

Susan M. Dombrowski, PhD 26 Oct 2018



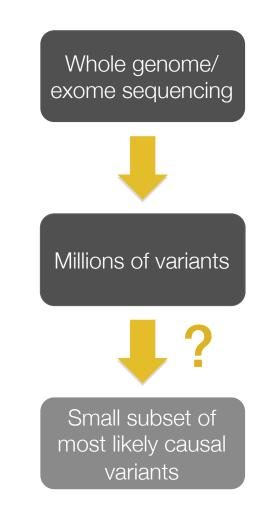
Basis

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?

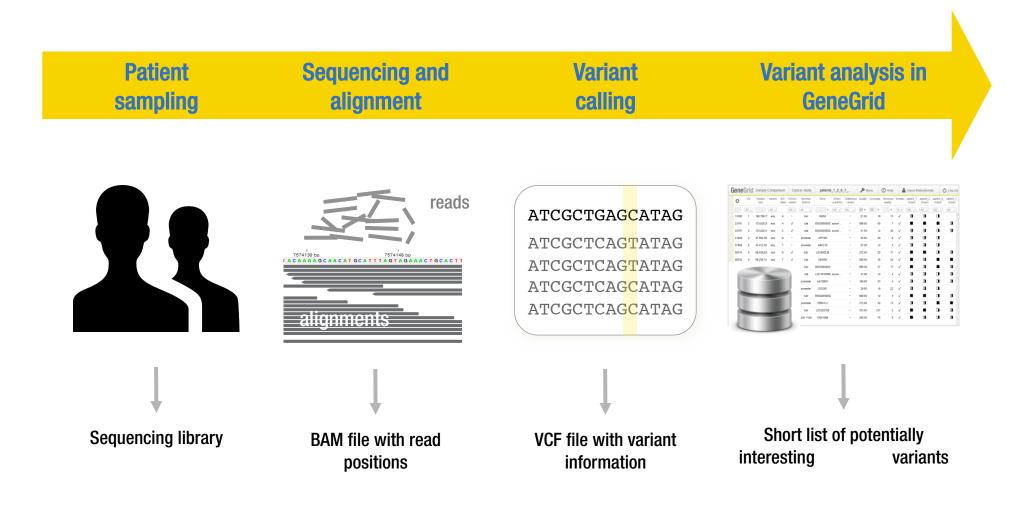


Variant analysis



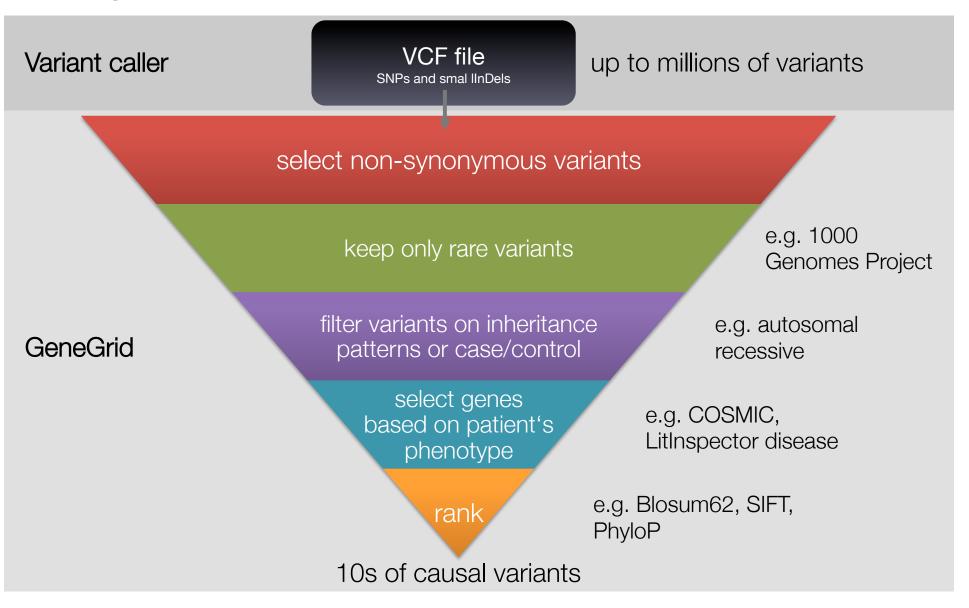
General workflow

Variant analysis





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



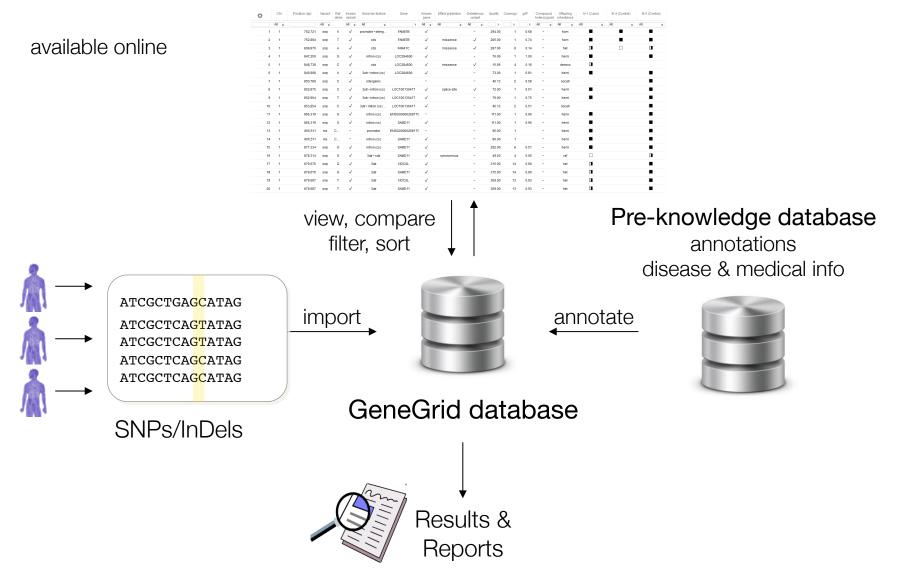
Selected GeneGrid filter fields

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



GeneGrid

The Genomatix GeneGrid technology





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

GeneGrid



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)

>>genomatix

Leber congenital amaurosis

Published in final edited form as: *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-Ogiso⁵, Chitra Kannabiran⁶, Zoe Fonseca-Kelly^{3,4}, Christina Chakarova⁷, Isabelle Audo^{8,9,10,11}, Donna S Mackay⁷, Christina Zeitz^{8,9,10}, Arundhati Dev Borman^{7,12}, Magdalena Staniszewska^{3,4}, Rachna Shukla⁶, Lakshmi Palavalli⁶, Saddek Mohand-Said^{8,9,10,11}, Naushin H Waseem⁷, Subhadra Jalali^{6,13}, Juan C Perin¹⁴, Emily Place^{1,3,4}, Julian Ostrovsky¹, Rui Xiao¹⁵, 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 Berson⁴, Qin Liu^{3,4}, Xiaowu Gai^{20,21,23}, and Eric A. Pierce^{3,4,23}

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⁶Kallam Anji Reddy Molecular Genetics Laboratory, LV Prasad Eye Institute (LVPEI), Kallam Anji Reddy Campus, LV Prasad Marg, Hyderabad, India

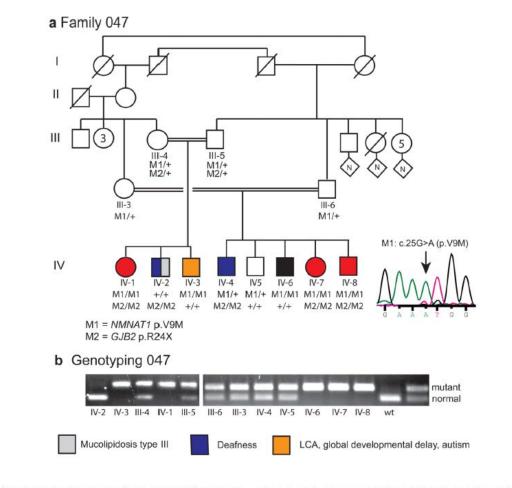
⁷Institute of Ophthalmology, University College of London, London, UK

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



GeneGrid example: trio

Consanguineous family



LCA, congenital deafness, global developmental delay, autism



GeneGrid example: trio

Step 1: load and annotate VCF files

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Getting started

The Genomatix GeneGrid technology enables you to quickly reduce millions of small variants to the few or even the single relevant one(s). All known & novel SNPs in your results can be annotated using our extensive annotation. You can filter the list for those variants of interest to you, perform trio analyses, compare case and control sets (using multiple samples) or identify somatic SNPs within minutes. Read more

Variant

Annotation

Load your VCF files with samples into GeneGrid to be automatically annotated.

Sample Comparison

Find the relevant small variants and identify disease-causing mutations by comparing samples.

Genome

Browser

Browse the human genome in context of your variants of interest and explore publicly available data.

Pathway

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System (GePS)

Browse, search and load canonical pathways and visualize affected genes on pathway level.



Step 1: load and annotate VCF files

𝒫 Filter samples	GeneGrid Variant Upload LCA047_Trio_Demo.38(1).vcf.gz
C Import samples & annotate variants	수 Variant Upload Job
Select your input file and import samples and automatically annotate the variants. <i>Note</i> : The required input file format is the VCI	several hours depending on the size of the input data. The output will become available in the Result Management. Thank you for using GeneGrid.
format. The genomic positions of the variants match the human genome build GRCh37/hg1 GRCh38/hg38. Read more	
Step 1: Select import workspace:	Analysis is running Refresh
Step 2: Define pre-filter settings for import:	Analysis progress 2018-10-19 15:34:03 Processing variants on chromosome 5 2018-10-19 15:34:01 Processing variants on chromosome 4
Minimum coverage: 1	2018-10-19 15:33:58 Processing variants on chromosome 3 2018-10-19 15:33:54 Processing variants on chromosome 2 2018-10-19 15:33:49 Processing variants on chromosome 1
Hint: Pre-filters are optional and can be used reduce the number of variants that will be	2018-10-19 15:33:49 Annotating variants 2018-10-19 15:33:48 Compiling general statistics
imported. Read more Step 3: Select the variant file from your comp	2018-10-19 15:33:48 Detected genome build GRCh38 2018-10-19 15:33:48 Matched 25 contigs with variants 2018-10-19 15:33:47 Validating variants with genome reference sequence
Browse No file selected.	2018-10-19 15:33:46 Creating index for VCF file 2018-10-19 15:33:44 Sorting VCF file 2018-10-19 15:33:43 Detected input file of size 3 MB
Cubmit Decet	2018-10-19 15:33:43 Preparing input file
Associate alignment files	



GeneGrid example: trio

Step 2: sample comparison

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Getting started

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Genome Browser

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Pathway

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System (GePS)

Browse, search and load canonical pathways and visualize affected genes on pathway level.

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Step 2: sample comparison

ımple ID 🖕	Input file			Samp	le			Number of n-ref variants		lass	Activa	ated	Associa alignme		Exome	filter	Minimum coverage
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1277 LCA	Trio_Demo.vcf	III-4			□ ■	Compare sar	nples			\sim	\checkmark		\checkmark		-		1
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Trio	ncer Other				Step	2: Assign the	e samp	oles to the	groups:								
Step 2: As	the samples to	e group				oring (1 assig											
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Please ent	er a result name				LCA	Trio											
Submit					Su	bmit 💦											

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.

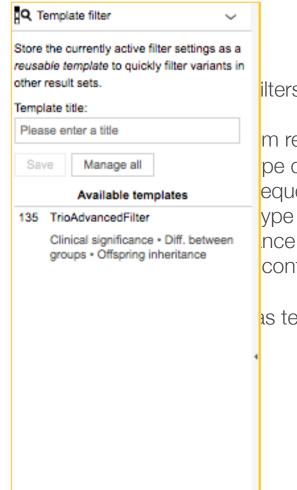
D Filter variants	\sim													پ Me	nu 🕐	Help	Susan Dombrowski	() Log out
	•		c Gene		(nown gene	Effect prediction	Deleterious variant	Consensus variation	Quality	Coverage	gAF	exacAF	Regulatory evidences	Compound heterozygo	Offspring inheritance	IV-1_1 (Case)	III-5_2 (Control)	III-4_1 (Control)
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			• i MR	AP2	\checkmark	missense	~	Arg125His	572.00	13	< 0.01	< 0.01		-	hom			
= Yes ▼	x		• i ATP6	V0A4	\checkmark	missense	~	Ser500Gly	434.00	3	< 0.01	< 0.01		-	hom			
			• i KLI	G2	\checkmark	missense	~	Ala311Val	416.00	4		< 0.01		-	hom			
gAF			on TRB	/7-9	\checkmark	missense	~	Asn26Asp	596.00	6				-	hom			
			on LOC10	377774	\checkmark	synonymous	\checkmark	Tyr28Ter	482.00	2	0.26		7	-	hom			
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			on FRM		~	missense	~	Asn1034Lys	647.00		< 0.01	< 0.01		-	hom	-	-	
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				'N3	v	nonsense	~	Arg620Ter	400.00	3		- 0.01		-	hom		0	0
III-5 (Control)				RA	v	missense	~	Arg172Cys	494.00	7	0.40	< 0.01		-	hom		0	
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Search Reset															Viewing: 1	to 45 Filter	ed: 45 Total va	ariants: 121,936



Filter history and template filters

Speed up the analysis and facilitate sample comparisons

O Filter variants			
S Filter history		~	
Тс	oday		
3 seconds ago	121,936	100.00%	
Unfiltered			
31 seconds ago	106	0.09%	
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7 minutes ago	45	0.04%	
exacAF • Deleterious • IV-1_1 (Case) • III- (Control)			
7 minutes ago	655	0.54%	
exacAF • Deleterious • IV-1_1 (Case)	s variant • Kr	nown gene	
7 minutes ago	3,361	2.76%	
exacAF • Deleterious	s variant • Kr	nown gene	
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Deleterious variant •	Known gen	8	4
7 minutes ago	113,625	93.18%	
Known gene			



ilters that are routinely used, e.g.

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

as template for use in other comparisons



Visualization in the Genomatix Genome Browser

	¢	Chr	Position (bp)	Variant	Ref allele	Known variant	Genomic feature	Gene	Knor gen		ect prediction	Deleterious variant	Quality	Covera	ge gAl	F			Literature diseases	
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25 bp



GeneGrid example: trio

Additional annotation / filter columns: Link-outs to transcript annotation,

dnSNP, ClinVar, COSMIC, Biomedical literature and Clinical information.

		allele	Alt allele	Known variant	Genomic feature	Gene symbol	gene		variant	Consensus variation	Quality	Coverage	gra ez		evidences	heterozygo	inheritance	IV-1 (Case	e) III-4 (Control)	
A	AII -	X	X	All \$	All	NMNAT1 († ×	All \$	All	All 🛊	X	×	X	X	x	All	All \$	All	All	All	All
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			Variant 39	Chr 6 1	Position (bp) 9,972,098	Variant Zygo snv he	osity Ref	Alt Alt2 allele A	Genotype	C Literatur Gene symbol NMNAT1	Known gene √	Effect predic missense	tion Delete	erious C	Quality Co 728.00	verage R cov 35	ef Alt erag coverag 16 19	Ref A fraction frac 0.46	Alt gAF ction 0.54	
			Variant	Chr 6 1 4 1	Position (bp)	Variant Zygo snv he snv he	osity Ref	Alt Alt2 allele	Genotype	IC Literatur Gene symbol	Known B gene	Effect predic	tion Delete	erious C	Quality Co	verage R cov	ef Alt erag coverag	Ref A fraction frac 0.46 0.60	Alt gAF	



Annotation detail views and links: ClinVar

ClinVar	ClinVar	C1837873 Create alert Advanced				Search
Home About - Acc	cess 🔻	Help Submit Statistics	FTP 🔻			
Gene Customize this list	Tal	bular ← 100 per page ← Sort by Location	*			
Clinical significance Conflicting interpretations (0) Benign (0) Likely benign (2) Uncertain significance (0)		earch results ms: 14				
Likely pathogenic (1) Pathogenic (12) Risk factor (0)		Variation Location	Gene(s)	Condition(s)	Clinical significance (Last reviewed)	Review status
Review status Practice guideline (0)	1.	NMNAT1, TRP169TER	NMNAT1	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided
Expert panel (0) Multiple submitters (1) Single submitter (4) At least one star (5)	2.	NM_022787.3(NMNAT1):c.25G>A (p. Val9Met) GRCh37: Chr1:10032156 GRCh38: Chr1:9972098	<u>NMNAT1</u>	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided
Conflicting interpretations (0) Allele origin Germline (14)	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
De novo (0) Somatic (0) Method type Research (1) Literature only (9)	4.	NM_022787.3(NMNAT1):c.451G>T (p.Val151Phe) GRCh37: Chr1:10042370 GRCh38: Chr1:9982312	<u>NMNAT1</u>	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided
Clinical testing (6)	5.	NM_022787.3(NMNAT1):c.457C>G (p.Leu153Val)	NMNAT1	Leber congenital amaurosis 9	Pathogenic (Sep 1, 2012)	no assertion criteria provided



GeneGrid example: trio

Report generator

GeneGrid Variant Report	NMNAT1
Print report	NMNAT1
🗘 Download report 🗸 🗸	
The report is available for download in the PDF format.	October 19, 2018
Note: The result should be communicated by a human	DNA variants
geneticist or by a genetic counselor.	Summary
Download	This report consists of 4 variants (ordered by genomic position):
Additionally, the PDF report can	1. NMNAT1 snv rs387907294 25G>A / Val9Met pathogenic
be sent as attachment directly	 ACTN3 snv rs1815739 1858C>T / Arg620Ter 1729C>T / Arg577Ter benign / pathogenic / C U21 snv rs1815739 1858C>T / Arg620Ter 1729C>T / Arg577Ter benign / pathogenic /
to your mail address.	 GJB2 snv rs104894396 71G>A / Trp24Ter pathogenic ARSA snv rs743616 1178C>G / Thr393Ser 920C>G / Thr307Ser 46C>G / Thr16Ser pathogenic /
Dent	benign
Send	
	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: A wid (201) 25 word - 0144 - 702 20 - 02 - 127
	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

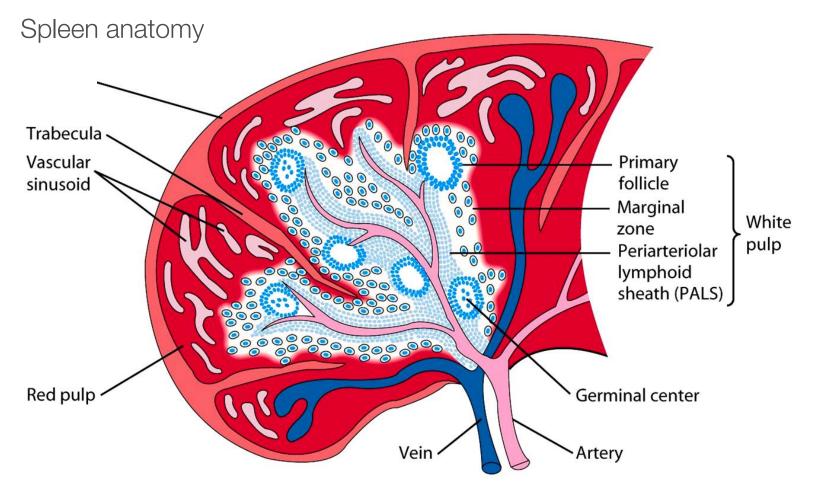
	Export va	riar	nts				-										
Ехро	ort the curr	ren	tly filtered	list of v	variants												
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			ct prediction, Genoma														
			of the alternative alle	ele (minimum)	, Customer												
	Coverage (minimum),																
	nes: Alternative allele																
##LiteratureD	Diseases: Associated d	lisease	terms based on litera	ature mining by	Genomatix (ge	ene level), L	tInspector, Sep 2014										
##LiteratureD ##ClinVarDise	Diseases: Associated d eases: Associated clini	lisease ical dis	e terms based on litera sease terms based on (ature mining by ClinVar databa	/ Genomatix (ge se (gene level),	ene level), L ClinVar, Oc	tInspector, Sep 2014										
##LiteratureD ##ClinVarDise ##OmimDisea	Diseases: Associated d eases: Associated clini ases: Associated disea	lisease ical dis	terms based on litera	ature mining by ClinVar databa	/ Genomatix (ge se (gene level),	ene level), L ClinVar, Oc	tInspector, Sep 2014										
##LiteratureD ##ClinVarDise ##OmimDisea ##SampleCase	Diseases: Associated d eases: Associated clini ases: Associated disea se: IV-1 (Case)	lisease ical dis	e terms based on litera sease terms based on (ature mining by ClinVar databa	/ Genomatix (ge se (gene level),	ene level), L ClinVar, Oc	tInspector, Sep 2014										
##LiteratureD ##ClinVarDise ##OmimDisea ##SampleCase ##SampleCon	Diseases: Associated d eases: Associated clini ases: Associated disea se: IV-1 (Case) ntrol: III-4 (Control)	lisease ical dis	e terms based on litera sease terms based on (ature mining by ClinVar databa	/ Genomatix (ge se (gene level),	ene level), L ClinVar, Oc	tInspector, Sep 2014										
##LiteratureD ##ClinVarDise ##OmimDisea ##SampleCas ##SampleCon ##SampleCon	Diseases: Associated d eases: Associated clini ases: Associated disea e: IV-1 (Case) htrol: III-4 (Control) htrol: III-5 (Control)	lisease ical dis ase ter	e terms based on litera sease terms based on ms based on OMIM da	ature mining by ClinVar databa: atabase (gene l	(Genomatix (ge se (gene level), evel), OMIM, Oo	ne level), L ClinVar, Oc ct 2014	itInspector, Sep 2014 t 2014		IsDalatasiau	Quality			ClinVerDiscore	OmimPianean			
##LiteratureD ##ClinVarDise ##ComimDisea ##SampleCos ##SampleCon ##SampleCon Number	Diseases: Associated d eases: Associated clini ases: Associated disea e: IV-1 (Case) htrol: III-4 (Control) htrol: III-5 (Control) Contig_ChrL Contig_C	lisease ical dis ase ter	e terms based on litera sease terms based on ms based on OMIM da osition Type	ature mining by ClinVar databas atabase (gene le Reference	(Genomatix (ge se (gene level), evel), OMIM, Oc KnownVaria Fu	ene level), L ClinVar, Oc ct 2014 unction	itInspector, Sep 2014 t 2014 Gene_Genel Gene_Gene		IsDeleteriou		Coverage	MafGenome LiteratureDiseases	ClinVarDiseases	OmimDiseases		e_SampleCo	
##LiteratureD ##ClinVarDise ##ComimDisea ##SampleCom ##SampleCom Number 290	Diseases: Associated d eases: Associated clini ases: Associated disea e: IV-1 (Case) htrol: III-4 (Control) htrol: III-5 (Control) Contig_Cht.d Contig_C 1	lisease ical dis ase terr Cont Po 1	eterms based on litera sease terms based on ms based on OMIM da osition Type 1684347 insertion	ature mining by ClinVar databas atabase (gene le Reference CCCTCCTCCT	r Genomatix (ge se (gene level), evel), OMIM, Oc KnownVariai Fu 0 3u	ne level), L ClinVar, Oc ct 2014 unction utr,intron,c	itinspector, Sep 2014 t 2014 Gene_Genel Gene_Gene 65220 NADK	insertion	1	30	4	2 0 Tuberculosis:Dysplast	ti Lung cancer		hom	het	het
##LiteratureD ##ClinVarDise ##OmimDisea ##SampleCase ##SampleCon Number 0 290 607	Diseases: Associated d eases: Associated clini ases: Associated disea ee: IV-1 (Case) htrol: III-4 (Control) htrol: III-5 (Control) Contig_ChrLiContig_C 1 1	lisease ical dis ase terr Cont Pc 1	eterms based on litera sease terms based on ms based on OMIM da osition Type 1684347 insertion 6637056 snp	ature mining by ClinVar databas atabase (gene la Reference CCCTCCTCCT G	r Genomatix (ge se (gene level), evel), OMIM, Oc KnownVariai Fu 0 3u 1 in	ene level), L ClinVar, Oc ct 2014 unction utr, intron, c ntron_cs, cd:	tinspector, Sep 2014 t 2014 Gene_Genel Gene_Gene 65220 NADK 80835 TASIR1	insertion missense	1	30 51	4	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste	ti Lung cancer r Malignant melanor	na	hom hom	het het	het het
##LiteratureD ##ClinVarDise ##SampleCas ##SampleCon Number 0 290 607 746	Diseases: Associated di eases: Associated clinia ases: Associated disea ie: IV-1 (Case) htrol: III-6 (Control) htrol: III-5 (Control) Contig_ChrLi Contig_C 1 1 1	lisease ical dis ase ter Cont Po 1 1	e terms based on litera sease terms based on o ms based on OMIM da osition Type 1684347 insertion 6637056 snp 10032156 snp	Ature mining by ClinVar databas atabase (gene la Reference CCCTCCTCCT G G	r Genomatix (ge se (gene level), evel), OMIM, Oo KnownVariai Fu 0 3u 1 in 0 cd	ene level), L ClinVar, Oc ct 2014 unction utr,intron,c ntron_cs,cd: ds	tinspector, Sep 2014 t 2014 Gene_Genel Gene_Genu 65220 NADK 80835 TASIR1 64802 NMNAT1	insertion missense missense	1 1 1	30 51 72	4	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 3 0 Frontotemporal Deme	ti Lung cancer r Malignant melanor e Leber congenital ar	na mi Leber congenital am	hom hom ni hom	het het het	het het het
##LiteratureD ##ClinVarDise ##SampleCas ##SampleCon Number 0 290 607 746 11097	Diseases: Associated di eases: Associated dini associated disea es: IV-1 (Case) ntrol: III-4 (Control) Contig_Chriz (Contig_C 1 1 1 2 2	lisease ical dis ase ten Cont Po 1 1 1 2	e terms based on litera sease terms based on 0 ms based on 0MIM da osition Type 1684347 insertion 6637056 snp 10032156 snp 1440078 snp	Ature mining by ClinVar database (gene la Reference CCCTCCTCCT G G C	r Genomatix (ge se (gene level), evel), OMIM, Oo KnownVaria Fu 0 3u 1 in 0 cd 1 3u	ene level), L ClinVar, Oc ct 2014 unction utr, intron, c ntron_cs, cd: ds utr, intron_c	tinspector, Sep 2014 t 2014 Gene_Genel Gene_Gene 65220 NADK 80835 TASIR1 64802 NMNAT1 7173 TPO	insertion missense missense missense	1 1 1 1	30 51 72 60	4	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 3 0 Frontotemporal Demo 0 0 Multiple System Atro	ii Lung cancer r Malignant melanor e Leber congenital ar p Deficiency of iodid	na Mi Leber congenital an e Thyroid dyshormon	hom hom n; hom no hom	het het het	het het het het
##LiteratureD ##ClinVarDise ##SampleCos ##SampleCon Number 0 290 607 746 11097 21791	Diseases: Associated di eases: Associated dini ases: Associated disea e: IV-1 (Case) htrol: III-4 (Control) htrol: III-5 (Control) Contig_ChrL (Control) 1 1 1 2 3	lisease ical dis ase ten Cont Po 1 1 1 2 3	e terms based on litera sease terms based on OMIM da ms based on OMIM da based on OMIM da b	Ature mining by ClinVar database (gene la Reference CCCTCCTCCT G G C TAAAAAAA	r Genomatix (ge se (gene level), evel), OMIM, OC KnownVarial Fu 0 3. 1 in 0 cd 1 3. 0 cd	unction utr, intron, c ds utr, intron, c ds utr, intron_ c ds	tinspector, Sep 2014 t 2014 Gene_Genel Gene_Gene 65220 NADK 80835 TASIRI 64802 NMNATI 7173 TPO 403278 OR5K4	insertion missense missense missense nonsense	1 1 1 1 1	30 51 72 60 20	4	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 3 0 Frontotemporal Demo 0 0 Multiple System Atro 1 0 0	ti Lung cancer r Malignant melanor e Leber congenital ar	na Mi Leber congenital an e Thyroid dyshormon	hom hom hom o hom hom	het het het het het	het het het het het
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##LiteratureD ##ClinVarDise ##SampleCase ##SampleCon Number 0 290 607 746 11097 21791 21793 25841	Diseases: Associated di eases: Associated dini ases: Associated disea er: IV-1 (Case) Introl: III-4 (Control) Contig_ChrLi Contig_C 1 1 1 2 3 3 4	lisease ical dis ase ten Cont Pc 1 1 2 3 3 4	eterms based on litera sease terms based on OMIM da ostition Type 1684347 insertion 6637056 snp 1440078 snp 98073591 deletion 98110406 insertion 10446604 snp	ture mining by ClinVar databas atabase (gene la Reference CCCTCCTCCT G G C TAAAAAAA T	r Genomatix (ge se (gene level), evel), OMIM, Oc KnownVarial FL 0 3u 1 in 0 cd 1 3u 0 cd 1 cd 0 cd 0 cd 0 cd 0 cd	ene level), L ClinVar, Oc ct 2014 unction utr, intron, c ntron_cs, cd: ds utr, intron_c ds ds ds, promote	tinspector, Sep 2014 t 2014 Gene_Genel Gene_Gene 65220 NADK 80835 TASIR1 64802 NMNAT1 7173 TPO 403278 OR5K4 403277 OR5K3 85460 ZNF518B	insertion missense missense missense nonsense frameshift missense	1 1 1 1 1 1 1	30 51 72 60 20 20 62	4	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 8 0 Frontotemporal Dem 0 0 Multiple System Atrop 1 0 3 0 4 0 0 0	il Lung cancer r Malignant melanor e Leber congenital ar p Deficiency of iodid Malignant melanor Malignant melanor	na m. Leber congenital an le Thyroid dyshormon na na	hom hom hom o hom hom hom hom	het het het het het het	het het het het het het
##LiteratureD ##ClinVarDise ##SampleCas ##SampleCon Number 0 290 290 290 290 2109 746 11097 21791 21793 21793 25841 25872	Diseases: Associated di eases: Associated dina ese: Associated disea e: IV-1 (Case) Introl: III-5 (Control) Contig_ChrLi Contig_C 1 1 2 3 3 3	lisease ical dis ase ter Cont Pc 1 1 1 2 3 3 3	e terms based on litera sease terms based on M ms based on OMIM da osition Type 1684347 insertion 6637056 snp 10032156 snp 10032156 snp 98073591 deletion 98110406 insertion 98110406 insertion 15542617 snp	ClinVar databas ClinVar databas tabase (gene la Reference CCCTCCTCCT G G C TAAAAAAA T C	r Genomatix (ge se (gene level), evel), OMIM, Oo KnownVaria FL 0 3u 1 in 0 cd 1 3u 0 cd 1 cd 0 cd 1 cd	ene level), L ClinVar, Oc ct 2014 unction utr,intron,c thron_cs,cd: ds utr,intron_c ds ds ds	Gene Gene <td< td=""><td>insertion missense missense missense nonsense frameshift missense missense</td><td>1 1 1 1 1</td><td>30 51 72 60 20 20 62 58</td><td>4</td><td>2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 3 0 Frontotemporal Demu 0 0 Multiple System Atro 1 0 3 0 4 0 7 0 Meckel syndrome typ</td><td>II Lung cancer Ir Malignant melanor I Leber congenital ar p Deficiency of iodid Malignant melanor Malignant melanor e Meckel syndrome,</td><td>na mi Leber congenital an le Thyroid dyshormon na ma ty COACH syndrome:N</td><td>hom hom o hom hom hom hom hom hom</td><td>het het het het het het het het</td><td>het het het het het het het</td></td<>	insertion missense missense missense nonsense frameshift missense missense	1 1 1 1 1	30 51 72 60 20 20 62 58	4	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 3 0 Frontotemporal Demu 0 0 Multiple System Atro 1 0 3 0 4 0 7 0 Meckel syndrome typ	II Lung cancer Ir Malignant melanor I Leber congenital ar p Deficiency of iodid Malignant melanor Malignant melanor e Meckel syndrome,	na mi Leber congenital an le Thyroid dyshormon na ma ty COACH syndrome:N	hom hom o hom hom hom hom hom hom	het het het het het het het het	het het het het het het het
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##LiteratureD ##ClinVarDise ##SampleCas ##SampleCon Number 0 290 607 746 11097 21791 21793 21791 21793 25841 225872 25608 31745	Diseases: Associated di eases: Associated dina ese: Associated disea e: IV-1 (Case) httrol: III-6 (Control) Contig_ChrLiContig_C 1 1 2 3 3 4 4 4 4 5	Cont Pc 1 1 2 3 3 4 4 4 5	eterms based on litera sease terms based on OMIM da obsition Type 1684347 Insertion 6637055 snp 1440078 snp 98073591 deletion 98110406 insertion 10446604 snp 15542617 snp 42403128 snp	ture mining by ClinVar databas ttabase (gene la Reference CCCTCCTCCT G G C TAAAAAAA T C C C C C	r Genomatix (ge se (gene level), evel), OMIM, OC 0 3. 1 in 0 cc 1 3. 0 cc 1 cc 1 cc 1 cc 1 cc 1 cc 1 cc 1 cc	ene level), L ClinVar, Oc ct 2014 unction utr, intron, c ntron_cs, cd: ds utr, intron_c ds ds, b, promote ds ds htron_cs, cs; ds htron_cs, cs; ds	titinspector, Sep 2014 t 2014 Gene_Genel Gene_Gene 65220 NADK 80835 TASIR1 64802 NMNAT1 7173 TPO 403277 ORSK3 85460 ZNF518B 57545 CC2D2A 152573 \$HISA3 4163 MCC	insertion missense missense nonsense frameshift missense missense splice-site	1 1 1 1 1 1 1 1 1 1 1	30 51 72 60 20 20 62 58 59 35	4	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 3 0 Frontotemporal Dem 0 0 Multiple System Atroj 1 0 3 0 4 0 7 0 Meckel syndrome typ 9 0 Neoplasms:Cell Trans 5 0 Colorectal carcinoma:	ii Lung cancer r Malignant melanor leber congenital ai poeficiency of iodid Malignant melanor Malignant melanor Malignant melanor f Malignant melanor N Carcinoma of color	ma mi Leber congenital an e E Thyroid dyshormon ma ty COACH syndrome:N ma n:L Colorectal cancer, si	hom hom o hom hom hom hom hom n/hom hom o hom	het het het het het het het het het	het het het het het het het het het
##LiteratureD ##ClinVarDise ##SampleCon Number 0 290 607 746 11097 21791 21793 25841 25872 26408 31745 39823	Diseases: Associated di eases: Associated dina ases: Associated disea e: IV-1 (Case) Itrol: III-5 (Control) Contig_ChrLi Contig_C 1 1 2 3 3 3 4 4 4 4	cont Pc 1 1 2 3 3 4 4 4 5 6	e terms based on litera sease terms based on OMIM da ms based on OMIM da based on OMIM da b	ClinVar databas tabase (gene la Reference CCCTCCTCCT G C C TAAAAAAAA GAAAAAAA T C C C C G G G G G G G G G G G G G G G	r Genomatix (ge se (gene level), evel), OMIM, Oo KnownVaria FL 0 3u 1 in 0 cd 1 3u 0 cd 1 cd 1 cd 1 cd 1 cd 1 cd 1 cd 1 cd 1	unction uurction utr, intron, c tron_cs, cd: ds ds, ds, promote ds ds ds ds, promote ds ds ds ds ds ds ds ds ds ds ds ds ds	Gene_Genel Gene_Genel 65220 NADK 8835 TASIRI 64802 NMNATI 7173 TPO 403276 OR5K4 85460 ZVFS188 57545 CC2D2A 152573 SHISA3 4163 MCC 112609 MRAP2	insertion missense missense nonsense frameshift missense missense splice-site missense	1 1 1 1 1 1 1 1 1 1 1 1	30 51 72 60 20 20 62 58 59 35 57	4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 8 0 Frontotemporal Demu 0 0 Multiple System Atro 1 0 3 0 4 0 7 0 0 Neoplasms:Cell Trans 5 0 2 Colorectal carinoma: 3 0	II Lung cancer Ir Malignant melanor I Leber congenital a p Deficiency of iodid Malignant melanor Malignant melanor e Meckel syndrome, fi Malignant melanor o Cacrinoma of color a Malignant melanor	ma mi Leber congenital an e E Thyroid dyshormon ma ty COACH syndrome:N ma n:L Colorectal cancer, si	hom hom o hom hom hom hom hom hom o hom li hom	het het het het het het het het het het	het het het het het het het het het het
##LiteratureD ##ClinVarDise ##SampleCos ##SampleCon Number 200 607 746 11097 21791 21793 21791 21793 21791 21793 21791 21793 21794 21793 21794 21793 21794 21793 21794 21793 21794 21793 21794 21795 21794 21795 2	Diseases: Associated di eases: Associated dine ases: Associated disea es: IV-1 (Case) ntrol: III-4 (Control) Contig_Chrit Contig_C 1 1 1 2 3 3 3 4 4 4 4 5 5 6	Lisease ical dis ase ten 1 1 1 2 3 3 4 4 4 4 5 6 6 6	terms based on litera sease terms based on Milera ms based on OMIM da obsition Type 1684347 insertion 6637056 snp 10032155 snp 10032155 snp 98073591 deletion 98110406 insertion 10446604 snp 11267428 snp 42403128 snp 11267428 snp 84798956 snp 84896313 deletion	ture mining by ClinVar databas tabase (gene la Reference CCCTCCTCCT G G G C C TAAAAAAA T C C C C C C C C C C C C	r Genomatix (ge se (gene level), evel), OMIM, Oo KnownVariar FL r 0 3t 1 in 0 cd 1 3t 0 cd 1 cd 1 cd 1 cd 1 cd 1 cd 1 cd 1 cd 1	unction utr, intron, cc ct 2014 unction utr, intron, cc ds ds ds ds, promote ds ds, promote ds ds utr, ncn_cs, cs_ ds utr, ncn_cs, cs_ utr, exon, cd utr, exon, cd	Itinspector, Sep 2014 12014 Gene Gene 65220 NADK 80835 TASIRI 64802 NMNATI 7173 TPO 403277 OR5K4 403277 OR5K4 65526 CC2D2A 152573 SHISA3 4163 MCC 112609 MRAP2 22832 KIAA1009	insertion missense missense nonsense frameshift missense missense splice-site missense deletion	1 1 1 1 1 1 1 1 1 1 1 1 1	30 51 72 60 20 20 62 58 59 35 57 72	4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	2 0 Tuberculosis:Dysplast 4 0.0093 Ageusia:Herpes Zoste 3 0 Frontotemporal Demi 0 Multiple System Atrop 1 0 3 0 4 0 7 0 0 Neoplasms:Cell Trans 5 0 0 Obesity:Adrenocortic 6 0	ii Lung cancer r Malignant melanor e Leber congenital ai p Deficiency of Iodid Malignant melanor Malignant melanor e Meckel syndrome, fi Malignant melanor N Carcinoma of color a Malignant melanor ses	ma mi Leber congenital an e E Thyroid dyshormon ma ty COACH syndrome:N ma n:L Colorectal cancer, si	hom hom o hom hom hom hom hom hom hom hom hom hom	het het het het het het het het het het	het het het het het het het het het het
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GeneGrid example 2

Cancer analysis



Splenic marginal zone lymphoma (SMZL)



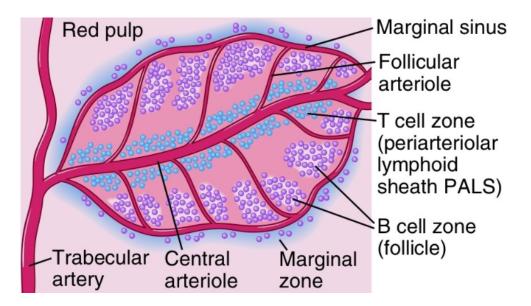
Source: Northern Arizona University http://www2.nau.edu/~fpm/immunology/spleen1.jpg



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)



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ORIGINAL ARTICLE

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

N Martínez¹, C Almaraz¹, JP Vaqué¹, I Varela², S Derdak³, S Beltran³, M Mollejo⁴, Y Campos-Martin⁴, L Agueda³, A Rinaldi⁵, I Kwee^{5,6,7}, M Gut³, J Blanc³, D Oscier⁸, JC Strefford⁹, J Martinez-Lopez¹⁰, A Salar¹¹, F Sole¹², JL Rodriguez-Peralto¹³, C Diez-Tascón¹⁴, JF García¹⁵, M Fraga¹⁶, E Sebastián¹⁷, J Alvés¹⁸, J Menárguez¹⁹, J González-Carreró²⁰, LF Casado⁴, M Bayes³, F Bertoni^{5,21}, I Gut³ 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 κ B (NF- κ B), 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- κ B, BCR, chromatin remodelling and the cytoskeleton.

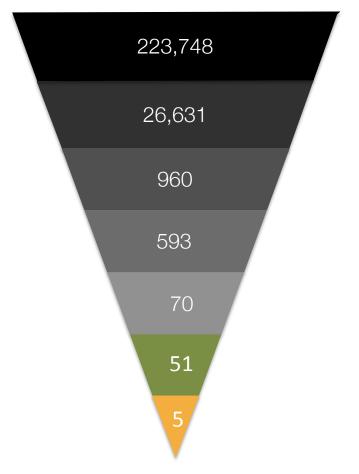
Leukemia (2014) 28, 1334–1340; doi:10.1038/leu.2013.365

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



Analysis example: SMZL in patient 7

Filter summary



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

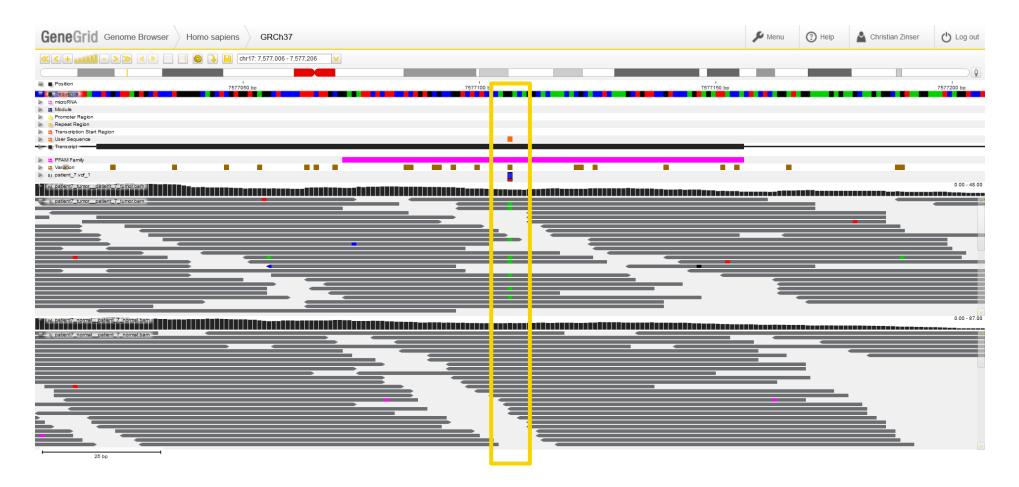


Filtering result

O Filter variants	-	≎	Variant			Known variant	Genomic feature	Gene symbol	Known gene	Effect prediction	Deleterious variant	Consensus variation	Quality	Coverage	Genoty: quality	gAF	exacAF	SIFT
Add column:			All	X	X	All \$	All	x	All \$	All	Yes \$	X	30 x	x	30 ×	X	.01 x	.05 x
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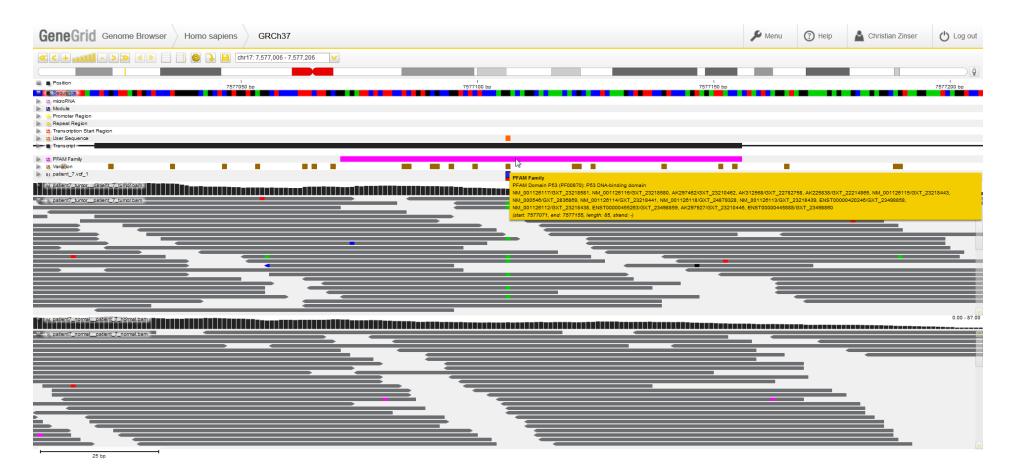
Visualization in the Genomatix Genome Browser



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



Visualization



The SNP is located in the P53 DNA-binding domain

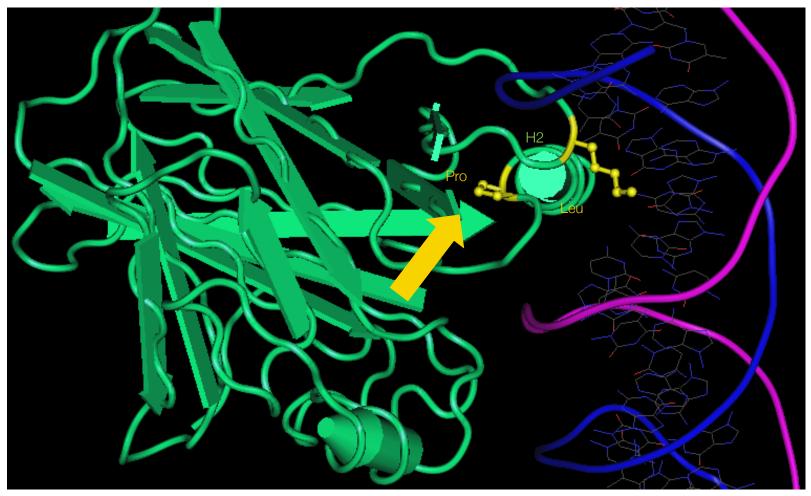


Visualization in the Genomatix Genome Browser

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P53 core domain in complex with DNA



Source: NCBI structure, MMDB ID: 106061

▶ the identified mutation could affect DNA binding or DNA affinity