International course: Training on strategies to foster solutions of undiagnosed rare disease cases

Polyweb : a Framework to analyse resequencing data

Patrick Nitschké

UNIVERSITÉ PARIS DESCARTES

imagine
INSTITUT DES MALADIES GÉNÉTIQUES

EUROPEAN JOINT PROGRAMME RARE DISEASES

Organised by National Centre for Rare Disease, Istituto Superiore di Sanità, Rome (Italy), April 27-29, 2020

TEAM

Patrick Nitschké
Technical manager

Jean-Philippe Jais
Scientific advisor

Bioinformatic

Biostatistic

Marc Bras
Study ingeneer

Cécile Masson
Study ingeneer

Cécile Fourrage
Research ingeneer

Fréderic Tores
Study ingeneer

Nicolas Cagnard
Study ingeneer

Quentin Brandao
Internship student

Emmanuelle Ollivier
Research ingeneer

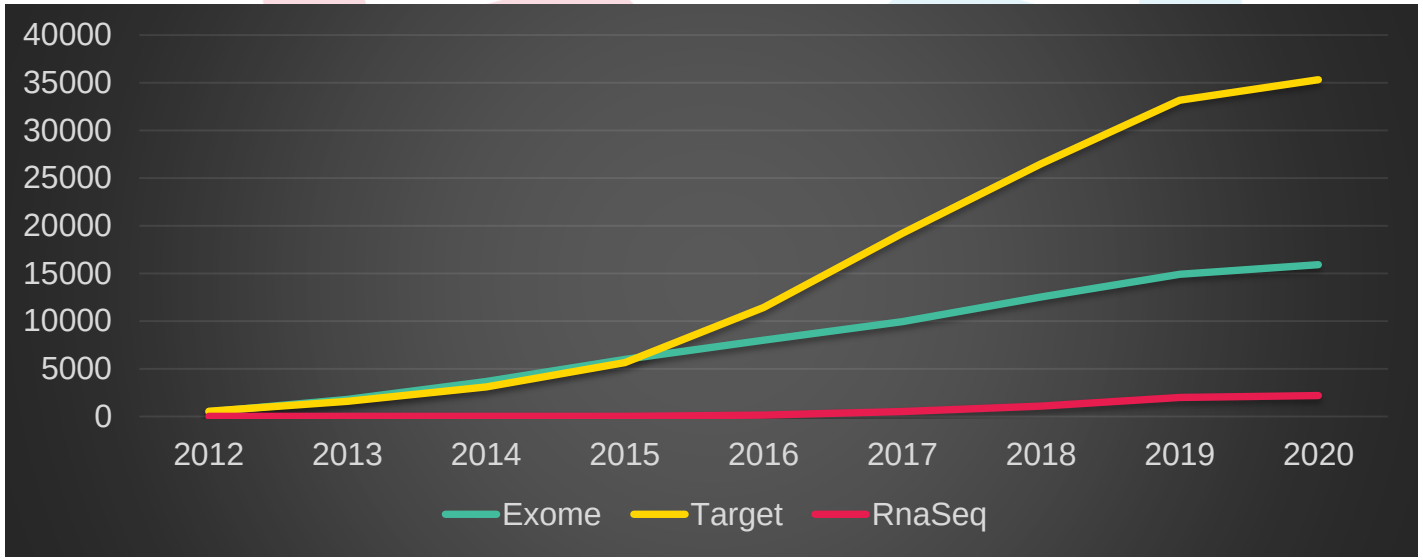
Jean-Marc Plaza
Study ingeneer

Fabienne Jabot-Hanin
Research ingeneer

Funded by the European Union
GA n°825575

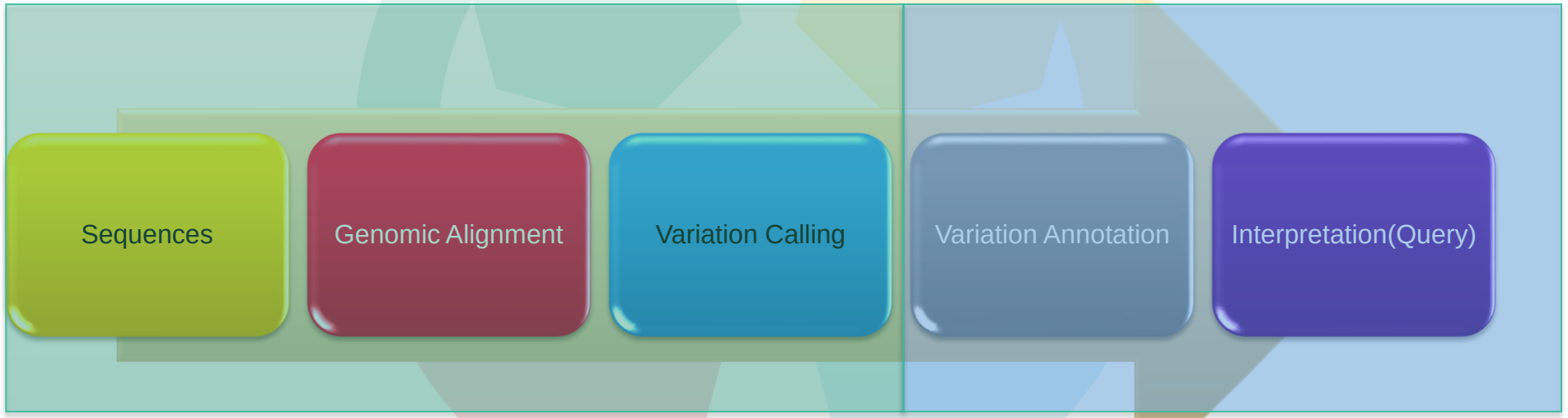
Sequencing project

	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Exomes	500	1300	1860	2325	2029	1945	2567	2405	1000	15932
Genomes				35	100(30)	225	124	228	405	1147
Target	556	1036	1519	2542	5764	7808	7257	6707	2354	33189
RnaSeq	-	-	-	-	151	370	573	913	200	2207



Funded by the European Union GA n°825575

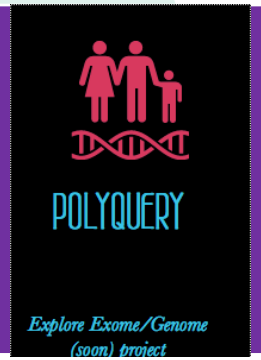
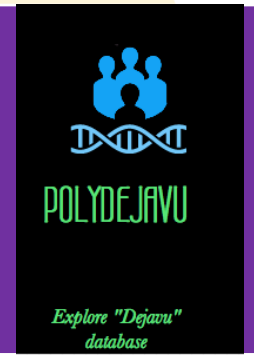
Target resequencing Pipeline



Funded by the European Union GA n°825575

Polyweb

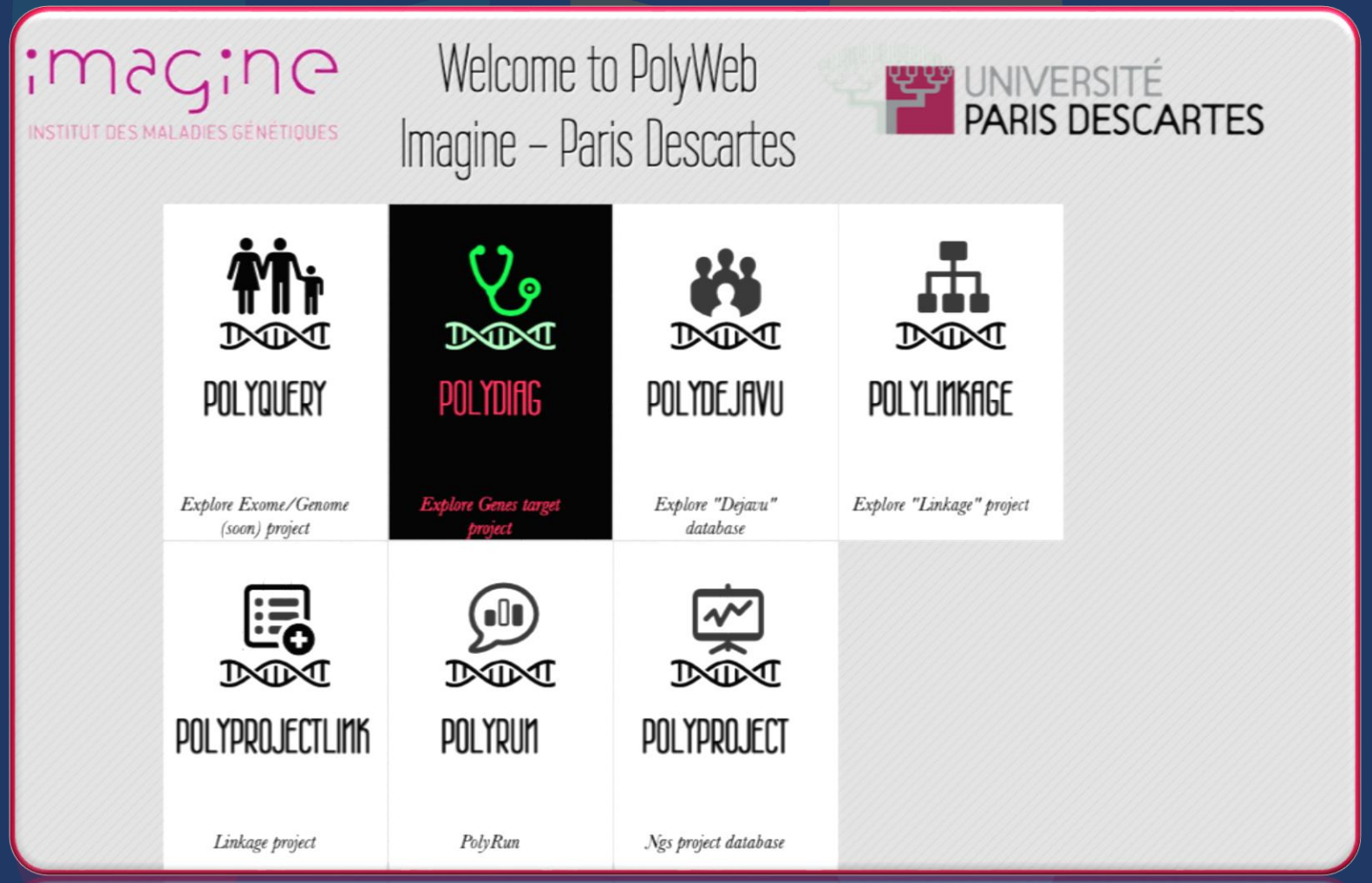
EUROPEAN JOINT PROGRAMME
RARE DISEASES

			
Project Type	Exomes and Full Genomes	Panels of genes	Variants Data Base
Objective:	Identification of new genes of interest related to a pathology ➔ Approach by gene	Identification of causal mutations ➔ Approach by patient	Query on all variants encounter ed in PolyWeb projects
Purpose	Research	Diagnostic	Minning

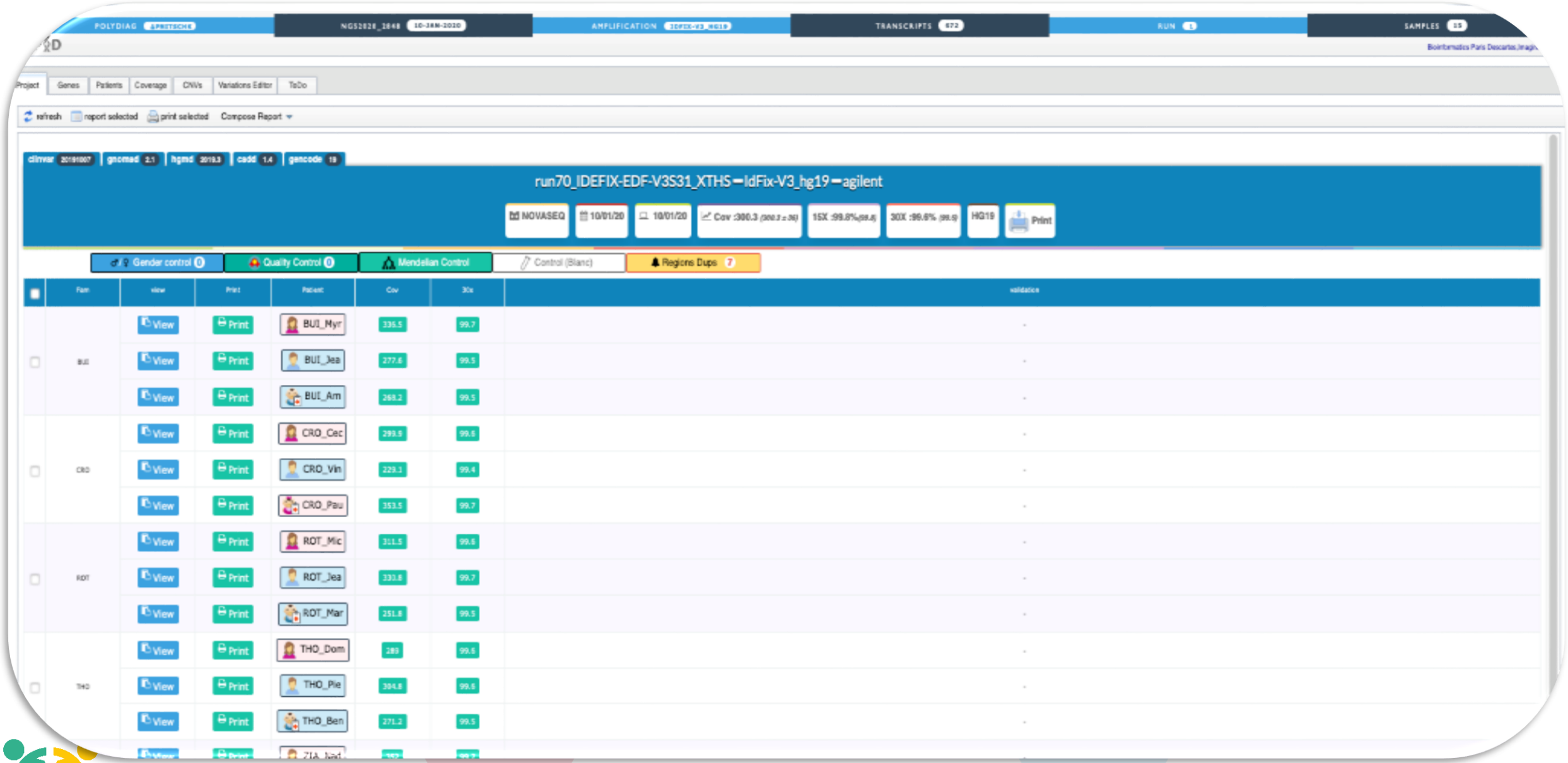
Déjà VU : 1500-16 000 – 35 000- 51 170 595

Funded by the European Union GA n°825575

PolyDiag

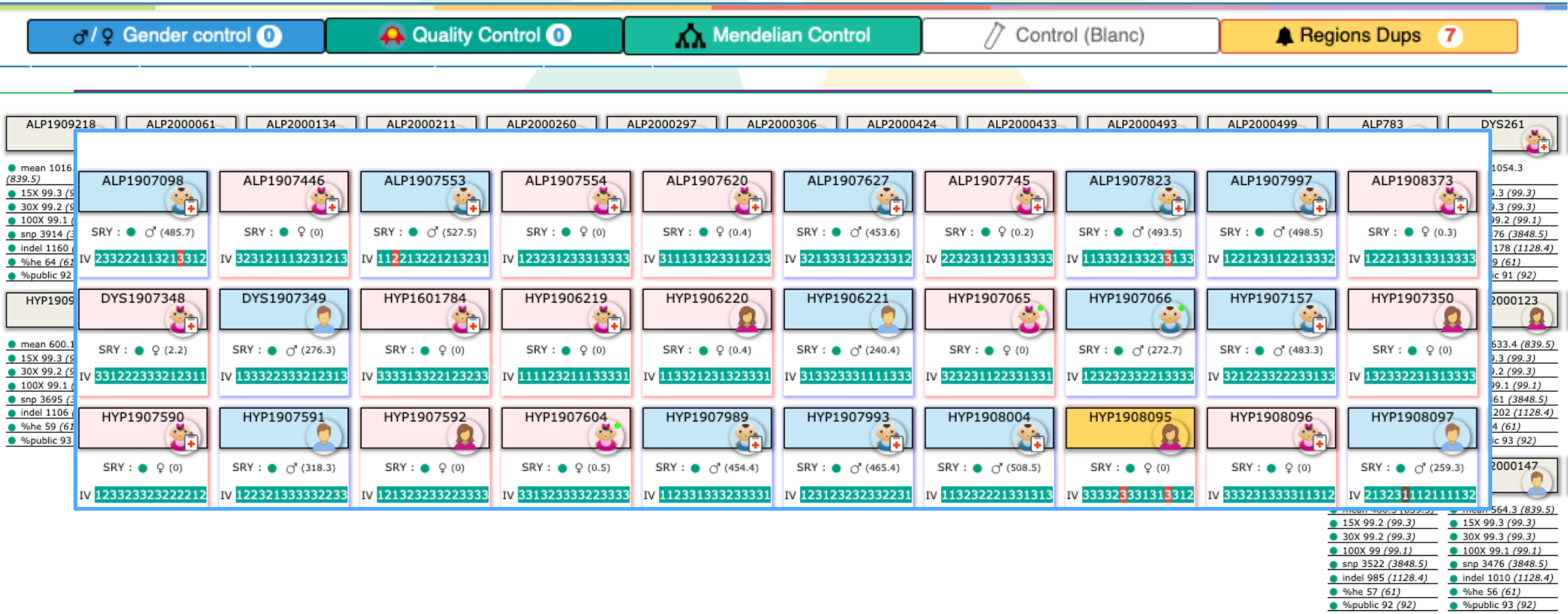


EUROPEAN JOINT PROGRAMME
RARE DISEASES



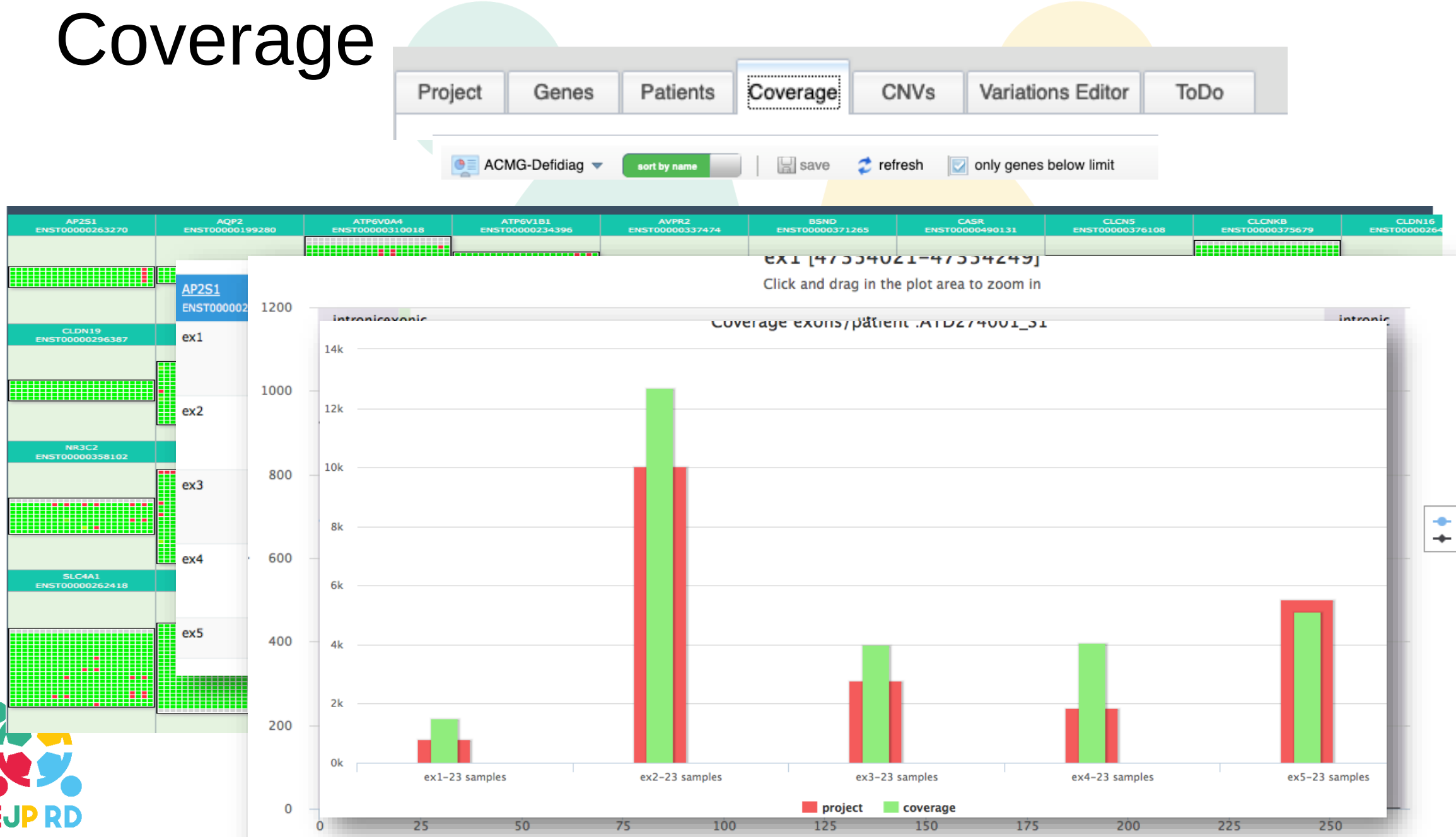
Funded by the European Union
GA n°825575

Quality Control

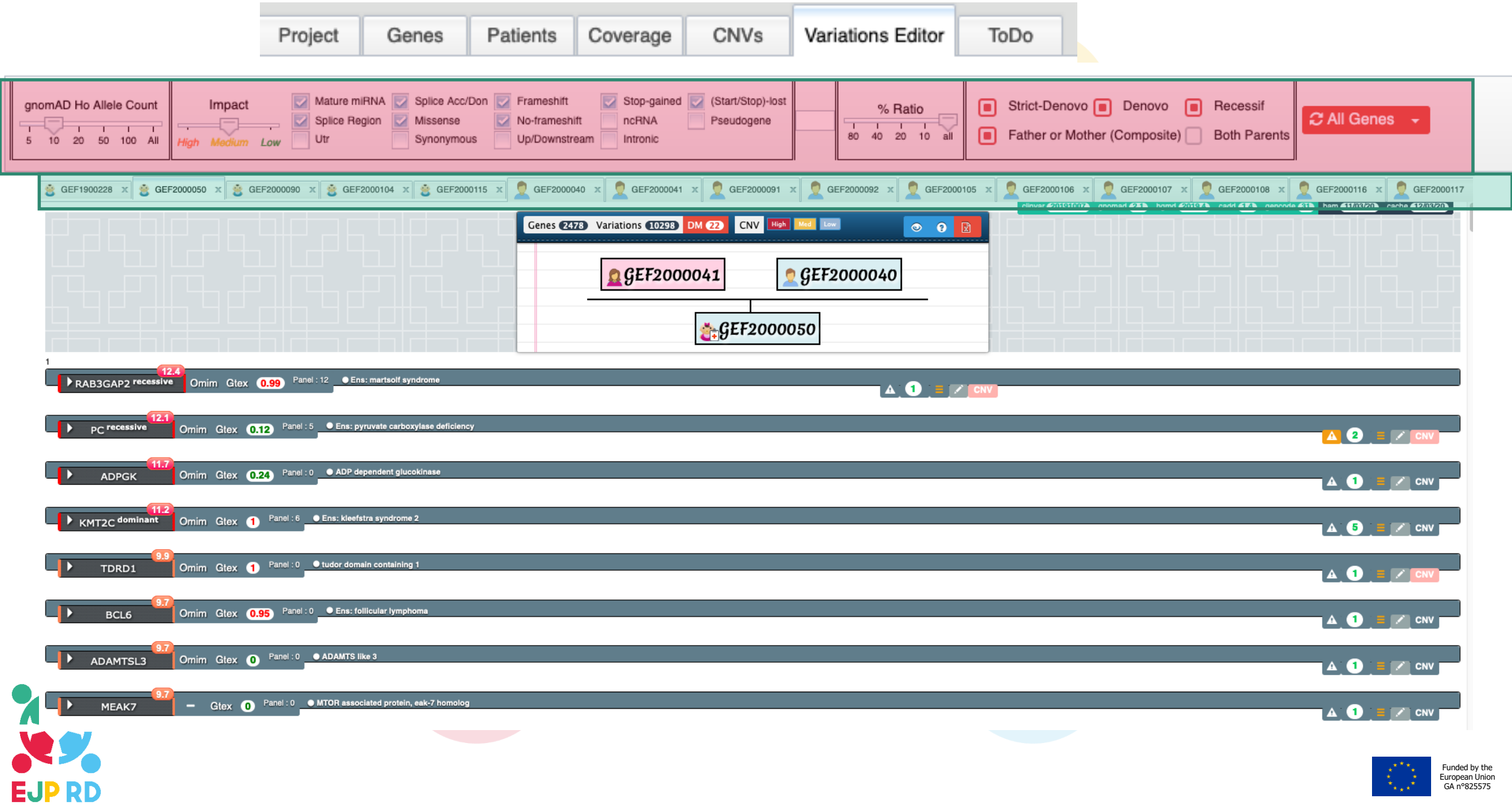


Funded by the European Union GA n°825575

Coverage

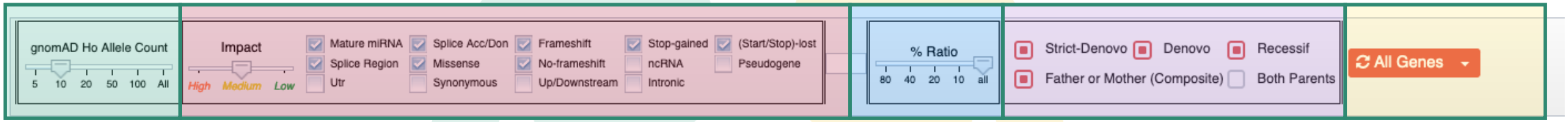


Funded by the European Union GA n°825575



Funded by the European Union GA n°825575

Variation filtering



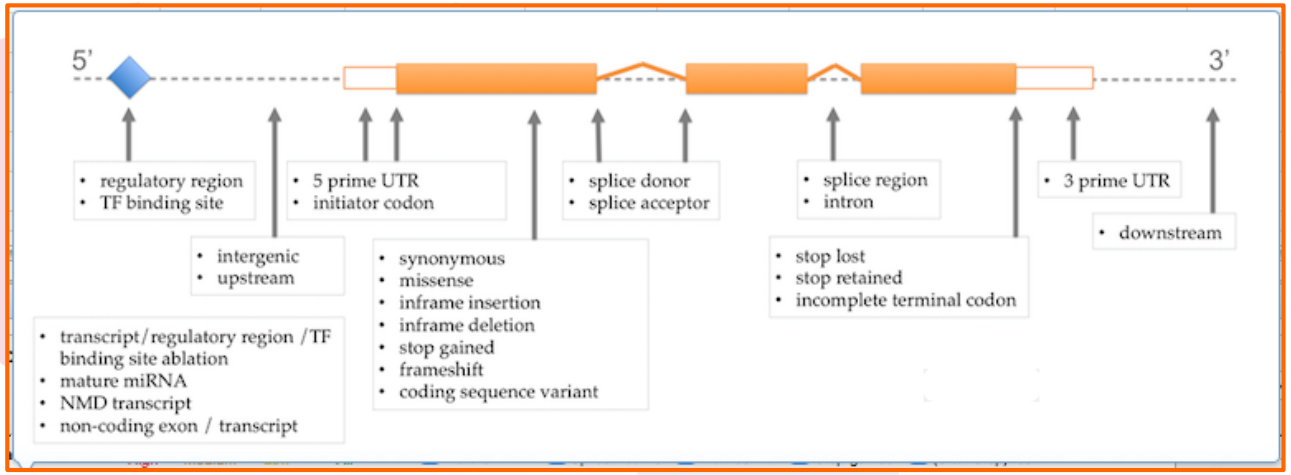
1- Frequency base on gnomad “homozygous allele count”

2-Impact

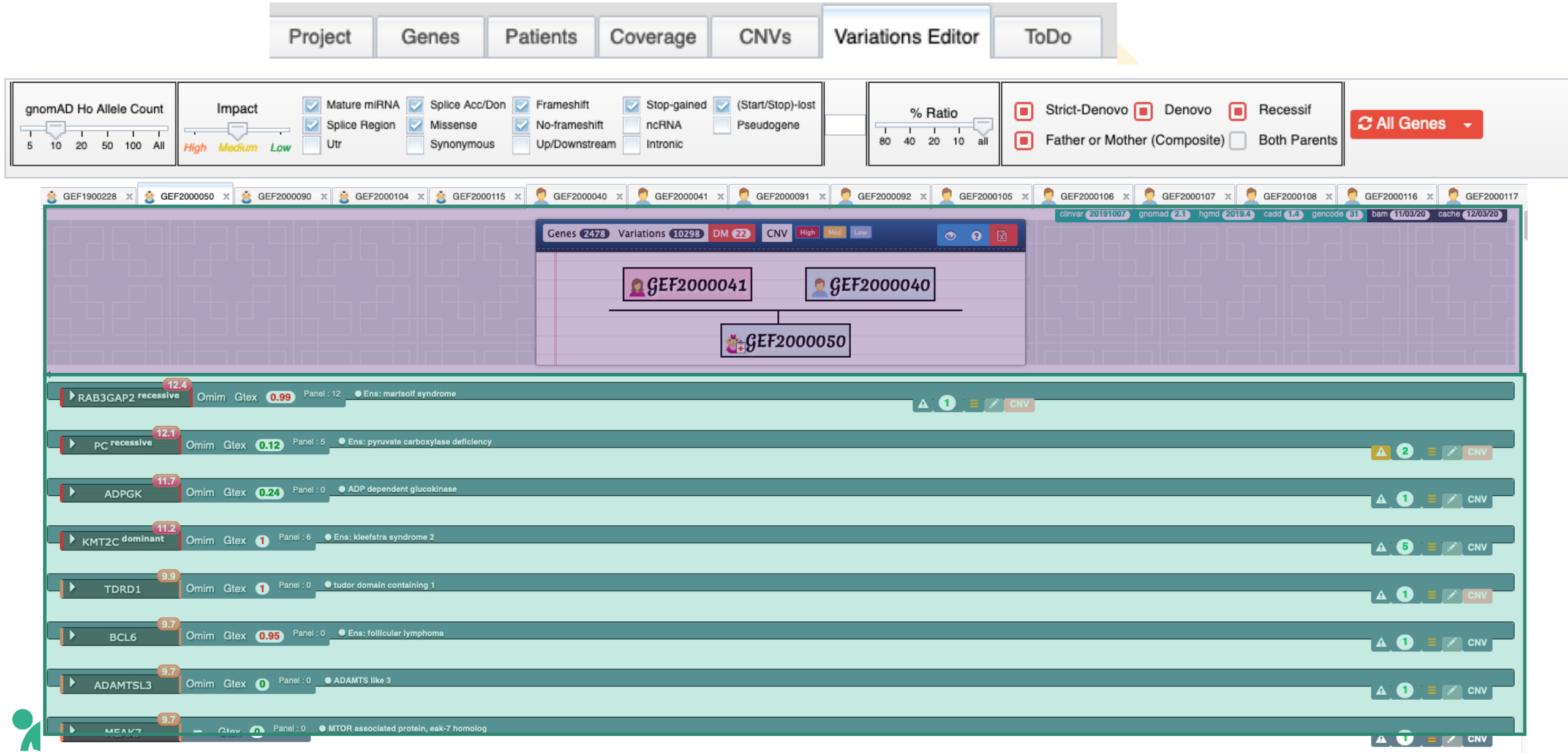
3-Allelique Ratio

4- Transmission Mode

5- Gene List

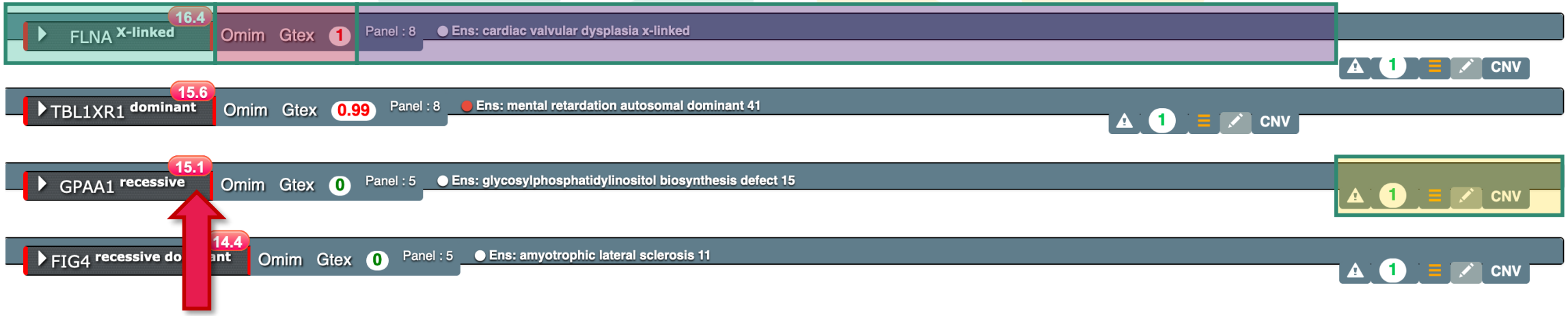


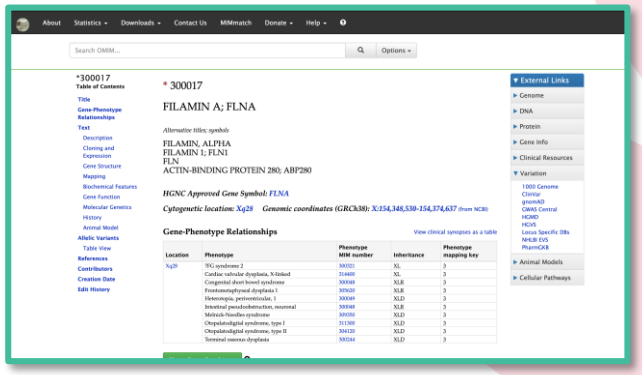
Funded by the European Union
GA n°825575



Funded by the European Union GA n°825575

Gene Informations panel





Funded by the European Union GA n°825575

Score

Variation

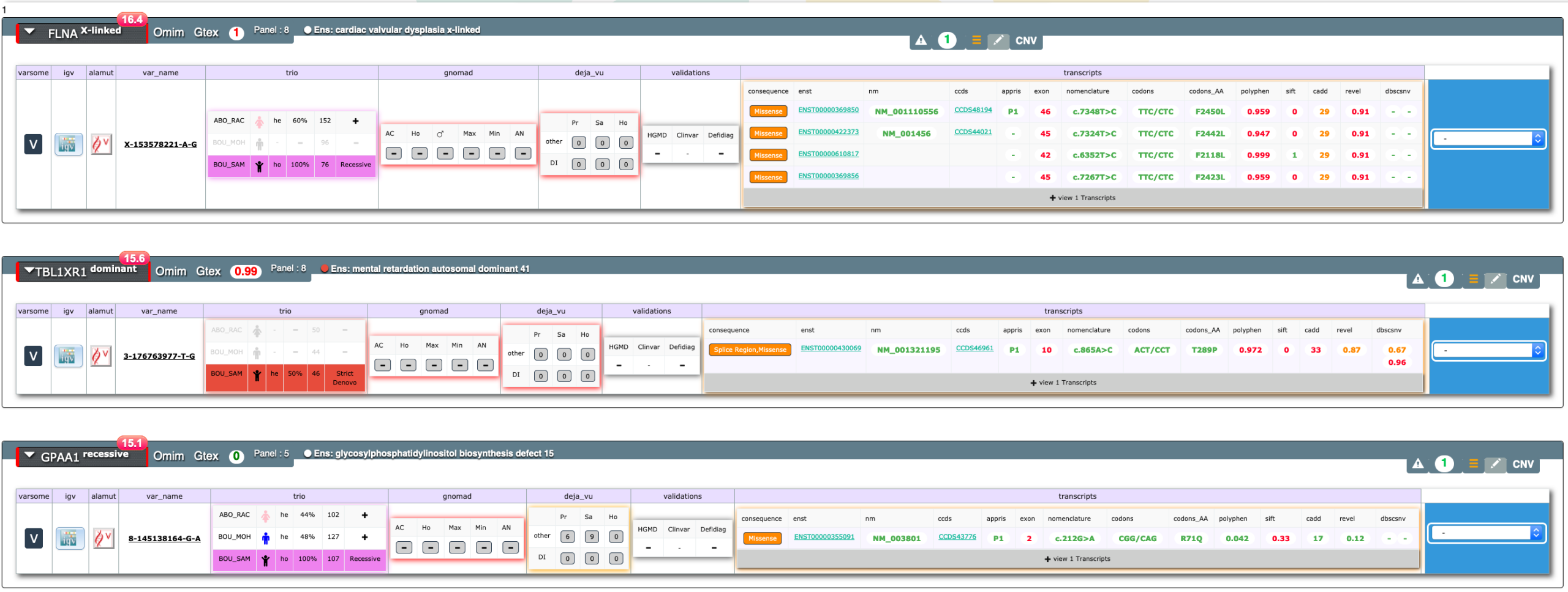
- Transmission
- Frequency public + dejavu
- Clinvar + local DB + (HGMD)
- Impact
- Prediction Score

Gene

- Phenotypes
  - Panels (DI: Imagine+PanelApp+SysID+Decipher)
  - Pli

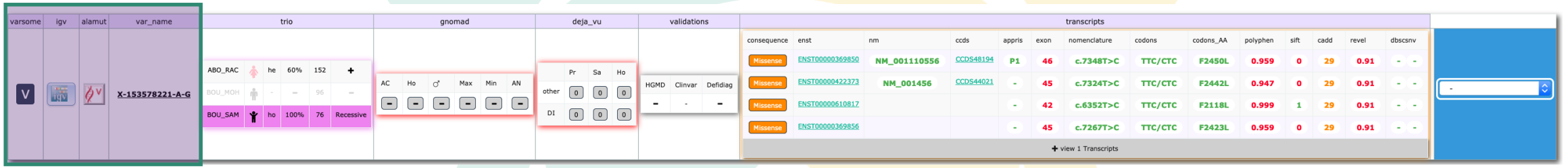
Funded by the European Union GA n°825575

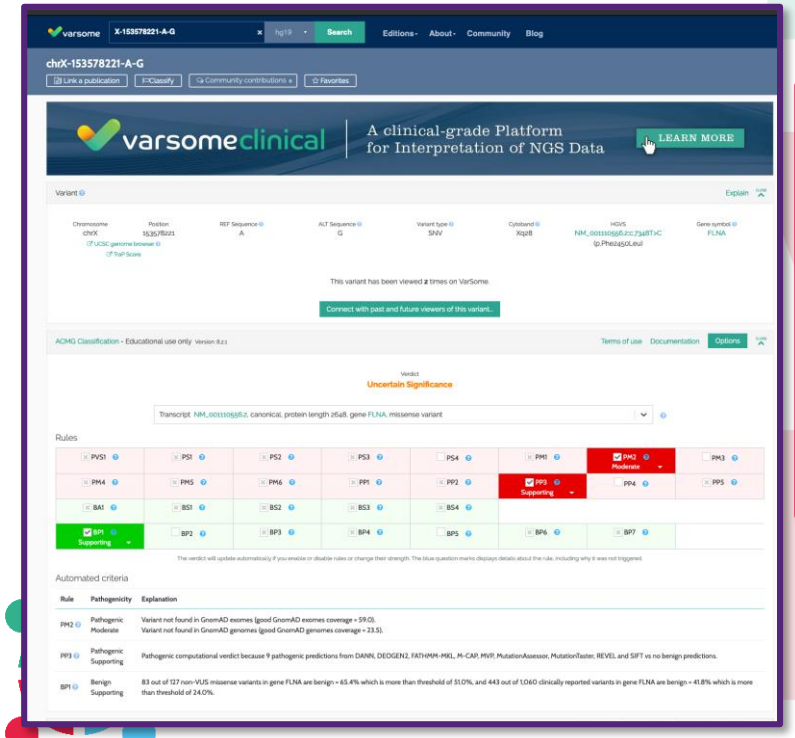
Variations Panels

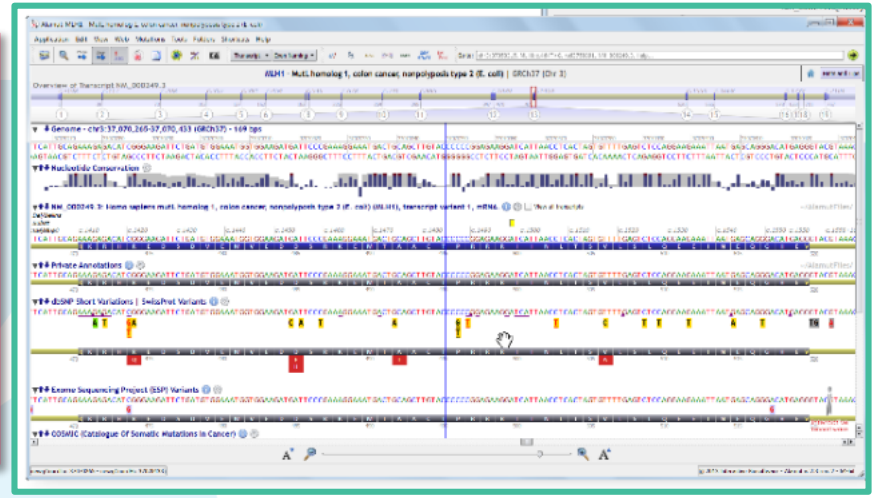


Funded by the European Union GA n°825575

Variations Panels : External Viewer

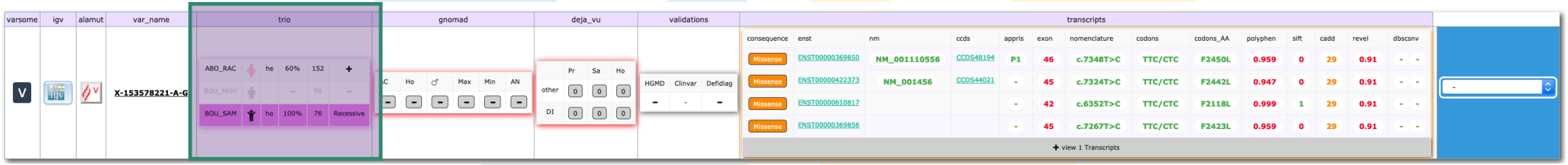






Funded by the European Union
GA n°825575

Variations Panel : Transmission Mode



Recessive

GEF2000107		he	45%	131	+
GEF2000108		he	52%	102	+
GEF1900228		ho	99%	135	Recessive

Denovo

GEF2000107		-	-	123	-
GEF2000108		-	-	95	-
GEF1900228		ho	94%	17	Denovo

Mosaic Parental

835_M		he	13%	149	+
835_P		-	-	129	-
835		he	50%	119	mosaic mother

MIL_Mam		he	30%	129	+
MIL_Pap		he	35%	160	+
MIL_Pil		he	33%	118	

Compound

GEF2000107		he	49%	179	+
GEF2000108		-	-	195	-
GEF1900228		he	53%	143	

GEF2000107		-	-	164	-
GEF2000108		he	52%	191	+
GEF1900228		he	46%	175	

Strict-Denovo

NCR4635_BIEM_F		-	-	62	-
NCR4634_BIEM_JP		-	-	45	-
NCR4452_BIEM_PH		he	55%	63	Strict Denovo

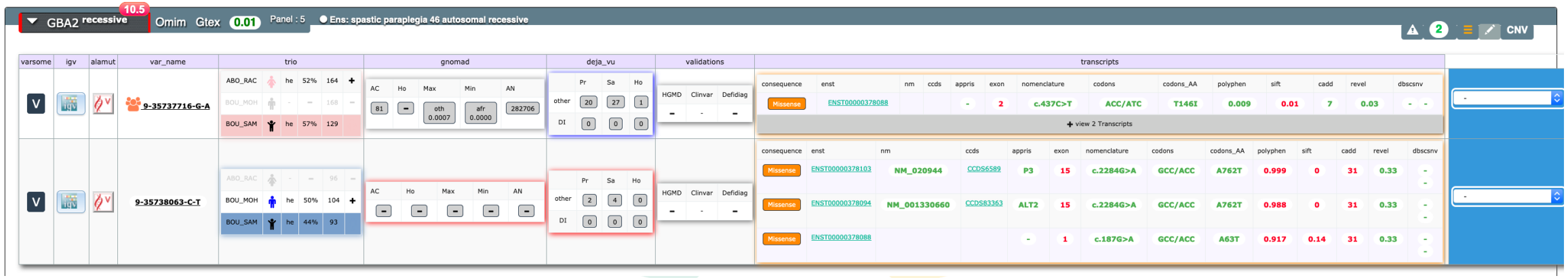
Unisomy Uniparental

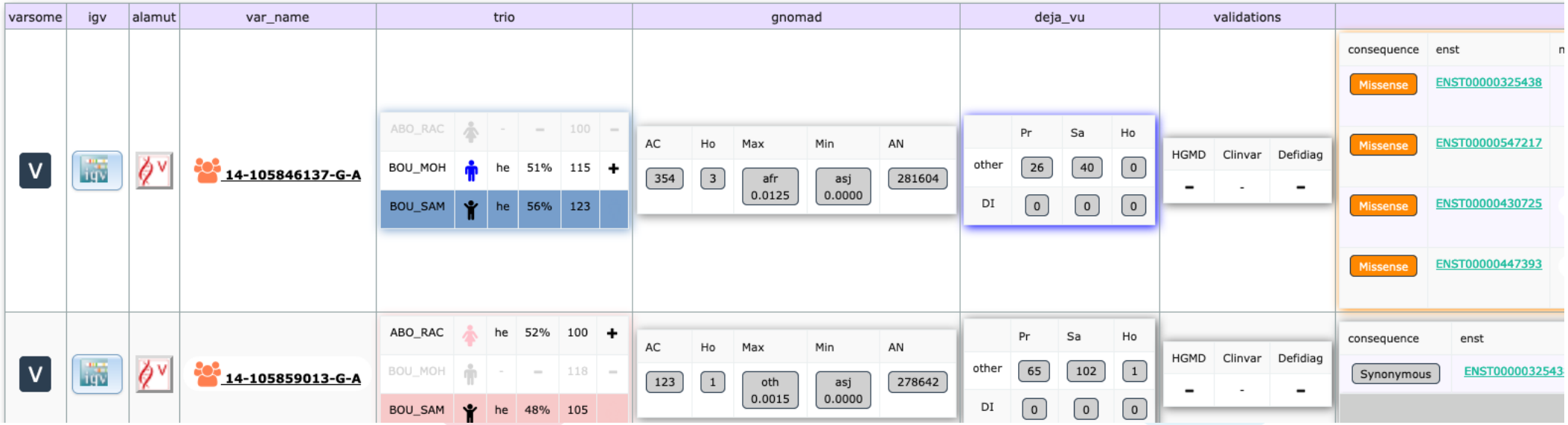
MIL_Mam		he	44%	75	+
MIL_Pap		-	-	81	-
MIL_Pil		ho	100%	49	Uniparental

EJP RD

Funded by the European Union
GA n°825575

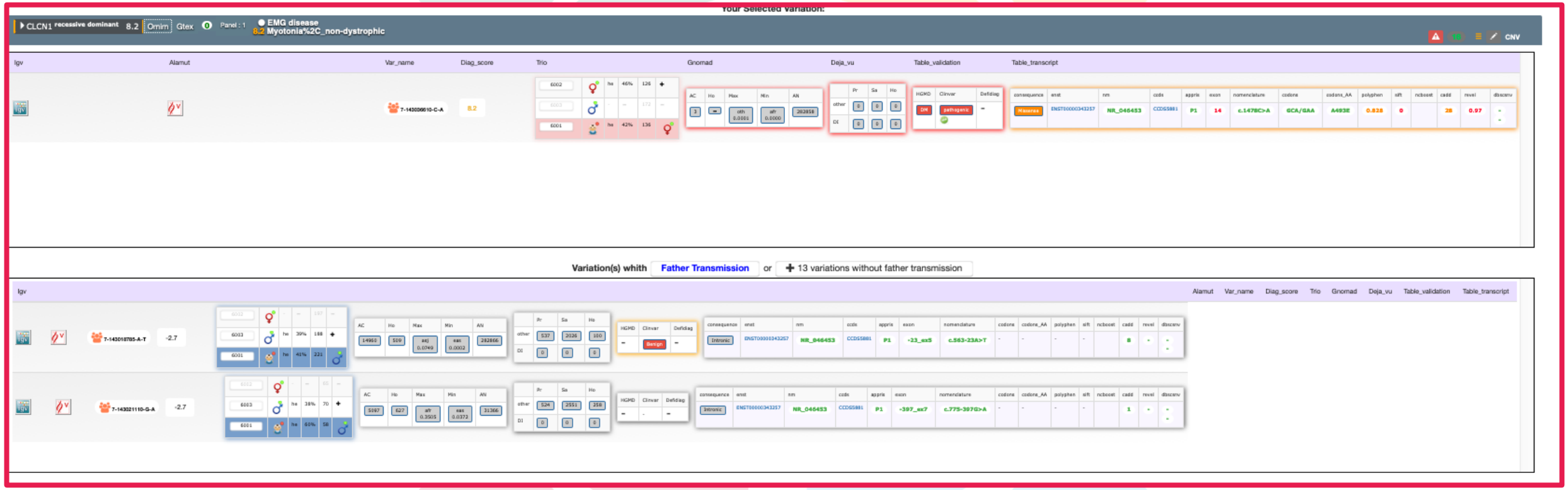
Heterozygous Compound





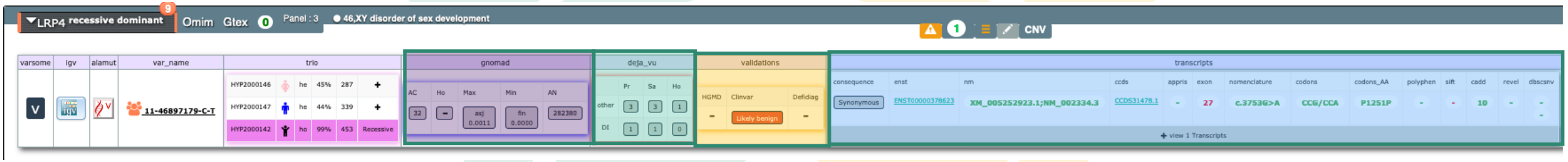
Funded by the European Union
GA n°825575

Heterozygous Coumpound



Funded by the European Union GA n°825575

Variation Panel



AC	Ho	Max	Min	AN
61	-	nfe 0.0004	afr 0.0000	276422

	Pr	Sa	Ho
other	1	1	0
DI	0	0	0

HGMD	Clinvar	Defidiag
DM?	Benign	-

consequence	enst	nm	ccds	appris	exon	nomenclature	codons	codons_AA	polyphen	sift	cadd	revel	dbscsnv
Missense	ENST00000391909		CCDS12691	P1	4	c.574G>A	GAC/AAC	D192N	0.066	0.55	14	0.42	- -

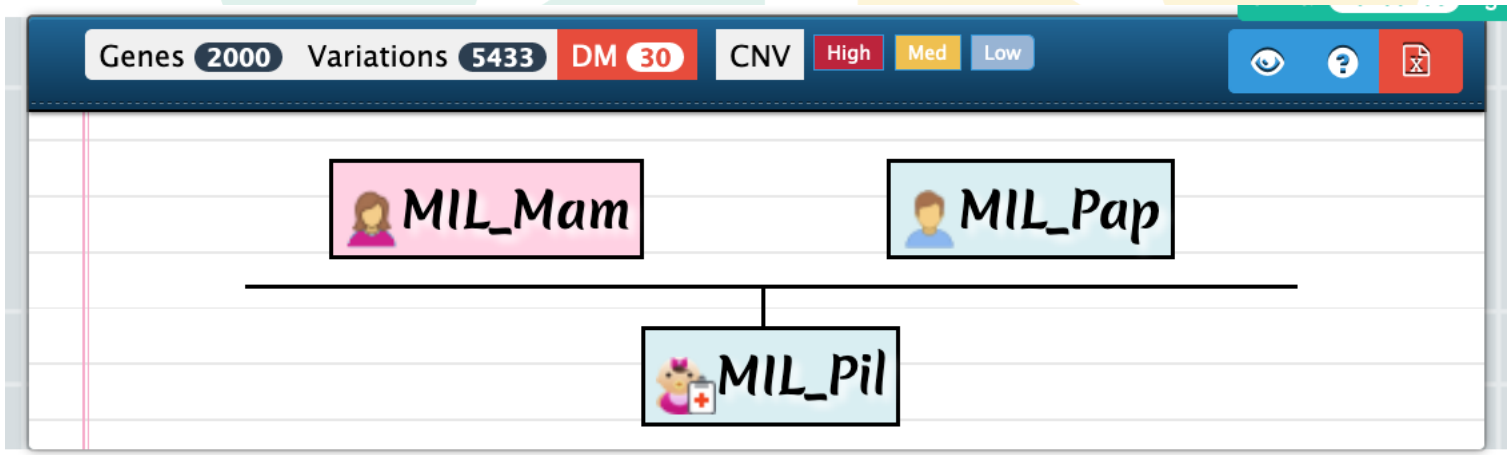
+ view 1 Transcripts

Funded by the European Union GA n°825575

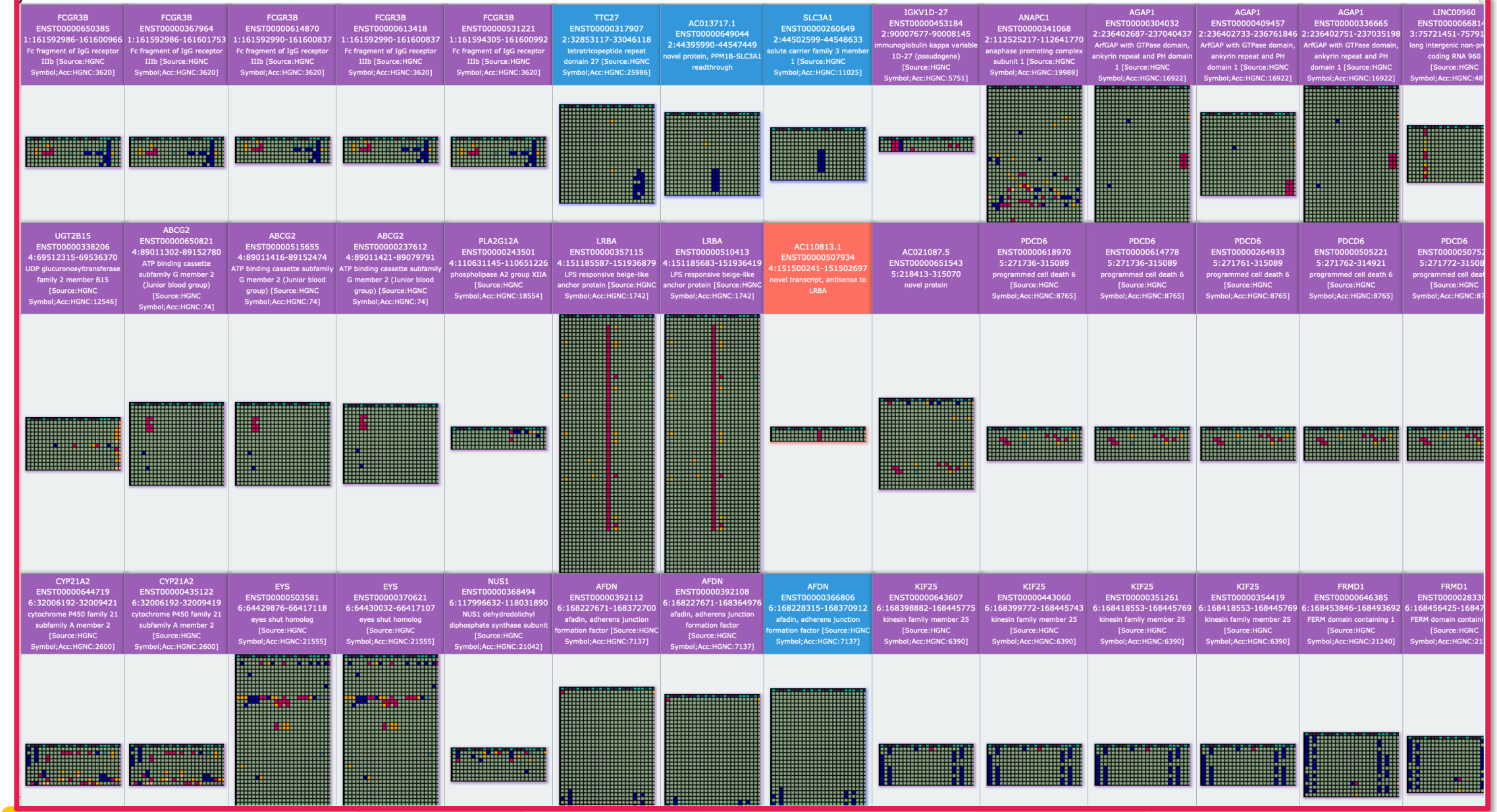
Structural Variations CNV

Part 1 : Capture

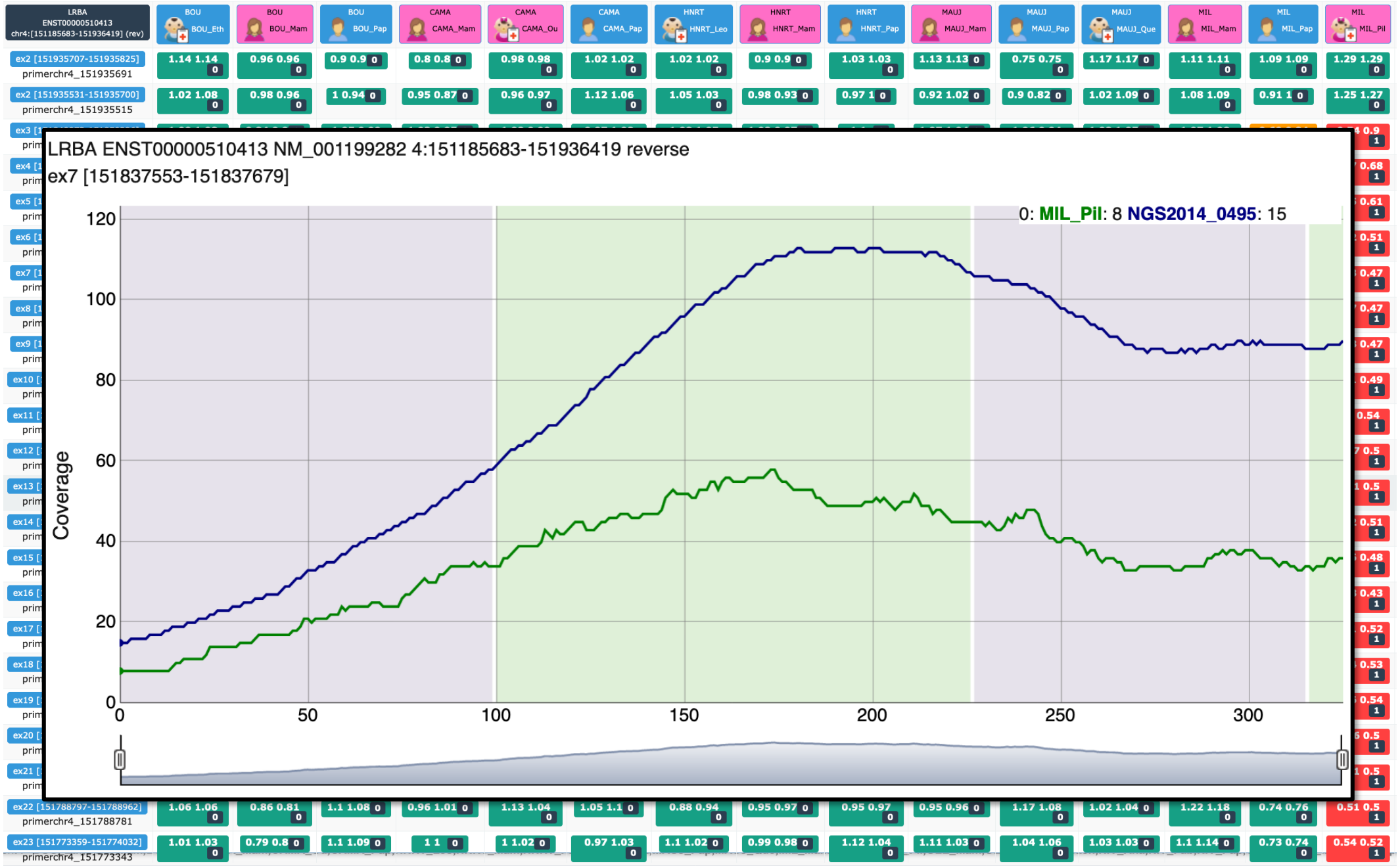
CNV (capture, exome and Panel)



Funded by the European Union
GA n°825575

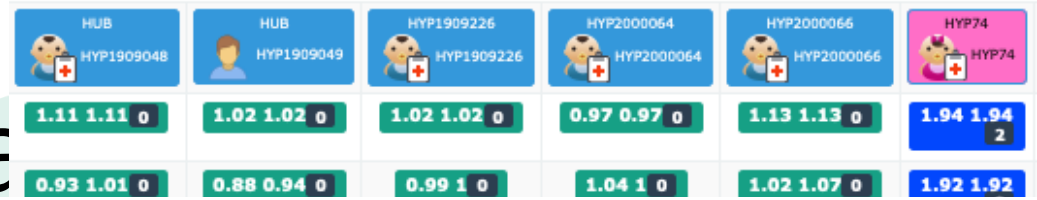


Funded by the European Union
GA n°825575



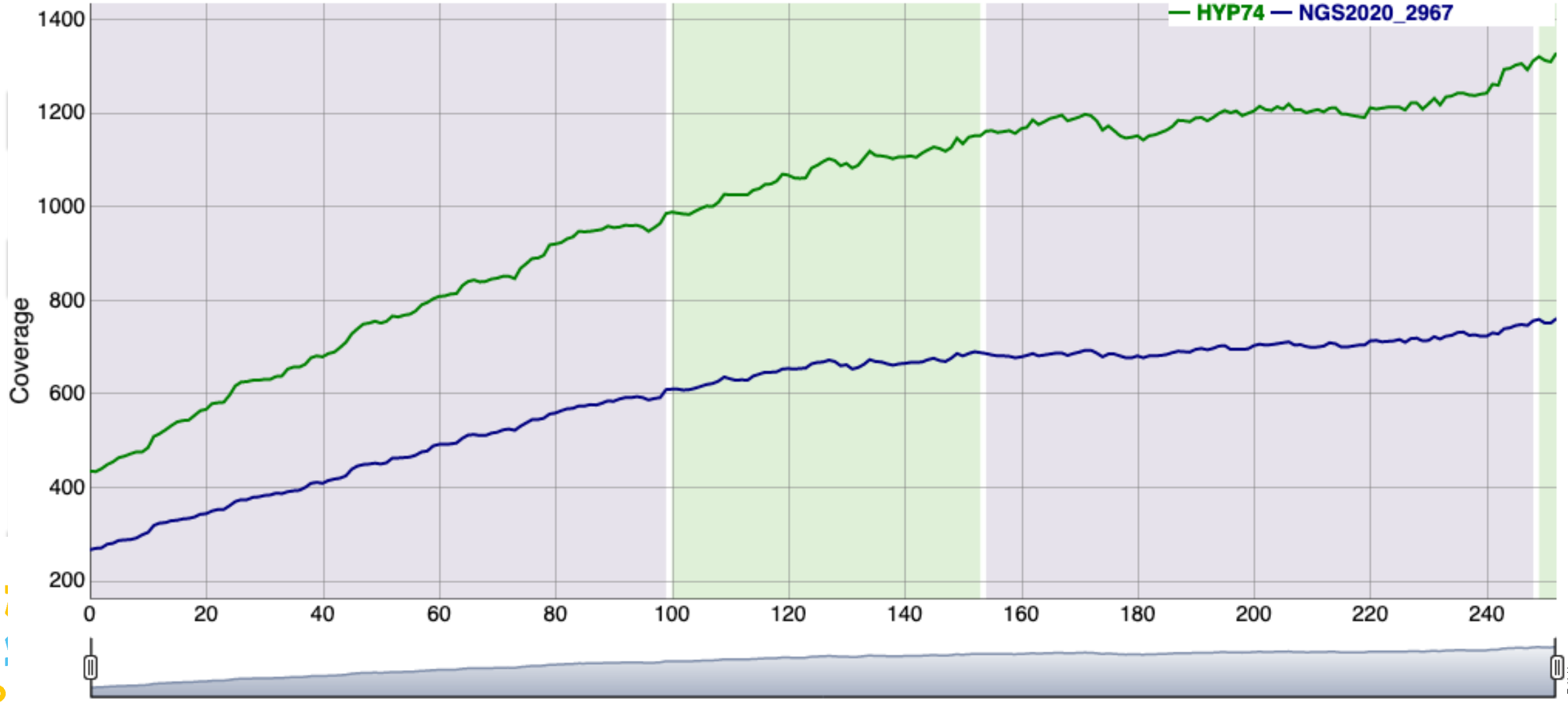
Funded by the European Union
GA n°825575

Structural Va



COL4A5 ENST00000328300 XM_005262070.1;NM_033380.2 X:107683112-107940771 forward

ex14 [107823763-107823816]



ded by the
pean Union
n°825575

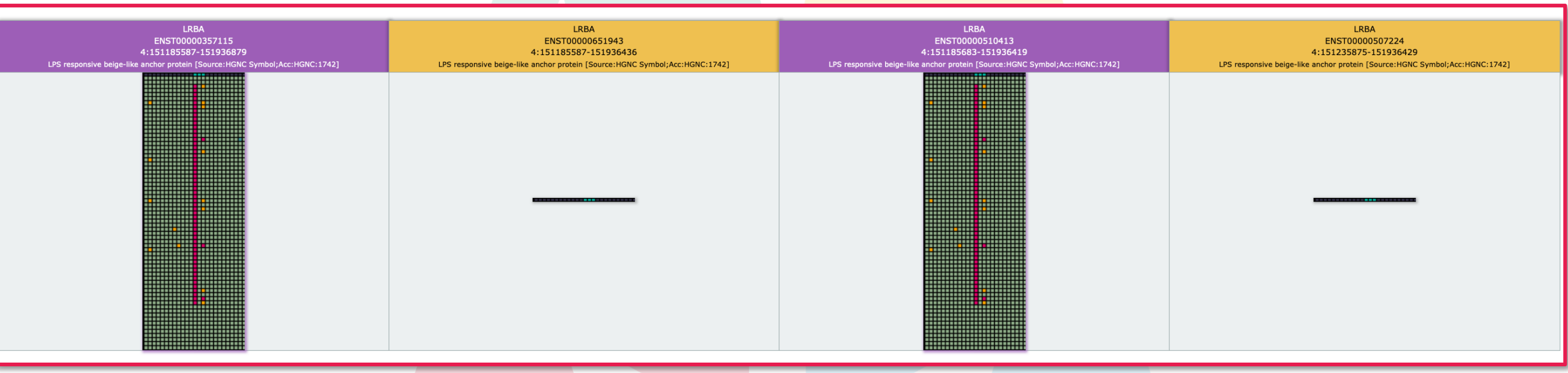
1

TRPM3 15 Omim Gtex 0.03 Panel : 2 Autism spectrum disorder 2 CNV

LRBA recessive 14.4 Omim Gtex 0 Panel : 2 Antibody deficiency, primary 49 CNV

FKRP recessive 12.6 Omim Gtex 0 Panel : 8 Cardiomyopathy, dilated 4 CNV

MAB21L2 recessive dominant 12.1 Omim Gtex 0.44 Panel : 9 Bilateral anophthalmia, intellectual disability & rhizomelic skeletal dysplasia 2 CNV



EJP RD

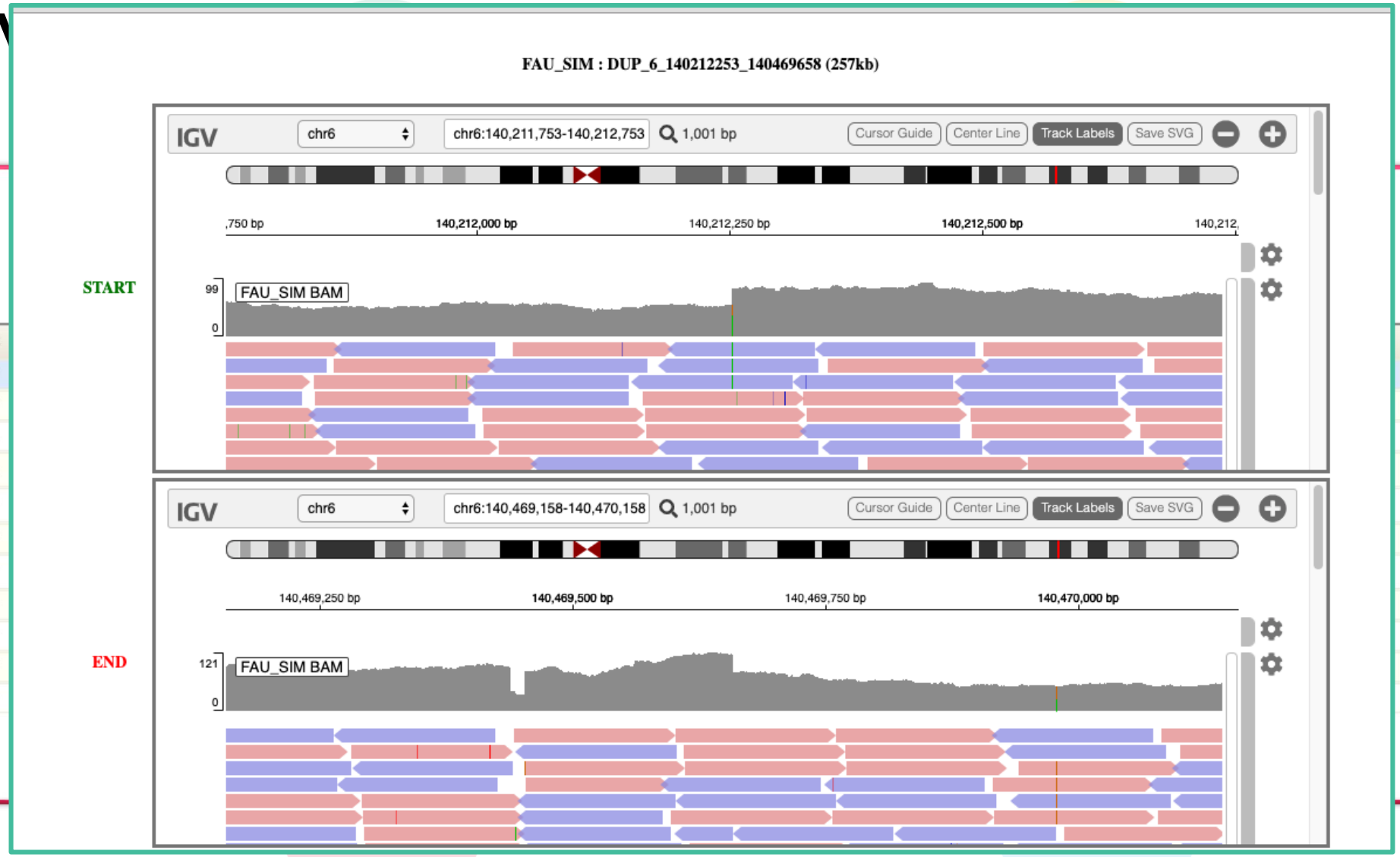
Funded by the European Union GA n°825575

Structural Variations CNV

Part 2 : Genome

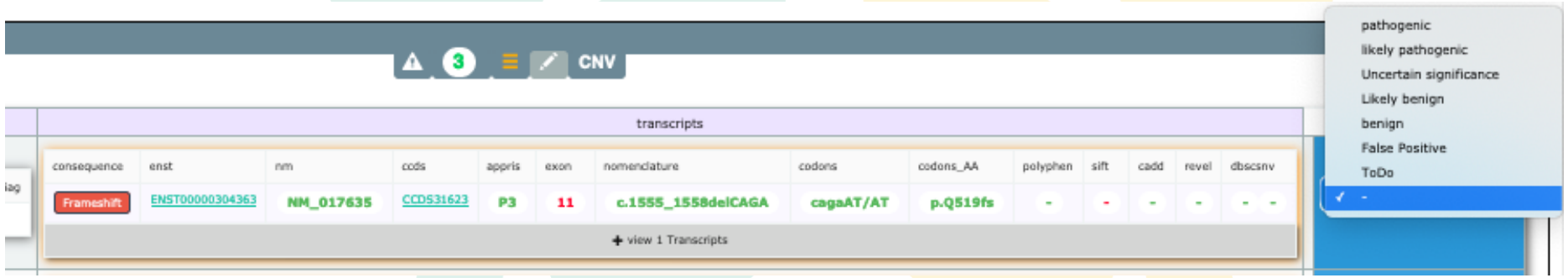
EUROPEAN JOINT PROGRAMME
RARE DISEASES

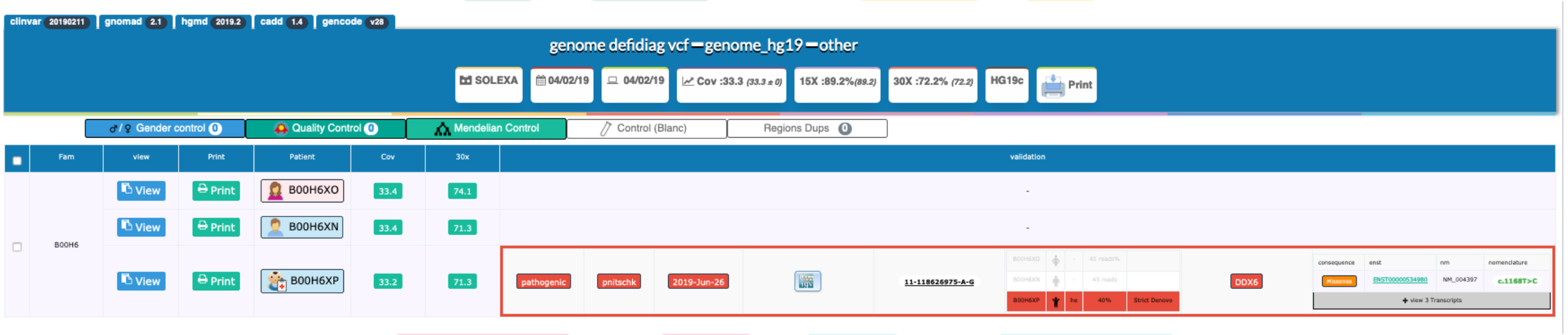
CNV



Funded by the European Union
GA n°825575

Validations :





Funded by the European Union GA n°825575

Rep

Patient Summary 2/2/2015

name	
identifiant	IMB
Validation	-

Run Summary

coverage limit=30 padding=20 1/4

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56

Other detected Variations

impact: [splice region - splice donor/acceptor - non coding transcript - stop gained - stop/start lost - missense - frameshift - inframe insertion/deletion - mature miRNA -] frequence:[<=1%]

ADCK4 XM_005259275.1;XM_005259274;XM_005259273;XM_005259272;XM_005259271;NM_024876.3

gene	var_name	sanger	ngs	ratio	caller	genomique	transcript	exon	nomenclature	consequence	codons	codons_AA	freq	deja_vu	similar_projects	in_this_run	polyphen	sift
ADCK4	rs113871093	-	he(2116/2174)	50%	uni	19:41220518	ENST00000324464	2	c.20G>A	coding	GGC/GAC	G7D	0.0012	3:3	0:0	1/16	0.092	0.08

CD151

gene	var_name	sanger	ngs	ratio	caller	genomique	transcript	exon	nomenclature	consequence	codons	codons_AA	freq	deja_vu	similar_projects	in_this_run	polyphen	sift
CD151	rs116211118	-	he(1350/1348)	49%	uni	11:836418	ENST00000397420	4	c.252G>T	coding	AAG/AAT	K84N	0.0029	12:18	2:2	1/16	0.081	0.09

COQ6 NM_182476.2

gene	var_name	sanger	ngs	ratio	caller	genomique	transcript	exon	nomenclature	consequence	codons	codons_AA	freq	deja_vu	similar_projects	in_this_run	polyphen	sift
COQ6	rs61743884	-	he(793/874)	52%	uni	14:74417180	ENST00000334571	1	c.145G>T	coding	GCC/TCC	A49S	0.0060	8:13	2:2	1/16	0.417	0.28

EMP2 NM_001424.4

gene	var_name	sanger	ngs	ratio	caller	genomique	transcript	exon	nomenclature	consequence	codons	codons_AA	freq	deja_vu	similar_projects	in_this_run	polyphen	sift
EMP2	rs140529660	-	he(2057/1982)	49%	uni	16:10641541	ENST00000359543	-7_ex2	c.-1-7T>A	splicing	T/A		0.0063	11:19	8:12	1/16	-	-

TTC21B NM_024753.4

gene	var_name	sanger	ngs	ratio	caller	genomique	transcript	exon	nomenclature	consequence	codons	codons_AA	freq	deja_vu	similar_projects	in_this_run	polyphen	sift
TTC21B	2_166810196_A_ACGCTCGCC	-	ho(74/273)	78%	uni	2:166810196	ENST00000243344	1	c.19_20insGGCGAGCG	splicing frameshift	AAG/AGGCGA	K7RR	-	0:0	17:58	2/16	0	0

TP53 NM_001126114.2;NM_001276696.1

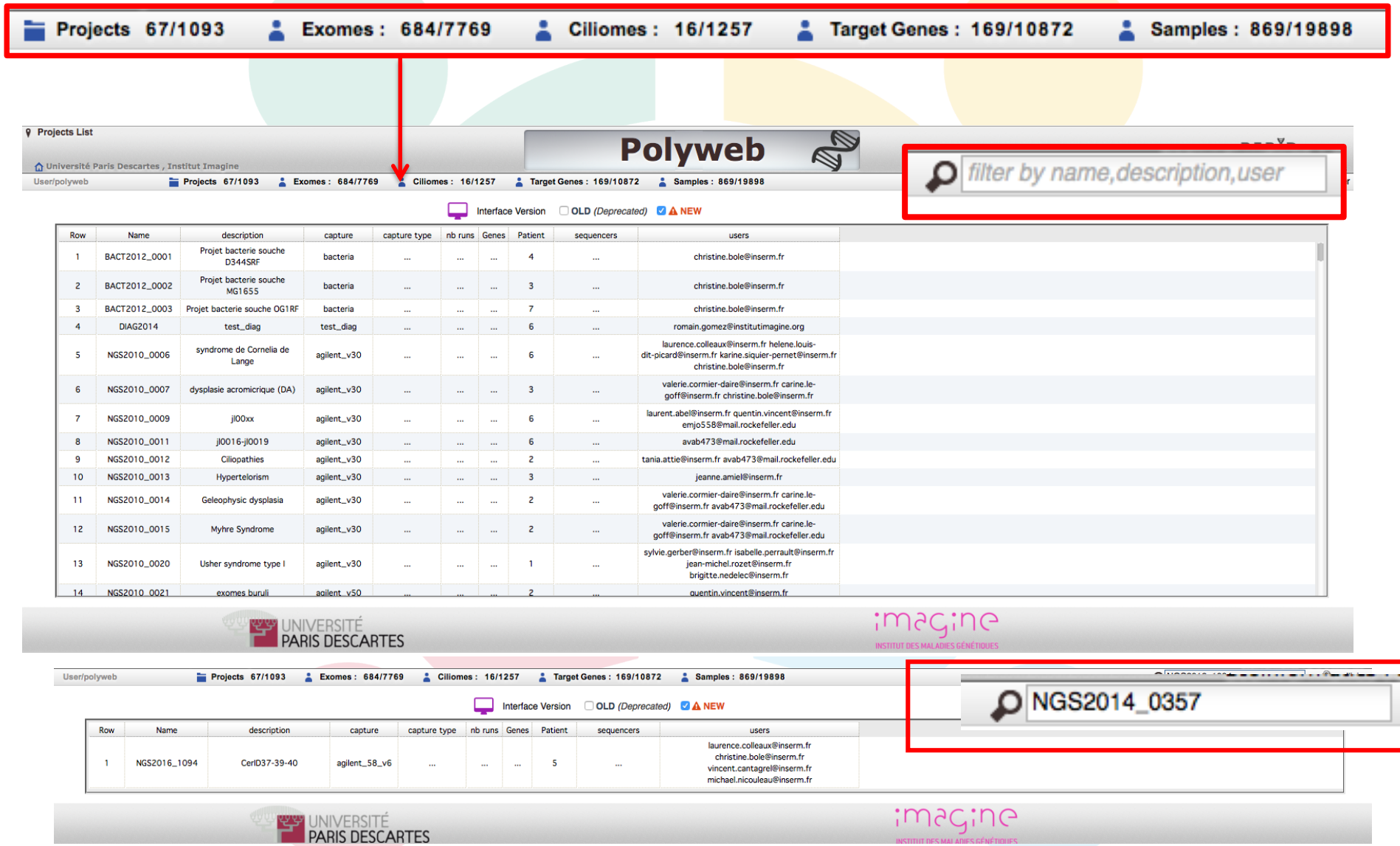
gene	var_name	sanger	ngs	ratio	genomique	transcript	exon	nomenclature	consequence	codons	codons_AA	freq	deja_vu	similar_projects	in_this_project	polyphen	sift
TP53	rs1042522	confirmed (he)	ho(1/401)	99%	17:7579472	ENST00000420246	4	c.215C>G	coding	CCC/CGC	P72R	0.63	367:4081	0:0	5/6	0.189	0.55

Funded by the European Union GA n°825575

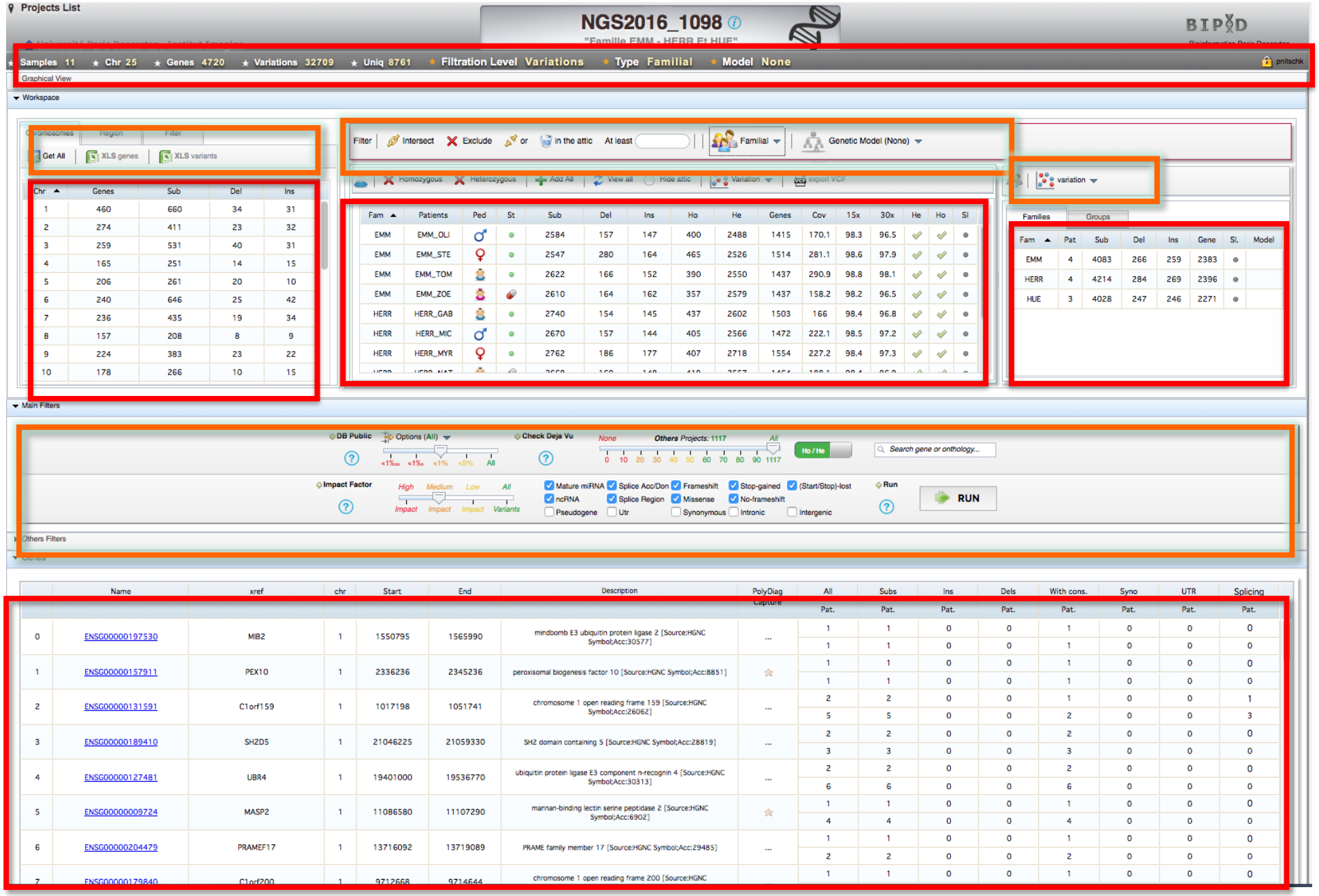
PolyQuery

EUROPEAN JOINT PROGRAMME
RARE DISEASES

PolyQuery: the home page

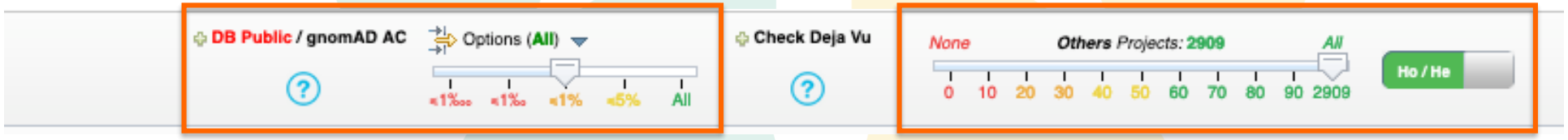


Funded by the European Union
GA n°825575

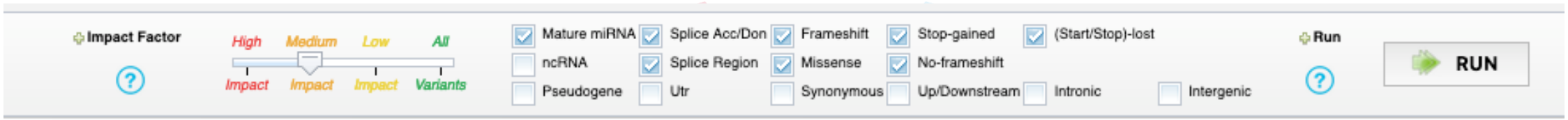


Funded by the European Union GA n°825575

Variations Filtering : Frequency

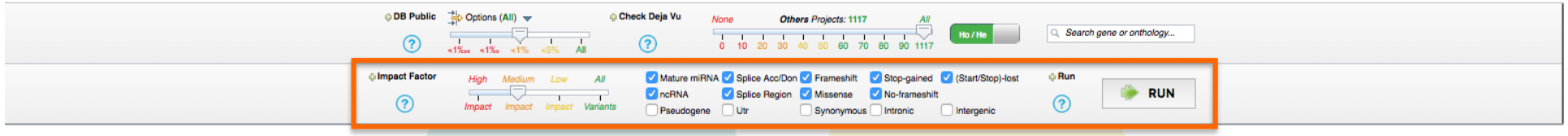


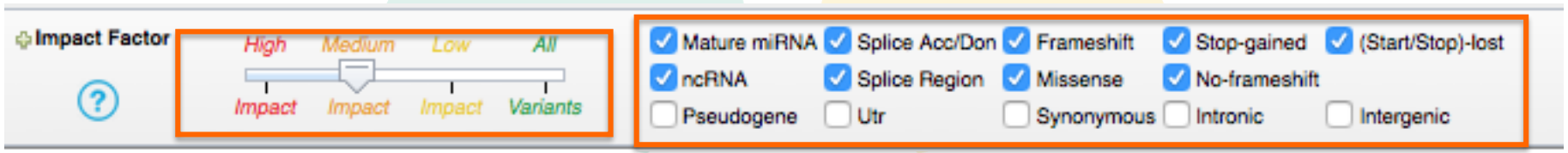
Variations Filtering :Annotation Impact

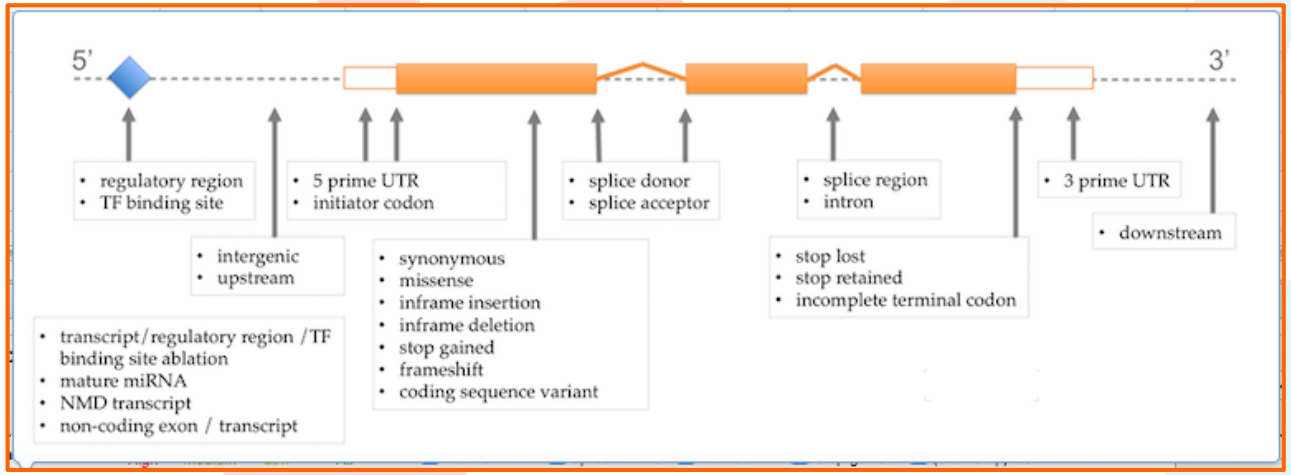


Funded by the European Union GA n°825575

Variant Annotation

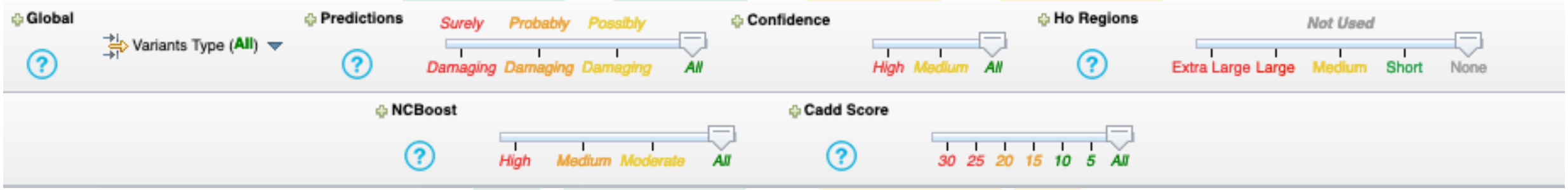






Funded by the European Union
GA n°825575

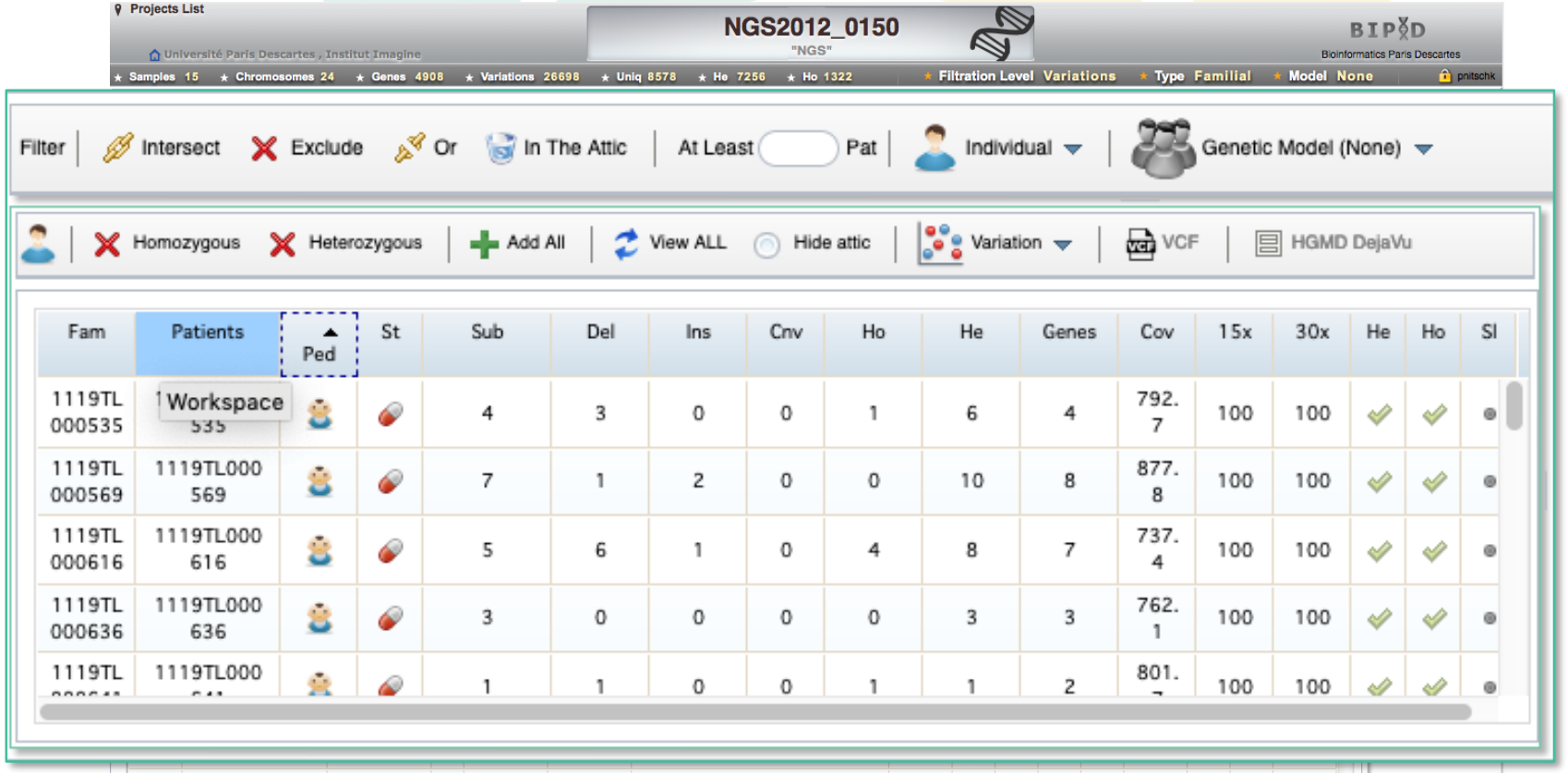
More variations Filter



Predictions Score	Sift
	Polyphen
	CADD
	NCBoost
Variant Quality	
Homozygous Region	

Funded by the European Union GA n°825575

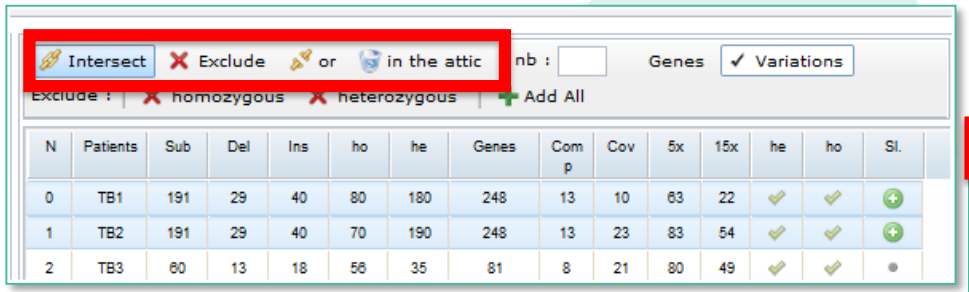
Samples Queries



Funded by the European Union GA n°825575

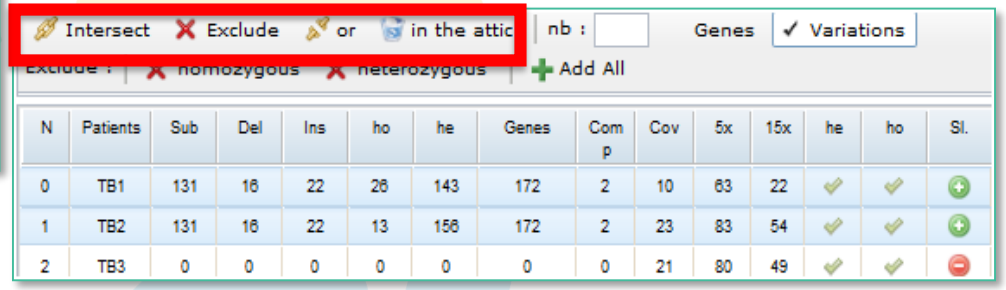
Query By Sample : Variation Level

Same Variation 2 patients



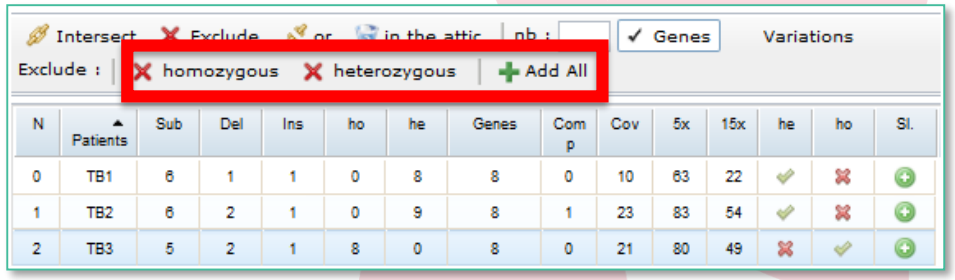
N	Patients	Sub	Del	Ins	ho	he	Genes	Comp	Cov	5x	15x	he	ho	Sl.
0	TB1	191	29	40	80	180	248	13	10	63	22	✓	✓	⊕
1	TB2	191	29	40	70	190	248	13	23	83	54	✓	✓	⊕
2	TB3	60	13	18	56	35	81	8	21	80	49	✓	✓	•

Ìdentical variation in 2 patients and never present in 1



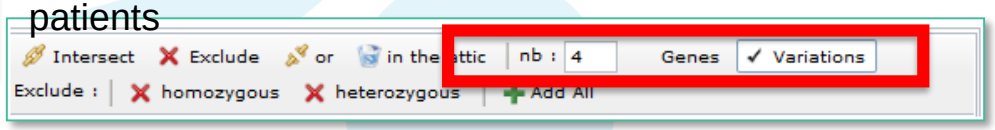
N	Patients	Sub	Del	Ins	ho	he	Genes	Comp	Cov	5x	15x	he	ho	Sl.
0	TB1	131	16	22	26	143	172	2	10	63	22	✓	✓	⊕
1	TB2	131	16	22	13	156	172	2	23	83	54	✓	✓	⊕
2	TB3	0	0	0	0	0	0	0	21	80	49	✓	✓	⊖

heterozygous variation in 2 patient
homozygoous Variation in 1 da s 1



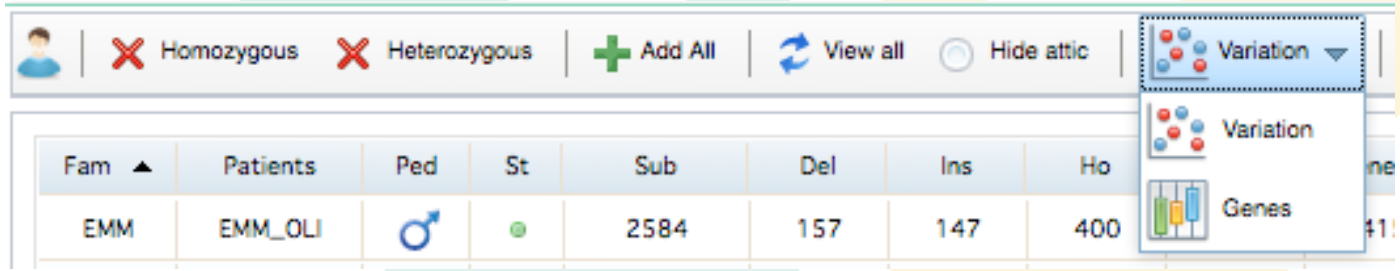
N	Patients	Sub	Del	Ins	ho	he	Genes	Comp	Cov	5x	15x	he	ho	Sl.
0	TB1	6	1	1	0	8	8	0	10	63	22	✓	✗	⊕
1	TB2	6	2	1	0	9	8	1	23	83	54	✓	✗	⊕
2	TB3	5	2	1	8	0	8	0	21	80	49	✗	✓	⊕

All Variations present in at least «N» patients

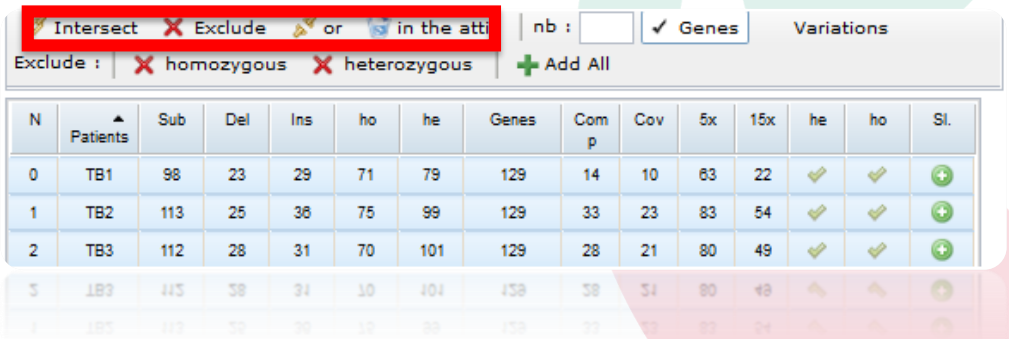


Funded by the European Union
GA n°825575

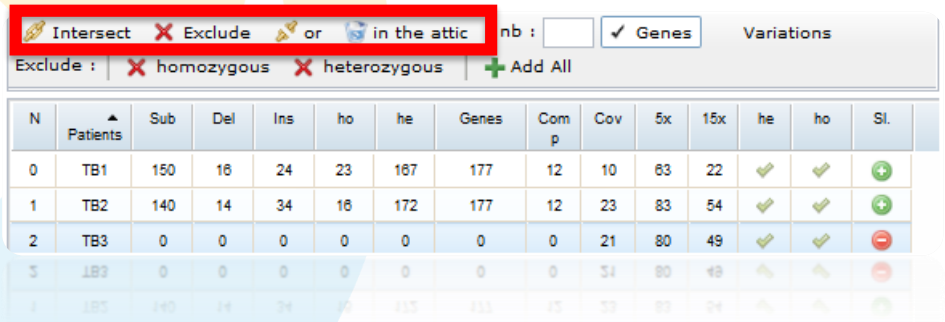
Query By Patients : Gene Level



Same "mutated" genes in 3 patients



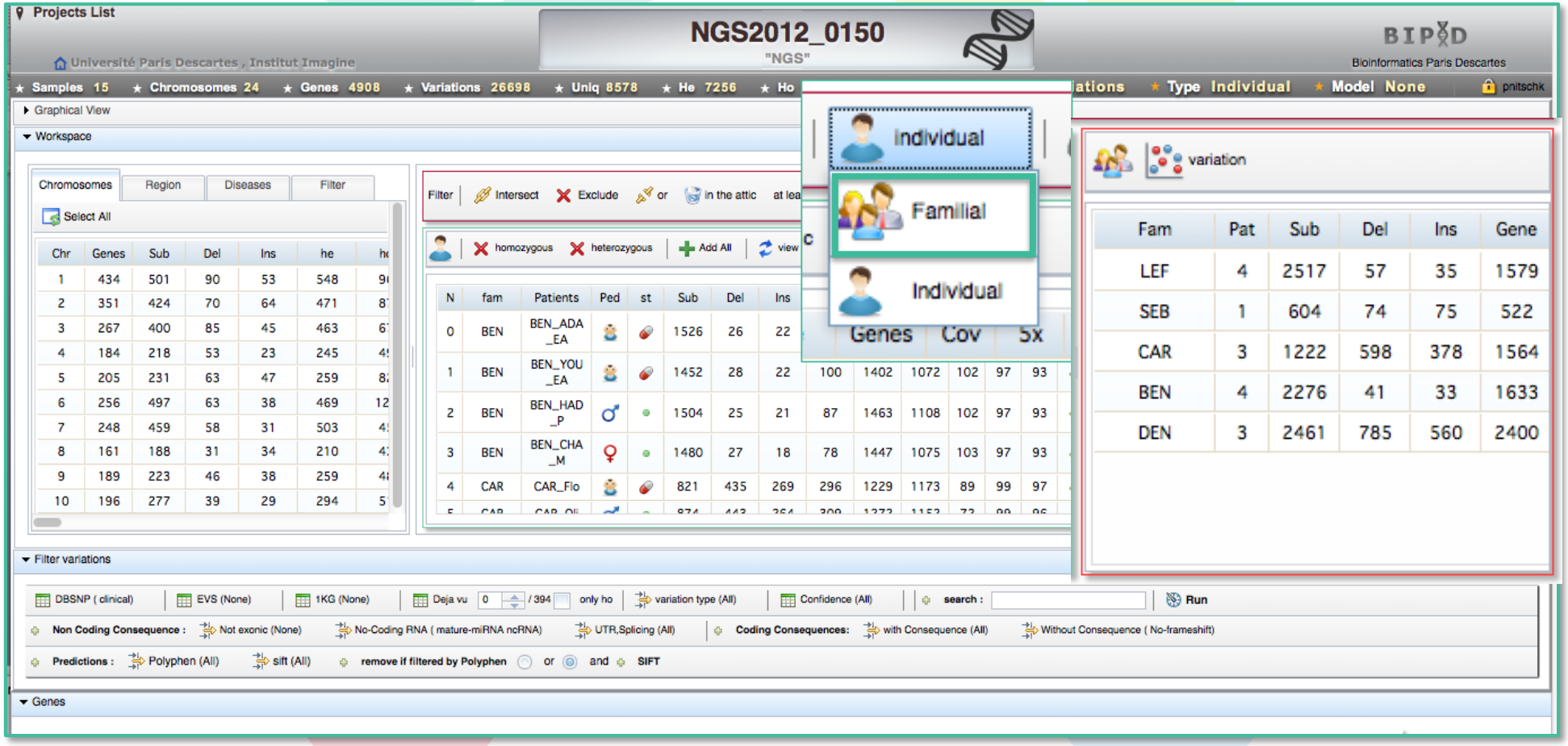
Excluded all gene from one patient



Genes in at least "N" patient

Funded by the European Union
GA n°825575

Familial Studies



Funded by the European Union GA n°825575

Famillial Studies : Intra-familial queries

Fam	Pat	Sub	Del	Ins	Gene	Sl.	Model
LEF	4	2517	57	35	1579		
SEB	1	604	74	75	522		
CAR	3	1222	598	378	1564		

homozygous | heterozygous | Add All | view all | hide attic | variation

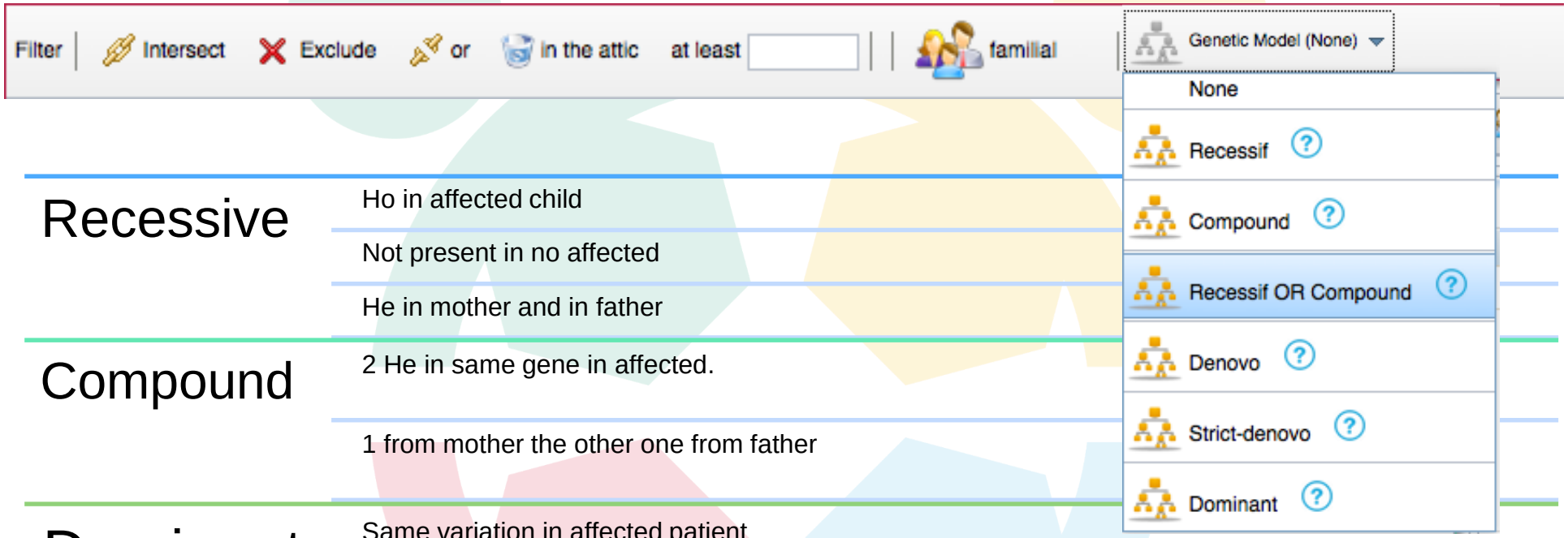
N	fam	Patients	Ped	st	Sub	Del	Ins	ho	he	Genes	Cov	5x	15x	he
0	LEF	LEF_Jul			1841	31	23	90	1805	1143	58	90	81	
1	LEF	LEF_Emi			1819	36	25	86	1794	1146	54	90	80	
2	LEF	LEF_Fre			1728	35	20	89	1694	1092	41	88	75	
3	LEF	LEF_Isa			1824	34	21	94	1785	1144	50	89	79	

Funded by the European Union GA n°825575

“inter-familial“ queries

Funded by the European Union
GA n°825575

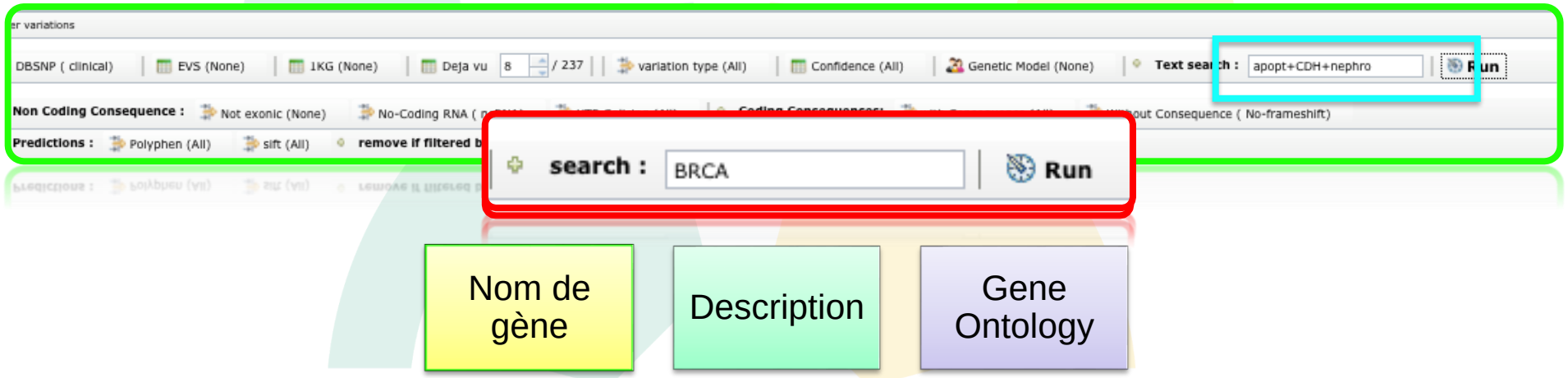
Transimission Model



Recessive	Ho in affected child
	Not present in no affected
	He in mother and in father
Compound	2 He in same gene in affected.
	1 from mother the other one from father
Dominant	Same variation in affected patient
De novo	Vairation only present in affected children
Strict-denovo	Denovo +correct covergae on parent alignment.

Funded by the European Union GA n°825575

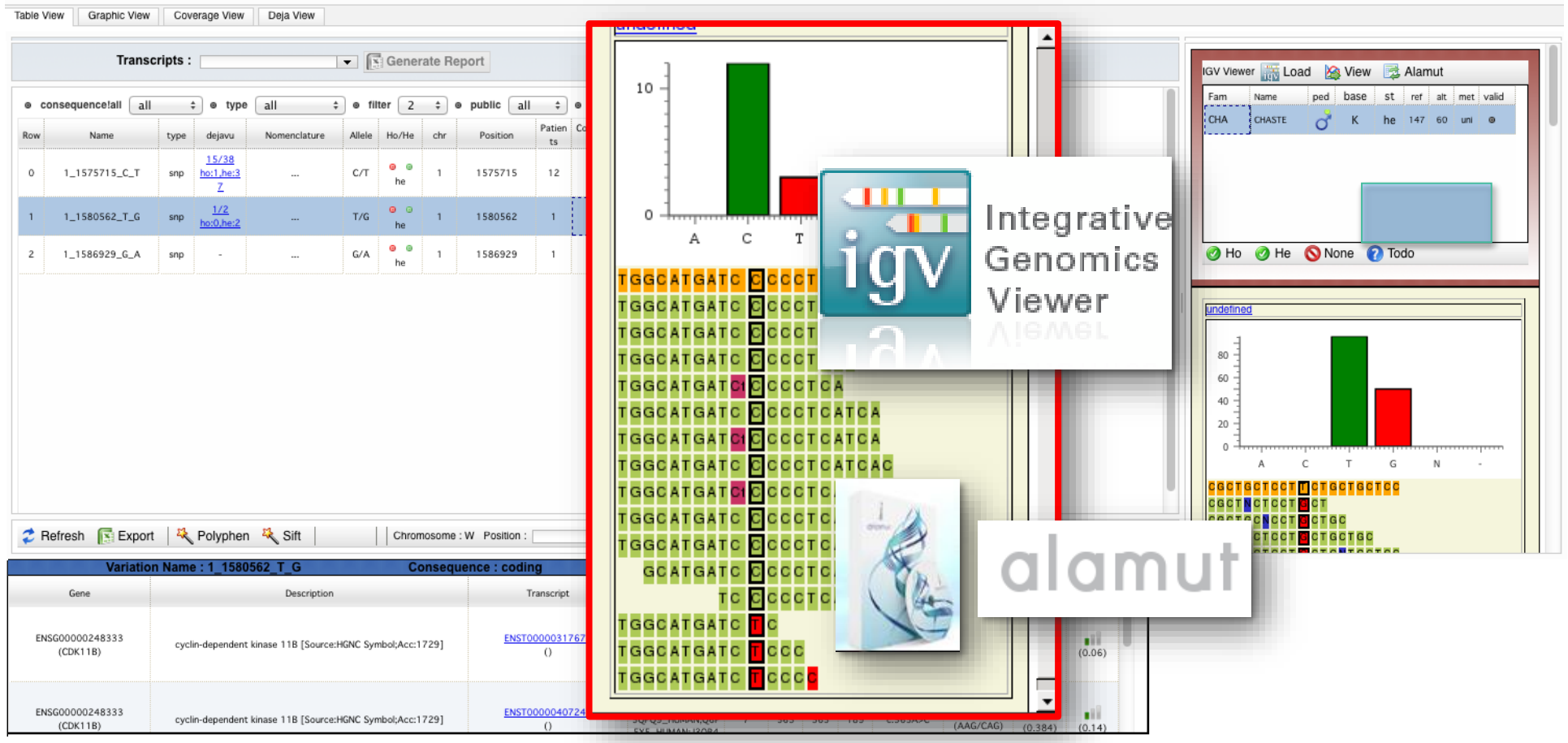
Textual search



1	ENSG00000204463	BAG6	6	31606805	31620482	BCL2-associated athanogene 6 [Source:HGNC Symbol;Acc:13919];kidney development	☆☆	1	1	0	0	1	0	2	0
								2	2	0	0	2	0	0	0
2	ENSG00000182580	EPHB3	3	184279572	184300197	EPH receptor B3 [Source:HGNC Symbol;Acc:3394];kidney development	☆☆	2	2	0	0	2	0	1	1
								2	2	0	0	2	0	0	0
3	ENSG00000135100	HNF1A	12	121416346	121440899	HNF1 homeobox A [Source:HGNC Symbol;Acc:11621];kidney development;renal absorption;renal glucose absorption	☆☆	2	2	0	0	2	0	2	0
								7	7	0	0	7	0	0	0
4	ENSG00000132130	LHX1	17	35294084	35301917	LIM homeobox 1 [Source:HGNC Symbol;Acc:6593];nephron development;kidney development;renal absorption	☆☆	1	1	0	0	1	0	0	0
								1	1	0	0	1	0	0	0

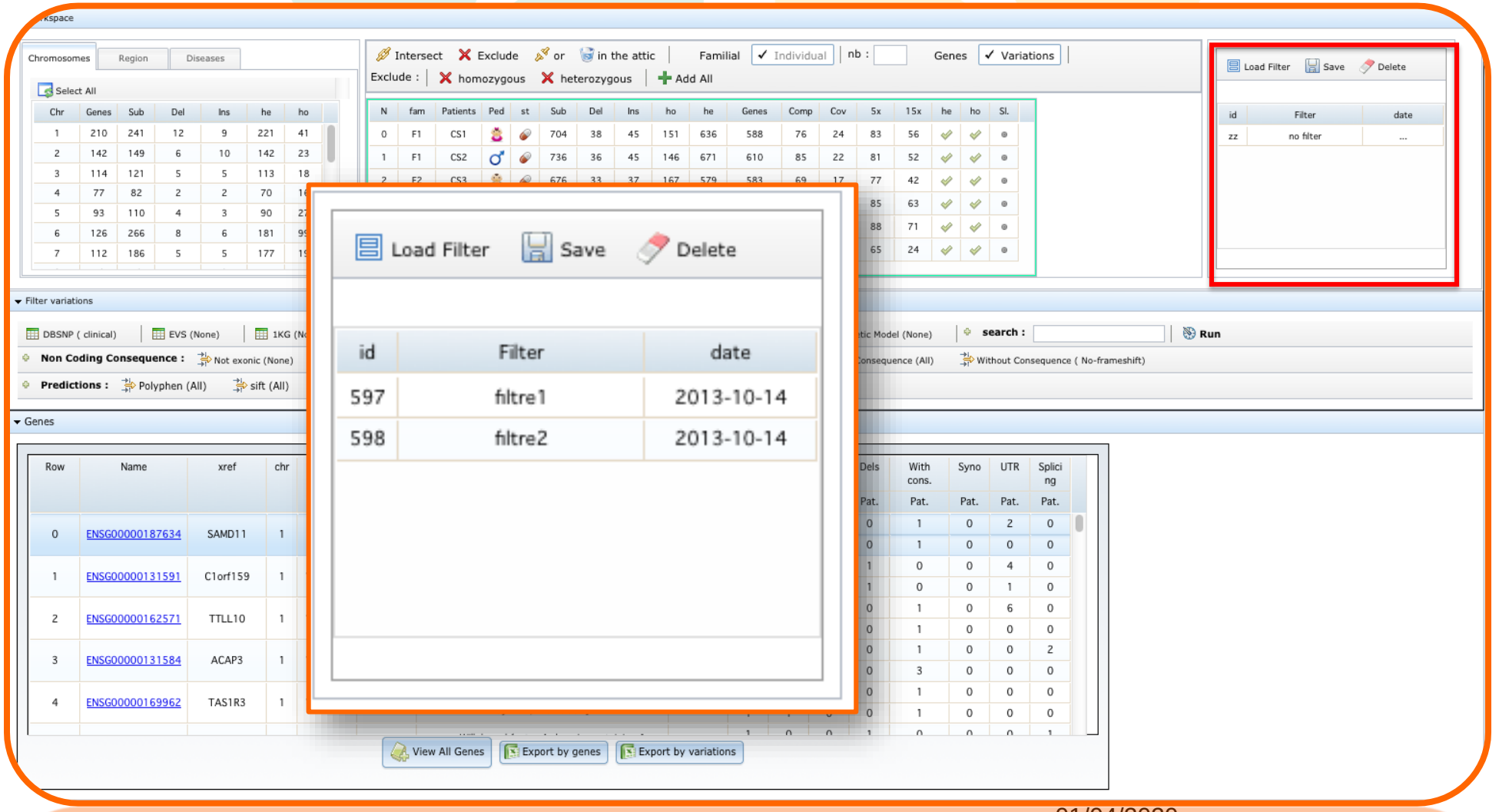
Funded by the European Union GA n°825575

Variation Visualisation and tools



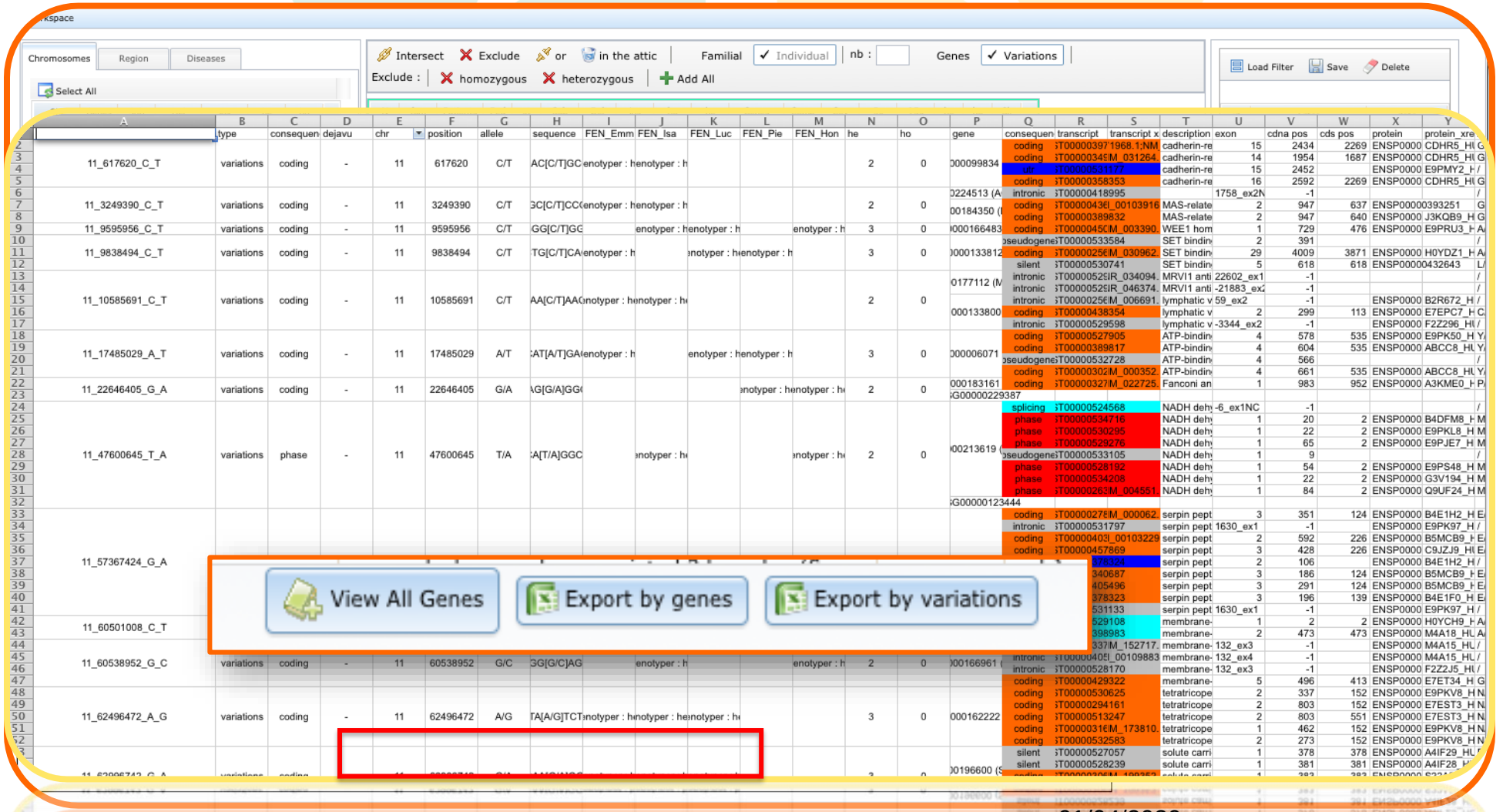
Funded by the European Union
GA n°825575

Save Filters



Funded by the European Union
GA n°825575

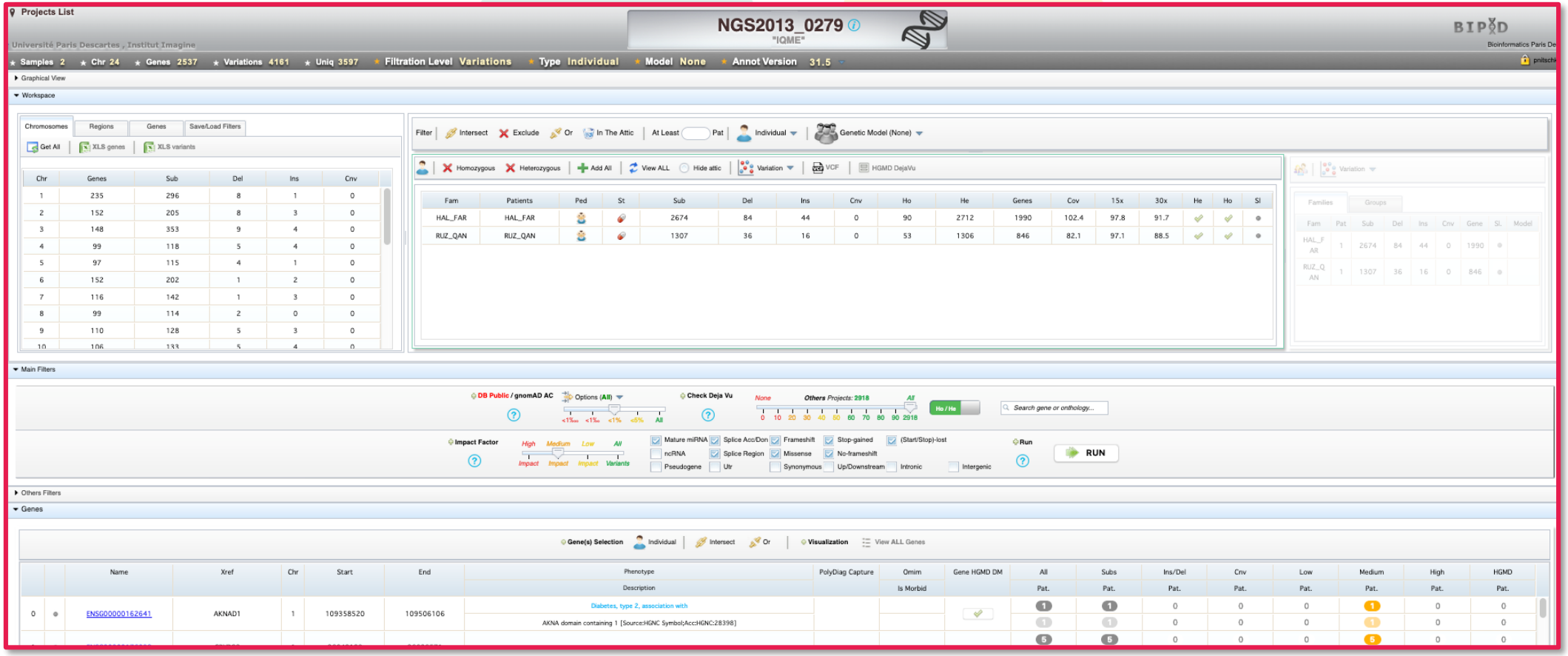
Export data



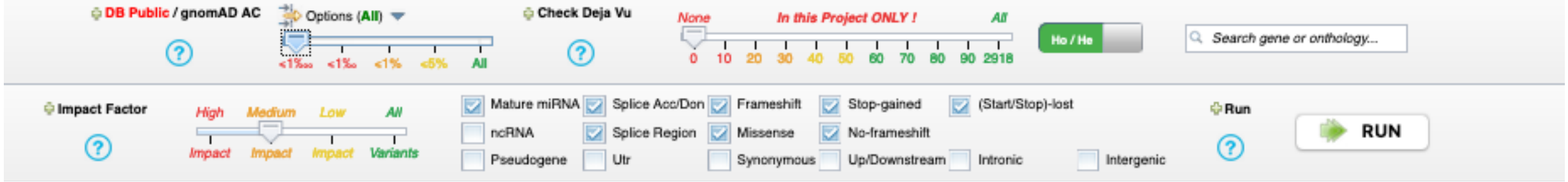
Funded by the European Union GA n°825575

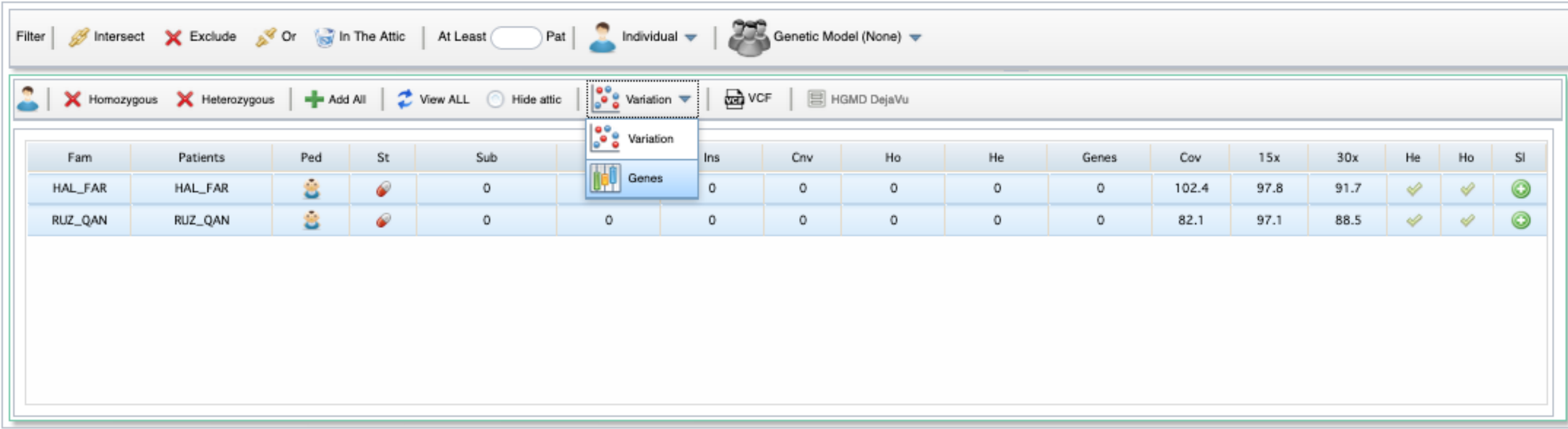
Example : 2 sporadic cases WES

Auriculocondylar syndrome (ACS) is a rare craniofacial disorder with mandibular hypoplasia and question-mark ears (QMEs) as major features.



Funded by the European Union
GA n°825575





Fam	Patients	Ped	St	Sub		Ins	Cnv	Ho	He	Genes	Cov	15x	30x	He	Ho	Sl
HAL_FAR	HAL_FAR			0		0	0	0	0	0	102.4	97.8	91.7			
RUZ_QAN	RUZ_QAN			0	0	0	0	0	0	0	82.1	97.1	88.5			

Funded by the European Union
GA n°825575

Fam	Patients	Ped	St	Sub	Del	Ins	Cnv	Ho	He	Genes	Cov	15x	30x	He	Ho	Sl
HAL_FAR	HAL_FAR			9	0	0	0	0	9	7	102.4	97.8	91.7			
RUZ_QAN	RUZ_QAN			7	0	0	0	0	7	7	82.1	97.1	88.5			

REPORT

Mutations in Endothelin 1 Cause Recessive Auriculocondylar Syndrome and Dominant Isolated Question-Mark Ears

Christopher T. Gordon,[1,2,*] Florence Petit,[3] Peter M. Kroisel,[4] Linda Jakobsen,[5] Roseli Maria Zechi-Ceide,[6] Myriam Oufadem,[1,2] Christine Bole-Feysot,[7] Solenn Pruvost,[7] Cécile Masson,[2,8] Frédéric Tores,[8] Thierry Hieu,[8] Patrick Nitschké,[2,8] Pernille Lindholm,[9] Philippe Pellerin,[10] Maria Leine Guion-Almeida,[6] Nancy Mizue Kokitsu-Nakata,[6] Siulan Vendramini-Pittoli,[6] Arnold Munnich,[1,2,11] Stanislas Lyonnet,[1,2,11] Muriel Holder-Espinasse,[12] and Jeanne Amiel[1,2,11,*]

		Name	Medium Pat.	High Pat.	HGMD Pat.
0		ENSG00000112837	2	0	0
			2	0	0
1		ENSG00000078401	1	1	2

Table View | Graphic View | Go

Export | Load App IG

Row	Name	Type	DejaVu	Allele	Ho/He	Chr	Position	Patients	Consequence	Gene	Omim	Polyphen status	Sift status	Cadd score	DB Freq	Is Clinical	Ncboost
0	6_12292700_T_A	snp	-	T/A	he	6	12292700	1	Missense	EDN1	Omim			33	0.000 %	Yes	-
1	6_12294189_T_G	snp	-	T/G	he	6	12294189	1	Stop-gained	EDN1	Omim			41	0.000 %	Yes	-

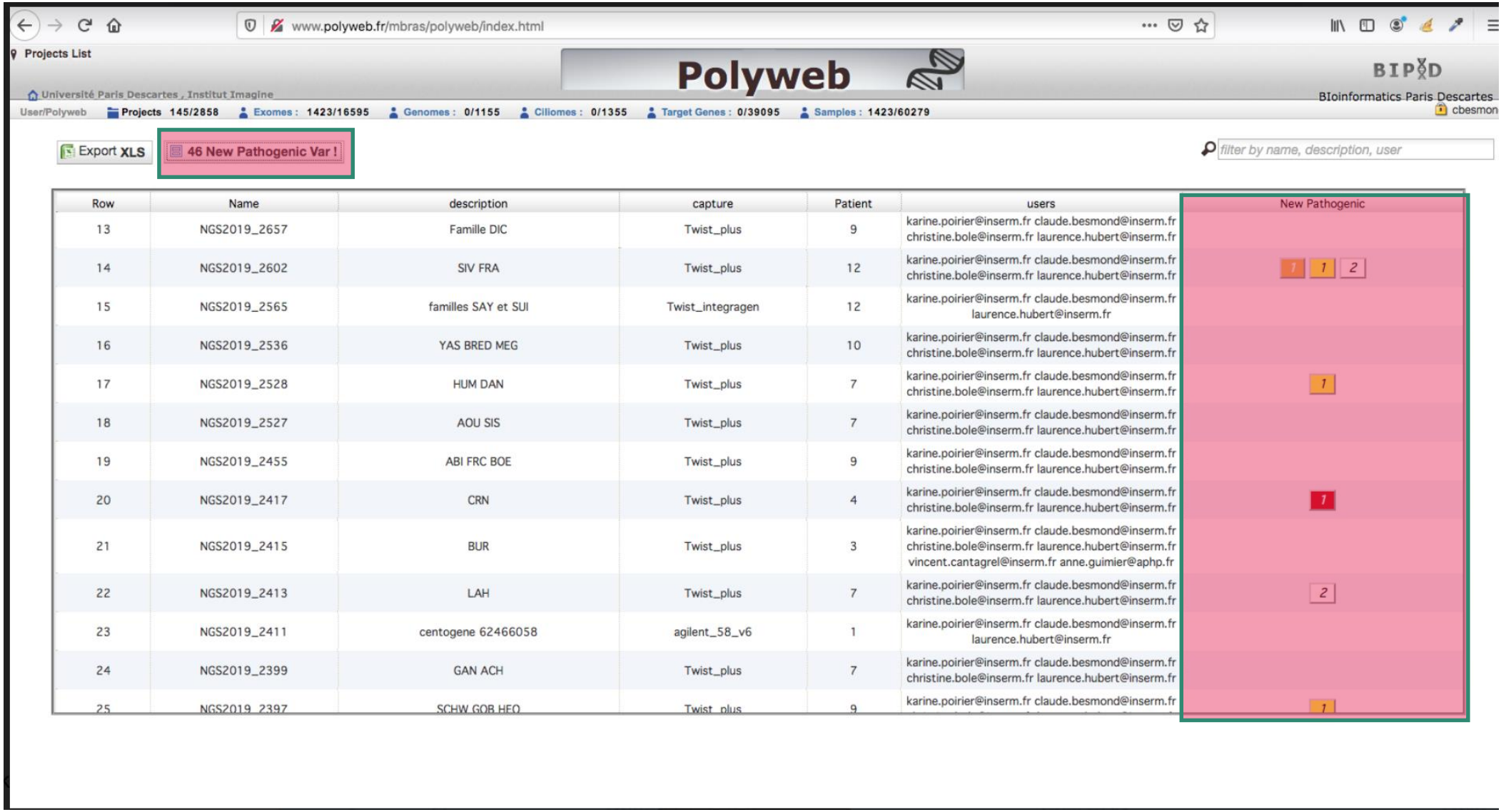
EJP RD

Funded by the European Union GA n°825575

Poly -BackToTheFuture

How to re-analyze data ? (DejaVu)

EUROPEAN JOINT PROGRAMME
RARE DISEASES



Row	Name	description	capture	Patient	users	New Pathogenic
13	NGS2019_2657	Famille DIC	Twist_plus	9	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	
14	NGS2019_2602	SIV FRA	Twist_plus	12	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	1 1 2
15	NGS2019_2565	familles SAY et SUI	Twist_integragen	12	karine.poirier@inserm.fr claude.besmond@inserm.fr laurence.hubert@inserm.fr	
16	NGS2019_2536	YAS BRED MEG	Twist_plus	10	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	
17	NGS2019_2528	HUM DAN	Twist_plus	7	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	1
18	NGS2019_2527	AOU SIS	Twist_plus	7	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	
19	NGS2019_2455	ABI FRC BOE	Twist_plus	9	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	
20	NGS2019_2417	CRN	Twist_plus	4	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	1
21	NGS2019_2415	BUR	Twist_plus	3	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr vincent.cantagrel@inserm.fr anne.guimier@aphp.fr	
22	NGS2019_2413	LAH	Twist_plus	7	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	2
23	NGS2019_2411	centogene 62466058	agilent_58_v6	1	karine.poirier@inserm.fr claude.besmond@inserm.fr laurence.hubert@inserm.fr	
24	NGS2019_2399	GAN ACH	Twist_plus	7	karine.poirier@inserm.fr claude.besmond@inserm.fr christine.bole@inserm.fr laurence.hubert@inserm.fr	
25	NGS2019_2397	SCHW GOB HEO	Twist_plus	9	karine.poirier@inserm.fr claude.besmond@inserm.fr	1

PolyBackToTheFuture

New Variants Pathogenic

Don't show me again

7457 New Pathogenic Variants in DataBases ***[HGMD: hgmd_pro-2020.1, Clinvar: 20200407]***

We found 381 New Pathogenic Variants in your project(s) !

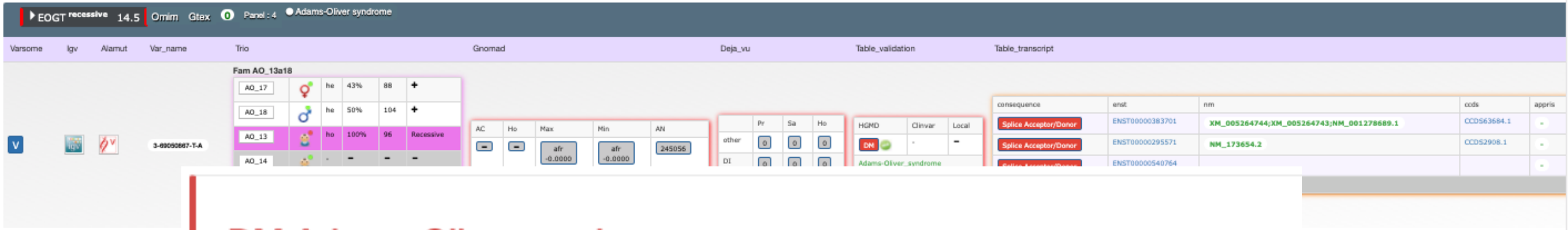
(with MAX DejaVu: **100** projects)

(with MAX gnomAD AC: **300**)

NGS2014_0480	CerlD18-19-egy5-egy6-egy11	1	1		
NGS2015_0665	syndrome ADAM-OLIVIER	1	3	1	1
NGS2013_0252	Projet Franck RM	1	1		
NGS2014_0527	RM set14	1	1	1	
NGS2018_1867	Exome-Diag-2017-Serie 1	1	1		
NGS2018_2090	Idefix_EDF_S23	1			
NGS2018_1866	THI BOU BESS MAR	1	1		
NGS2011_0061	neuropathie optique	1			
NGS2011_0084	quebec	1	12	8	
NGS2013_0310	MAR MET	1	1		
NGS2013_0327	Myocapture-J	1			
NGS2014_0381	Anemie de Blackfan-Diamond DBA	1	2	6	6

Funded by the European Union GA n°825575

NGS2015_0665 syndrome ADAM-OLIVIER 1 3 1 1



DM Adams-Oliver syndrome :

Ref : Expanding the phenotype in Adams-Oliver syndrome correlating with the genotype.

OMIM: 614789 **dbsnp:**rs1312622774 **HGMD:** CS200536 (2020-02-07)

3p14.1: chr3:69050867-69050867

EOGT: EGF domain specific O-linked N-acetylglucosamine transferase

Expanding the phenotype in Adams-Oliver syndrome correlating with the genotype.

Dudoignon B[1], Huber C[2,3], Michot C[1,2,3], Di Rocco F[4], Girard M[5], Lyonnet S[1], Rio M[1], Rabia SH[6], Daire VC[1,2,3], Baujat G[1,2,3].

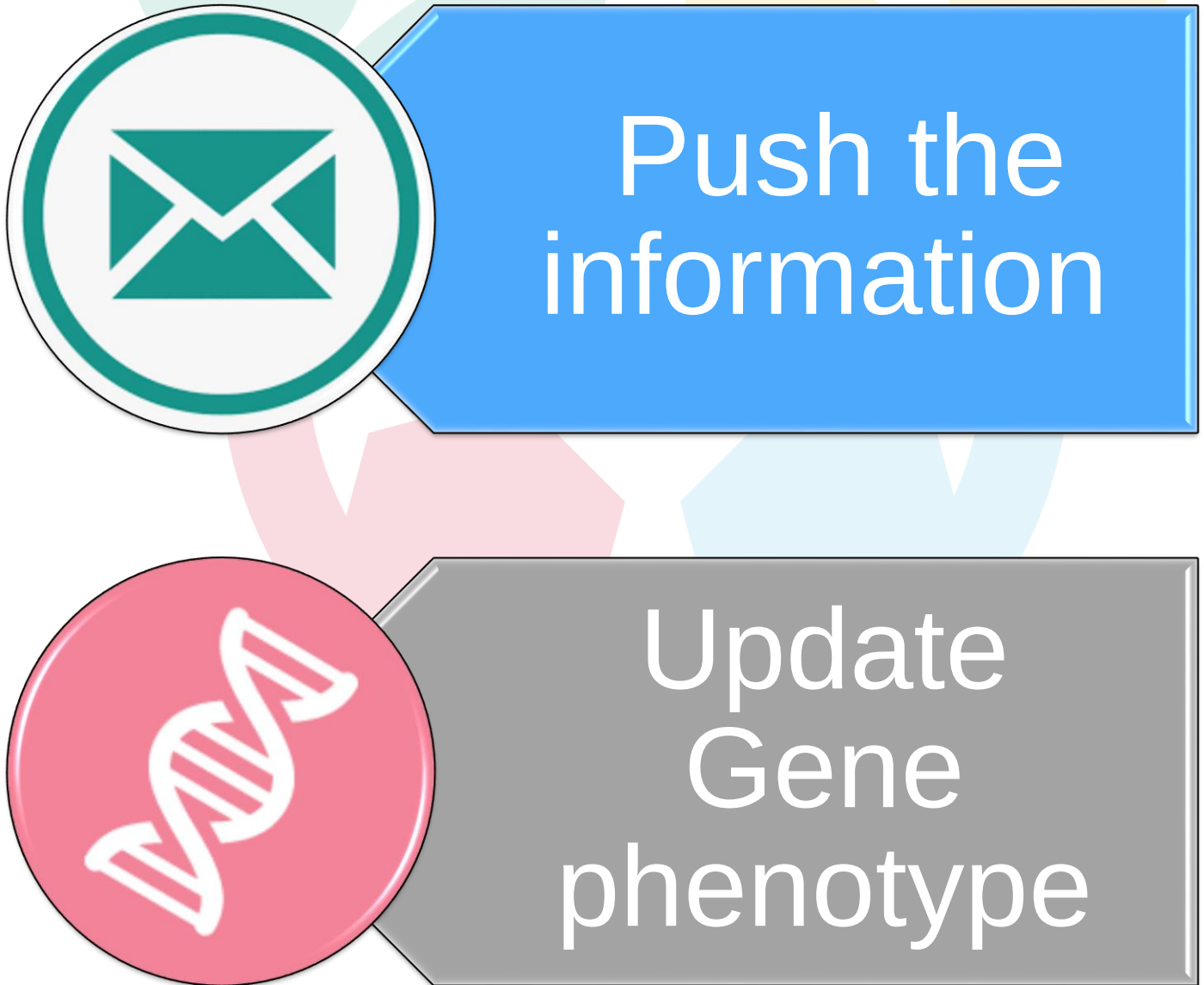
Author information

1 AP-HP, Service de Génétique Clinique, Necker-Enfants malades University Hospital, Paris, France.
2 INSERM, UMR1163, Imagine Institute, Paris, France.
3 AP-HP, Reference Center for Skeletal Dysplasia, Paris, France.
4 Hopital Femme Mere Enfant, Bron, France.
5 AP-HP, Liver Unit, National Reference Center for Biliary Atresia and Genetic Cholestasis, INSERM U1151/CNRS UMR 8253, Institut Necker-Enfants malades (INEM), Assistance Publique Hopitaux de Paris, Necker-Enfants malades Hospital, Paris, France.
6 AP-HP, Department of Dermatology, Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC), INSERM U1163, Descartes-Sorbonne Paris Cité University, Imagine Institute, Necker-Enfants malades University Hospital, Paris, France.

EJP RD

Funded by the European Union GA n°825575

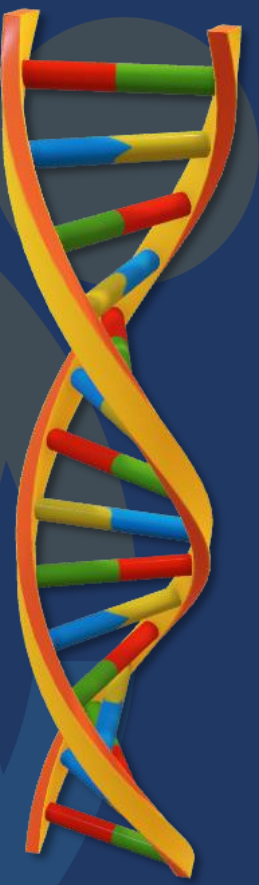
PolyBackToTheFuture : Perspectives



Funded by the European Union
GA n°825575

UNIVERSITÉ PARIS DESCARTES

Thank You



imagine
INSTITUT DES MALADIES GÉNÉTIQUES

EUROPEAN JOINT PROGRAMME
RARE DISEASES

EJP RD

Funded by the
European Union
GA n°825575