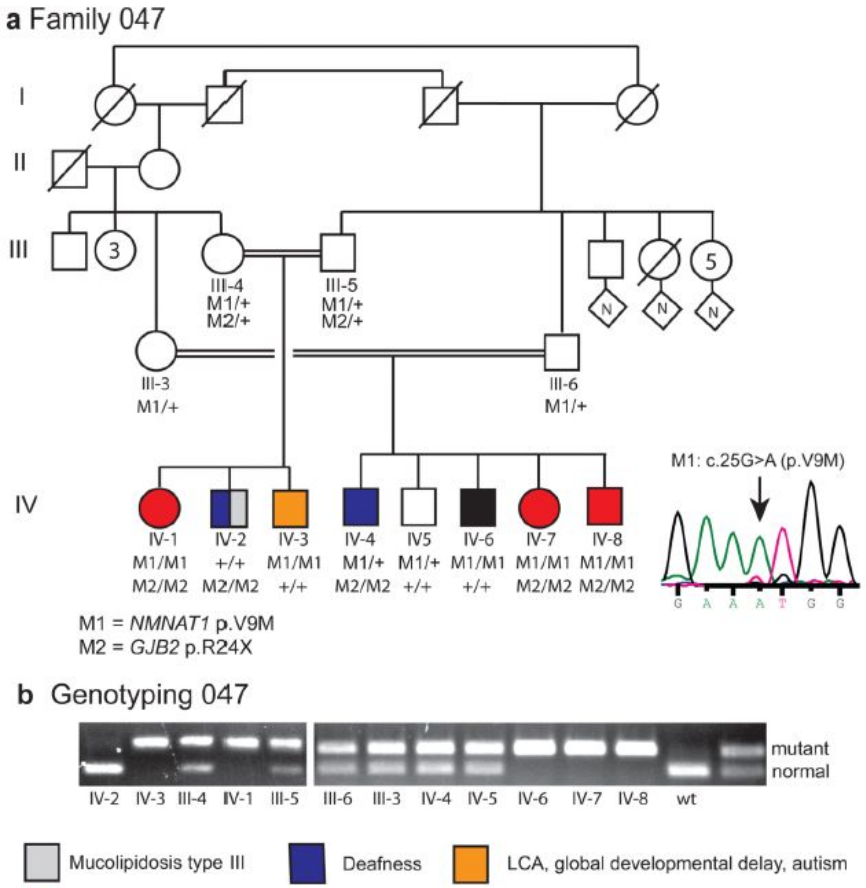
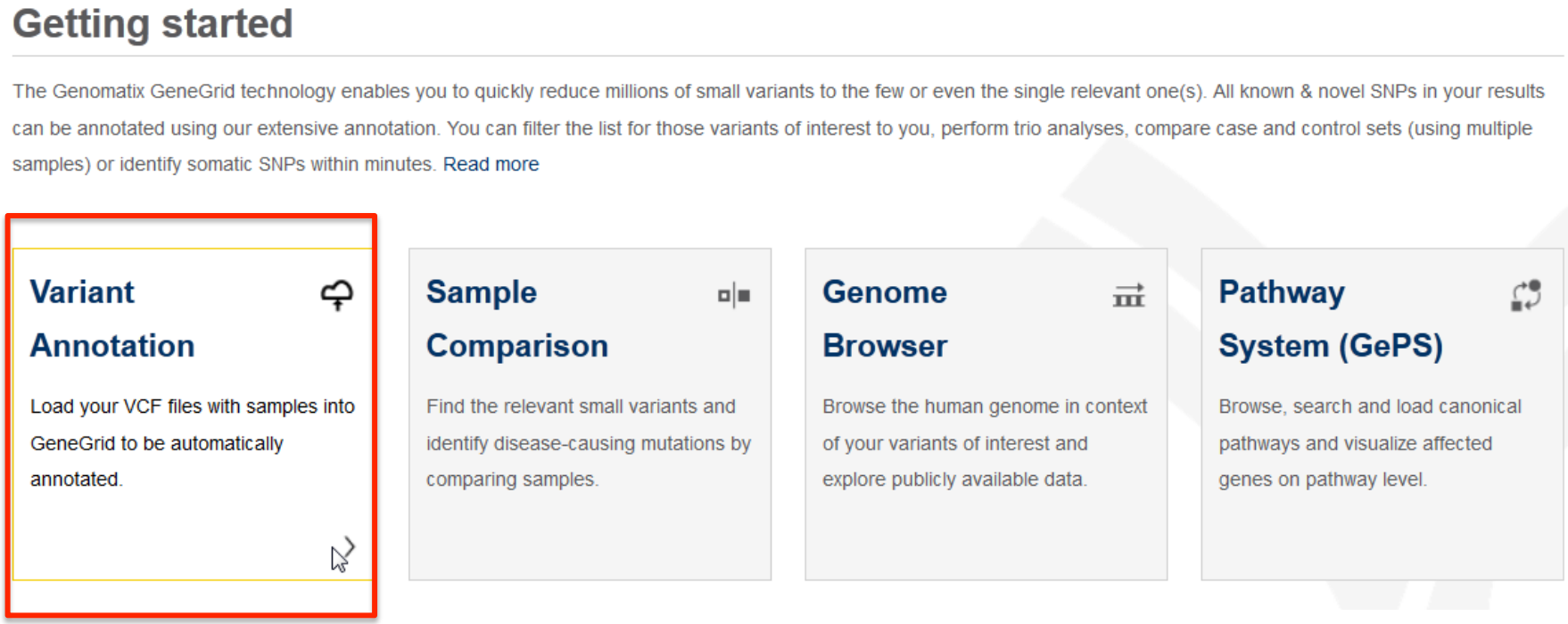
[8]Institut National de la Santé et de la Recherche Médicale, U968, Paris, France

Consanguineous family

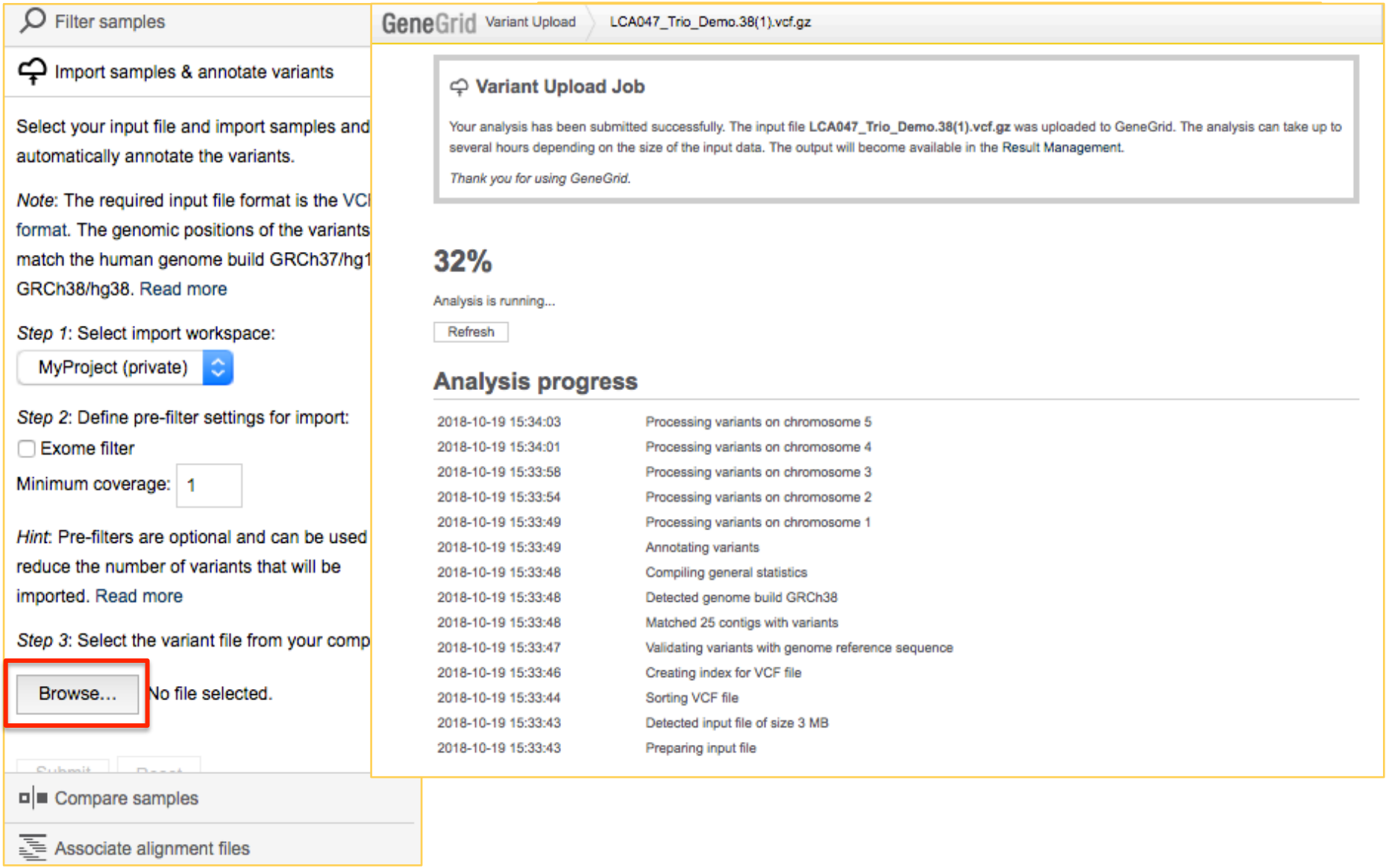


LCA, congenital deafness, global developmental delay, autism

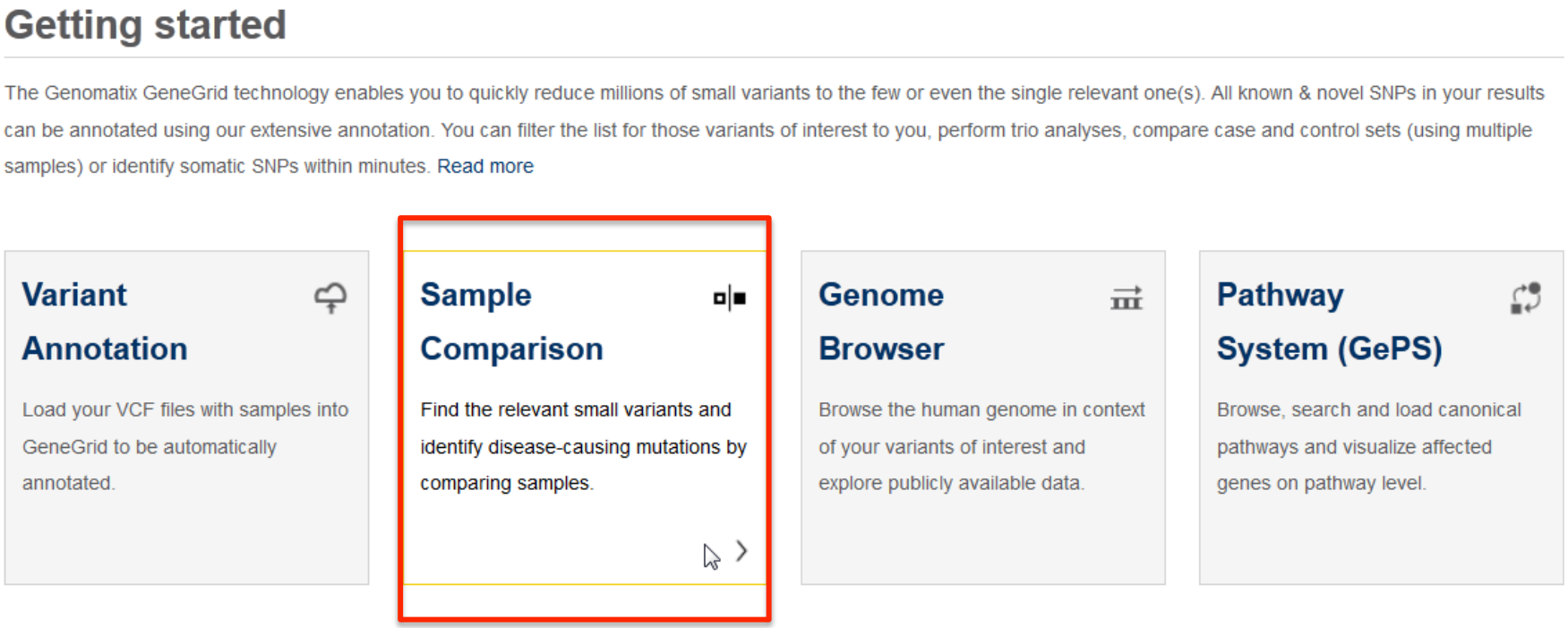
Step 1: load and annotate VCF files



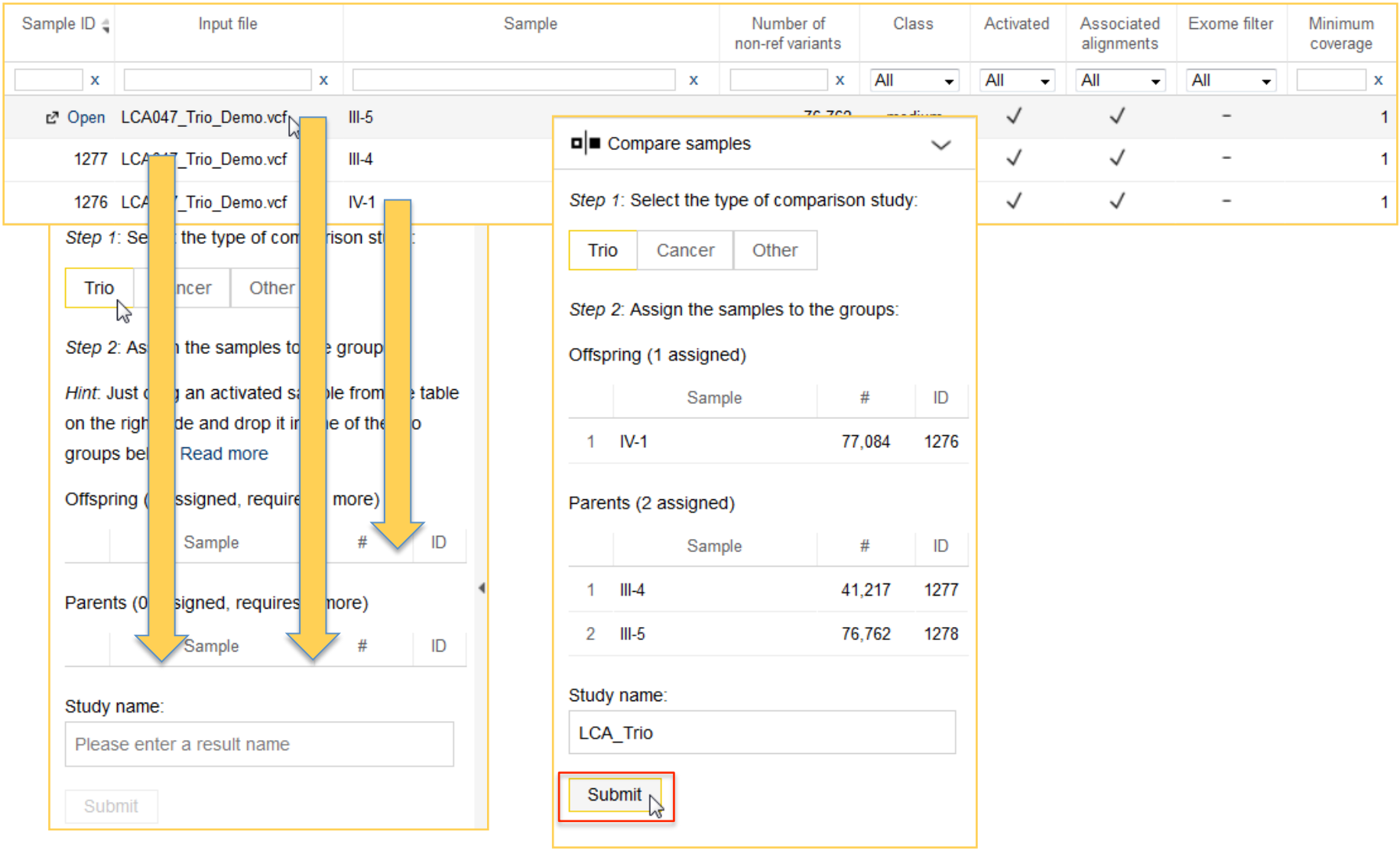
Step 1: load and annotate VCF files



Step 2: sample comparison



Step 2: sample comparison



Step 3: filtering

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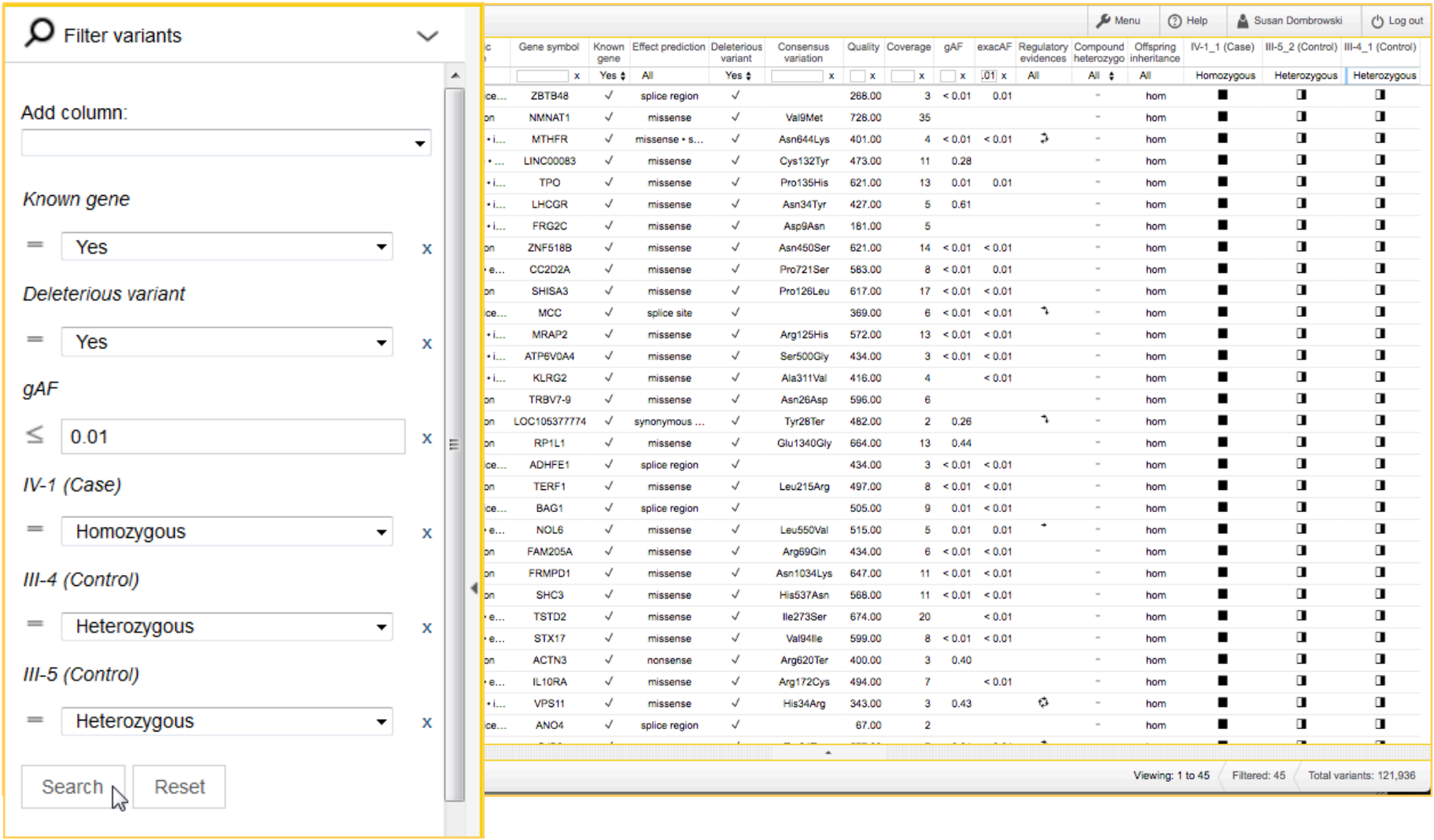
GeneGrid example: trio

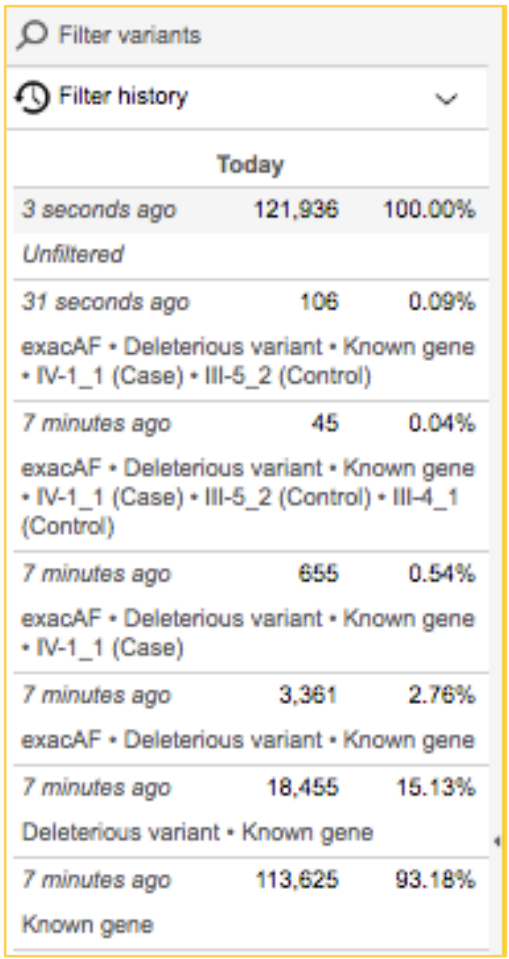
***Apply filtering criteria to search for low frequency (rare) variants that are deleterious and found in known (annotated) genes.**

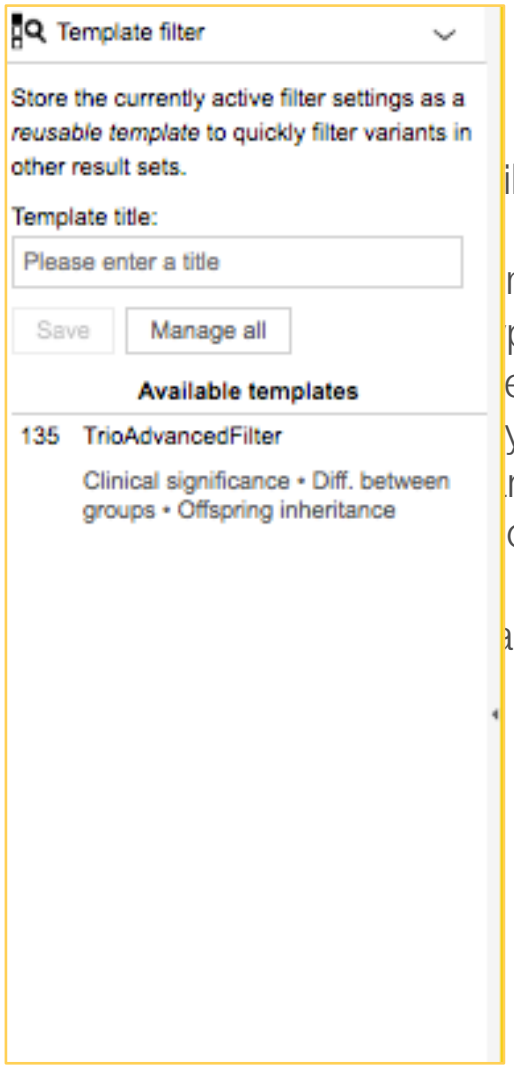
***This leaves the top 6% variants in the list.**



Filter history and template filters

Speed up the analysis and facilitate sample comparisons





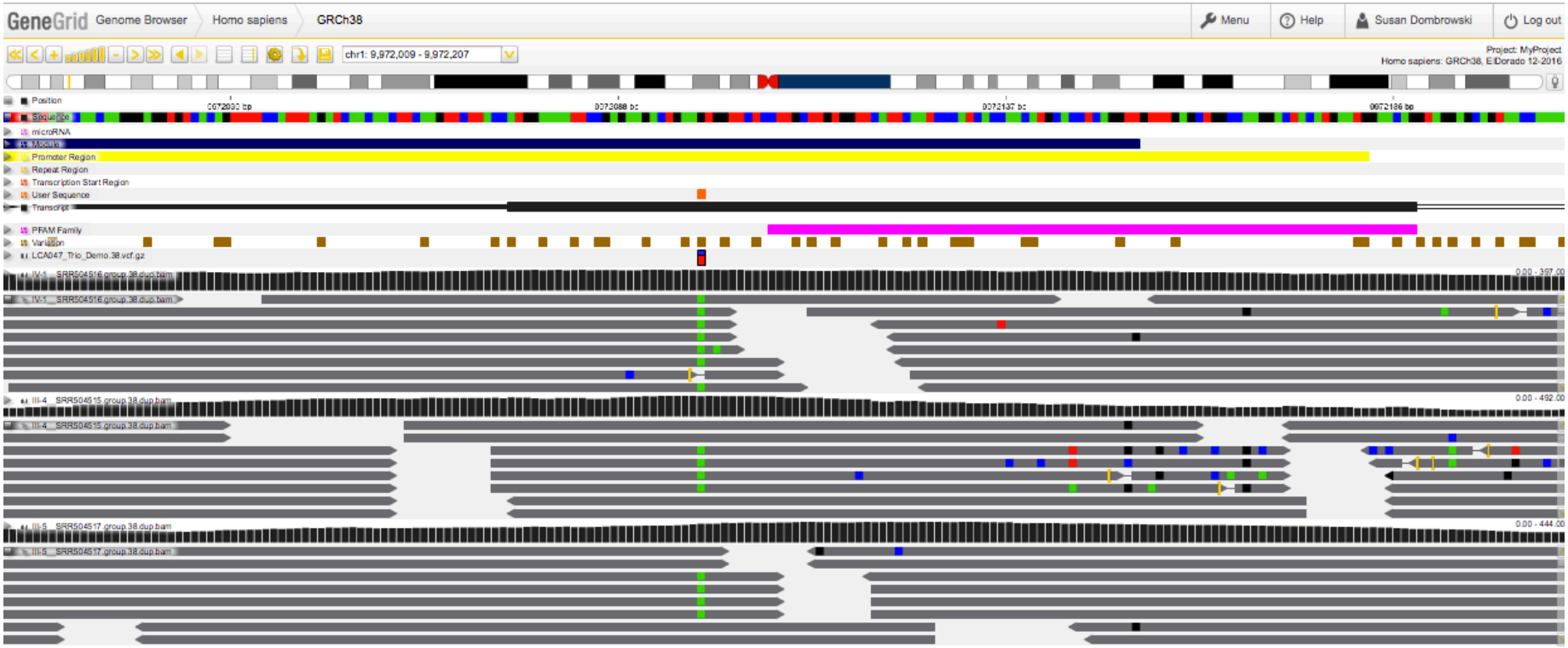
ilters that are routinely used, *e.g.*

m read coverage
pe quality
equency (gAF)
ype annotation
nce patterns
control genotypes

s template for use in other comparisons

Visualization in the Genomatix Genome Browser

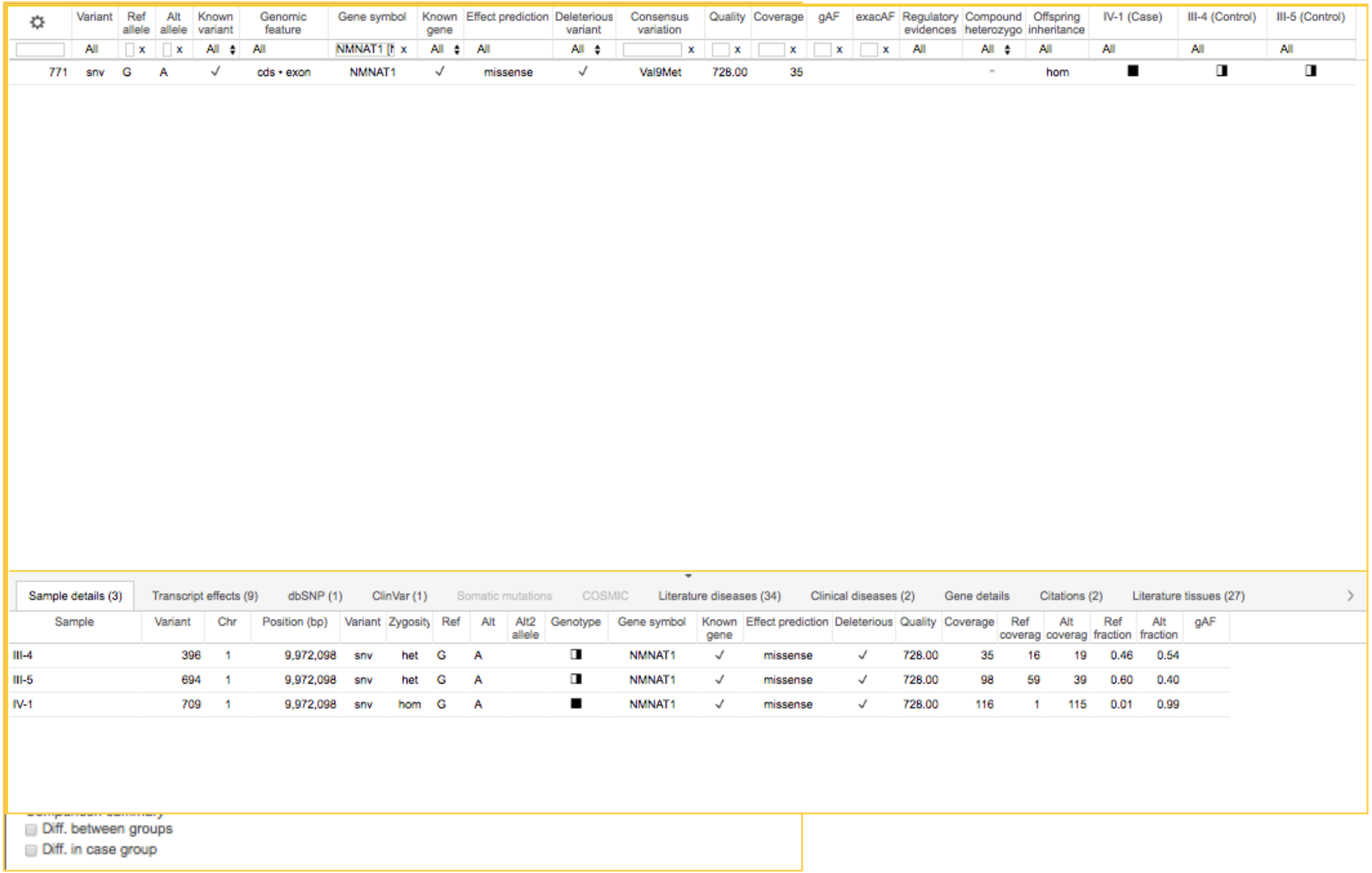
	Chr	Position (bp)	Variant	Ref allele	Known variant	Genomic feature	Gene	Known gene	Effect prediction	Deleterious variant	Quality	Coverage	gAF	Literature diseases
	All		All		All	All		All	All	Yes			0.01	Leber Congenital Amaurosis [Leber Congenital Amaurosis, 33
Browse	1	10,032,156	snp	G	-	cds	NMNAT1	✓	missense	✓	728.00	33		Frontotemporal Dementia • Leber Congenital Amaurosis • Anet



genomatix

GeneGrid example: trio

Additional annotation / filter columns: Link-outs to transcript annotation, dnSNP, ClinVar, COSMIC, Biomedical literature and Clinical information.



	Variant	Ref allele	Alt allele	Known variant	Genomic feature	Gene symbol	Known gene	Effect prediction	Deleterious variant	Consensus variation	Quality	Coverage	gAF	exacAF	Regulatory evidences	Compound heterozygo	Offspring inheritance	IV-1 (Case)	III-4 (Control)	III-5 (Control)
	All	x	x	All	All	NMNAT1 [N x	All	All	All	x	x	x	x	x	All	All	All	All	All	All
771	snv	G	A	✓	cds • exon	NMNAT1	✓	missense	✓	Val9Met	728.00	35				-	hom	■	◨	◨

Sample details (3) | Transcript effects (9) | dbSNP (1) | ClinVar (1) | Somatic mutations | COSMIC | Literature diseases (34) | Clinical diseases (2) | Gene details | Citations (2) | Literature tissues (27)

Sample	Variant	Chr	Position (bp)	Variant	Zygosity	Ref	Alt	Alt2 allele	Genotype	Gene symbol	Known gene	Effect prediction	Deleterious	Quality	Coverage	Ref coverag	Alt coverag	Ref fraction	Alt fraction	gAF
III-4	396	1	9,972,098	snv	het	G	A		◨	NMNAT1	✓	missense	✓	728.00	35	16	19	0.46	0.54	
III-5	694	1	9,972,098	snv	het	G	A		◨	NMNAT1	✓	missense	✓	728.00	98	59	39	0.60	0.40	
IV-1	709	1	9,972,098	snv	hom	G	A		■	NMNAT1	✓	missense	✓	728.00	116	1	115	0.01	0.99	

Diff. between groups

Diff. in case group

Annotation detail views and links: ClinVar

ClinVar | ClinVar | C1837873 | Search

Create alert | Advanced

Home | About | Access | Help | Submit | Statistics | FTP

Gene
Customize this list...

Clinical significance
Conflicting interpretations (0)
Benign (0)
Likely benign (2)
Uncertain significance (0)
Likely pathogenic (1)
Pathogenic (12)
Risk factor (0)

Review status
Practice guideline (0)
Expert panel (0)
Multiple submitters (1)
Single submitter (4)
At least one star (5)
Conflicting interpretations (0)

Allele origin
Germline (14)
De novo (0)
Somatic (0)

Method type
Research (1)
Literature only (9)
Clinical testing (6)

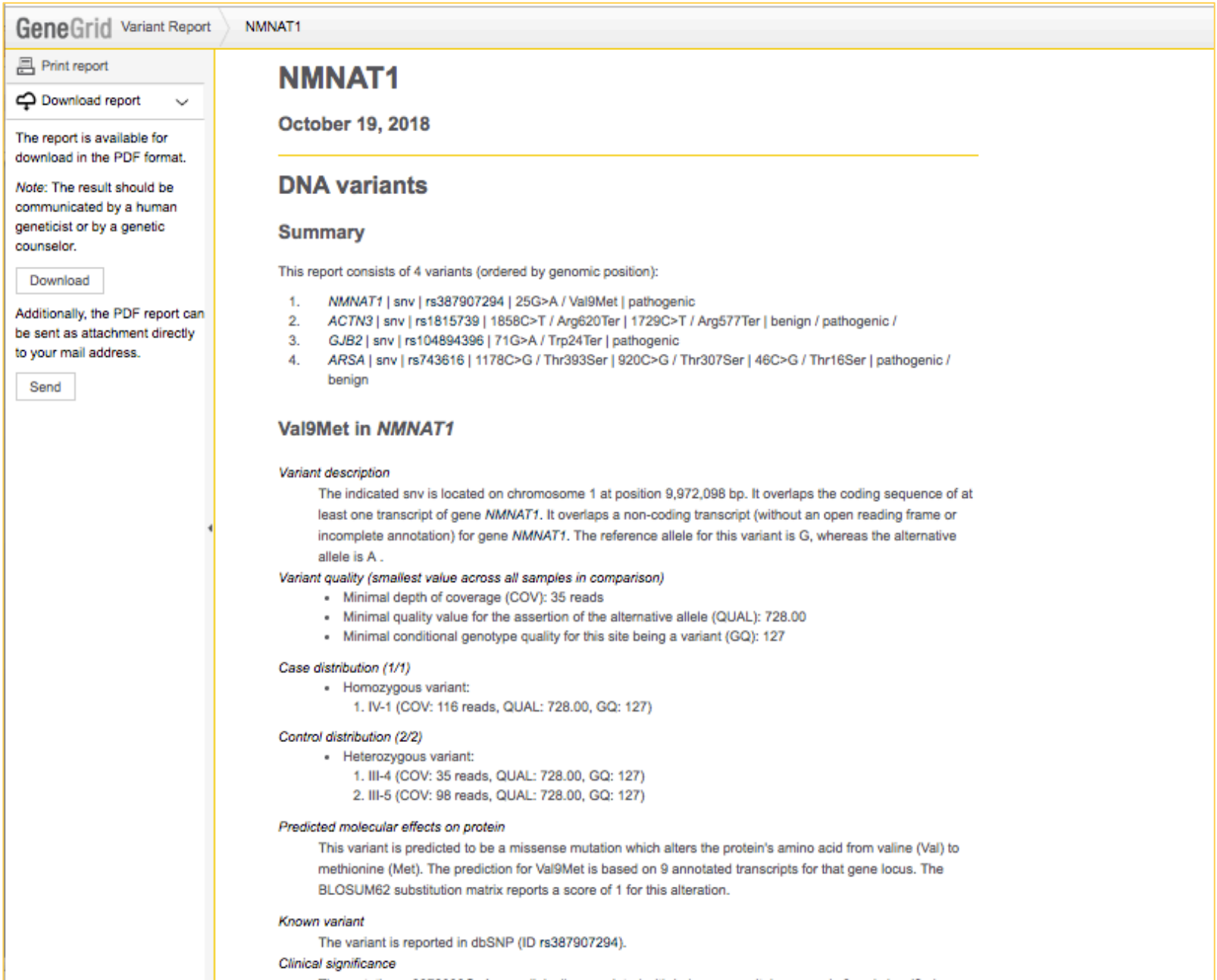
Tabular | 100 per page | Sort by Location

Search results

Items: 14

	Variation *Location*	Gene(s)	Condition(s)	Clinical significance (Last reviewed)	Review status
1.	NMNAT1, TRP169TER	NMNAT1	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided
2.	NM_022787.3(NMNAT1):c.25G>A (p.Val9Met) *GRCh37:* Chr1:10032156 *GRCh38:* Chr1:9972098	NMNAT1	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided
3.	NM_022787.3(NMNAT1):c.115+3A>G *GRCh37:* Chr1:10032249 *GRCh38:* Chr1:9972191	NMNAT1	Leber congenital amaurosis 9	Likely benign (Jun 23, 2017)	criteria provided, single submitter
4.	NM_022787.3(NMNAT1):c.451G>T (p.Val151Phe) *GRCh37:* Chr1:10042370 *GRCh38:* Chr1:9982312	NMNAT1	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided
5.	NM_022787.3(NMNAT1):c.457C>G (p.Leu153Val)	NMNAT1	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided

Report generator



GeneGrid Variant Report | NMNAT1

Print report

Download report

The report is available for download in the PDF format.

Note: The result should be communicated by a human geneticist or by a genetic counselor.

Download

Additionally, the PDF report can be sent as attachment directly to your mail address.

Send

NMNAT1

October 19, 2018

DNA variants

Summary

This report consists of 4 variants (ordered by genomic position):

1. *NMNAT1* | snv | rs387907294 | 25G>A / Val9Met | pathogenic
2. *ACTN3* | snv | rs1815739 | 1858C>T / Arg620Ter | 1729C>T / Arg577Ter | benign / pathogenic /
3. *GJB2* | snv | rs104894396 | 71G>A / Trp24Ter | pathogenic
4. *ARSA* | snv | rs743616 | 1178C>G / Thr393Ser | 920C>G / Thr307Ser | 46C>G / Thr16Ser | pathogenic / benign

Val9Met in *NMNAT1*

Variant description

The indicated snv is located on chromosome 1 at position 9,972,098 bp. It overlaps the coding sequence of at least one transcript of gene *NMNAT1*. It overlaps a non-coding transcript (without an open reading frame or incomplete annotation) for gene *NMNAT1*. The reference allele for this variant is G, whereas the alternative allele is A .

Variant quality (smallest value across all samples in comparison)

- Minimal depth of coverage (COV): 35 reads
- Minimal quality value for the assertion of the alternative allele (QUAL): 728.00
- Minimal conditional genotype quality for this site being a variant (GQ): 127

Case distribution (1/1)

- Homozygous variant:
  1. IV-1 (COV: 116 reads, QUAL: 728.00, GQ: 127)

Control distribution (2/2)

- Heterozygous variant:
  1. III-4 (COV: 35 reads, QUAL: 728.00, GQ: 127)
  2. III-5 (COV: 98 reads, QUAL: 728.00, GQ: 127)

Predicted molecular effects on protein

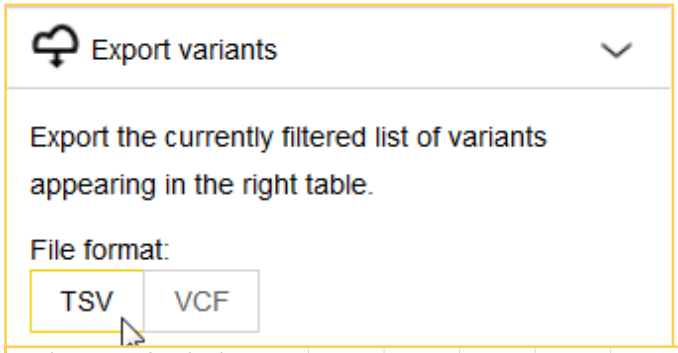
This variant is predicted to be a missense mutation which alters the protein's amino acid from valine (Val) to methionine (Met). The prediction for Val9Met is based on 9 annotated transcripts for that gene locus. The BLOSUM62 substitution matrix reports a score of 1 for this alteration.

Known variant

The variant is reported in dbSNP (ID rs387907294).

Clinical significance

Export of annotated variants



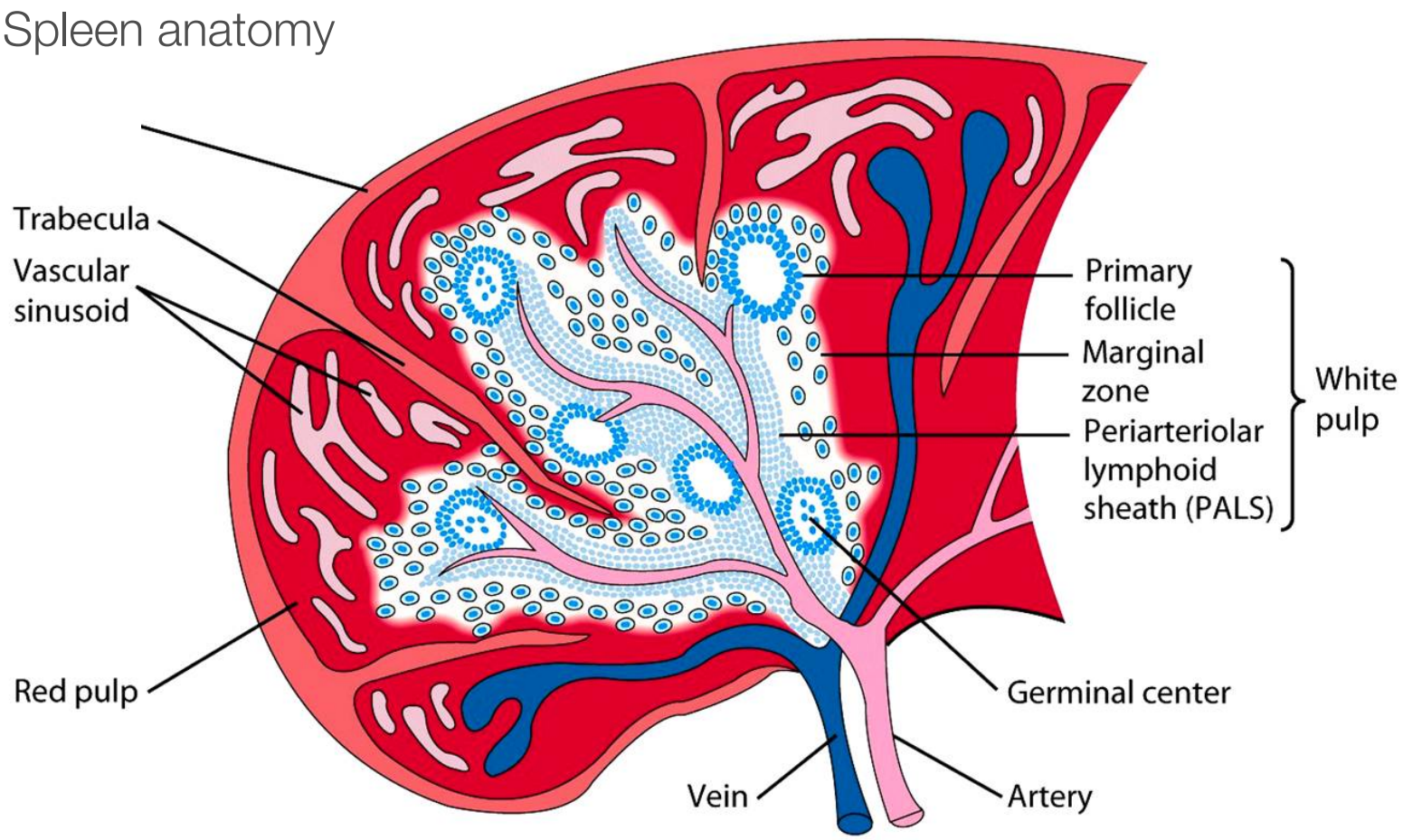
##Number: Consecutively numbered variants
##Contig: Contig numbers in karyotypic order, Genomatix
##Position: Position on the contig, Customer
##Type: Type of variation, Customer
##Reference: Sequence for reference, Customer
##KnownVariant: Known variant, dbSNP, Build 138
##Function: Genomic feature, ElDorado, May 2013
##Gene: Preferred symbol for gene, ElDorado, May 2013
##Category: Predicted effects, Genomatix
##IsDeleterious: Deleterious variant effect prediction, Genomatix
##Quality: Quality value for the assertion of the alternative allele (minimum), Customer
##Coverage: Coverage (minimum), Customer
##MafGenomes: Alternative allele frequency from the whole 1000 genomes project, 1000 Genomes Project, Apr 2012
##LiteratureDiseases: Associated disease terms based on literature mining by Genomatix (gene level), LitInspector, Sep 2014
##ClinVarDiseases: Associated clinical disease terms based on ClinVar database (gene level), ClinVar, Oct 2014
##OmimDiseases: Associated disease terms based on OMIM database (gene level), OMIM, Oct 2014
##SampleCase: IV-1 (Case)
##SampleControl: III-4 (Control)
##SampleControl: III-5 (Control)

Number	Contig_ChrLa	Contig_Cont	Position	Type	Reference	KnownVaria	Function	Gene_GeneI	Gene_Gene	Category	IsDeleteriou	Quality	Coverage	MafGenome	LiteratureDiseases	ClinVarDiseases	OmimDiseases	SampleCase_	SampleConti	SampleControl_2
290	1	1	1684347	insertion	CCCTCCTCCT	0	3utr,intron,c	65220	NADK	insertion	1	304	2	0	Tuberculosis:Dysplasti	Lung cancer		hom	het	het
607	1	1	6637056	snp	G	1	intron_cs,cd	80835	TAS1R1	missense	1	511	4	0.0093	Ageusia:Herpes Zoster	Malignant melanoma		hom	het	het
746	1	1	10032156	snp	G	0	cds	64802	NMNAT1	missense	1	728	33	0	Frontotemporal Deme	Leber congenital am	Leber congenital am	hom	het	het
11097	2	2	1440078	snp	C	1	3utr,intron_c	7173	TPO	missense	1	608	10	0	Multiple System Atrop	Deficiency of iodide	Thyroid dyshormono	hom	het	het
21791	3	3	98073591	deletion	TAAAAAAA	0	cds	403278	OR5K4	nonsense	1	203	11	0		Malignant melanoma		hom	het	het
21793	3	3	98110406	insertion	GAAAAAAA	1	cds	403277	OR5K3	frameshift	1	200	13	0				hom	het	het
25841	4	4	10446604	snp	T	0	cds,promote	85460	ZNF518B	missense	1	621	14	0		Malignant melanoma		hom	het	het
25872	4	4	15542617	snp	C	1	cds	57545	CC2D2A	missense	1	586	7	0	Meckel syndrome type	Meckel syndrome, ty	COACH syndrome:M	hom	het	het
26408	4	4	42403128	snp	C	1	cds	152573	SHISA3	missense	1	593	9	0	Neoplasms:Cell Transf	Malignant melanoma		hom	het	het
31745	5	5	112676428	snp	C	1	intron_cs,cs_	4163	MCC	splice-site	1	356	5	0	Colorectal carcinoma:N	Carcinoma of colon:L	Colorectal cancer, so	hom	het	het
39823	6	6	84798956	snp	G	1	cds	112609	MRAP2	missense	1	572	13	0.0005	Obesity:Adrenocortica	Malignant melanoma	Obesity, susceptibili	hom	het	het
39832	6	6	84896313	deletion	TTTCTT	0	5utr,exon,cd	22832	KIAA1009	deletion	1	728	16	0	Communicable Diseases			hom	het	het
40963	6	6	142738314	deletion	CTTCTTTTC	0	intron_cs,int	57211	GPR126	nonsense	1	571	4	0	Peripheral neuropathy	Lung cancer		hom	het	het
44143	7	7	65444359	insertion	TGAGAG	0	intron_cs	2990	GUSB	splice-site	1	553	3	0	Mucopolysaccharidosis	Mucopolysaccharido	Mucopolysaccharido	hom	het	het
46432	7	7	138424359	snp	T	1	intron,cds	50617	ATP6V0A4	missense	1	434	3	0.0009	Renal Tubular Acidosis	Renal tubular acidos	Renal tubular acidos	hom	het	het
46467	7	7	139164446	snp	G	1	intron_cs,cd	346689	KLRG2	missense	1	402	2	0	Prostate Cancer			hom	het	het
47886	8	8	10467589	snp	T	1	cds	94137	RP1L1	missense	1	664	12	0	Occult macular dystrop	Malignant melanoma	Occult macular dystr	hom	het	het
49527	8	8	67369047	snp	T	1	intron_cs	137872	ADHFE1	splice-site	1	434	3	0	D-2-hydroxyglutaric ac	Malignant melanoma		hom	het	het
49733	8	8	73937076	snp	T	0	5utr,cds	7013	TERF1	missense	1	497	8	0	Low Grade Prostatic Intraepithelial Neoplasia:Acute leukemias:A			hom	het	het
52162	9	9	33255933	snp	A	0	intron_cs	573	BAG1	splice-site	1	505	9	0	Breast cancer:Invasive Breast Carcinoma:Periampullary Adenocar			hom	het	het

GeneGrid example 2

Cancer analysis

Splenic marginal zone lymphoma (SMZL)

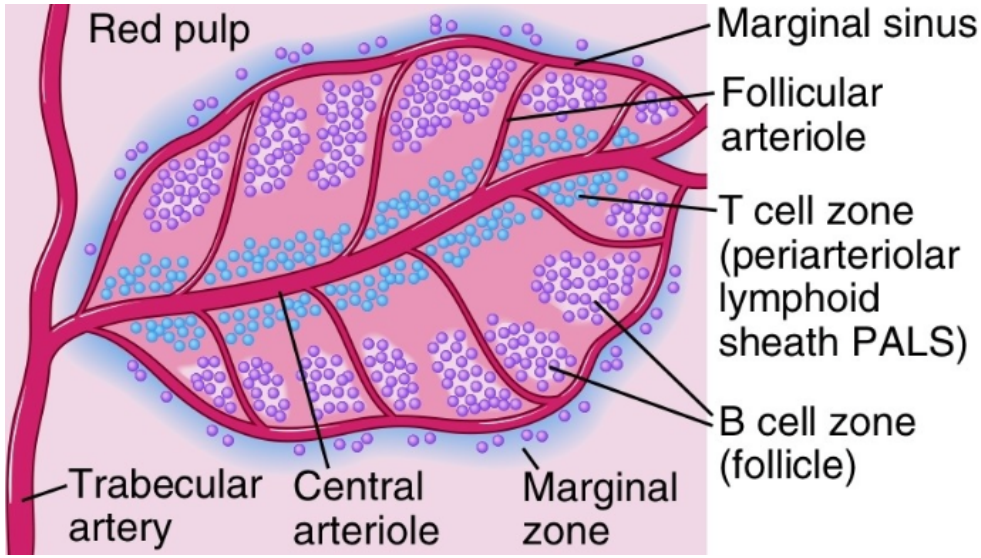


Source: Northern Arizona University http://www2.nau.edu/~fpm/immunology/spleen1.jpg

Splenic marginal zone lymphoma (SMZL)

B cell lymphoma consisting of small lymphocytes and larger blasts

- Starts in white pulp of the spleen
- Invades mantle zone of splenic follicles
- Erodes marginal zone
- Ultimately invades red pulp of the spleen



Frequent clonal rearrangements of immunoglobulin genes

Splenic marginal zone lymphoma (SMZL)

Leukemia (2014) **28**, 1334–1340

www.nature.com/leu

ORIGINAL ARTICLE

Whole-exome sequencing in splenic marginal zone lymphoma reveals mutations in genes involved in marginal zone differentiation

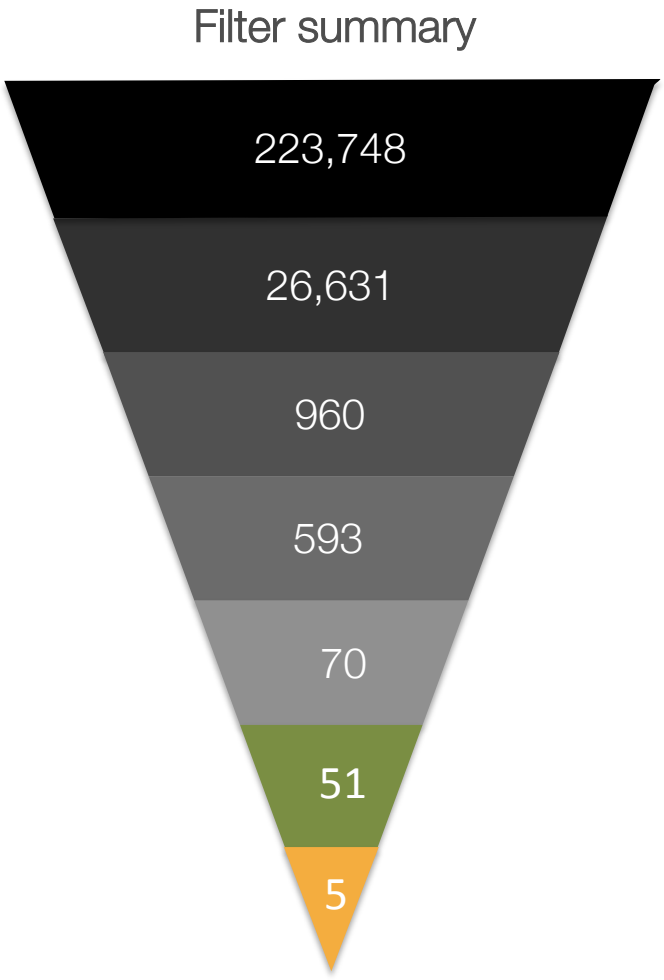
N Martínez[1], C Almaraz[1], JP Vaqué[1], I Varela[2], S Derdak[3], S Beltran[3], M Mollejo[4], Y Campos-Martin[4], L Agueda[3], A Rinaldi[5], I Kwee[5,6,7], M Gut[3], J Blanc[3], D Oscier[8], JC Strefford[9], J Martinez-Lopez[10], A Salar[11], F Sole[12], JL Rodriguez-Peralto[13], C Diez-Tascón[14], JF García[15], M Fraga[16], E Sebastián[17], J Alvés[18], J Menárguez[19], J González-Carreró[20], LF Casado[4], M Bayes[3], F Bertoni[5,21], I Gut[3] and MA Piris[1,22]

Splenic marginal zone lymphoma (SMZL) is a B-cell neoplasm whose molecular pathogenesis remains fundamentally unexplained, requiring more precise diagnostic markers. Previous molecular studies have revealed 7q loss and mutations of nuclear factor κB (NF-κB), B-cell receptor (BCR) and Notch signalling genes. We performed whole-exome sequencing in a series of SMZL cases. Results confirmed that SMZL is an entity distinct from other low-grade B-cell lymphomas, and identified mutations in multiple genes involved in marginal zone development, and others involved in NF-κB, BCR, chromatin remodelling and the cytoskeleton.

Leukemia (2014) **28,** 1334–1340; doi:10.1038/leu.2013.365

Keywords: whole-exome sequencing; splenic; lymphoma; marginal zone

Analysis example: SMZL in patient 7



total number

somatic variants

select deleterious variants

select rare variants (exacAF < 1%)

quality and genotype quality > 30

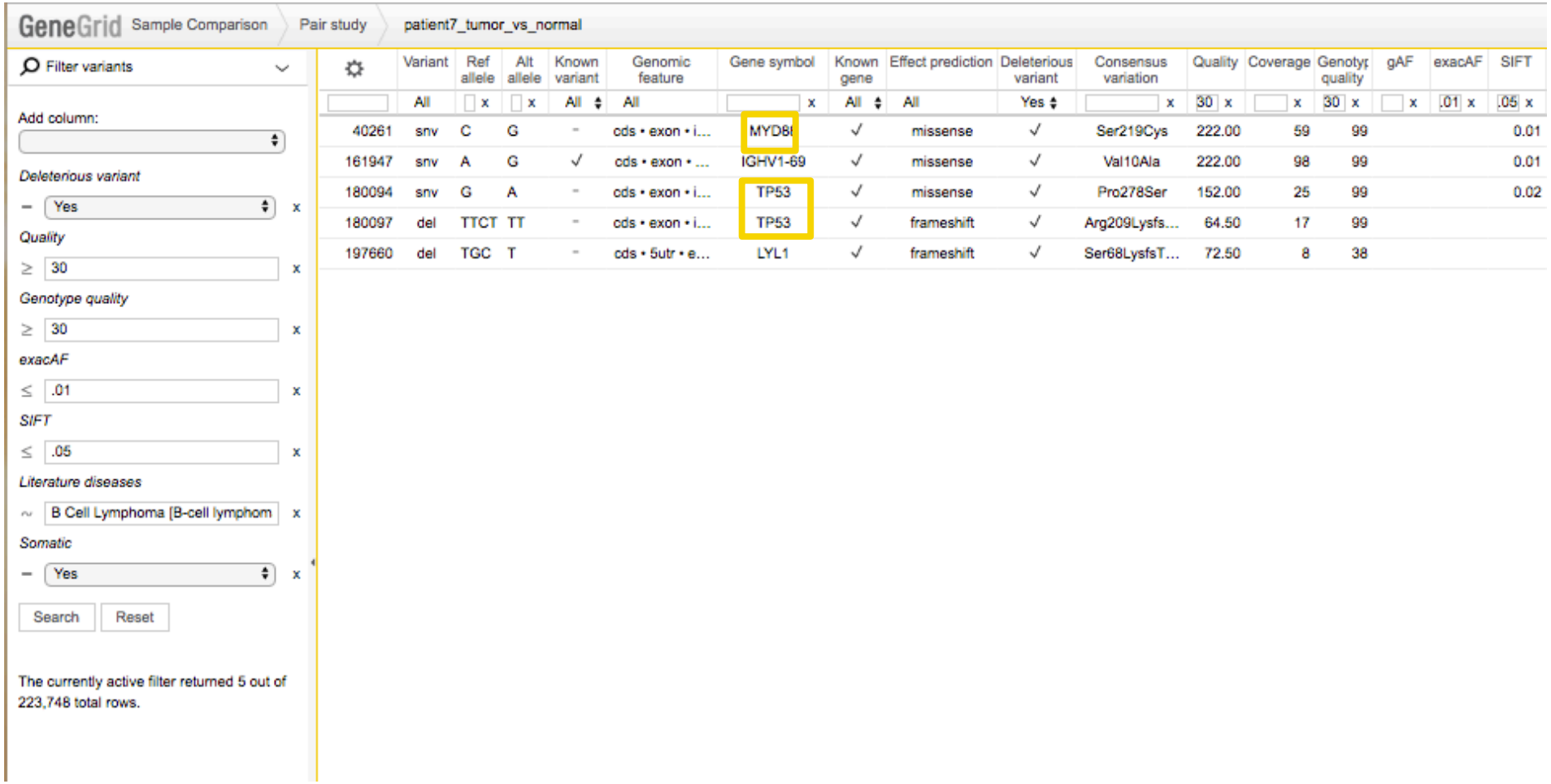
only high-confidence predicted protein effects (SIFT <.05)

select genes associated with "B-Cell Lymphoma" in the literature

genomatix

GeneGrid example: cancer

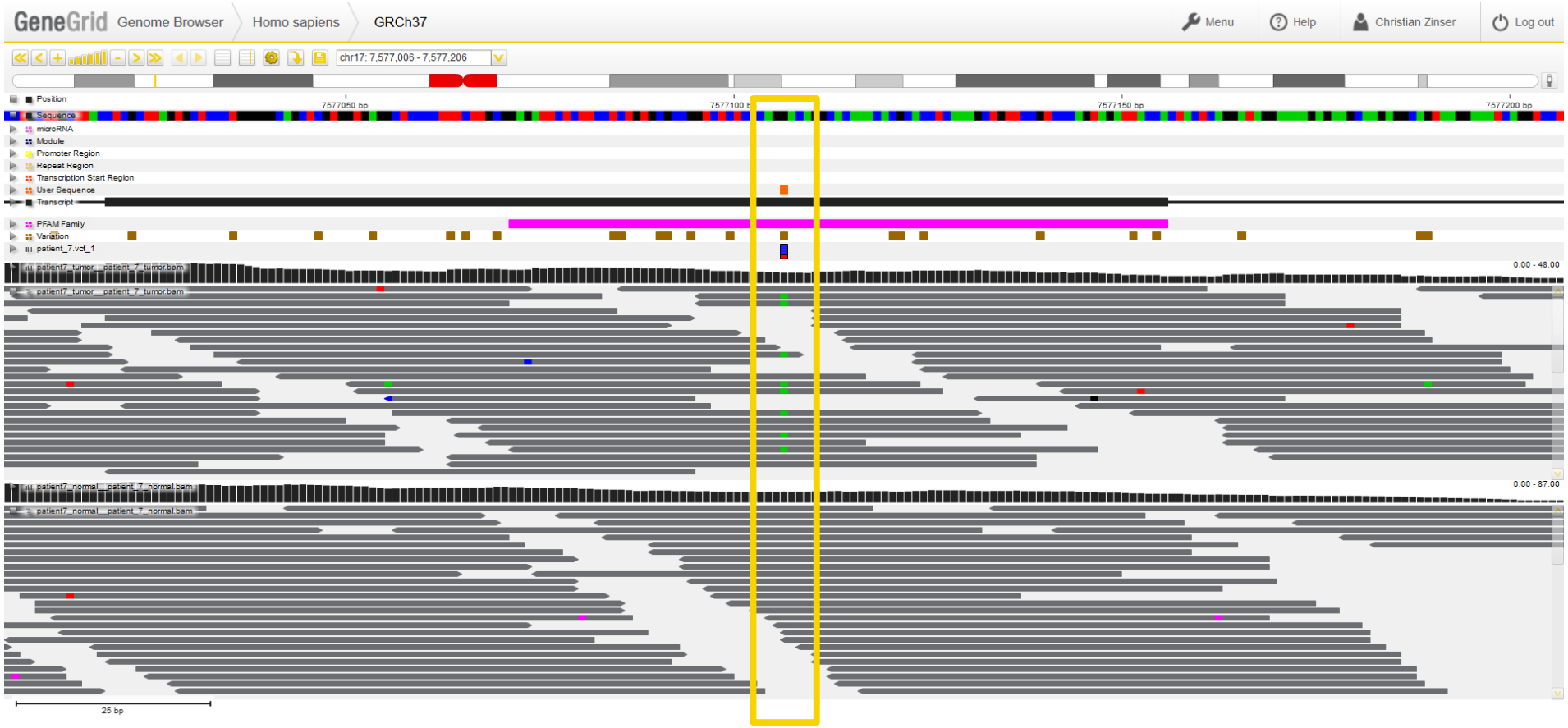
Filtering result



genomatix

GeneGrid example: cancer

Visualization in the Genomatix Genome Browser



Read coverage at SNP position chr17: 7,577,106 (GRCh37) in TP53 for tumor and control

genomatix

GeneGrid example: cancer

Visualization

The SNP is located in the P53 DNA-binding domain

genomatix

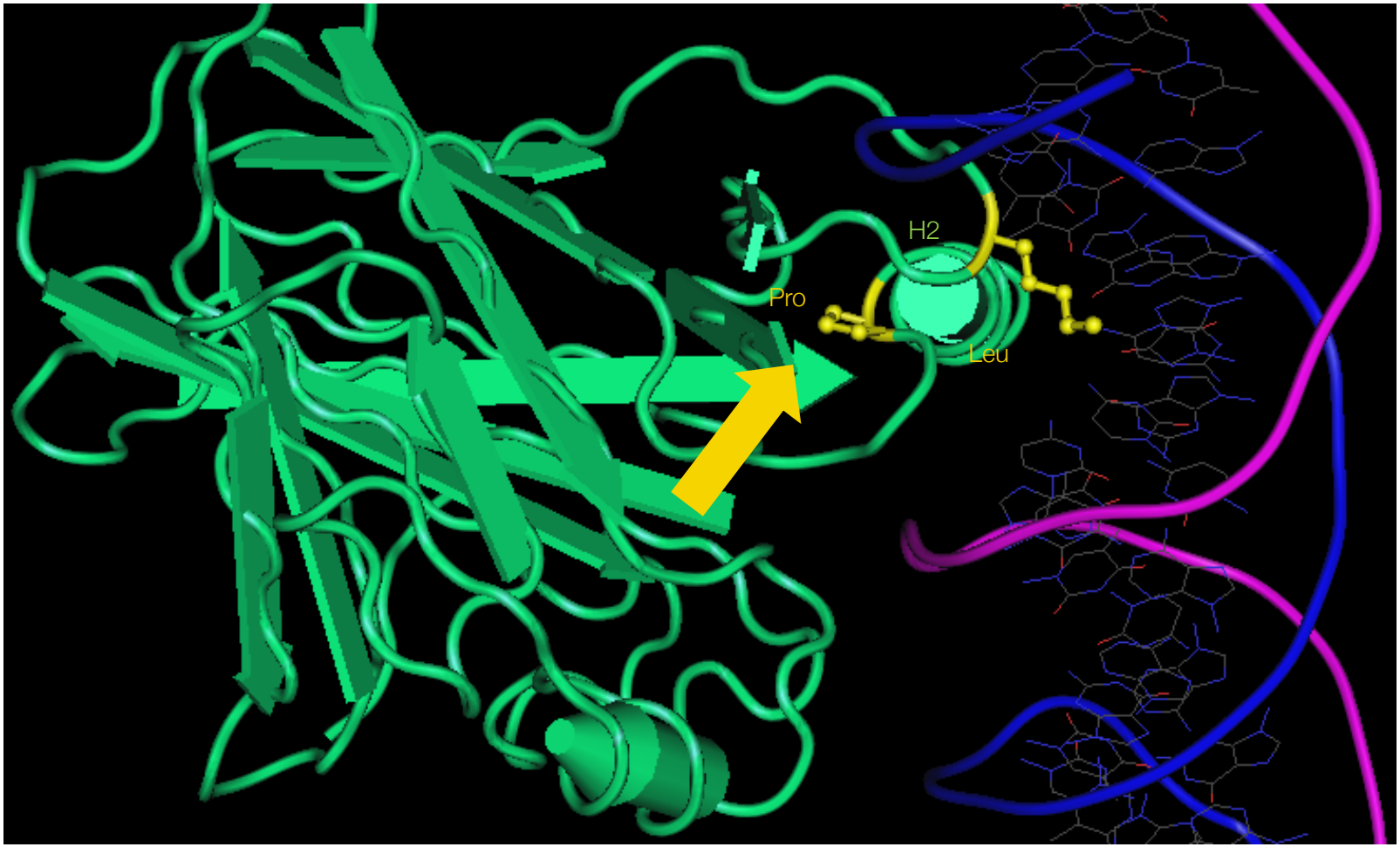
GeneGrid example: cancer

Visualization in the Genomatix Genome Browser

Sample details (2) | Transcript effects (66) | dbSNP (1) | ClinVar | Somatic mutations (20) | COSMIC (12) | Literature diseases (100+) | Clinical diseases (44) | Gene details | Citations (100) | Literature tissues (100+) | Canonic

Ref allele	Alt allele	Ref protein sequence	Alt protein sequence	Gene symbol	Transcript accession	Transcri version	Strand	Type	Genomic feature	Effect prediction	Deleterious	Low confidence	Variation coding	Variation protein	Coding position	Relative coding	BLOSUM	SIFT score
G	A	P	S	TP53	NM_001126112	2	-	protein cod	cds • exon	missense	✓	-	832C>T	Pro278Ser	832	0.70	-1	0.03
G	A	P	S	TP53	NM_000546	5	-	protein cod	cds • exon	missense	✓	-	832C>T	Pro278Ser	832	0.70	-1	0.03
G	A	P	S	TP53	NM_001126113	2	-	protein cod	cds • exon	missense	✓	-	832C>T	Pro278Ser	832	0.80	-1	0.02
G	A	P	S	TP53	NM_001126114	2	-	protein cod	cds • exon	missense	✓	-	832C>T	Pro278Ser	832	0.81	-1	0.02
G	A	P	S	TP53	ENST00000269	4	-	protein cod	cds • exon	missense	✓	-	832C>T	Pro278Ser	832	0.70	-1	0.03
G	A	P	S	TP53	ENST00000359	4	-	protein cod	cds • exon	missense	✓	-	832C>T	Pro278Ser	832	0.81	-1	0.02
G	A	P	S	TP53	ENST00000420	2	-	protein cod	cds • exon	missense	✓	-	832C>T	Pro278Ser	832	0.81	-1	0.02

P53 core domain in complex with DNA



Source: NCBI structure, MMDB ID: 106061

▶ the identified mutation could affect DNA binding or DNA affinity