Les Variants de Signification Incertaine (VSI)
Une classe très hétérogène

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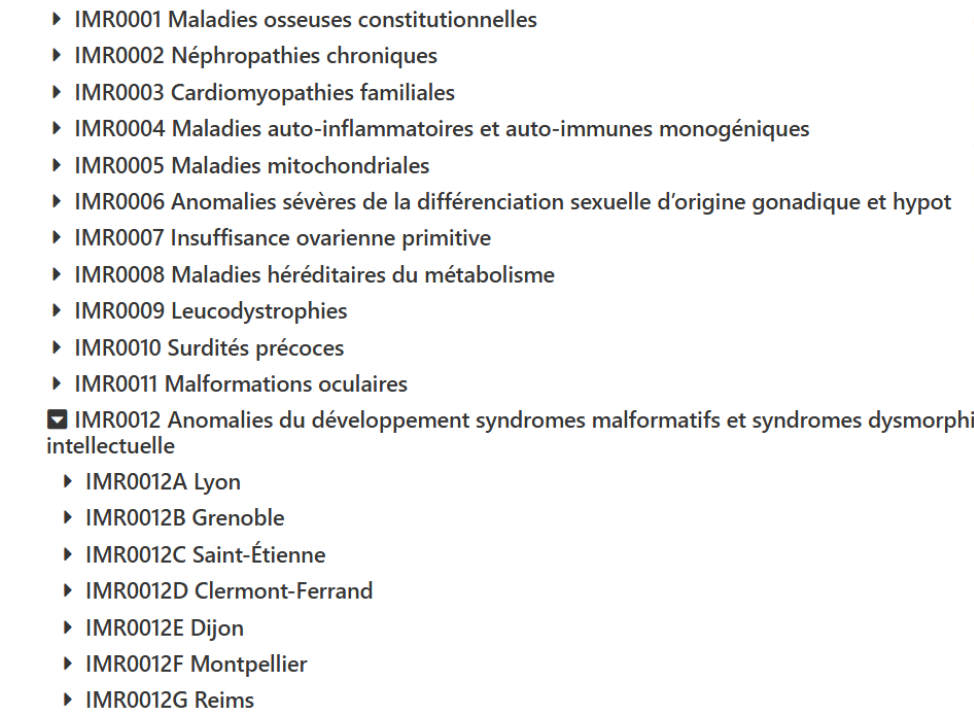
Contexte

- Laboratoire de Biologie Médicale AURAGEN à Lyon, PFMG2025
- Maladies Rares (MR) : Génome trio, duo, solo, quatuor
- 67 préindications
- Lecteurs dans les CHU/CH
- Equipe de biologistes Auragen



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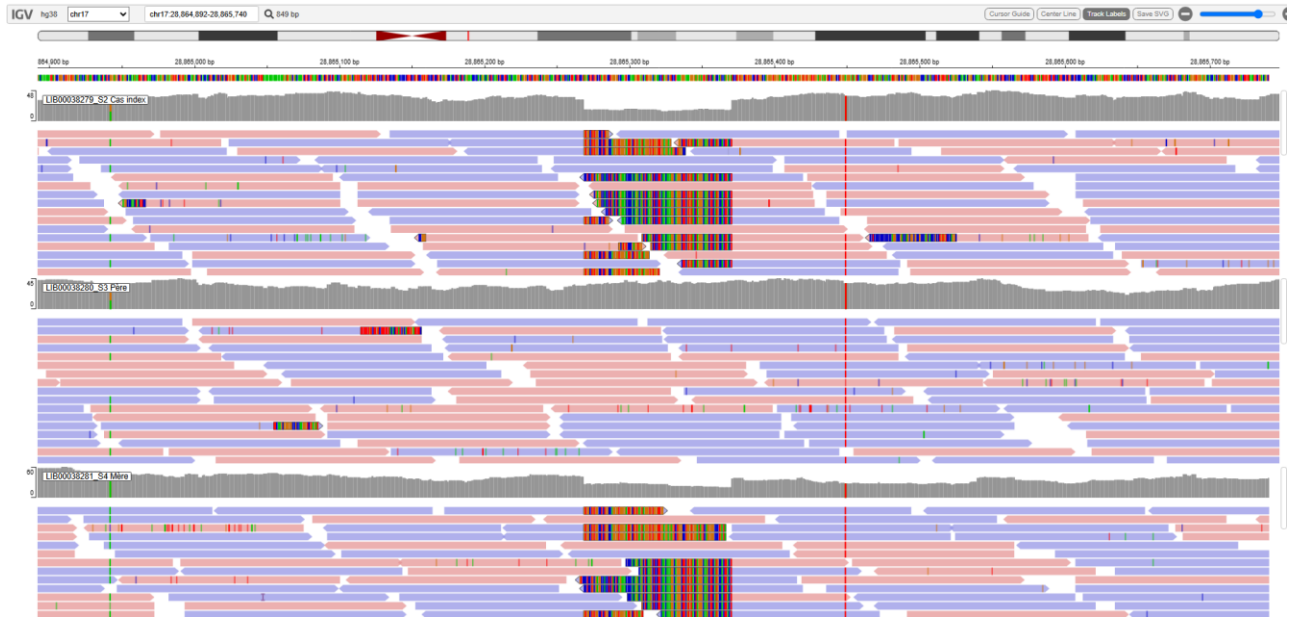
Quelques rappels

- SNV

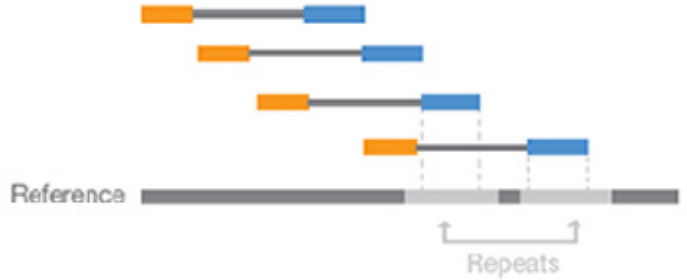
- SV/CNV
- Points de cassures (breakpoint BP)
- Split-reads
- Paires-discordantes
- Profondeur



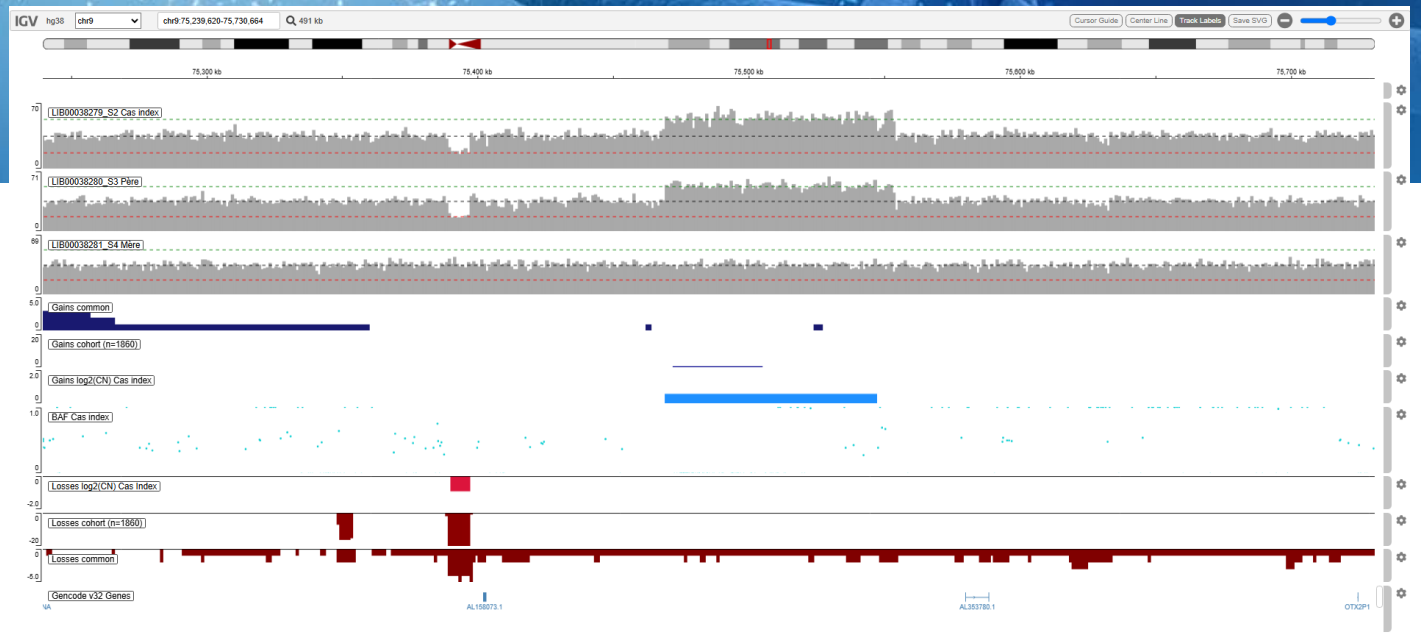
- HPO : Human Phenotype Ontology

Quelques rappels

- **Séquençage short reads paired-end**



Quelques rappels



- SNV

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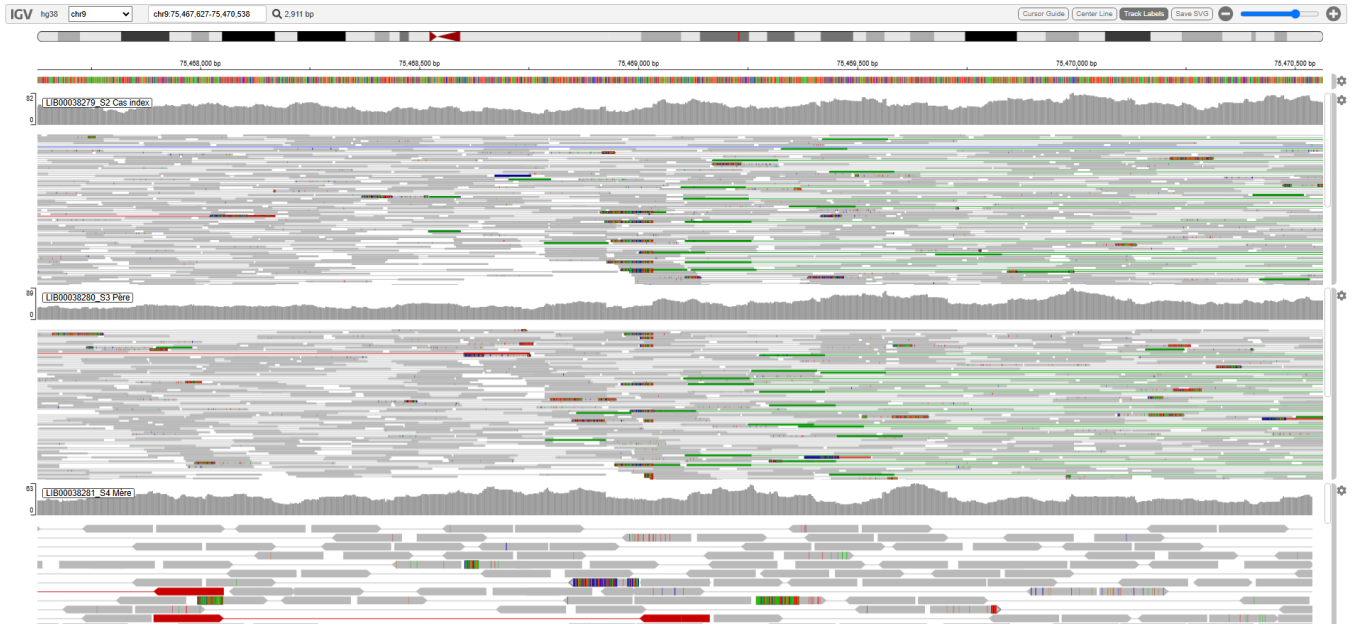


- HPO : Human Phenotype Ontology

Contexte

Aurapport version…

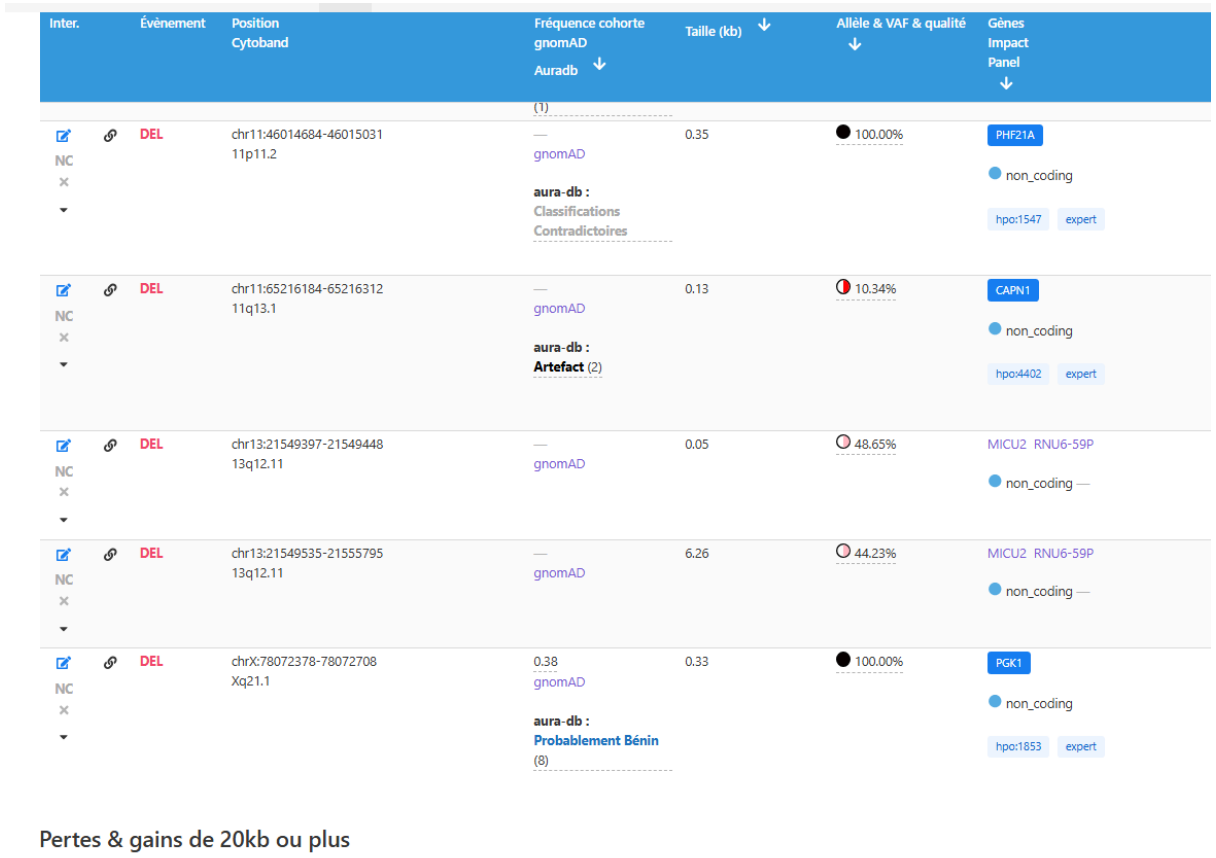
Sommaire | SNV | CNV | SV | Autres | QC Ciblé

NC	**CEP290** hpo:348 green	0.49	chr12:g.88079228G>A c.5228C>T e.39/54 p.Ala1743Val	gnomAD —	CADD GERP++ UTR SpliceAI	32 5.19 — — AG: 0.01 (-7)	Signification Incertaine 5 maladies OMIM
NC	**RERE** hpo:31 green	0.61	chr1:g.8360194C>G c.3313G>C e.18/23 p.Glu1105Gln	gnomAD —	CADD GERP++ UTR SpliceAI	24.2 5.56 — — —	— Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart
NC	**VPS13B** hpo:293 amber	0.58	chr8:g.99854115G>A c.10726G>A e.56/62 p.Ala3576Thr	gnomAD 0.0003	CADD GERP++ UTR SpliceAI	28.3 5.5 — — —	Signification Incertaine Cohen syndrome
NC	**TRMT5** hpo:2133	0.54	chr14:g.60979584_60979587del c.312_315del e.2/5 p.Ile105SerfsTer4	0.0008 0.0013	CADD GERP++ UTR SpliceAI	— — — — —	Conflicting_classifications_of_pathogenicity Peripheral neuropathy with variable spasticity, exercise intolerance, and developmental delay
NC	**GATA6** hpo:106 green	0.41	chr18:g.22200758G>C c.1723G>C e.7/7 p.Ala575Pro	0.0004 0.0003	CADD GERP++ UTR SpliceAI	23.5 3.68 — — —	Conflicting_classifications_of_pathogenicity 5 maladies OMIM

Contexte

Aurapport version…

Sommaire | SNV | CNV | SV | Autres | QC Ciblé



Inter.	Évènement	Position Cytoband	Fréquence cohorte gnomAD Auradb (1)	Taille (kb)	Allèle & VAF & qualité	Gènes Impact Panel
NC	DEL	chr11:46014684-46015031 11p11.2	— gnomAD aura-db : Classifications Contradictoires	0.35	100.00%	PHF21A non_coding hpo:1547 expert
NC	DEL	chr11:65216184-65216312 11q13.1	— gnomAD aura-db : Artefact (2)	0.13	10.34%	CAPN1 non_coding hpo:4402 expert
NC	DEL	chr13:21549397-21549448 13q12.11	— gnomAD	0.05	48.65%	MICU2 RNU6-59P non_coding —
NC	DEL	chr13:21549535-21555795 13q12.11	— gnomAD	6.26	44.23%	MICU2 RNU6-59P non_coding —
NC	DEL	chrX:78072378-78072708 Xq21.1	0.38 gnomAD aura-db : Probablement Bénin (8)	0.33	100.00%	PGK1 non_coding hpo:1853 expert

Pertes & gains de 20kb ou plus

Contexte

Aurapport version…

Sommaire | SNV | CNV | SV | Autres | QC Ciblé

Points de cassure

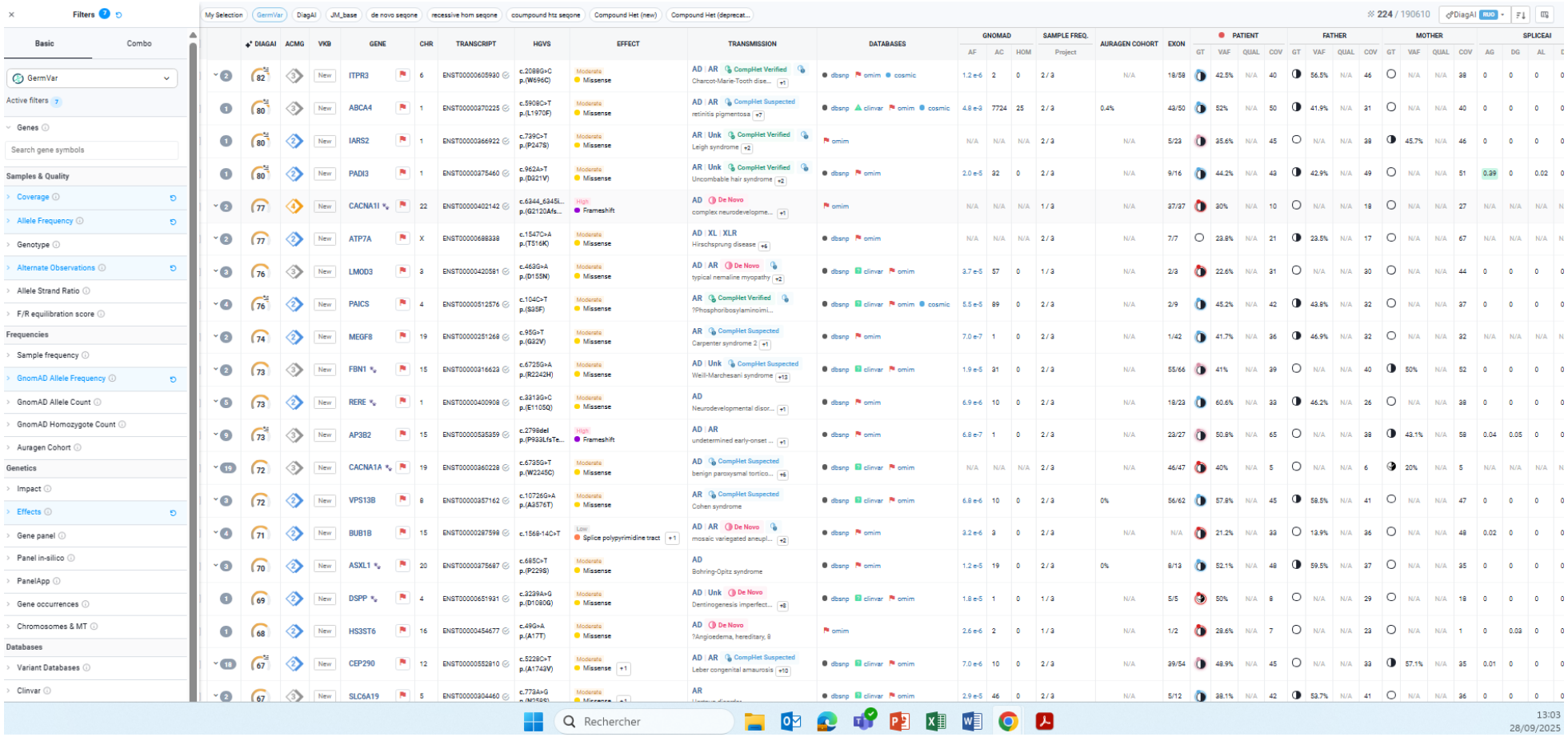
Cette section regroupe des variations candidates comportant des faux positifs. Le filtrage sera amélioré progressivement.

Code couleur allèle : De novo · Homozygote · Hérité du père · Hérité de la mère · Probablement hérité du père · Probablement hérité de la mère · De novo mosaic · Héritage non déterminé · Autre

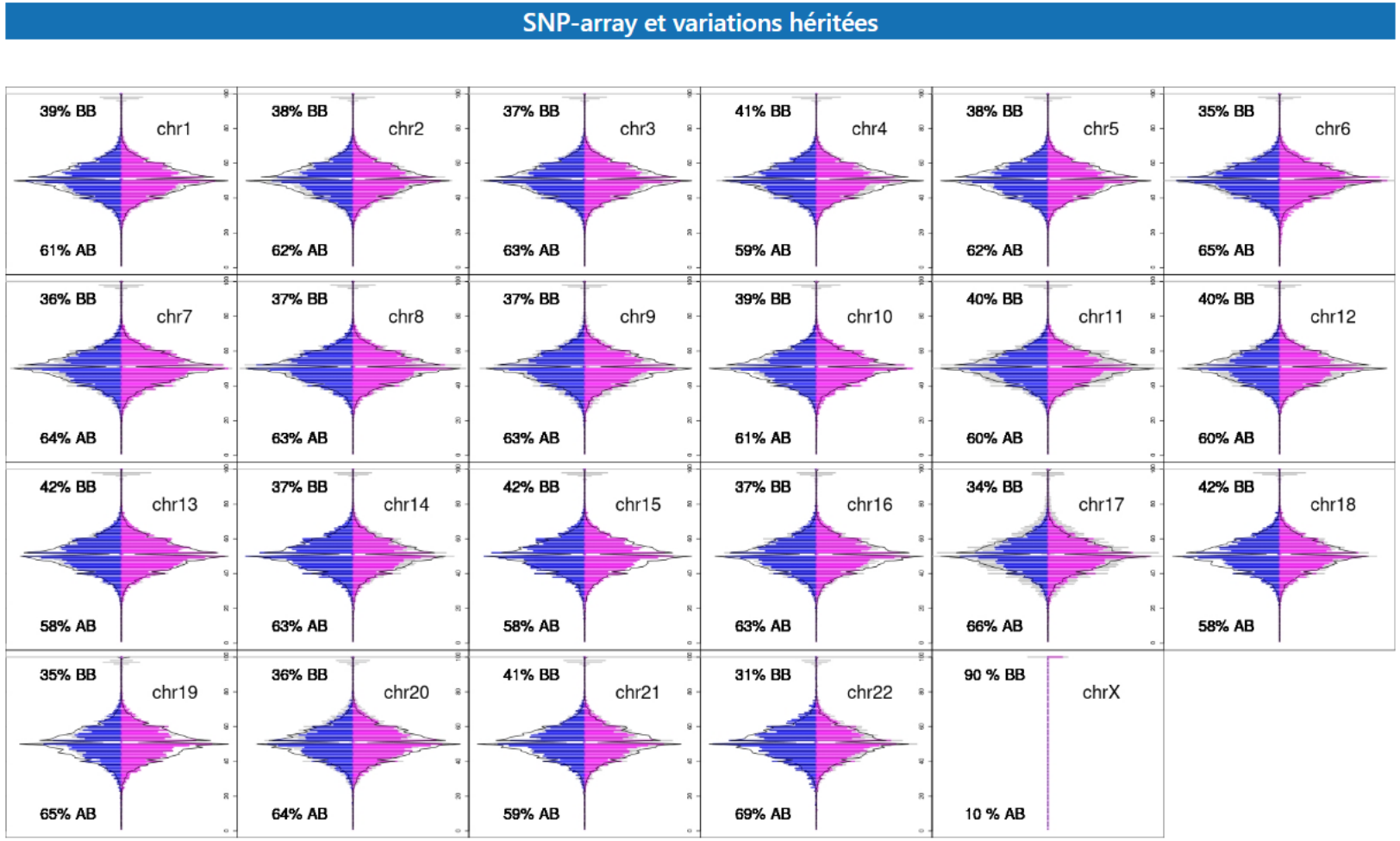
Réinitialiser les filtres

Inter.	Qualité	Position(Cytobande)	Fréquence cohorte	Balance allélique	Génotype / Ségrégation familiale	Distance (bp)	Gènes Panel
NC	445	**chrX:23645152 (Xp22.11)** chr10:80978300 (10q23.1)	— gnomAD 0.11 gnomAD	20.59 (27, 7)	heterozygous inherited_parental_lineage_2	inter-chromosomique	—
—	944	chr8:41034377 (8p11.21) chr8:41018434 (8p11.21)	0.54 0.54 gnomAD	19.18 (59, 14)	heterozygous inherited_parental_lineage_1	15942	RNU6-356P
—	999	**chrX:26782035 (Xp21.3)** **chrX:26792668 (Xp21.3)**	0.75 0.43 gnomAD	43.33 (17, 13)	heterozygous inherited_parental_lineage_2	10634	RNU1-142P
NC	999	**chrX:34216587 (Xp21.1)** **chrX:34217637 (Xp21.1)**	— — gnomAD	50.00 (15, 15)	heterozygous inherited_parental_lineage_2	1051	—
—	858	chr10:104438337 (10q25.1) chr6:62495212 (6q11.1)	0.11 gnomAD 0.11 gnomAD	43.14 (29, 22)	heterozygous inherited_parental_lineage_2	inter-chromosomique	CFAP58
NC	999	chr15:33739648 (15q14) chr4:70106104 (4q13.3)	— gnomAD — gnomAD	63.08 (24, 41)	heterozygous inherited_parental_lineage_1	inter-chromosomique	RYR3

Contexte seqone



Profil normal :



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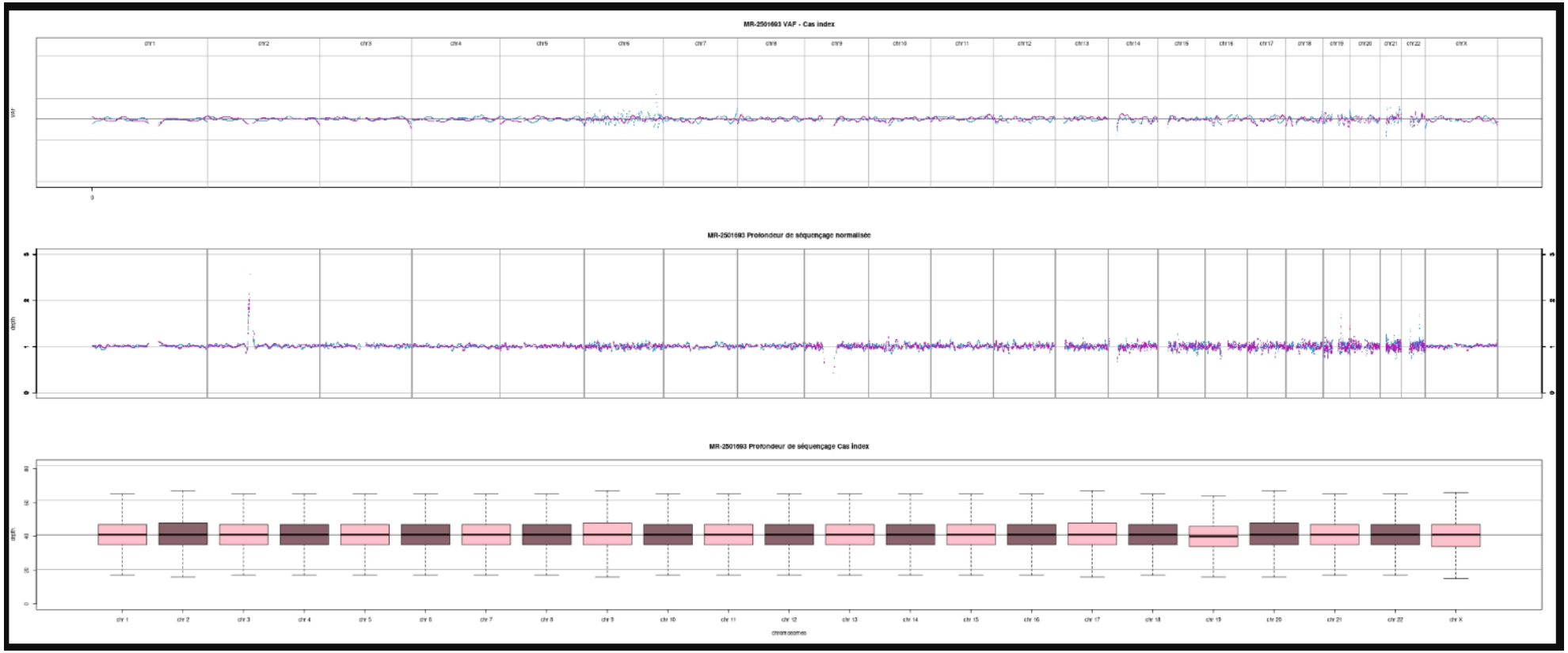

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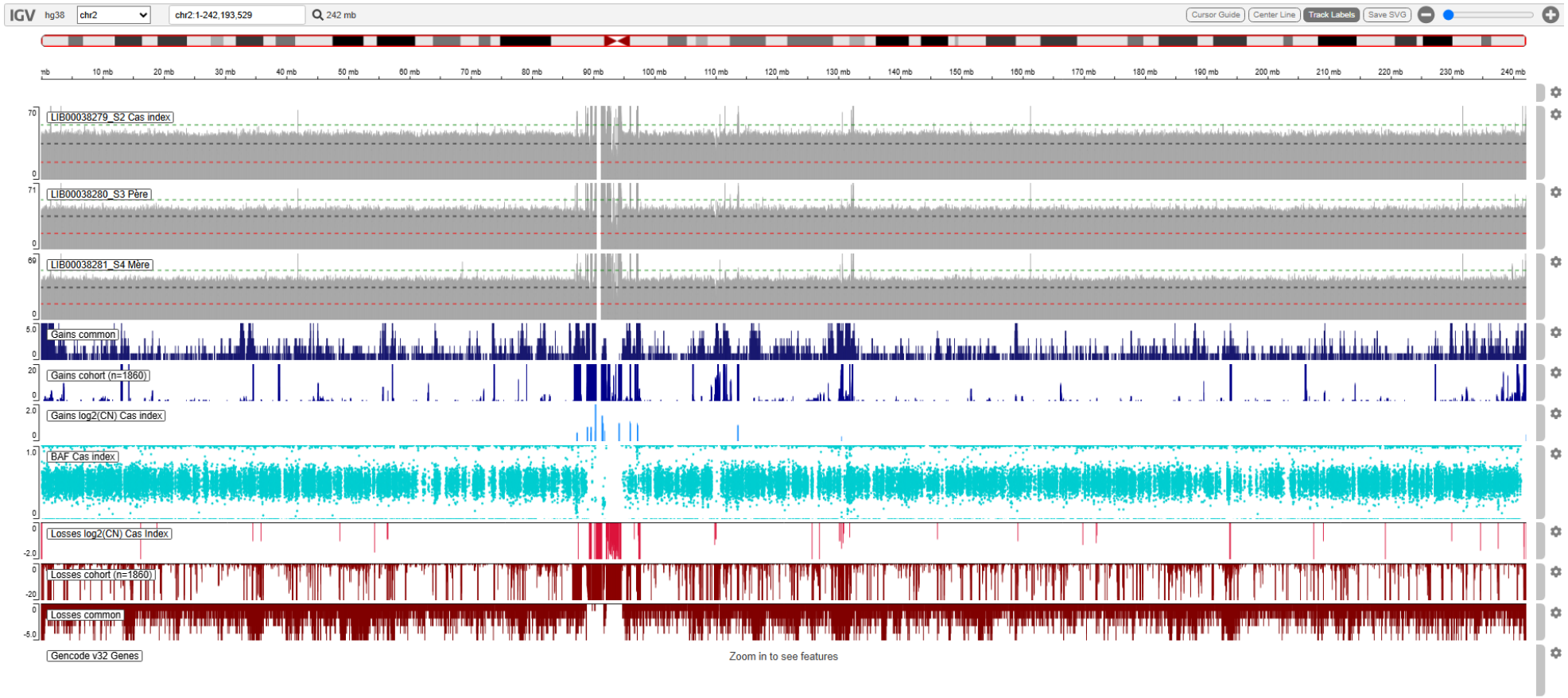
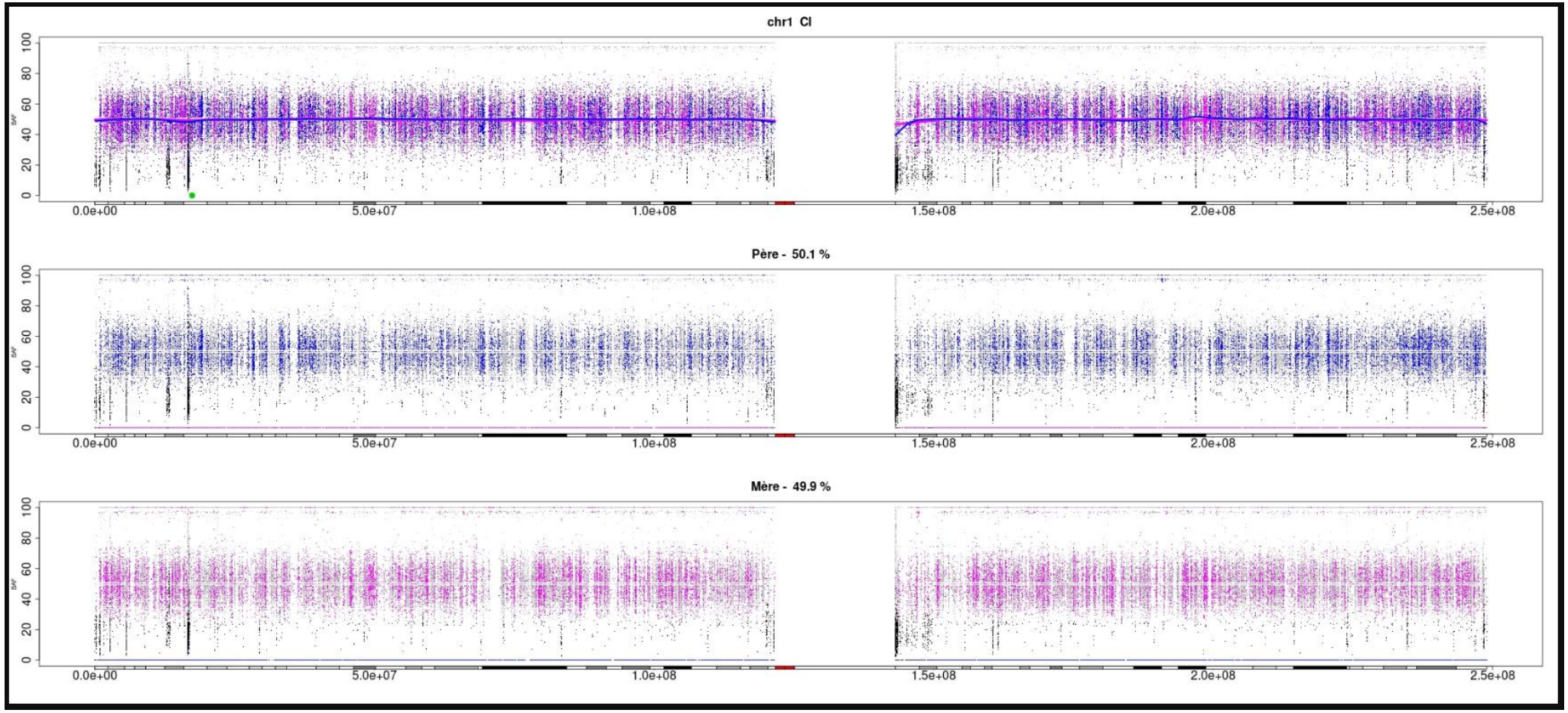
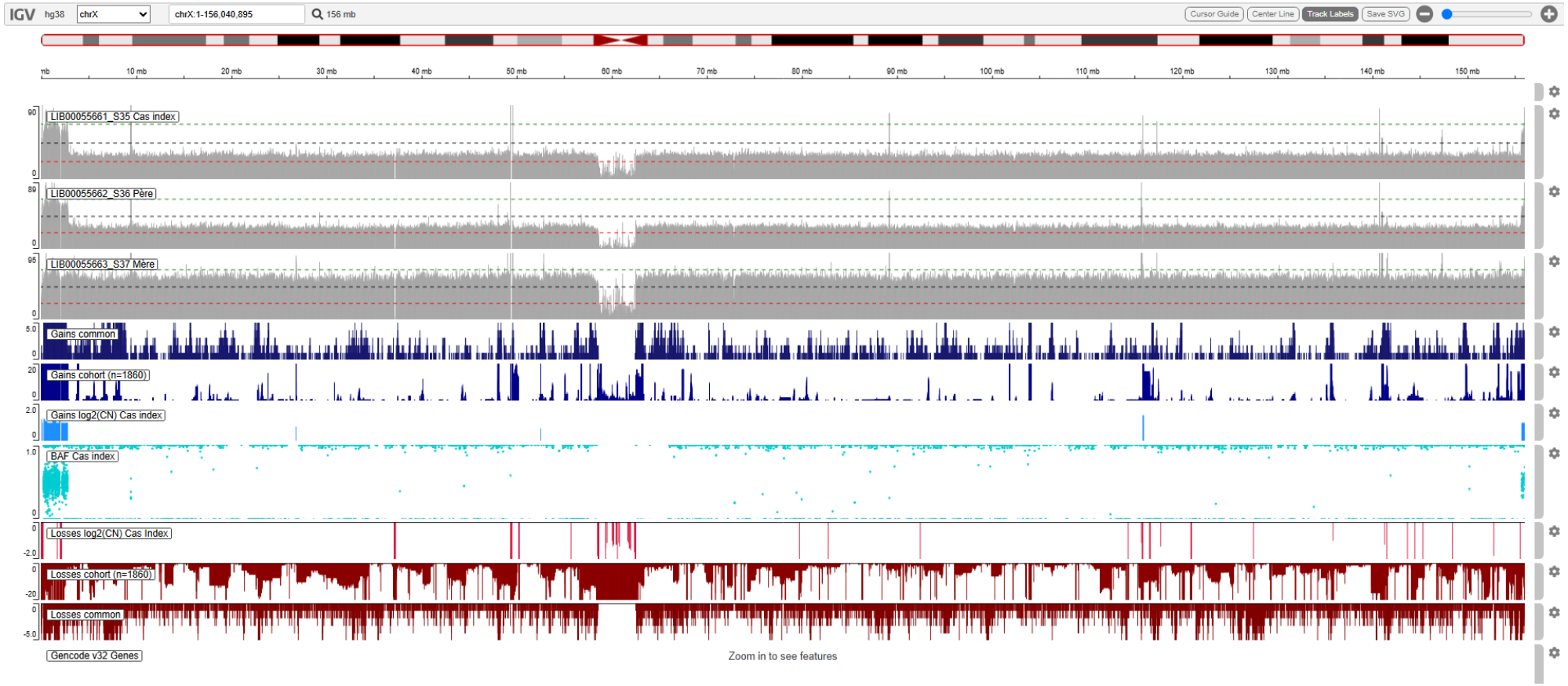


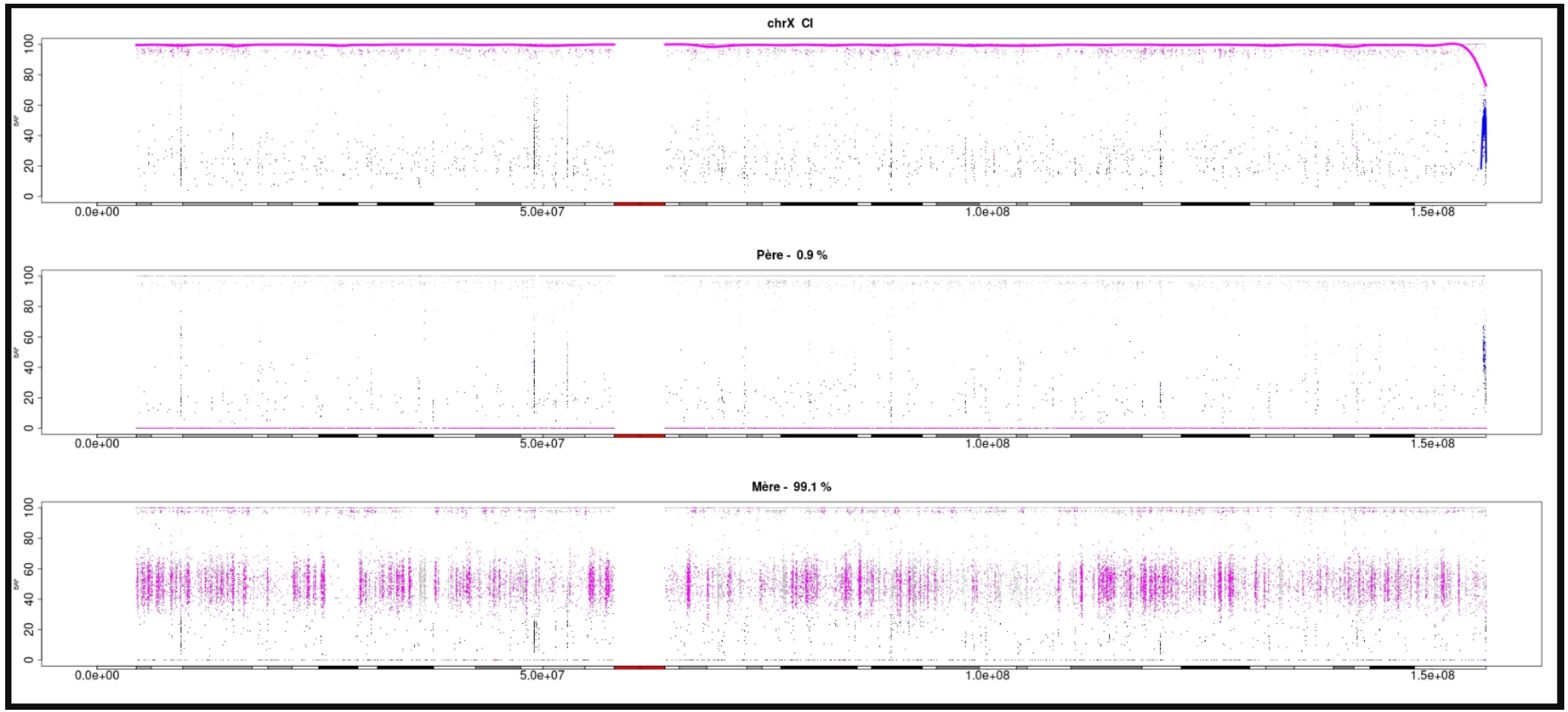
Profil normal :



Profil normal chrX chez un garçon :



Profil normal chrX chez un garçon :



Classification des variations ACMG

- **Pathogène Classe 5**
- **Probablement pathogène Classe 4**

- **Signification incertaine VSI Classe 3**

- **Probablement Bénigne Classe 2**
- **Bénigne Classe 1**

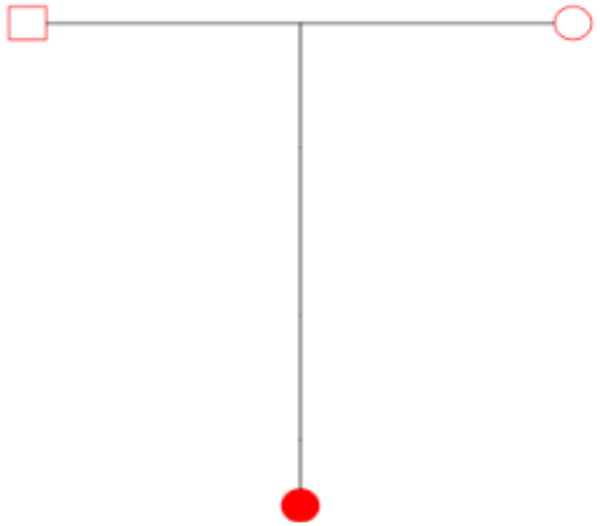
- **PIEV**
- **Hypomorphe**
- **Modificateur**
- **…**

Cas 1

Cas 1

Garçon de 4 ans
Exome et ACPA ras
trio parents

Symptômes renseignés :
Retard moteur
Fente



VSI

chr19:47300001-47960000
19q13.32q13.33
+ SNV

3 copies
1.73
Ségrégation familiale

gnomAD
—

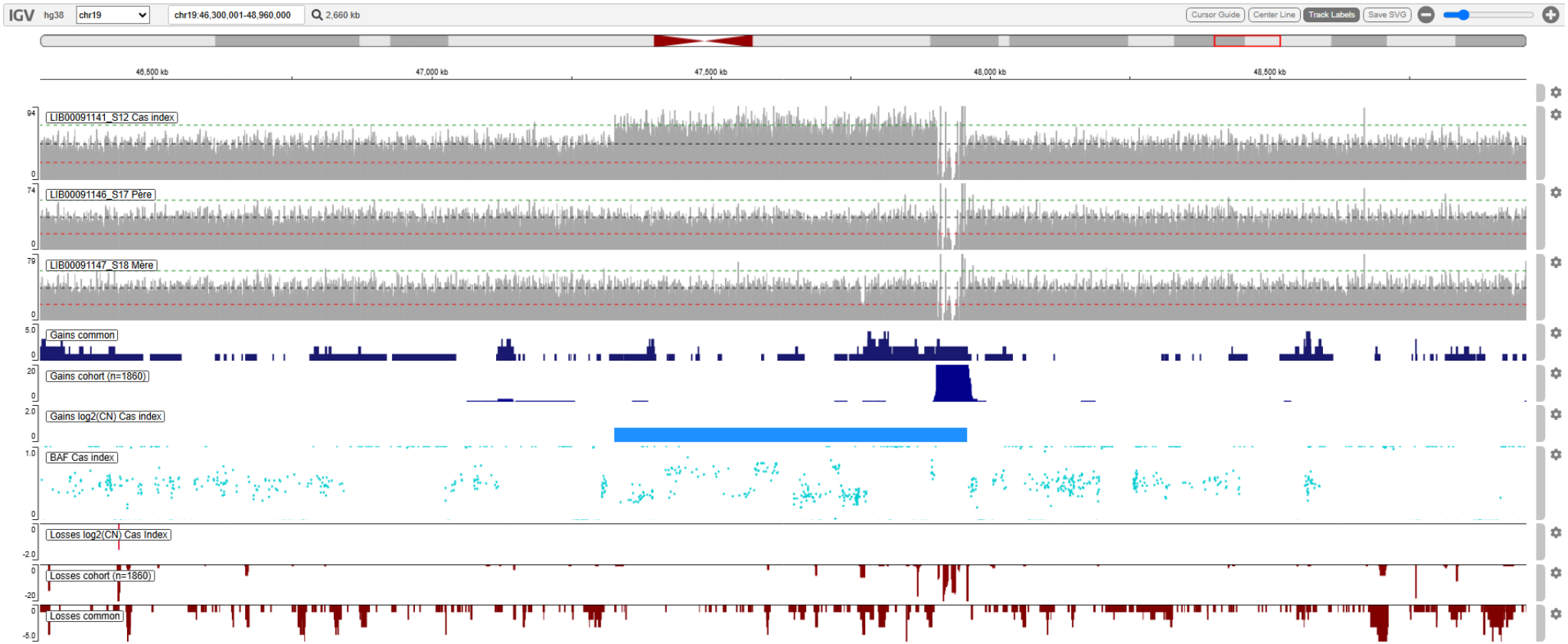
aura-db :
VSI (1)

660.00

BICRA (AD) CRX (AD&NA) KPTN (AR)

génique

hpo:42 expert



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chr19:47300001-47960000
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gnomAD
—

aura-db :
VSI (1)

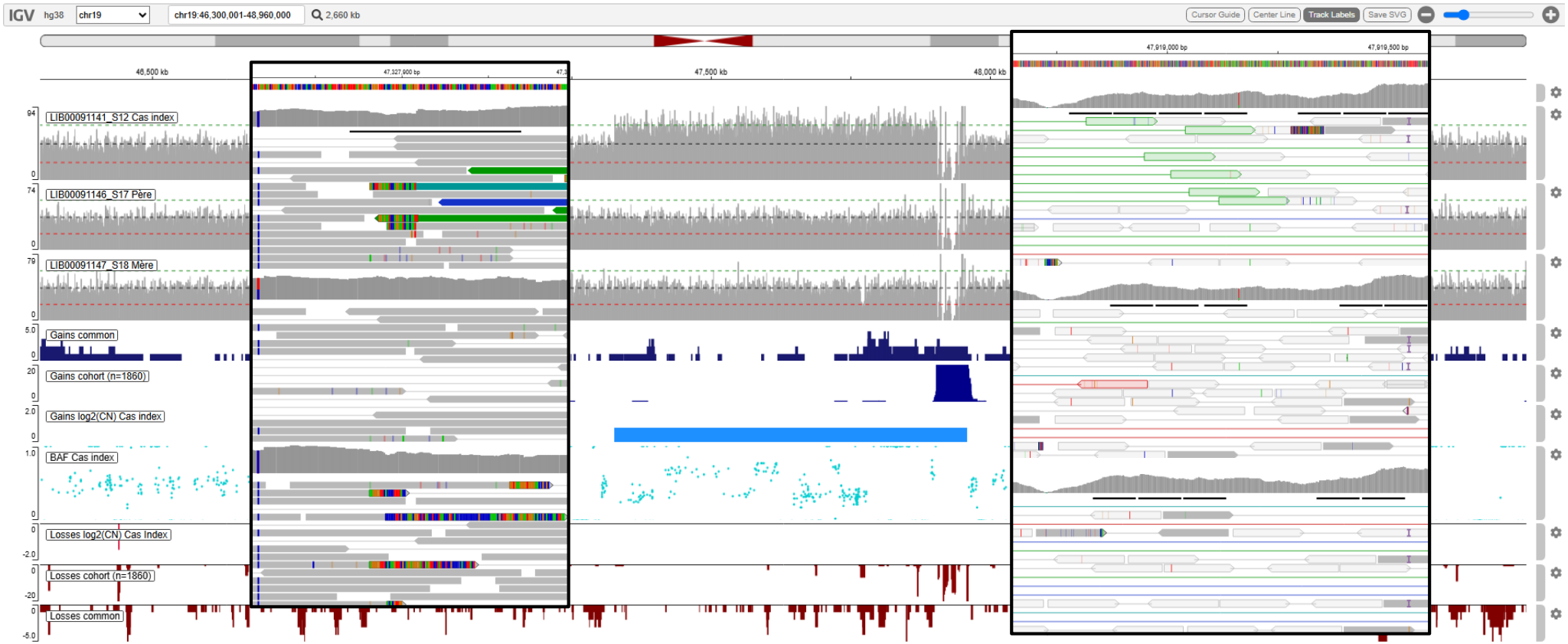
660.00

BICRA (AD) CRX (AD&NA) KPTN (AR)

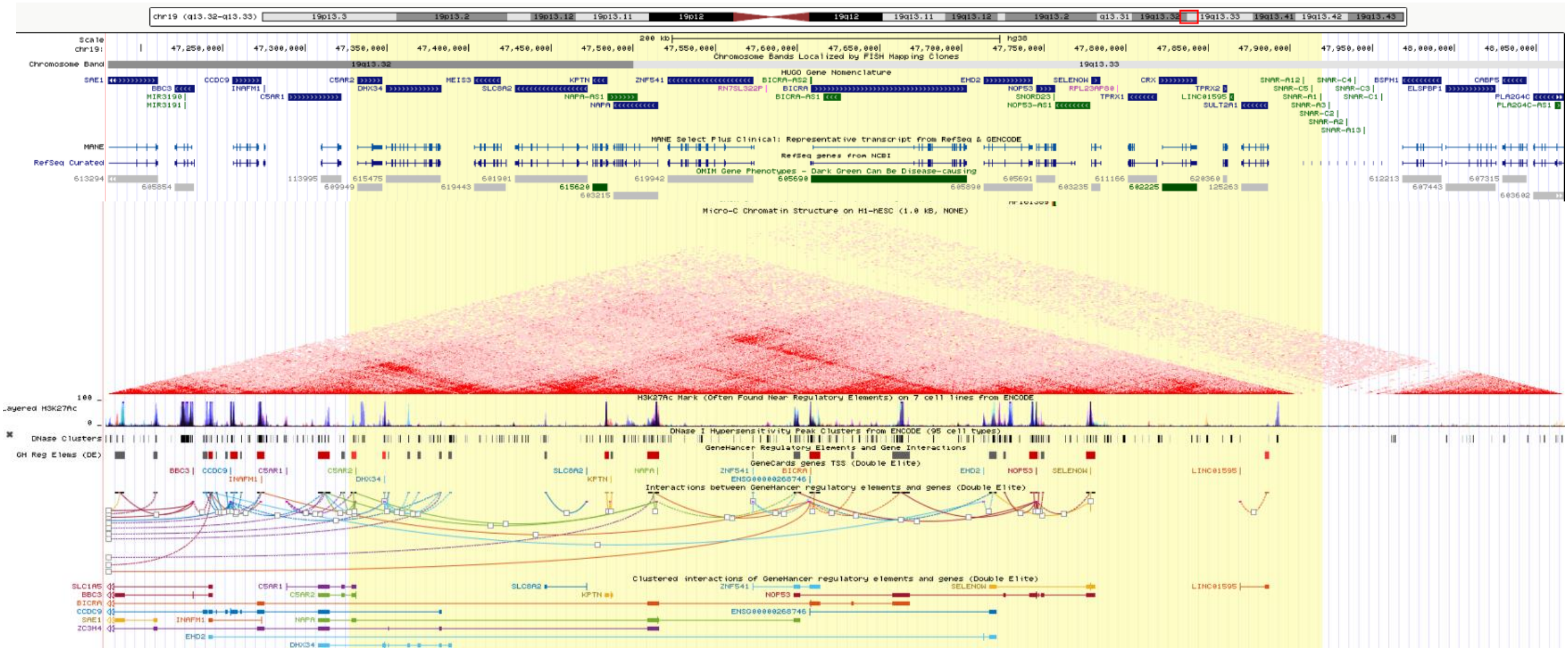
génique

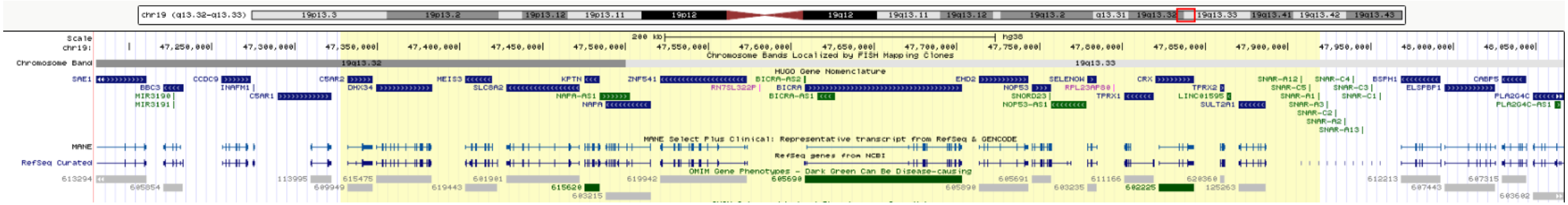
Duplication hétérozygote en tandem, de novo, BPD incertain car LCR

hpo:42 expert



chr19 (q13.32-q13.33)
Scale
chr19:
Chromosome Band
Chromosome Bands Localized by FISH Mapping Clones
HUGO Gene Nomenclature
MANE Select Plus Clinical: Representative transcript from RefSeq & GENCODE
RefSeq Curated
RefSeq genes from NCBI
OMIM Gene Phenotypes - Dark Green Can Be Disease-causing
OMIM Cytogenetic Loci Phenotypes - Gene Unknown
DECIPHER CNVs (Merged 18 items)
Merged 18 items
Database of Genomic Variants: Structural Var Regions (CNV, Inversion, In/del)
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Microarray Probesets and OGM sites


chr19 (q13.32-q13.33)
Chromosome Bands Localized by FISH Mapping Clones
HUGO Gene Nomenclature
MANE Select Plus Clinical: Representative transcript from RefSeq & GENCODE
RefSeq genes from NCBI
OMIM Gene Phenotypes - Dark Green Can Be Disease-causing
Micro-C Chromatin Structure on H1-hESC (1.0 kB, NONE)
H3K27Ac Mark (Often Found Near Regulatory Elements) on 7 cell lines from ENCODE
DNase I Hypersensitivity Peak Clusters from ENCODE (95 cell types)
GeneHancer Regulatory Elements and Gene Interactions
GeneCards genes TSS (Double Elite)
Interactions between GeneHancer regulatory elements and genes (Double Elite)
Clustered interactions of GeneHancer regulatory elements and genes (Double Elite)

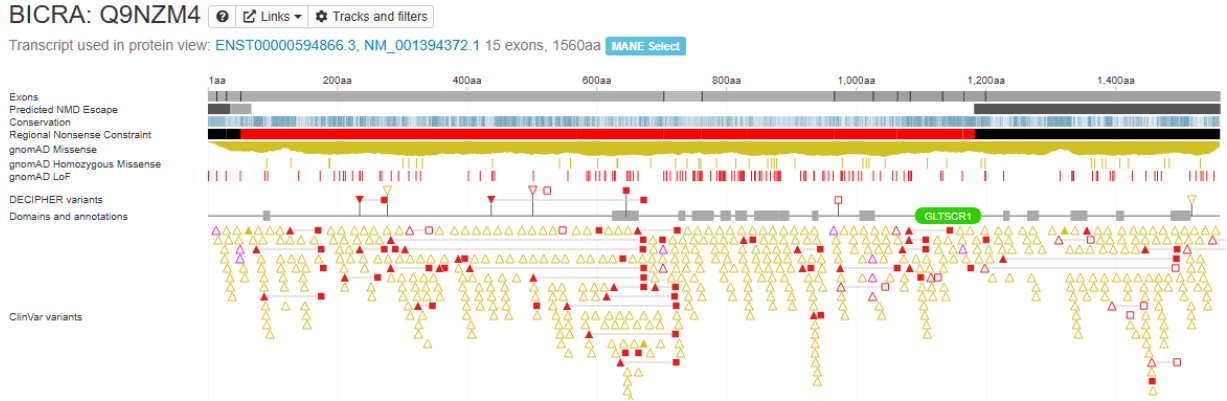


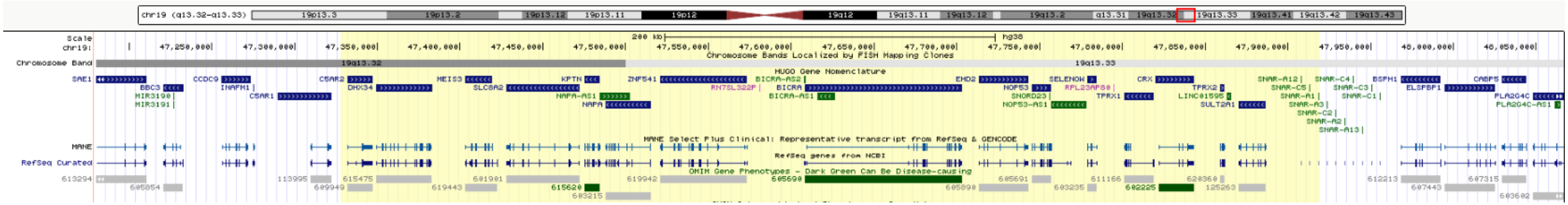
619325

COFFIN-SIRIS SYNDROME 12; CSS12

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
19q13.33	Coffin-Siris syndrome 12	619325	AD	3	BICRA	605690





Review > Genes (Basel). 2023 Nov 29;14(12):2157. doi: 10.3390/genes14122157.

Duplication at 19q13.32q13.33 Segregating with Neuropsychiatric Phenotype in a Three-Generation Family: Towards the Definition of a Critical Region

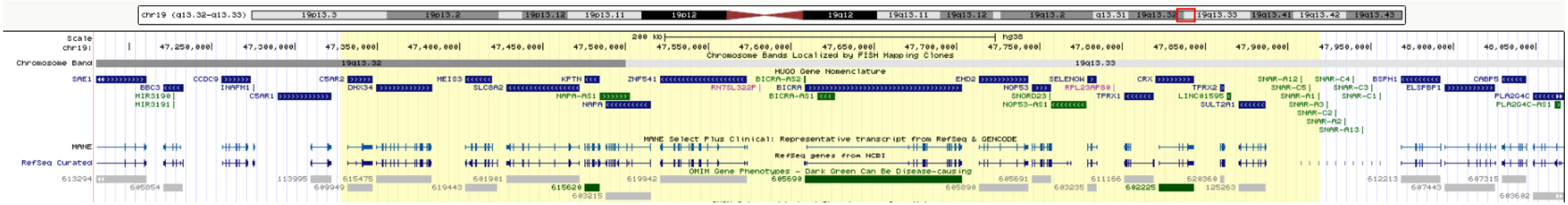
Daniele Guadagnolo [1], Gioia Mastromoro [1], Barbara Torres [2], Enrica Marchionni [1], Francesca di Palma [1], Marina Goldoni [2], Dario Cocciadiferro [3], Antonio Novelli [3], Laura Bernardini [2], Antonio Pizzuti [1 2]

Affiliations + expand

PMID: **38136979** PMCID: PMC10742575 DOI: 10.3390/genes14122157

A review of the reported microduplications allowed to propose *BICRA* (MIM *605690) and *KPTN* (MIM *615620) as candidates for the neurodevelopmental delay susceptibility in 19q13.32q13.33 copy number gains. The peculiarities of this case are the small extension of the duplication, the three-generation segregation, and the full penetrance of the phenotype.

1 publication avec 1 famille : peu étayé



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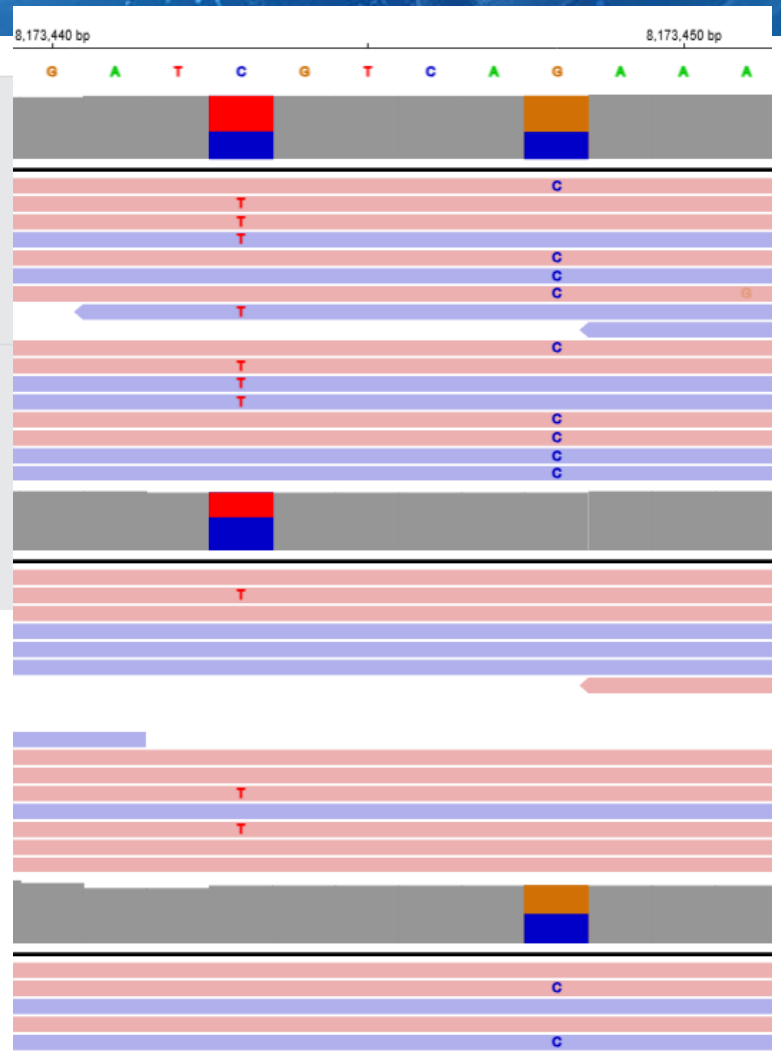
Votre avis ?

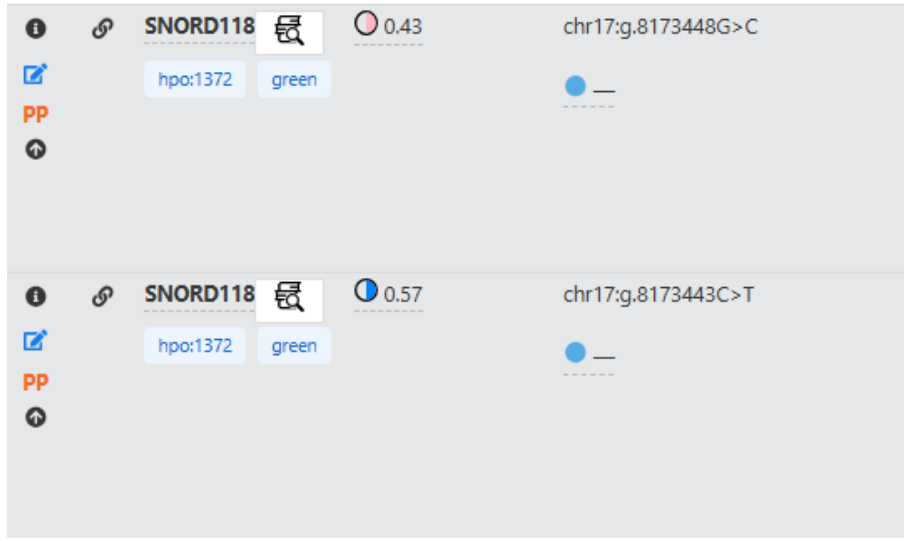
VSI	chr19:47300001-47960000 19q13.32q13.33 + SNV	3 copies 1.73 Ségrégation familiale	gnomAD —	**aura-db :** VSI (1)		660.00	BICRA (AD) CRX (AD&NA) KPTN (AR) génique hpo:42 expert	

Et dans les SNV :

PP	SNORD118 hpo:1372 green	0.43	chr17:g.8173448G>C —	**v4.** 0.0007 gnomADv3 All of Us **coh.** 0.0011	CADD GERP+ UTR SpliceAI	7.46 — — — —	Pathogène/Probablement Pathogène Leukoencephalopathy, brain calcifications, and cysts(AR) **aura-db :** Probablement Pathogène (1)	
PP	SNORD118 hpo:1372 green	0.57	chr17:g.8173443C>T —	**v4.** 0.0001 gnomADv3 All of Us **coh.** 0.0003	CADD GERP+ UTR SpliceAI	9.89 — — — —	Probablement Pathogène Leukoencephalopathy, brain calcifications, and cysts(AR) **aura-db :** Probablement Pathogène (1)	

SNORD118	0.43	chr17:g.8173448G>C	**v4.** 0.0007	CADD	7.46
hpo:1372 green			gnomADv3	GERP+	—
PP			All of Us	UTR	
			coh. 0.0011		—
				SpliceAI	—
					—
SNORD118	0.57	chr17:g.8173443C>T	**v4.** 0.0001	CADD	9.89
hpo:1372 green			gnomADv3	GERP+	—
PP			All of Us	UTR	
			coh. 0.0003		—
				SpliceAI	—
					—





Nat Genet. 2016 Oct;48(10):1185-92. doi: 10.1038/ng.3661. Epub 2016 Aug 29.

Mutations in SNORD118 cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts

Emma M Jenkinson [1], Mathieu P Rodero [2], Paul R Kasher [1], Carolina Uggenti [2], Anthony Oojageer [1], Laurence C Goosey [1], Yoann Rose [2], Christopher J Kershaw [3], Jill E Urquhart [1], Simon G Williams [1], Sanjeev S Bhaskar [1], James O'Sullivan [1], Gabriela M Baerlocher [4 5], Monika Haubitz [4 5], Geraldine Aubert [6 7], Kristin W Barañano [8 9], Angela J Barnicoat [10], Roberta Battini [11], Andrea Berger [12 13], Edward M Blair [14], Janice E Brunstrom-Hernandez [15 16], Johannes A Buckard [17], David M Cassiman [18], Rosaline Caumes [19], Duccio M Cordelli [20], Liesbeth M De Waele [21 22], Alexander J Fay [16], Patrick Ferreira [23], Nicholas A Fletcher [24], Alan E Fryer [25], Himanshu Goel [26 27], Cheryl A Hemingway [28], Marco Henneke [29], Imelda Hughes [30], Rosalind J Jefferson [31], Ram Kumar [32], Lieven Lagae [22], Pierre G Landrieu [33], Charles M Lourenço [34], Timothy J Malpas [35], Sarju G Mehta [36], Imke Metz [37], Sakkubai Naidu [38], Katrin Õunap [39 40], Axel Panzer [41], Prab Prabhakar [28], Gerardine Quaghebeur [42], Raphael Schiffmann [43], Elliott H Sherr [44], Kanaga R Sinnathuray [45], Calvin Soh [46], Helen S Stewart [14], John Stone [47], Hilde Van Esch [48], Christine E G Van Mol [49], Adeline Vanderver [50 51], Emma L Wakeling [52], Andrea Whitney [53], Graham D Pavitt [3], Sam Griffiths-Jones [3], Gillian I Rice [1], Patrick Revy [54 55], Marjo S van der Knaap [56 57], John H Livingston [58], Raymond T O'Keefe [3], Yanick J Crow [1 2 55]

Affiliations + expand

PMID: 27571260 PMCID: PMC5045717 DOI: 10.1038/ng.3661

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
17p13.1	Leukoencephalopathy, brain calcifications, and cysts	614561	AR	3	SNORD118	616663

Clinical Synopsis | PheneGene Graphics

INHERITANCE
- Autosomal recessive

NEUROLOGIC

Central Nervous System
- Developmental delay
- Seizures
- Gait abnormalities
- Spasticity
- Dystonia
- Ataxia
- Dysarthria
- Hemiplegia
- Tremor
- Cognitive decline
- Extrapyramidal signs
- Pyramidal signs
- Intracerebral cysts
- Intracranial calcifications
- Leukodystrophy

MISCELLANEOUS
- Onset usually in childhood
- Later onset has been reported
- Highly variable severity
- Progressive disorder

MOLECULAR BASIS
- Caused by mutation in the small nucleolar RNA, C/D box, 118 gene (SNORD118, 616663.0001)

Pathogène/Probablement Pathogène

Leukoencephalopathy, brain calcifications, and cysts(AR)

aura-db :
Probablement Pathogène (1)

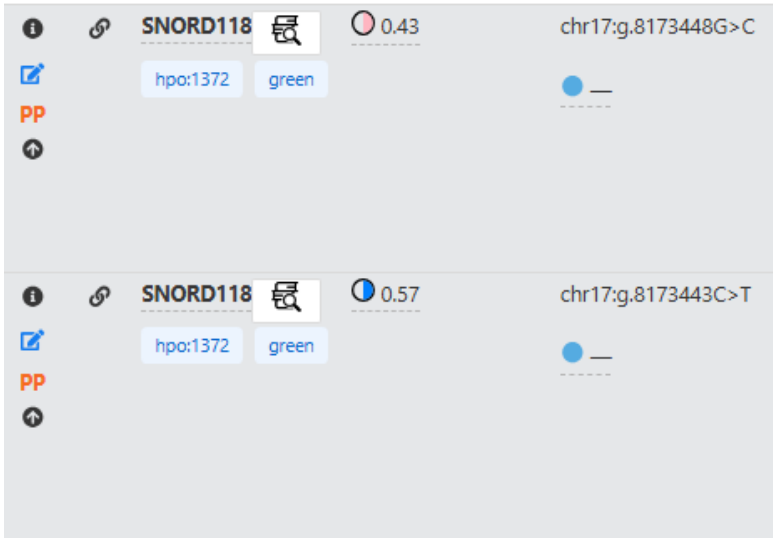
Probablement Pathogène

Leukoencephalopathy, brain calcifications, and cysts(AR)

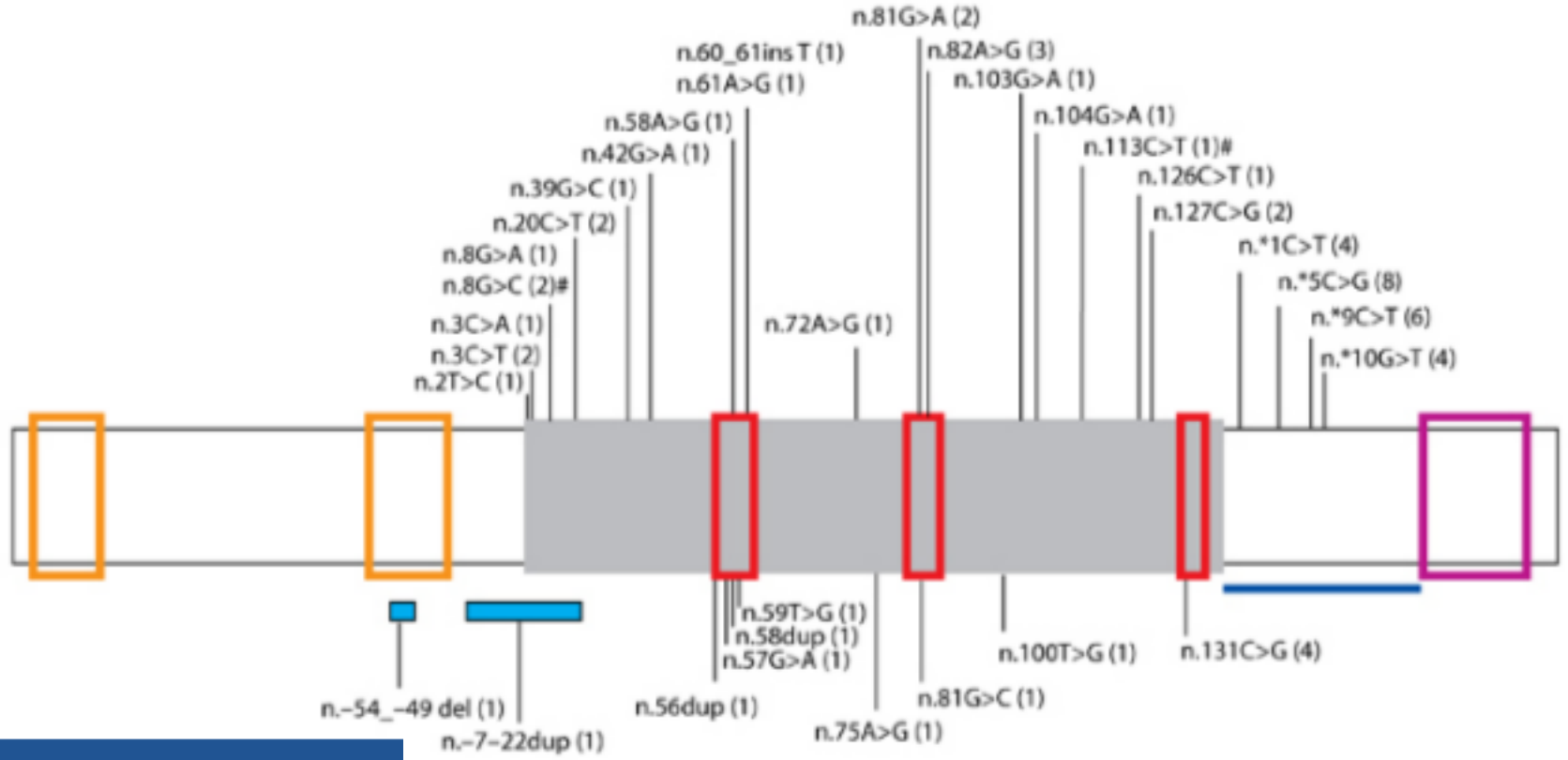
aura-db :
Probablement Pathogène (1)

Nat Genet. 2016 Oct;48(10):1185-92. doi: 10.1038/ng.3661. Epub 2016 Aug 29.

Mutations in SNORD118 cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts



NR_033294.1:n.[*5C>G];[*10G>A]
*10 Pas la même que celle de la publi



NC_000017.11:g.8173443C>T

Germline

Classification

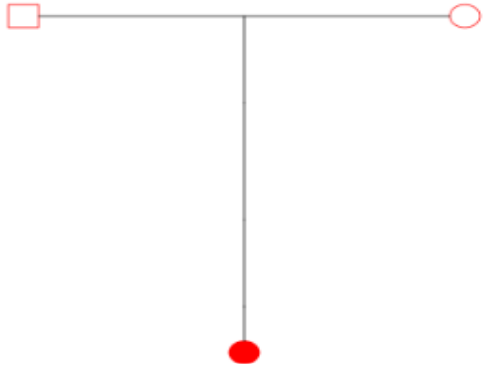
Likely pathogenic
Likely pathogenic (1)
This classification is based on the single submission received

Nat Genet. 2016 Oct;48(10):1185-92. doi: 10.1038/ng.3661. Epub 2016 Aug 29.

Mutations in SNORD118 cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts

Garçon de 4 ans
Exome et ACPA ras
trio parents

Symptômes renseignés :
Retard moteur
Fente



Génome trio :
- VSI CNV duplication hétérozygote de novo incluant BICRA
- SNORD118 htz composite P/VSI

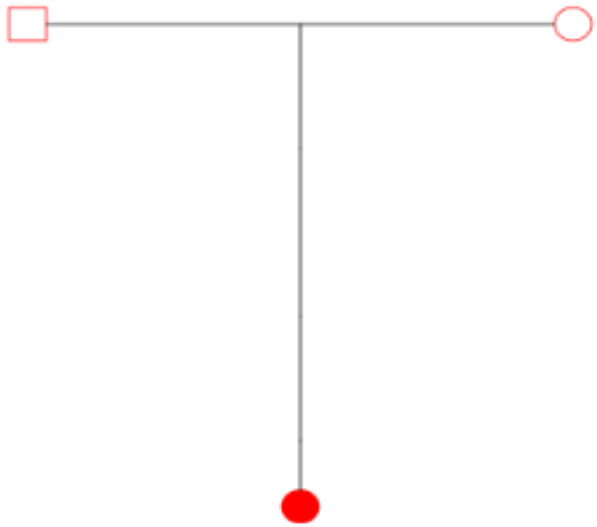
→ Avis expert SNORD118, IRM cérébrale
→ Pour la duplication : appel à collaboration, genematcher…

→ RAS pour expliquer la fente à priori

Cas 2

Cas 2

Fille de 12 ans
Exome trio : variant DHX30 hétérozygote de novo



Symptômes renseignés

0007018: Déficit de l'attention avec hyperactivité
0002474: Retard de langage, de type expressif
0000717: Autisme
0002360: Trouble du sommeil
0001273: Anomalie du corps calleux

Fille de 12 ans
Exome trio : variant DHX30 hétérozygote de novo

VSI

DHX30

hpo:386 green

0.34
Ségrégation familiale

chr3:g.47818115G>C
c.122G>C e.4/22
p.Arg41Pro

gnomAD

—

CADD 27.6
GERP+ 5.61
UTR —
SpliceAI — — —

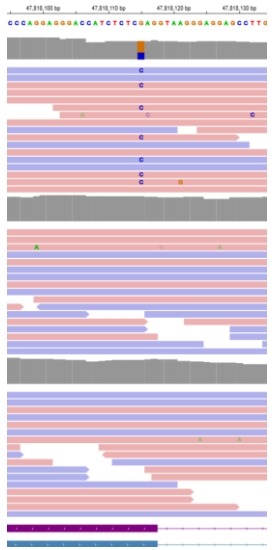
—

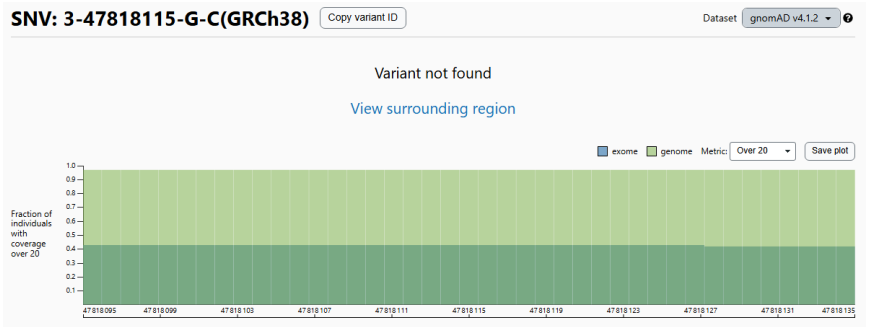
Neurodevelopmental disorder with variable motor and speech impairment(AD)

aura-db :
VSI (1)

Missense predictions: p.(Arg41Pro)

Features	Values	Prediction
SIFT:	0.01 *	Damaging
Polyphen 2 HumDiv:	0.989	Probably Damaging
Polyphen 2 HumVar:	0.969	Probably Damaging
Fathmm-XF:	0.790	Damaging
AlphaMissense:	0.168	Likely Benign
popEVE:	-3.375 *	Benign
BayesDel (with MaxAF):	0.004	Tolerated
REVEL:	0.204	Uncertain
ClinPred:	0.627	Damaging
Meta SVM:	-1.066 (10)	Tolerated
Meta LR:	0.029 (10)	Tolerated
Mistic:	0.30	Tolerated



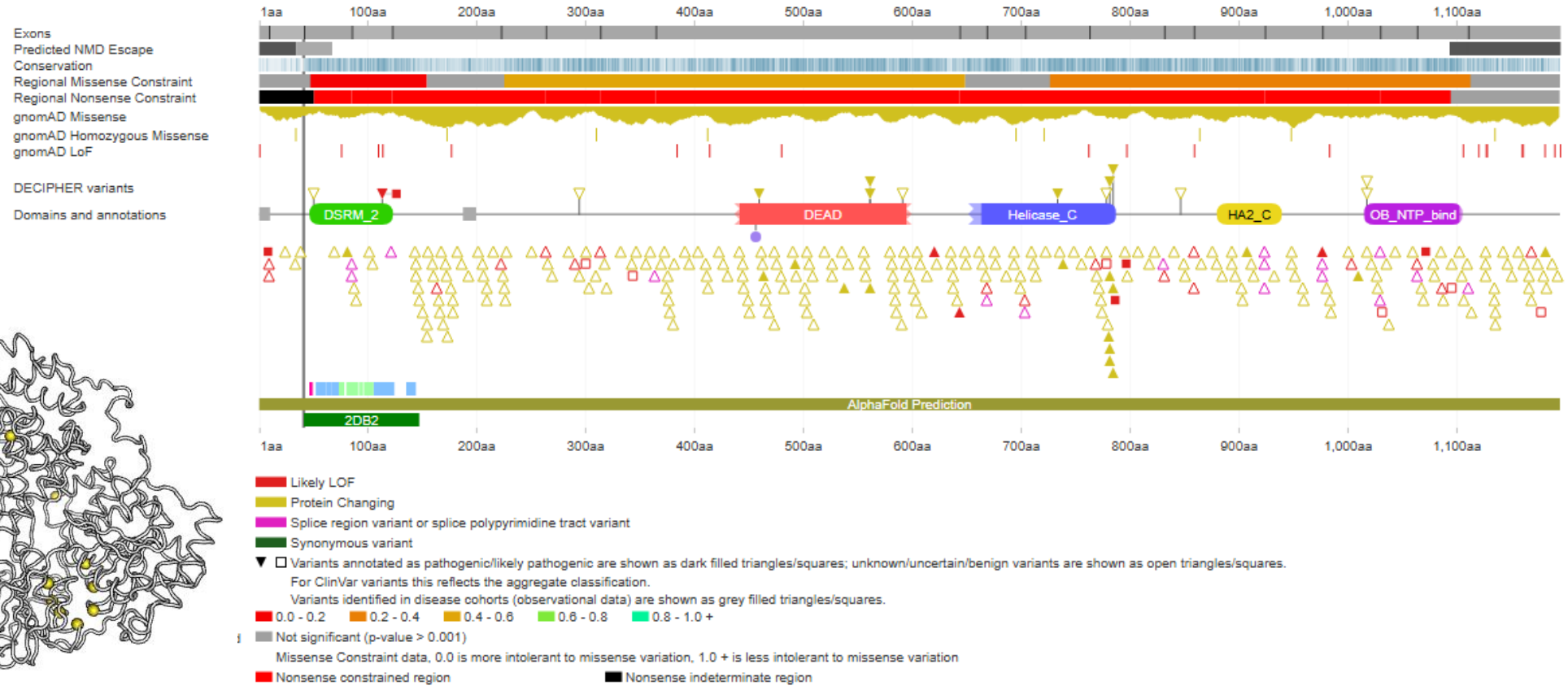


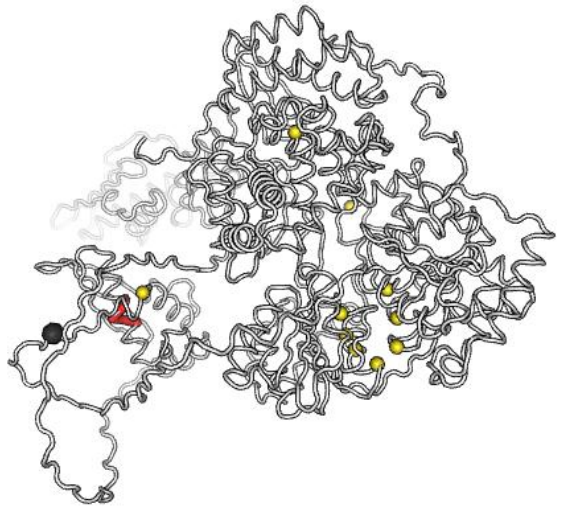
DHX30: Q7L2E3

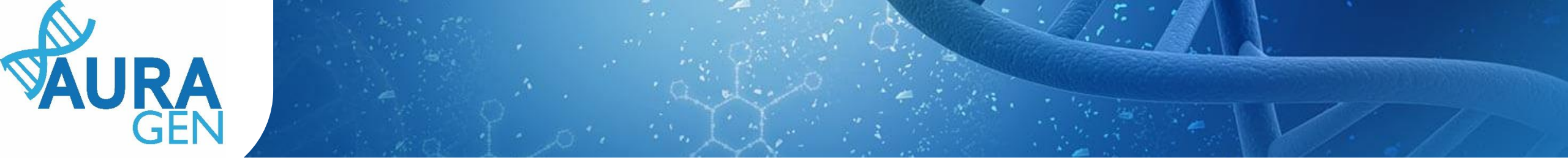
Links ▾ | Tracks and filters

Transcript used in protein view: ENST00000445061.6, NM_138615.3 22 exons, 1194aa MANE Select

ProtVar Functional Annotations Structure







VSI

DHX30

hpo:386 green

0.34
Ségrégation familiale

chr3:g.47818115G>C
c.122G>C e.4/22
p.Arg41Pro

gnomAD

—

CADD	27.6
GERP+	5.61
UTR	—
SpliceAI	—
	—

Neurodevelopmental disorder with variable motor and speech impairment(AD)

aura-db :
VSI (1)

617804
NEURODEVELOPMENTAL DISORDER WITH VARIABLE MOTOR AND LANGUAGE IMPAIRMENT; NEDMIAL
DHX30 - 616423
- Autosomal dominant

Central Nervous System
- Global developmental delay
- Impaired intellectual development
- Absent speech (in most patients)
- Speech delay
- Delayed walking
- Inability to walk
- Ataxia
- Poor fine motor skills
- Seizures (in some patients)
- Involuntary movements
- Dystonia
- Chorea
- Sleep disorder
- Brain imaging abnormalities (in some patients)
- Cerebral atrophy
- Cerebellar atrophy
- Enlarged ventricles
- Delayed myelination

Behavioral Psychiatric Manifestations
- Behavioral abnormalities, variable
- Sleep disturbances
- Autistic features

- Onset in infancy
- Variable dysmorphic features
- Most patients are severely impaired
- De novo mutation
- Recurrent variants at codons 782 and 785

Symptômes renseignés

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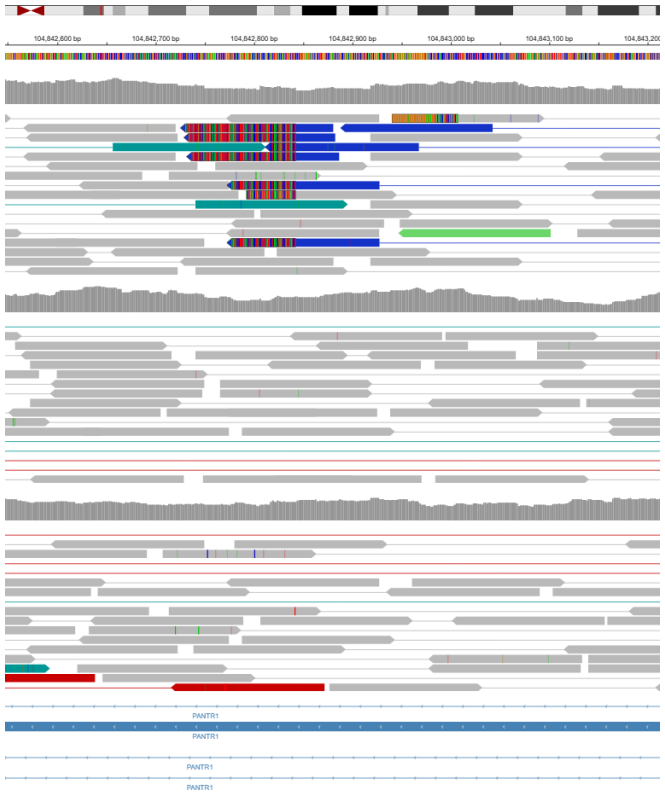
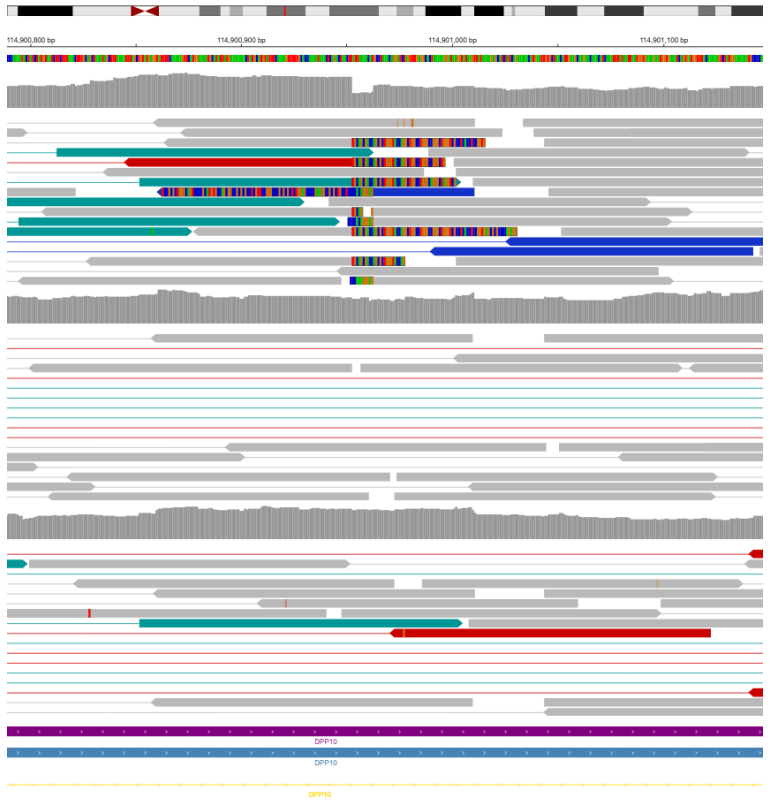
0002474: Retard de langage, de type expressif
0000717: Autisme
0002360: Trouble du sommeil
0001273: Anomalie du corps calleux

Inversion paracentrique hétérozygote de novo d'environ 10 Mb, pas de del

VSI	999	chr2:104842842 (2q12.1) chr2:114900952 (2q14.1)	— — gnomAD	40.00 (30, 20)	heterozygous de_novo	10058111	PANTR1 DPP10 expert



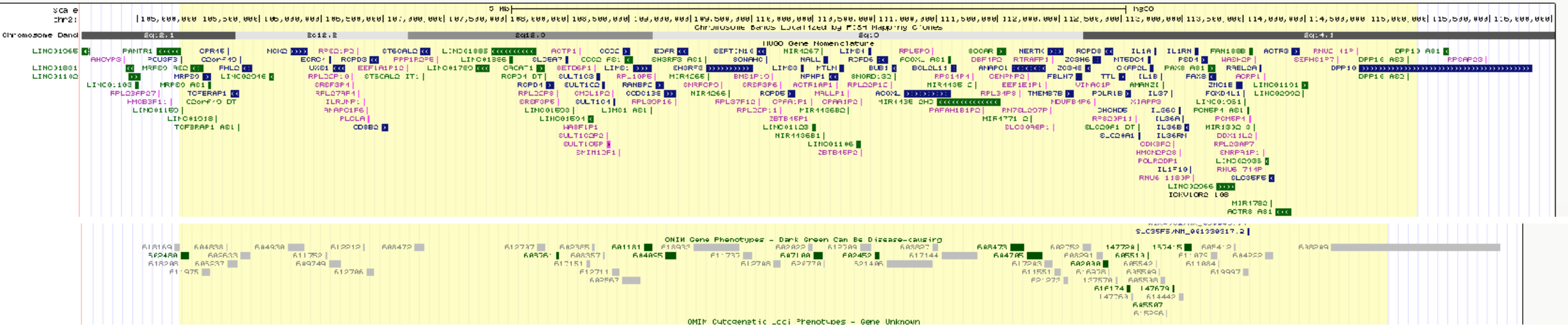


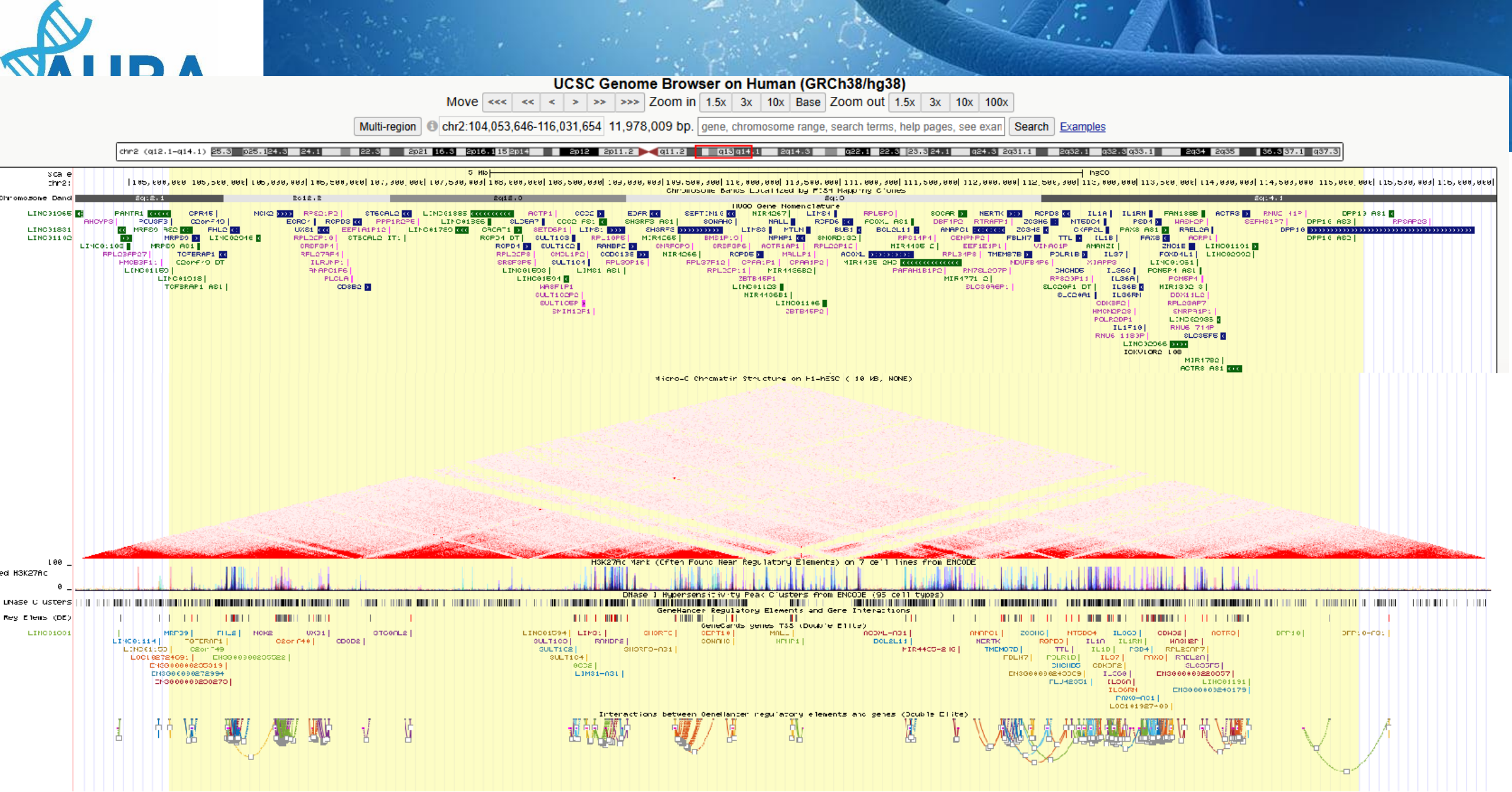
	999	chr2:104842842 (2q12.1) chr2:114900952 (2q14.1)	— —	40.00 (30, 20)	heterozygous de_novo	10058111	PANTR1 DPP10
VSI			gnomAD				

UCSC Genome Browser on Human (GRCh38/hg38)

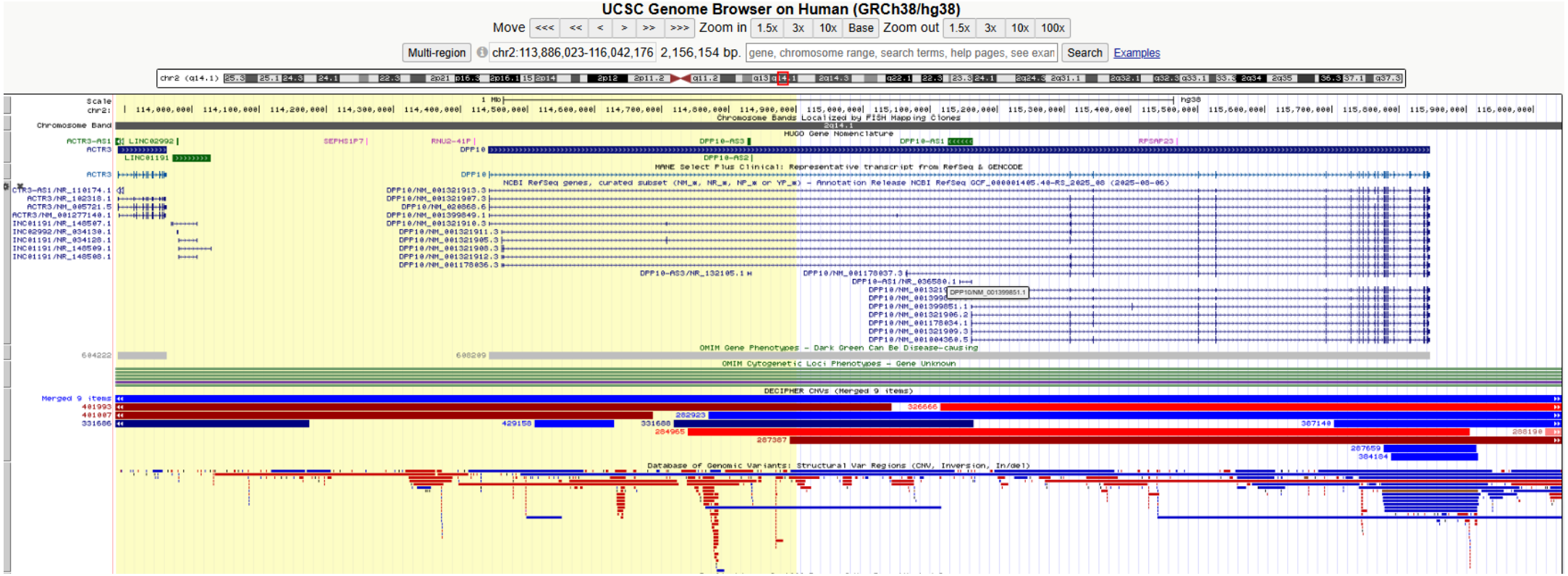
Move <<< << < > >> >>> Zoom in 1.5x 3x 10x Base Zoom out 1.5x 3x 10x 100x

Multi-region chr2:104,053,646-116,031,654 11,978,009 bp. gene, chromosome range, search terms, help pages, see exan Search Examples

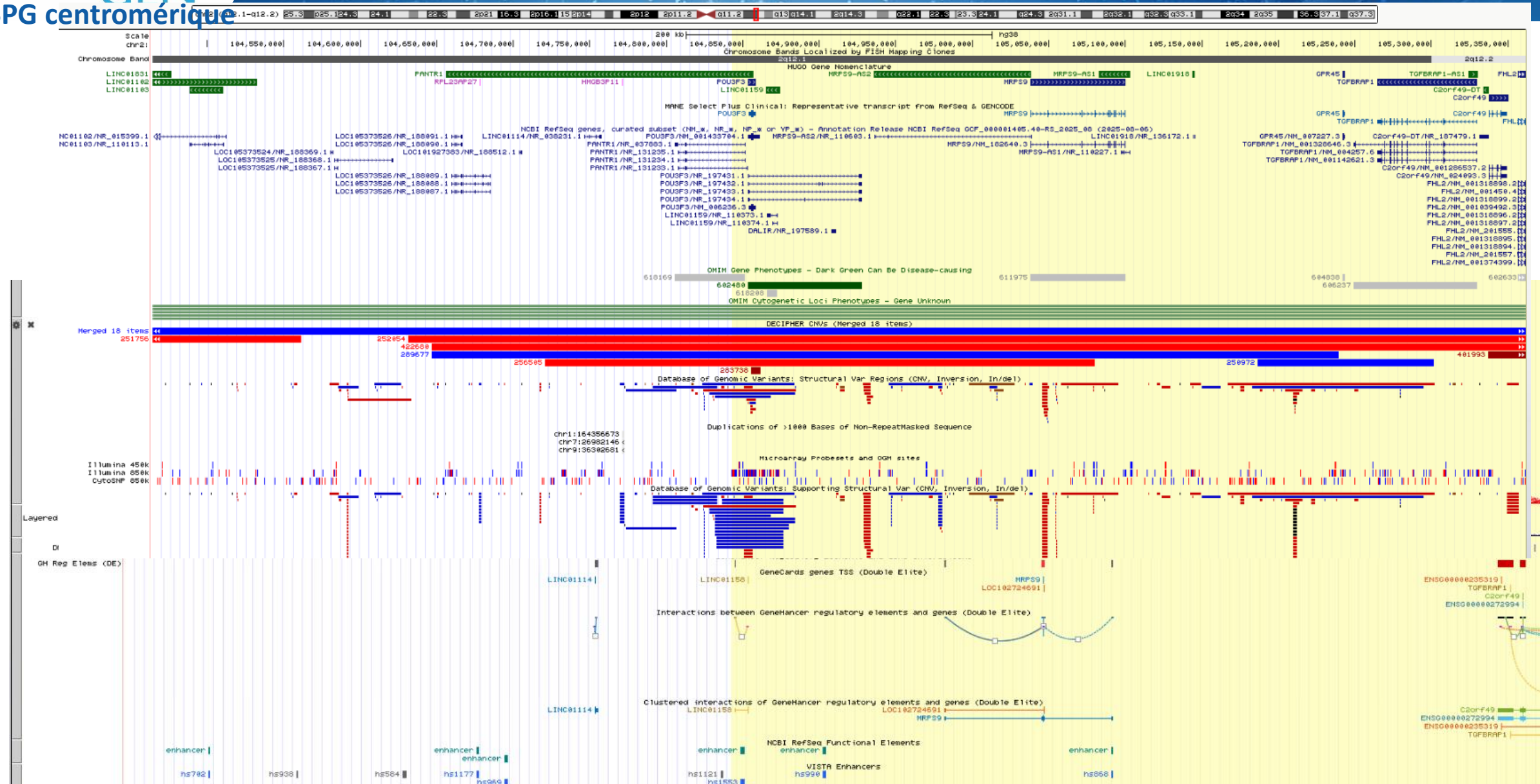


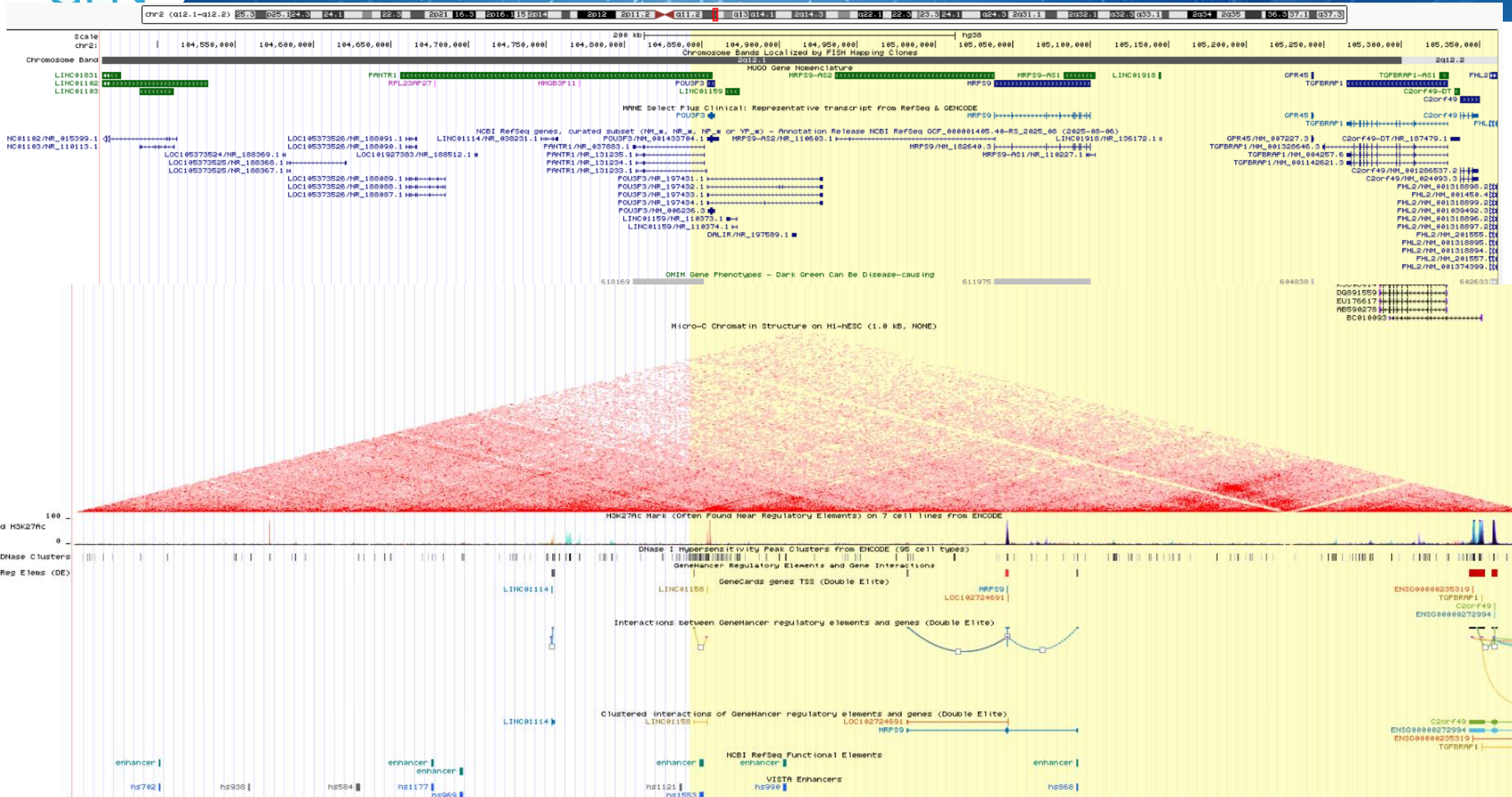

UCSC Genome Browser on Human (GRCh38/hg38)
Move <<< << < > >> >>> Zoom in 1.5x 3x 10x Base Zoom out 1.5x 3x 10x 100x
Multi-region chr2:104,053,646-116,031,654 11,978,009 bp. gene, chromosome range, search terms, help pages, see exan Search Examples
chr2 (q12.1-q14.1)
5 Mb
HUGO Gene Nomenclature
Micro-C Chromatin Structure on H1-hESC (10 KB, NONE)
H3K27Ac Mark (Often Found Near Regulatory Elements) on 7 Cell Lines from ENCODE
DNase I HyperSensitivity Peak Clusters from ENCODE (95 cell types)
GeneHancer Regulatory Elements and Gene Interactions
GeneCards genes TSS (Double Elite)
Interactions between GeneHancer regulatory elements and genes (Double Elite)

BPD télomérique



BPG centromérique




chr2 (q12.1-q12.2)
Scale
chr2:
Chromosome Band
Chromosome Bands Localized by FISH Mapping Clones
HUGO Gene Nomenclature
MANE Select Plus Clinical: Representative transcript from RefSeq & GENCODE
NCBI RefSeq genes, curated subset (NM_w, NR_w, NP_w or YP_w) - Annotation Release NCBI RefSeq GCF_000001405.40-RS_2025_08 (2025-08-06)
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Micro-C Chromatin Structure on H1-hESC (1.0 kB, NONE)
Layered H3K27Ac
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Clustered interactions of GeneHancer regulatory elements and genes (Double Elite)
NCBI RefSeq Functional Elements
VISTA Enhancers

VSI		999	chr2:104842842 (2q12.1) chr2:114900952 (2q14.1)	— — gnomAD	40.00 (30, 20)	heterozygous de_novo	10058111	PANTR1 DPP10 expert

Clin Genet. 2023 Aug;104(2):186-197. doi: 10.1111/cge.14353. Epub 2023 May 10.

POU3F3-related disorder: Defining the phenotype and expanding the molecular spectrum

Alessandra Rossi [1 2], Lot Snijders Blok [3], Sonja Neuser [4], Chiara Klöckner [4], Konrad Platzer [4], Laurence Olivier Faivre [5 6], Heike Weigand [7], Maria L Dentici [8 9], Marco Tartaglia [8], Marcello Niceta [8], Paolo Alfieri [10], Siddharth Srivastava [11], David Coulter [11], Lacey Smith [11], Kristin Vinorum [12], Gerarda Cappuccio [13 14], Nicola Brunetti-Pierri [13 14 15], Deniz Torun [16], Mutluay Arslan [17], Mathilde F Lauridsen [18], Oliver Murch [19], Rachel Irving [19], Sally A Lynch [20], Sarju G Mehta [21], Jenny Carmichael [21], Evelien Zonneveld-Huijssoon [22], Bert de Vries [3], Tjitske Kleefstra [3], Katrine M Johannesen [1 23], Ian T Westphall [24], Susan S Hughes [25], Sarah Smithson [26], Julie Evans [27], Tracy Dudding-Byth [28], Marleen Simon [29], Ellen van Binsbergen [29], Johanna C Herkert [22], Gea Beunders [22], Henry Oppermann [4], Mert Bakal [30], Rikke S Møller [1 31], Guido Rubboli [1 32], Allan Bayat [1 31 33]

Affiliations + expand

PMID: 37165752 PMCID: PMC10330344 DOI: 10.1111/cge.14353

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				gnomAD				

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POU3F3-related disorder: Defining the phenotype and expanding the molecular spectrum

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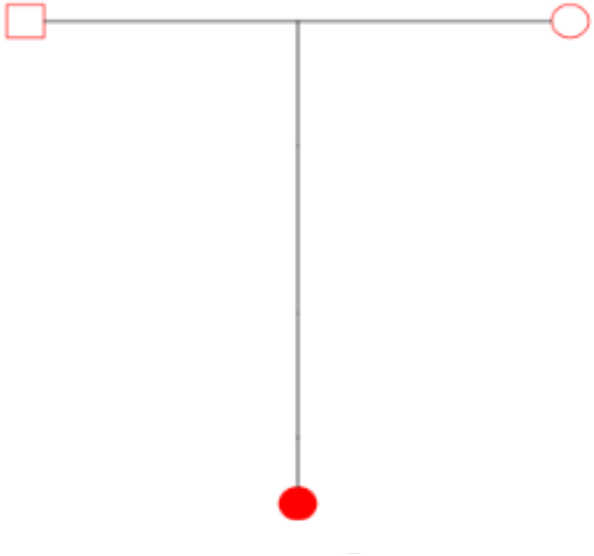
0002474: Retard de langage, de type expressif
0000717: Autisme
0002360: Trouble du sommeil
0001273: Anomalie du corps calleux

Abstract

POU3F3 variants cause developmental delay, behavioral problems, hypotonia and dysmorphic features. We investigated the phenotypic and genetic landscape, and genotype-phenotype correlations in individuals with **POU3F3**-related disorders. We recruited unpublished individuals with **POU3F3** variants through international collaborations and obtained updated clinical data on previously published individuals. Trio exome sequencing or single exome sequencing followed by segregation analysis were performed in the novel cohort. Functional effects of missense variants were investigated with 3D protein modeling. We included 28 individuals (5 previously published) from 26 families carrying **POU3F3** variants; 23 de novo and one inherited from an affected parent. Median age at study inclusion was 7.4 years. All had developmental delay mainly affecting speech, behavioral difficulties, psychiatric comorbidities and dysmorphisms. Additional features included gastrointestinal comorbidities, hearing loss, ophthalmological anomalies, epilepsy, sleep disturbances and joint hypermobility. Autism, hearing and eye comorbidities, dysmorphisms were more common in individuals with truncating variants, whereas epilepsy was only associated with missense variants. In silico structural modeling predicted that all (likely) pathogenic variants destabilize the DNA-binding region of **POU3F3**. Our study refined the phenotypic and genetic landscape of **POU3F3**-related disorders, it reports the functional properties of the identified pathogenic variants, and delineates some genotype-phenotype correlations.

Keywords: POU3F3; autism; cupped ears; epilepsy; neurodevelopmental disorder.

Fille de 12 ans
Exome trio : variant DHX30 hétérozygote de novo



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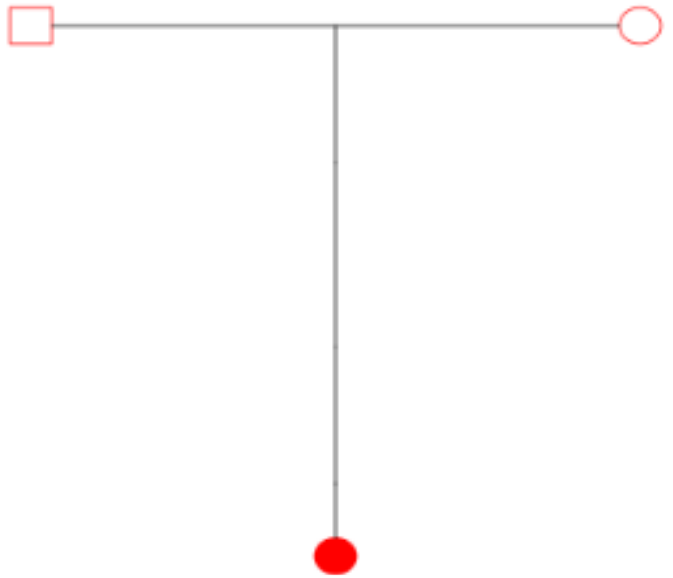
Génome trio :
- VSI SNV DHX30 hétérozygote de novo
- VSI SV inversion chr2 10 Mb hétérozygote de novo avec BP proche de POU3F3

→ Étude ARN à prévoir
→ Etude en cours pour DHX30 avec équipe de recherche

Cas 3

Cas 3

Garçon de 10 ans
Trio



Symptômes renseignés

0001249: Retard mental

0000717: Autisme

0002121: Absences épileptiques

0011149: Absences épileptiques avec myoclonie des paupières

0002376: Régression du développement

0100034: Tics moteurs

0100035: Tics phoniques

0010526: Dysgraphie

VSI

chr11:57435001-57772000
11q12.1

3 copies
1.31

gnomAD
—

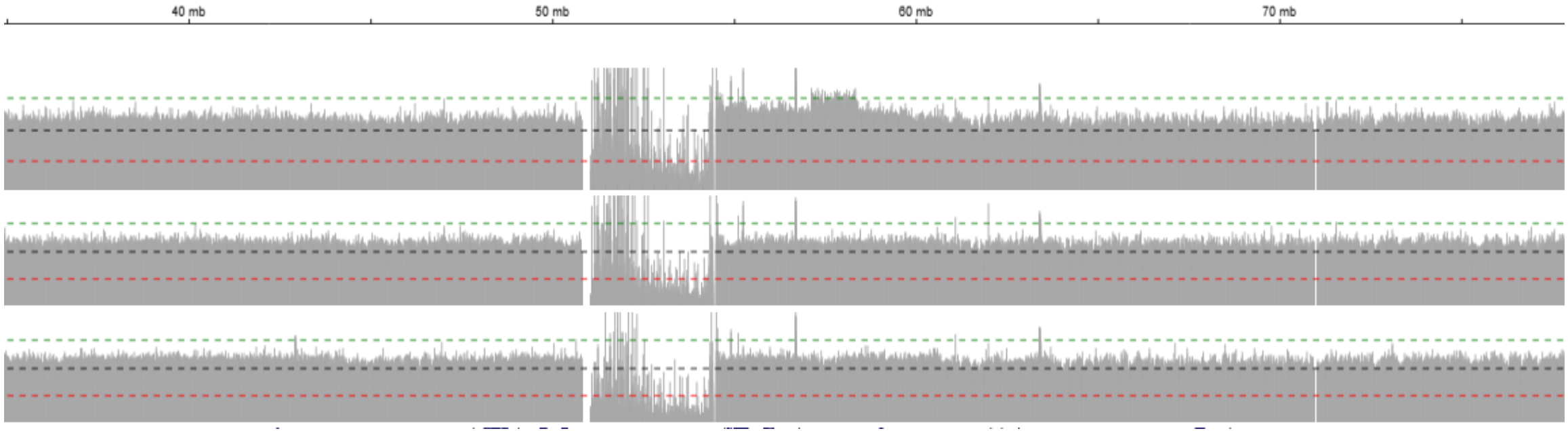
aura-db :
VSI (1)

337.00

SERPING1 (AD, AR) CLP1 (AR)
CTNND1 (AD) TMX2 (AR)

génique

hpo:643 expert



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3 copies
1.31

gnomAD
—

aura-db :
VSI (1)

337.00

SERPING1 (AD, AR) CLP1 (AR)
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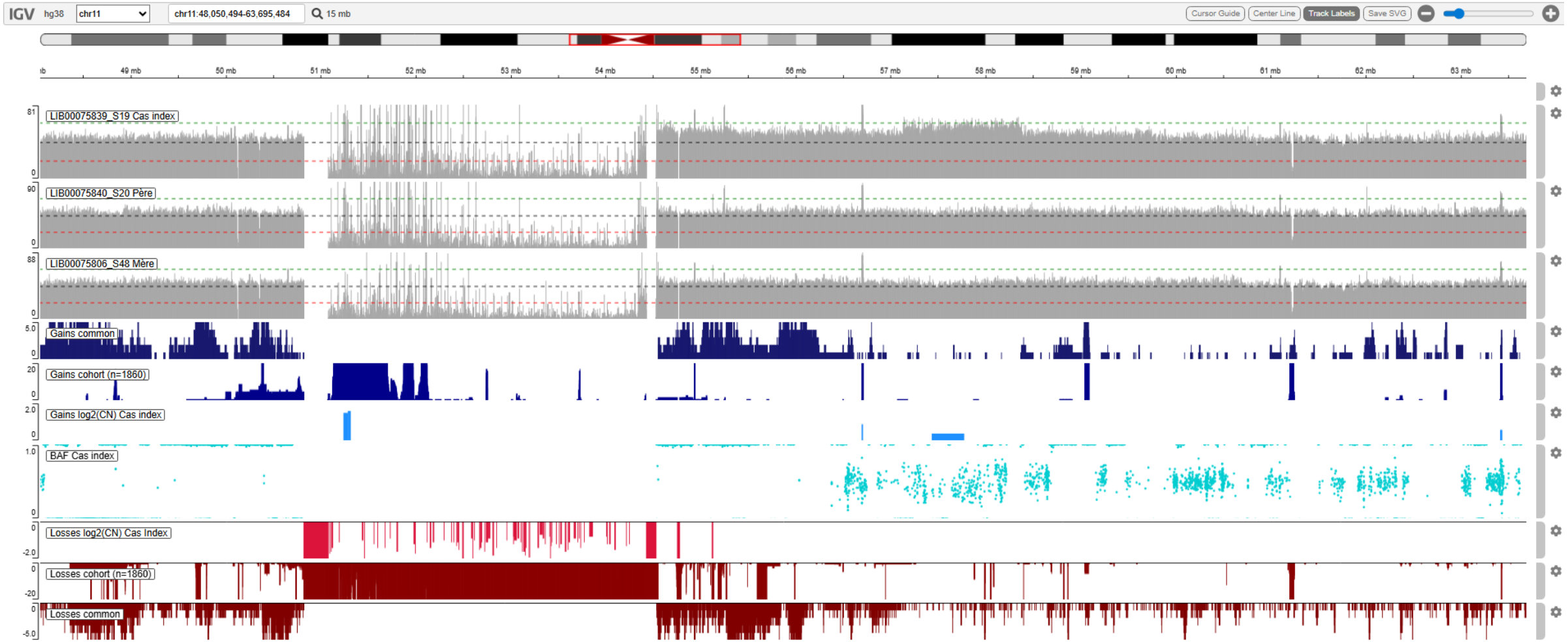
hpo:643 expert



chr11:57435001-57772000
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3 copies
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gnomAD
—

aura-db :
VSI (1)

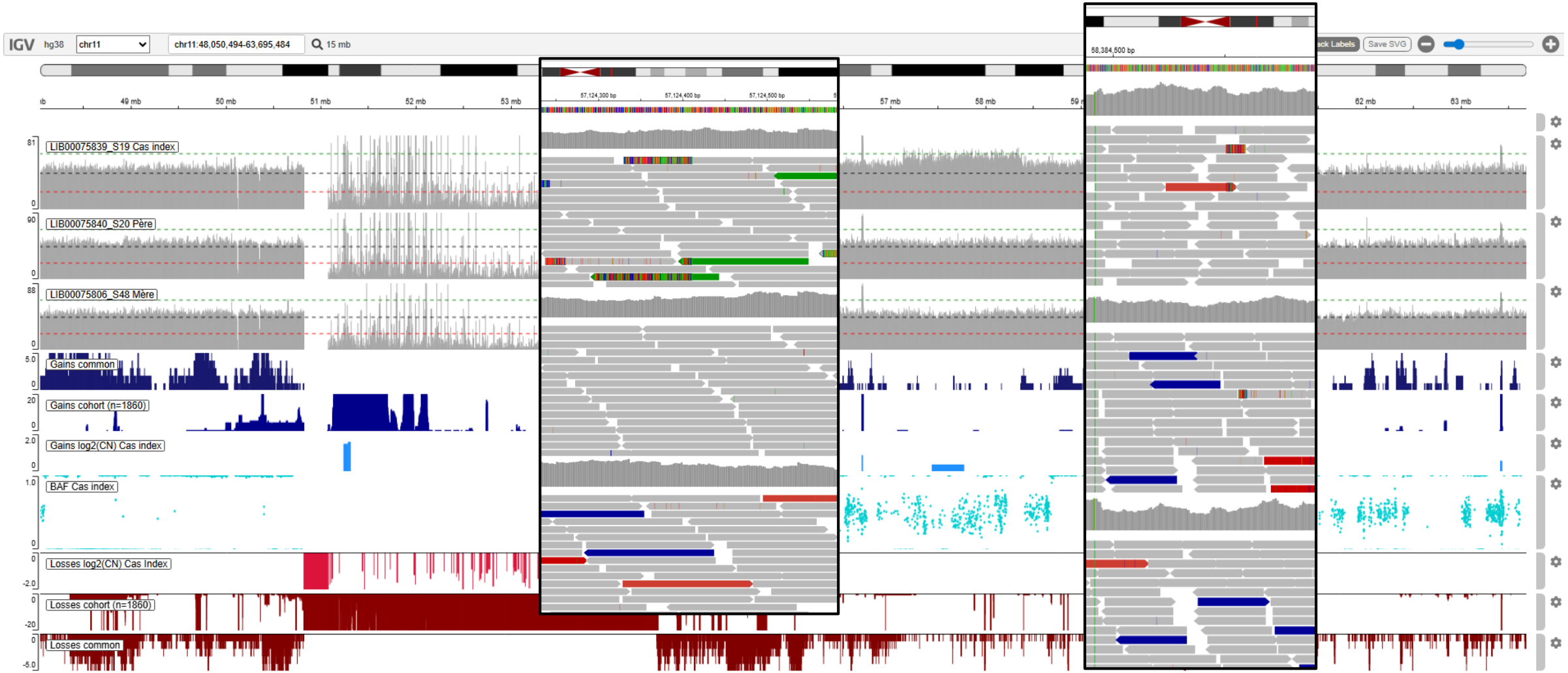
337.00

SERPING1 (AD, AR) CLP1 (AR)
CTNND1 (AD) TMX2 (AR)

génique

hpo:643 expert

Mosaïque avec BPG 3/53 reads et BPD 4/39 reads portant un split reads, de novo



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3 copies
1.31

gnomAD
—

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337.00

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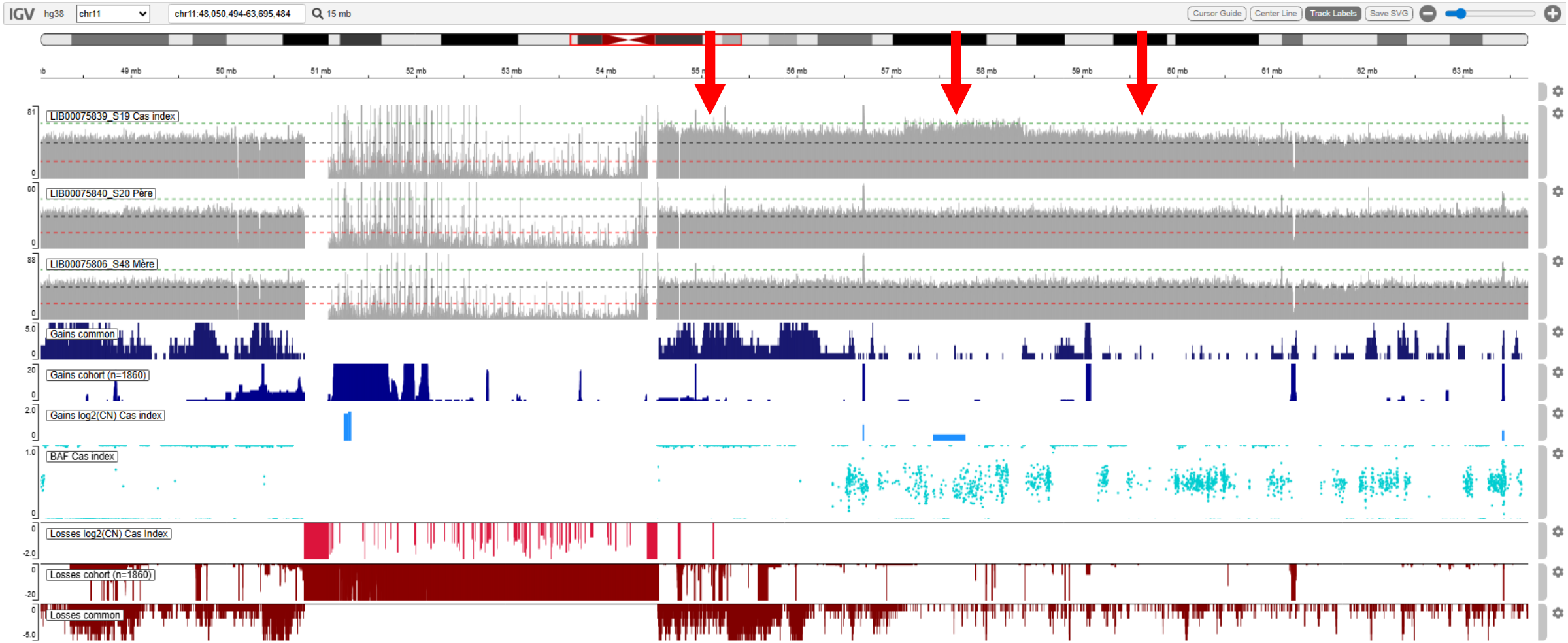
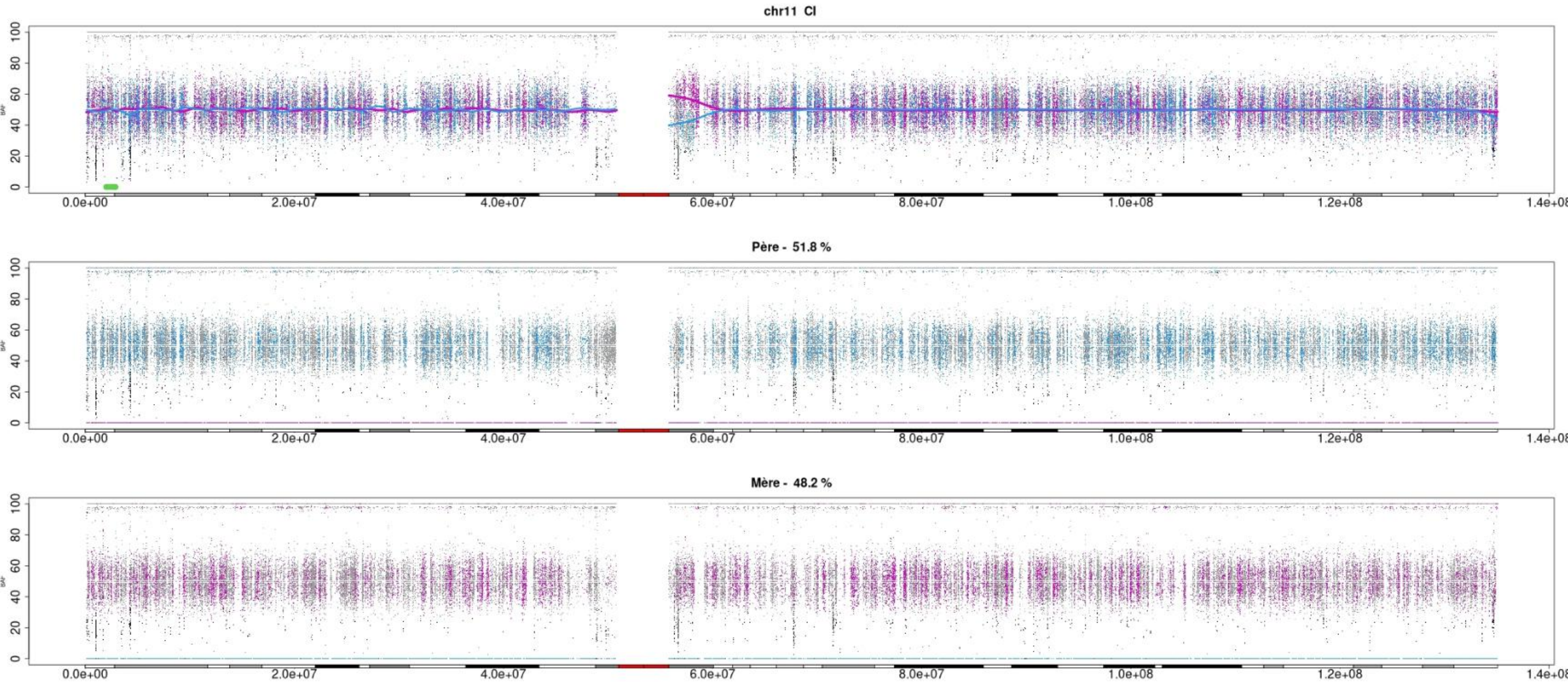
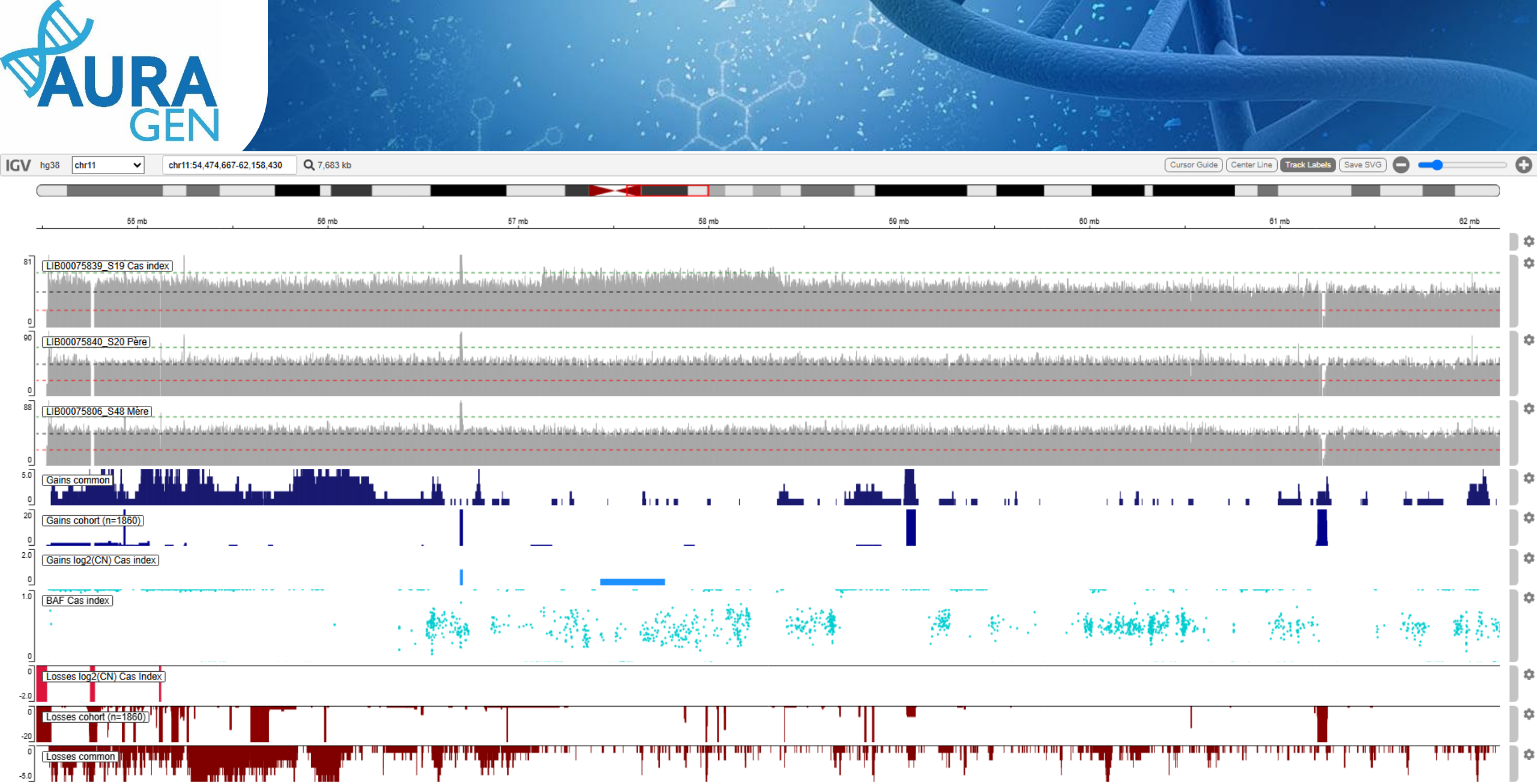
hpo:643 expert

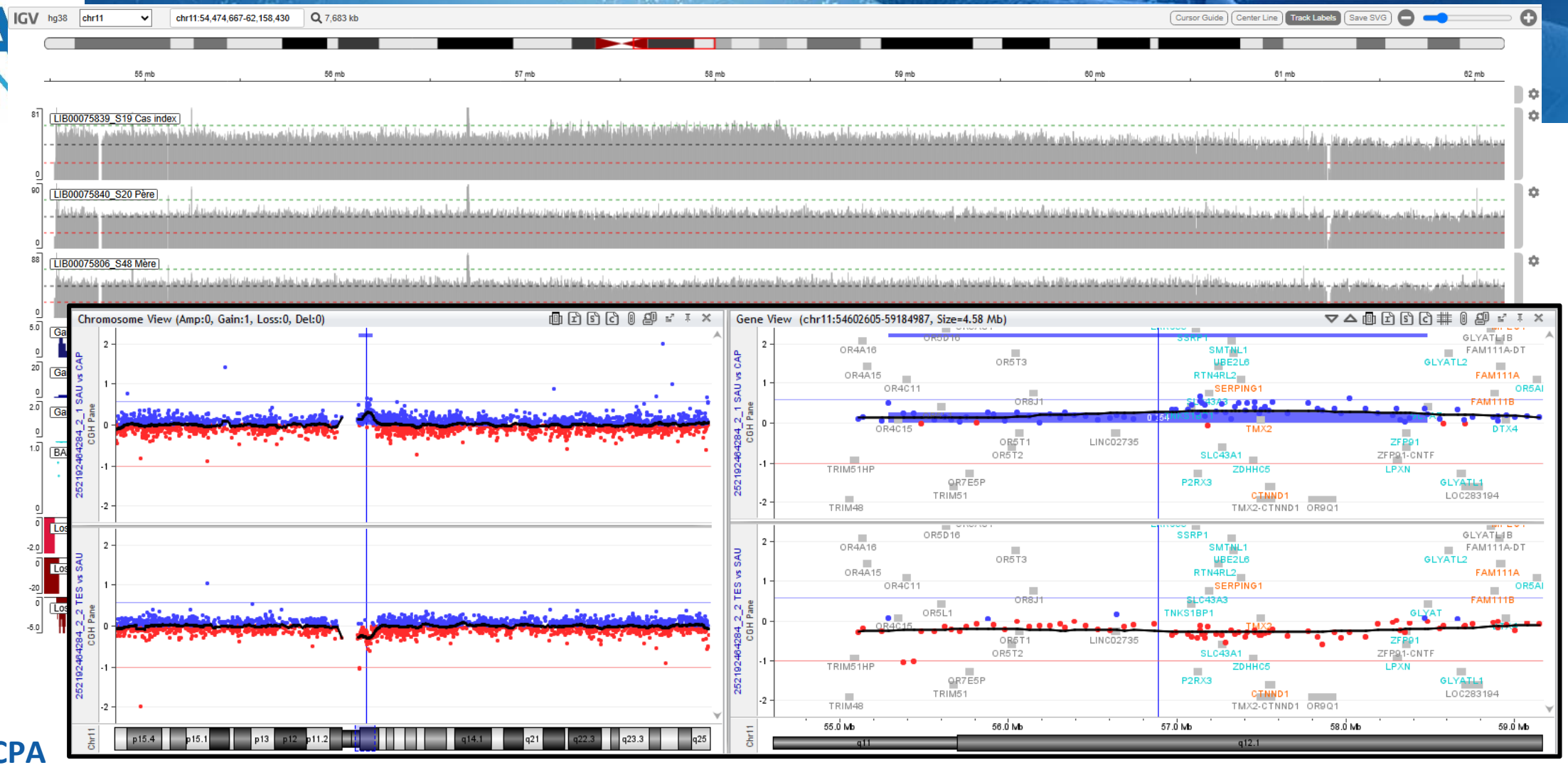



chr11 CI
BAF
0
20
40
60
80
100
0.0e+00
2.0e+07
4.0e+07
6.0e+07
8.0e+07
1.0e+08
1.2e+08
1.4e+08
Père - 51.8 %
Mère - 48.2 %


IGV
hg38
chr11
chr11:54,474,667-62,158,430
7,683 kb
Cursor Guide
Center Line
Track Labels
Save SVG
55 mb
56 mb
57 mb
58 mb
59 mb
60 mb
61 mb
62 mb
LIB00075839_S19 Cas index
LIB00075840_S20 Père
LIB00075806_S48 Mère
Gains common
Gains cohort (n=1860)
Gains log2(CN) Cas index
BAF Cas index
Losses log2(CN) Cas Index
Losses cohort (n=1860)
Losses common

Pas de gène d'intérêt

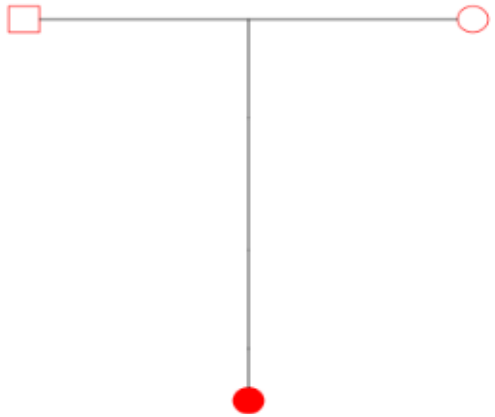
Decipher : dup en VSI



Visible en ACPA

Non rendu (limite de la résolution)

Garçon de 10 ans
Trio



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0002376: Régression du développement
0100034: Tics moteurs
0100035: Tics phoniques
0010526: Dysgraphie

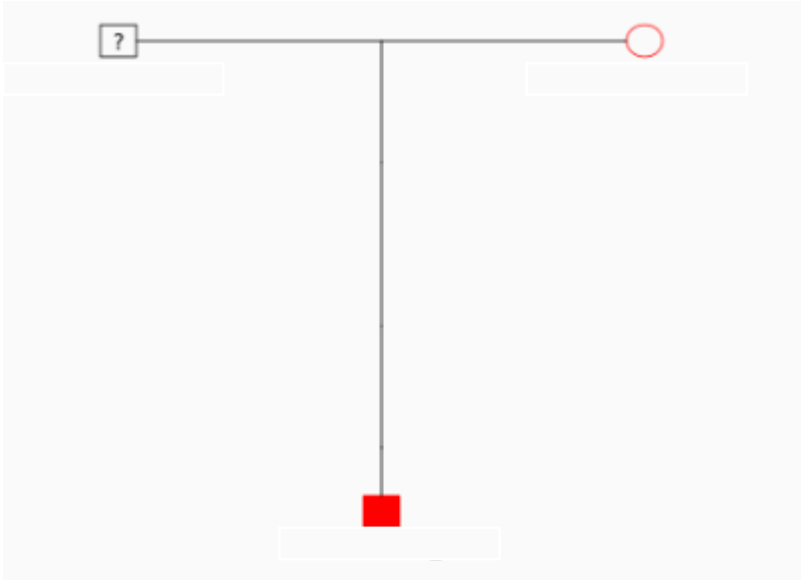
Génome trio :
VSI dup 11q12 htz mos dn 1.3 Mb minimum et possible remaniement chromosomique plus complexe (anneau ?)

→ Poursuivre explorations (confirmer et caractériser)
→ Bionano, FISH, caryotype, Nanopore…

Cas 4

Cas 4

Garçon de 6 ans
Duo avec mère



Symptômes renseignés

0011344: Retard de développement global sévère

0001344: Développement du langage absent

0001250: Crises épileptiques

0001270: Retard moteur

0200134: Encéphalopathie épileptique

0003248: Tissu gonadique inapproprié au système génital externe ou le sexe chromosomique

Garçon de 6 ans
Duo avec mère

Caryotype 46,XX, t(3;11)

Cartographie optique :

Résultat :
Variation de signification incertaine
ogm[GRCh38] ins(11;3)(q22.3;
q26.33q24.3)(103,203,716~103,218,264;179,315,579_144,229,903
),inv(3)(q26.33q26.33)(181,993,276_179,328,662)
La cartographie optique a révélé:
Un Profil chromosomique XX,

- Une insertion d'un fragment du chromosome 3, situé en 3q24.3q26.33 (position génomique hg38 : 179,315,579-144,229,903) d'une taille d'environ 35 Mb, sur le bras long du chromosome 11 en q22.3 (position génomique hg38 : 103,203,716 à 103,218,264). Ce fragment est inséré dans le chromosome 11 en orientation inversée.

- Une inversion supplémentaire d'un segment voisinant le point de cassure distal de l'insertion, d'une taille d'environ 266 kb, a également été identifiée en 3q26.33 (position génomique hg38 : 181,993,276-179,328,662),

ce segment s'est fusionné avec la région chromosomique 3q24.3 au niveau de la position de fusion 144,233,903 à 181,993,276.

Un point de cassure de ces remaniements affecte le gène DYNC2H1 en 11q22.3, référencé sous OMIM 603297 et de transmission autosomique récessive. Le gène DYNC2H1 est associé au syndrome de dysplasie thoracique à côtes courtes

Symptômes renseignés

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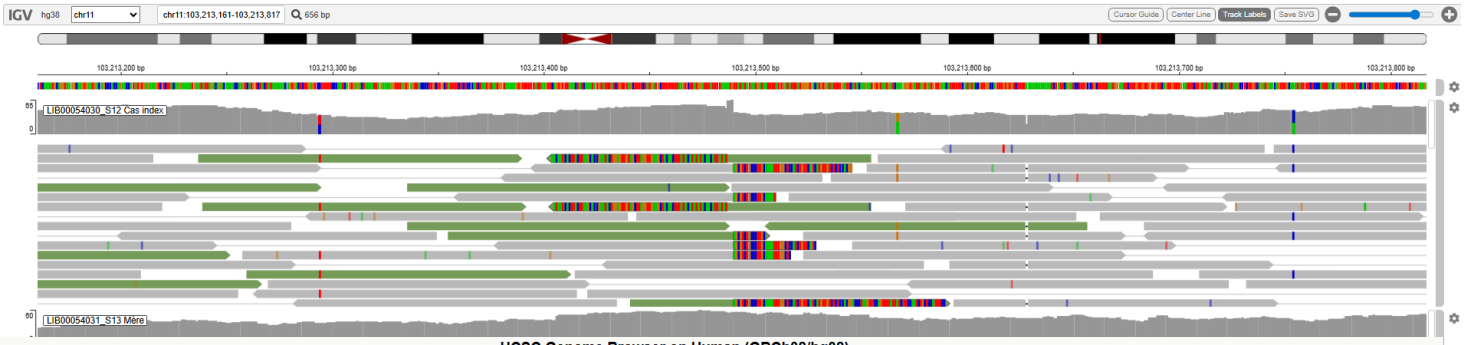
Garçon de 6 ans
Duo avec mère

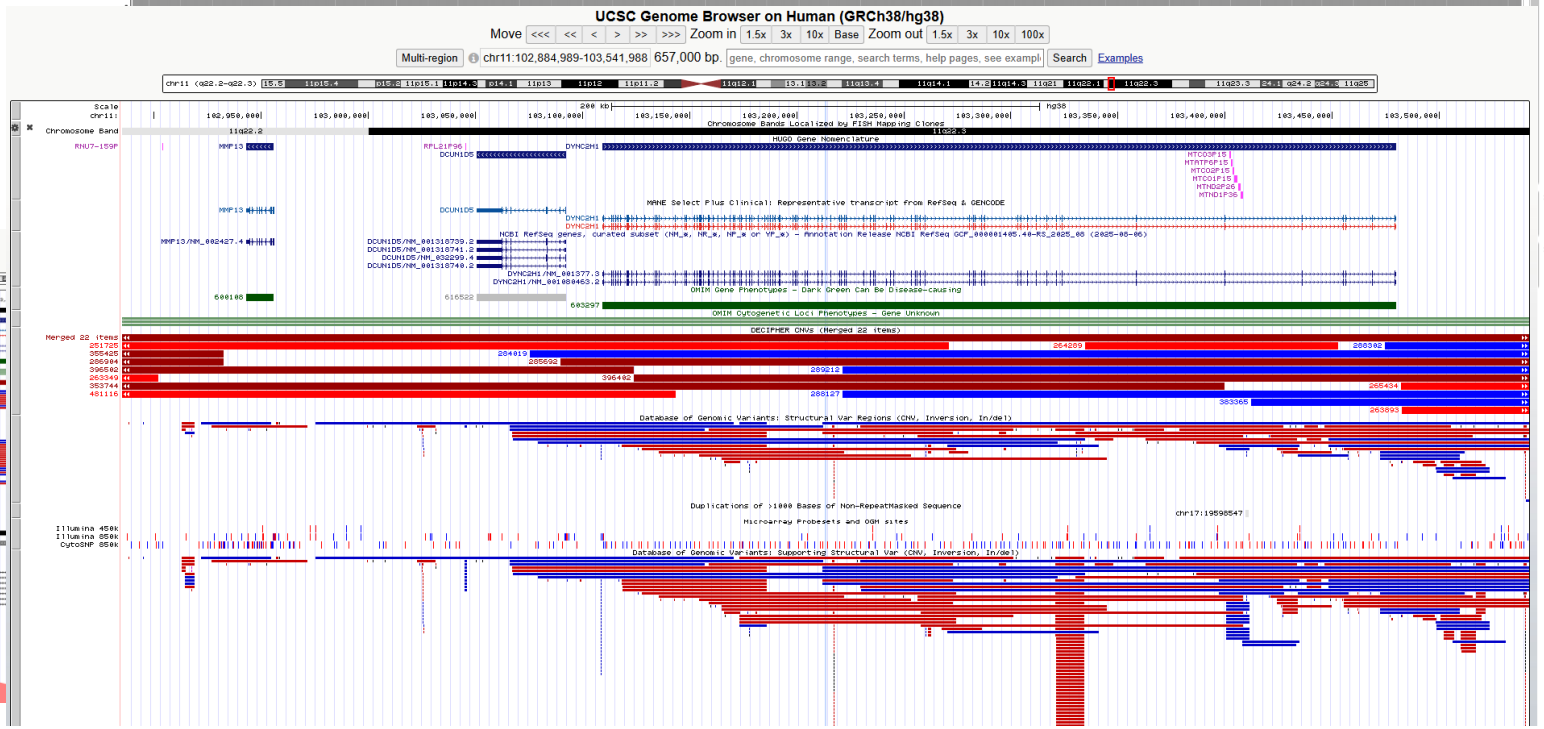
SV 4 BP détectés

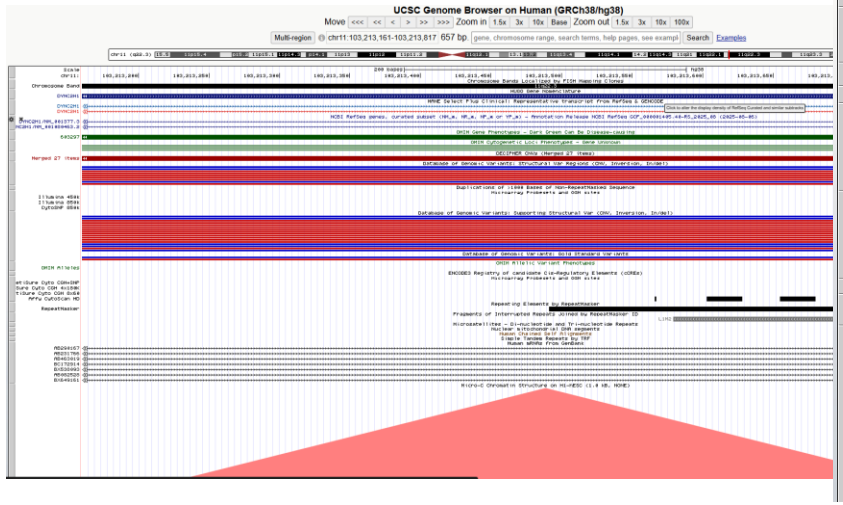
VSI		822	chr3:181994085 (3q26.33) chr3:179319483 (3q26.33)	— — gnomAD	36.36 (28, 16)	heterozygous undetermined	2674601	LINC01206 ZNF639 —
VSI		999	chr11:103213489 (11q22.3) chr3:179319479 (3q26.33)	— gnomAD — gnomAD	42.11 (33, 24)	heterozygous undetermined	inter-chromosomique	DYNC2H1 (AR,DR) ZNF639 —
VSI		924	chr11:103213487 (11q22.3) chr3:144229941 (3q24)	— gnomAD — gnomAD	32.26 (42, 20)	heterozygous undetermined	inter-chromosomique	DYNC2H1 (AR,DR) — —

Garçon de 6 ans
Duo avec mère

Point de cassure BP
Chr11:103213489
Intron 54/88 DYNC2H1

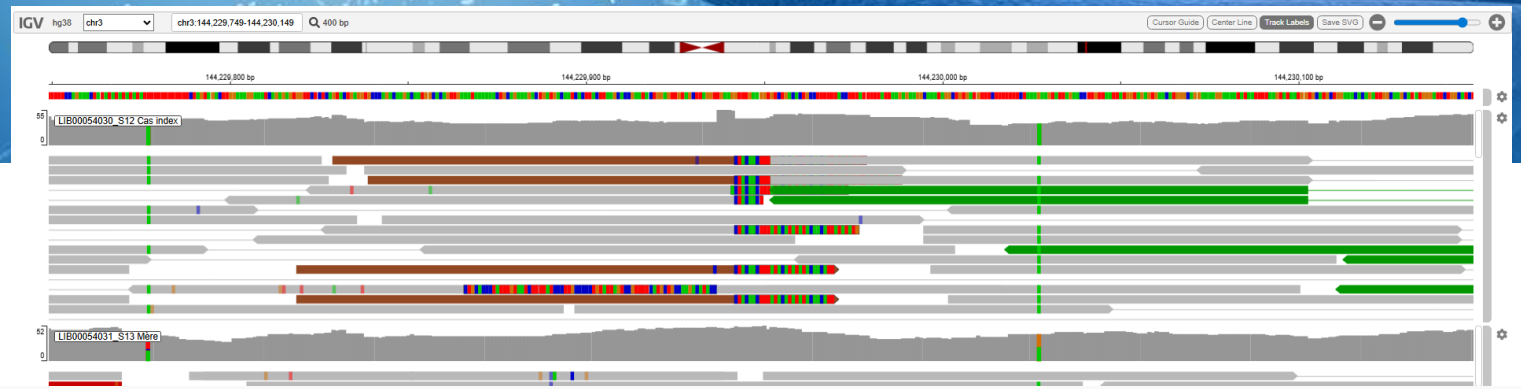


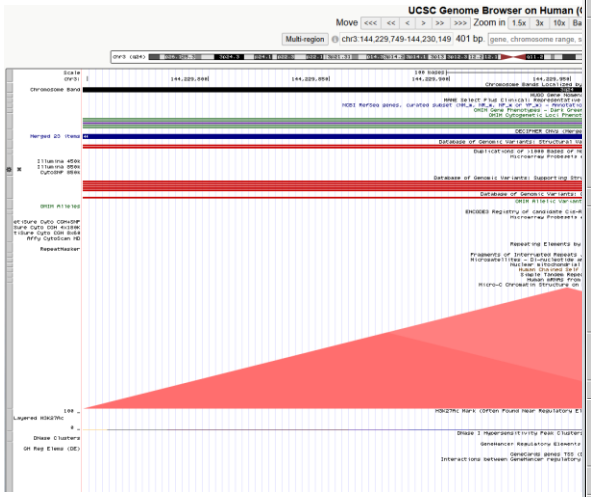




Garçon de 6 ans
Duo avec mère

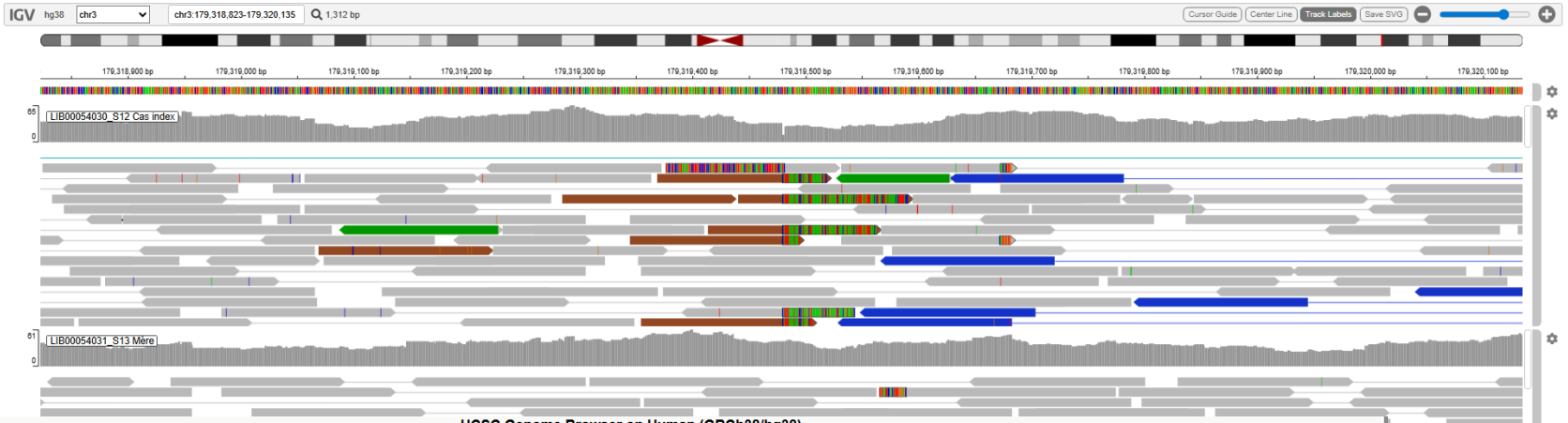
Point de cassure BP
Chr3:144229937
RAS

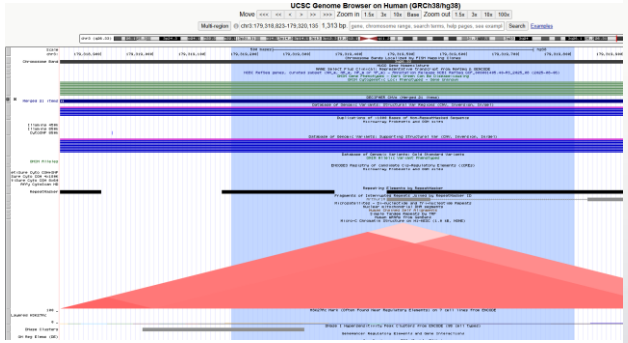




Garçon de 6 ans
Duo avec mère

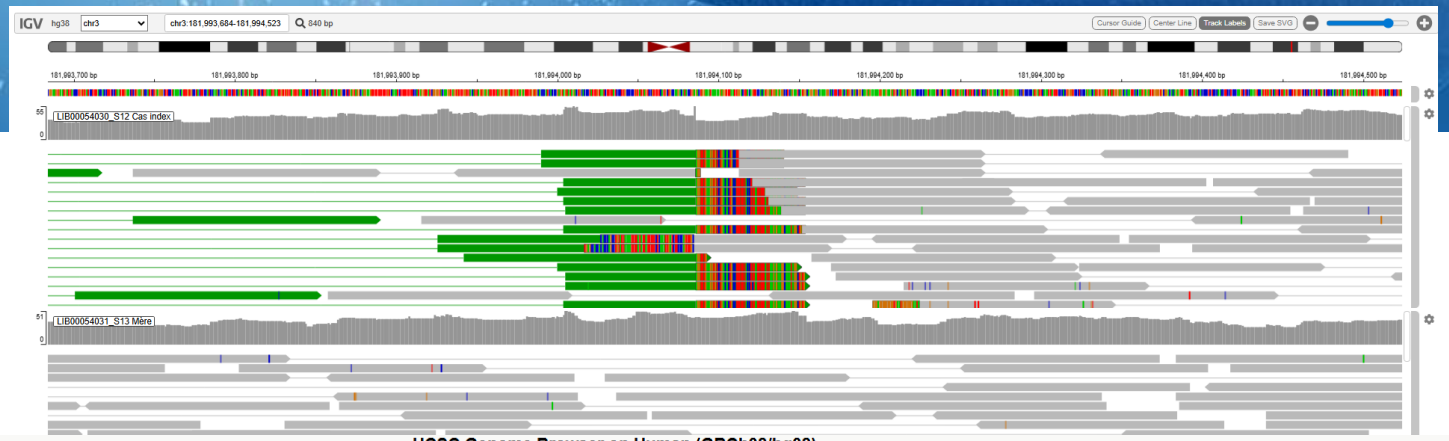
Point de cassure BP
Chr3:179319479
RAS

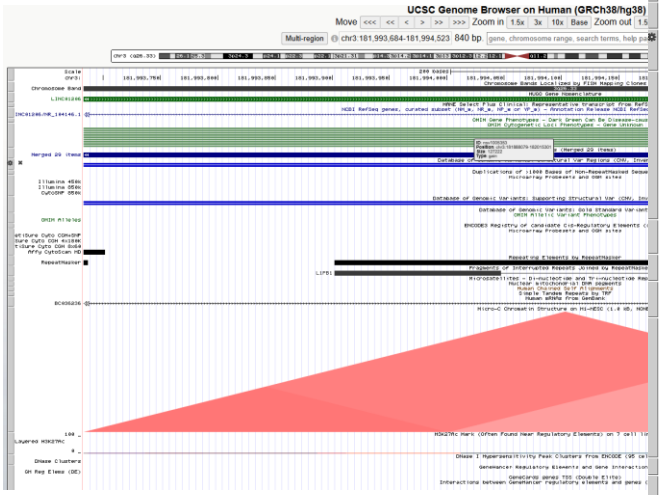




Garçon de 6 ans
Duo avec mère

Point de cassure BP
Chr3:181994085
à distance de SOX2





Garçon de 6 ans
Duo avec mère

4 Points de cassure BP

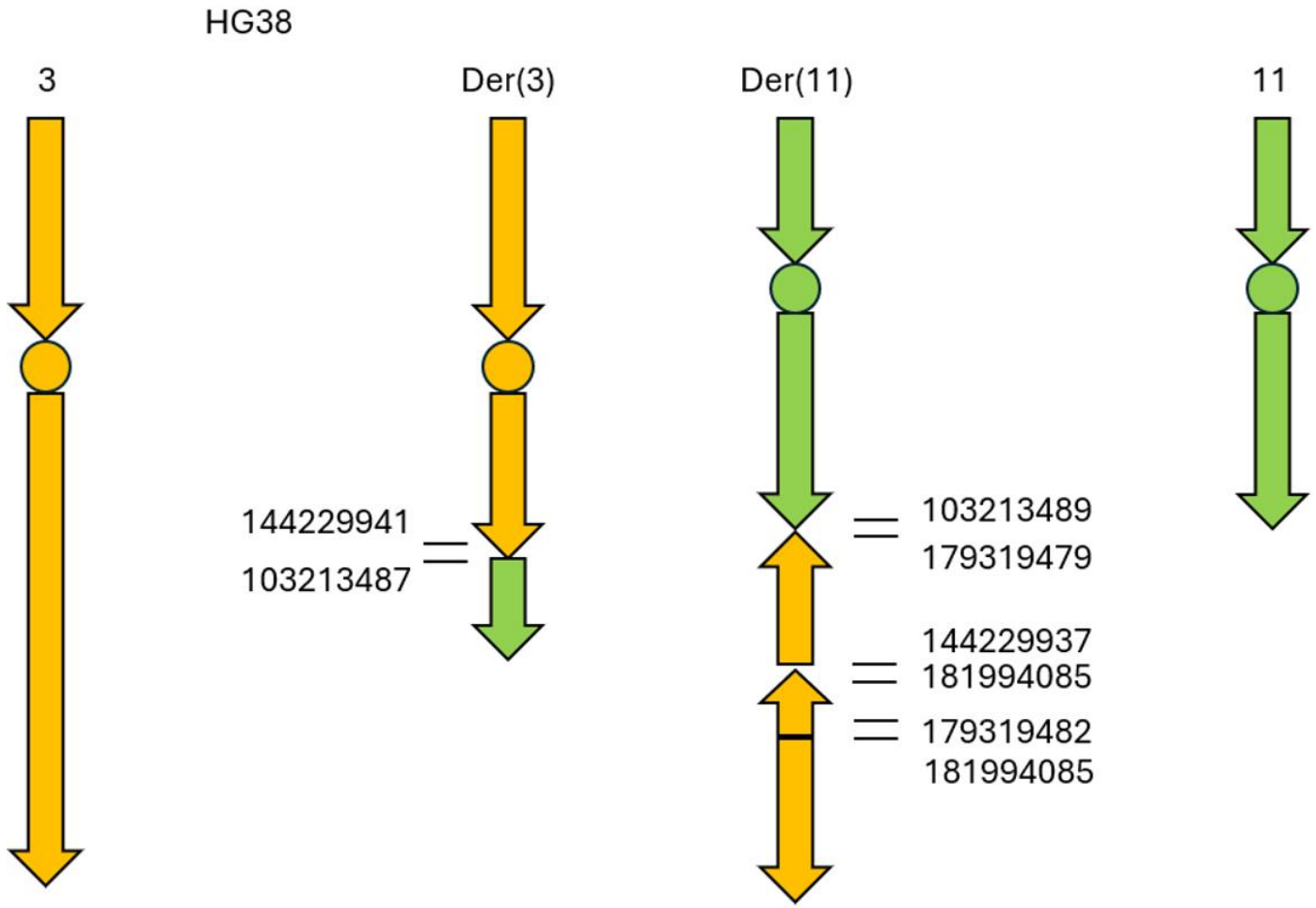


Image construite par le Dr. J Puechberty

Garçon de 6 ans
Duo avec mère

seq[GRCh38] t(3;11)(q24;q22.3)dn
NC_000003.12:g.144229941_qterdelins[NC_000011.10:g.103213489_qter]
NC_000011.10:g.103213489_qterdelins[NC_000003.12:g.[144229941_179319479inv;
179319482_181994085inv;181994085_qter]]

HPO:
Retard de développement global sévère
Développement du langage absent
Crises épileptiques
Retard moteur
Encéphalopathie épileptique
Tissu gonadique inapproprié au système génital externe ou le sexe chromosomique

Remaniement chromosomique complexe 4 BP
De Novo (père testé dans un autre laboratoire)

Aucun gène ni élément régulateur d'intérêt mis en évidence proche des BP

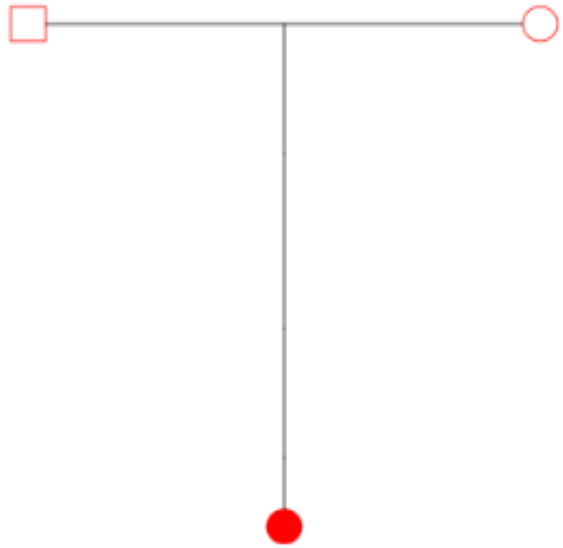
2 chrX normaux, pas de chrY ni *SRY* : pas d'explication au phénotype ou au sexe phénotypique avec caryotype 46XX

→ VSI
→ Transcriptome pour poursuivre

Cas 5

Cas 5

Garçon de 4 ans
trio parents



Symptômes renseignés

0001520: Macrosomie

0001263: Retard global du développement

0000256: Macrocéphalie

0000076: Reflux vésico-urétéral

0000767: Pectus excavatum

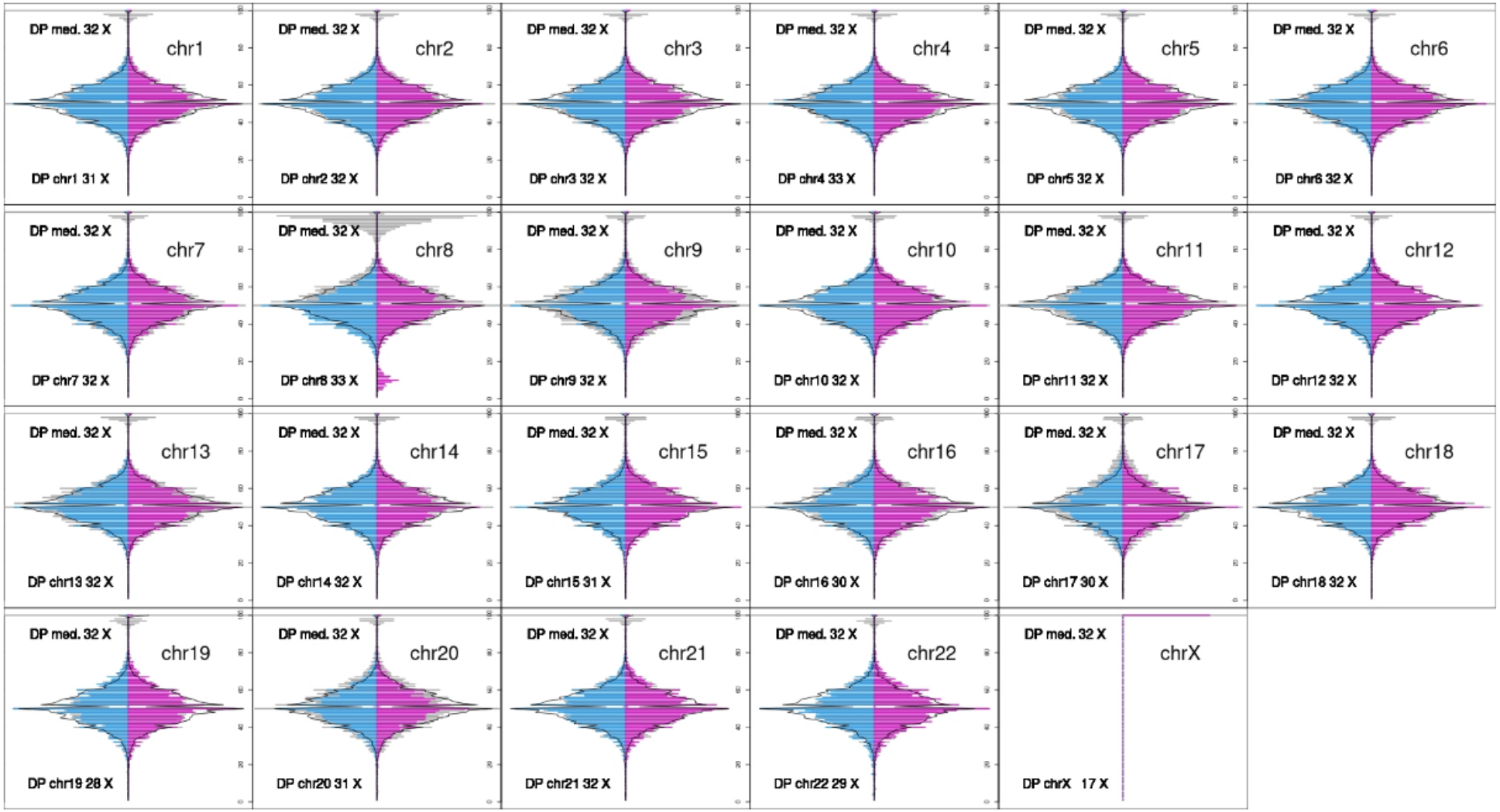
0010490: Anomalie des plis palmaires

0000034: Hydrocèle du testicule

0001869: Plis plantaires profonds

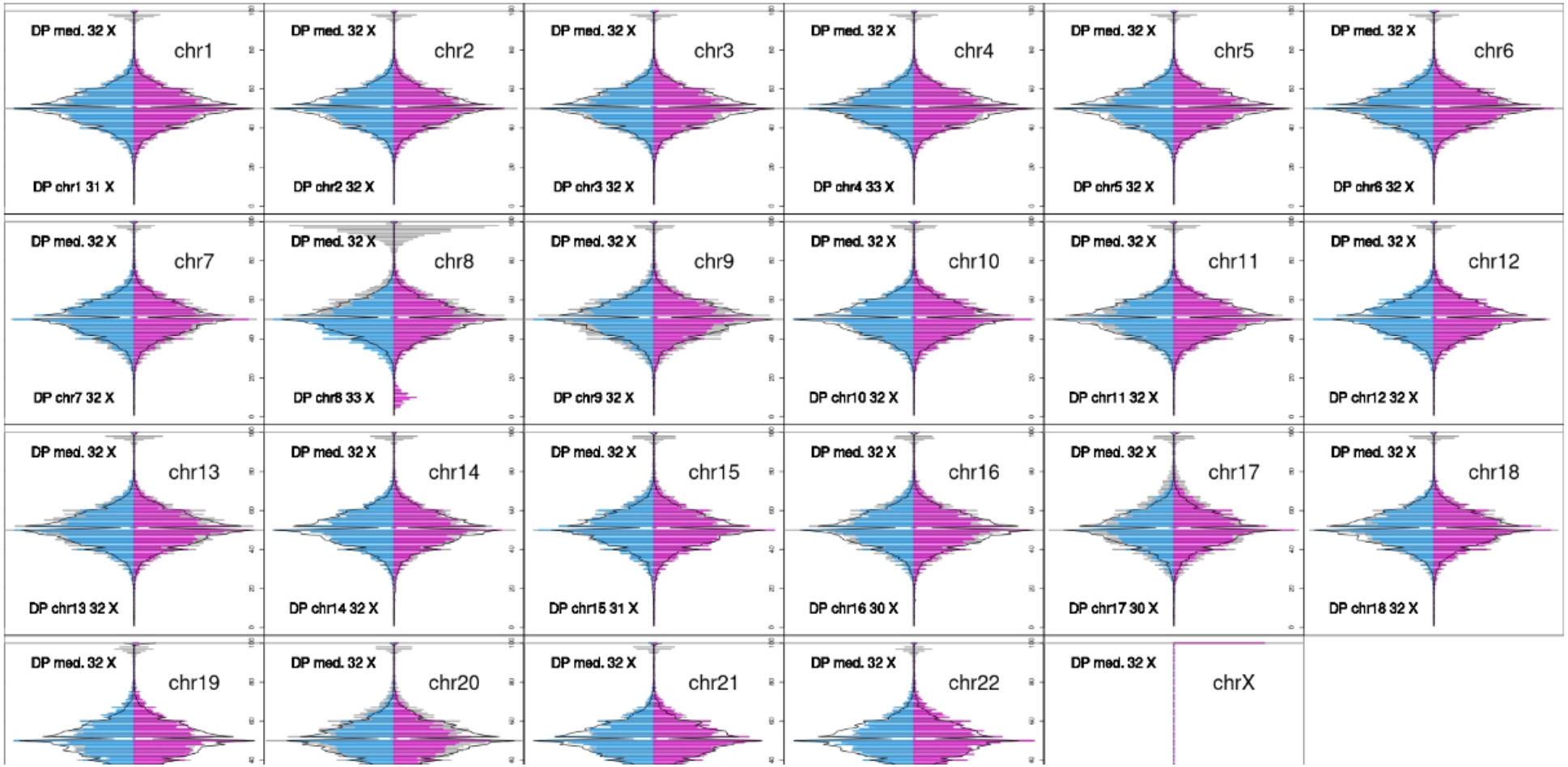
SNP-array et variations héritées

Garçon de 4 ans
trio parents

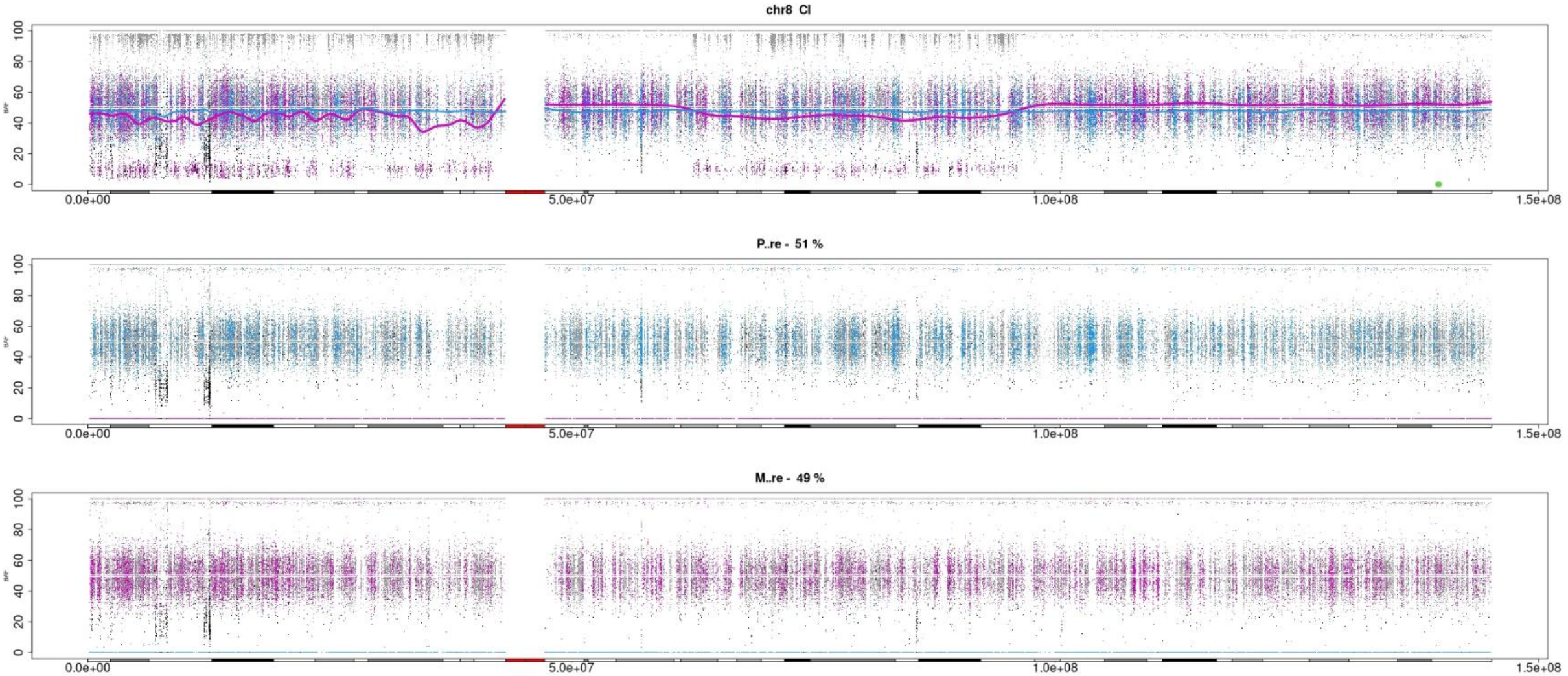


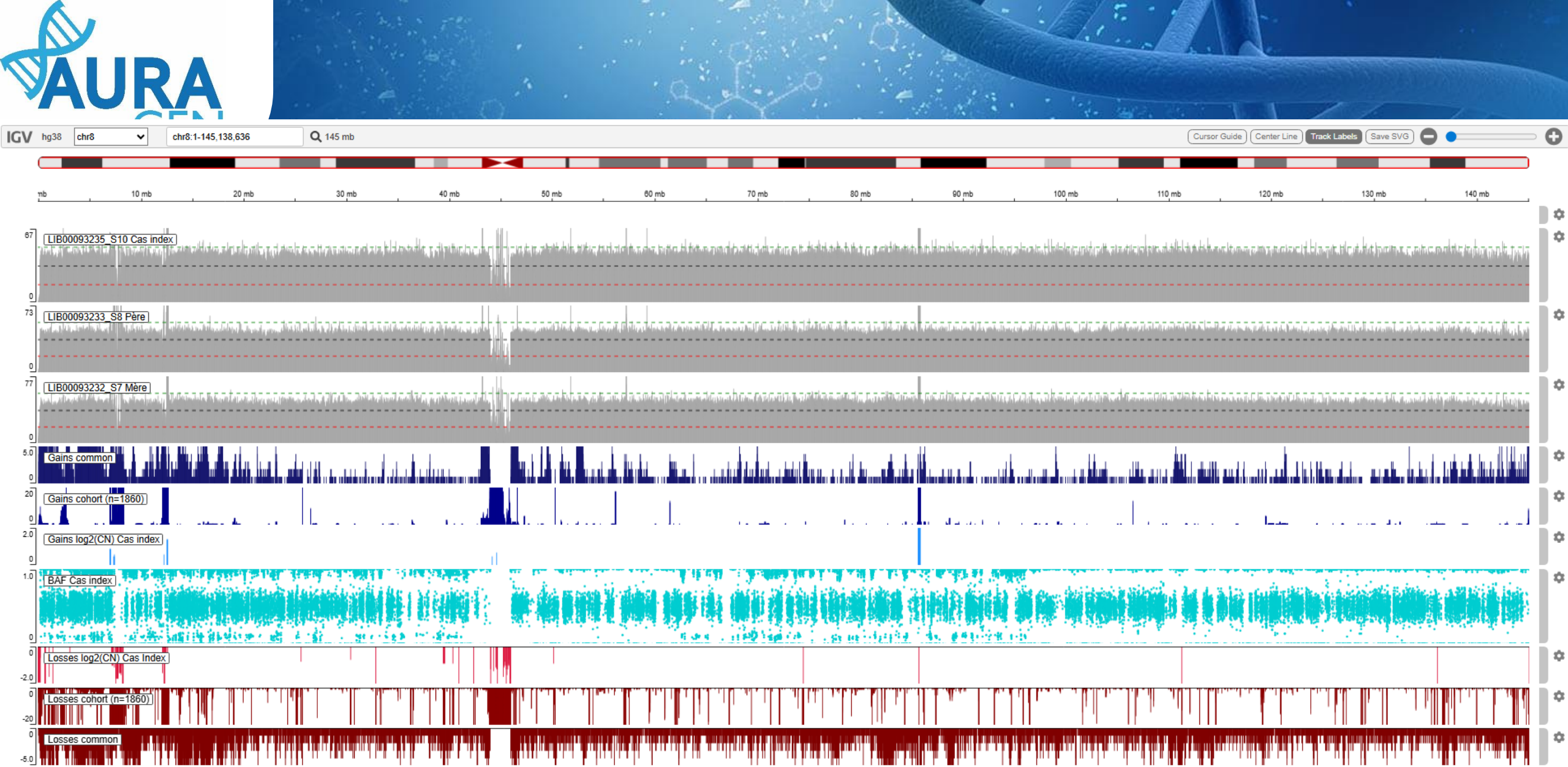
SNP-array et variations héritées

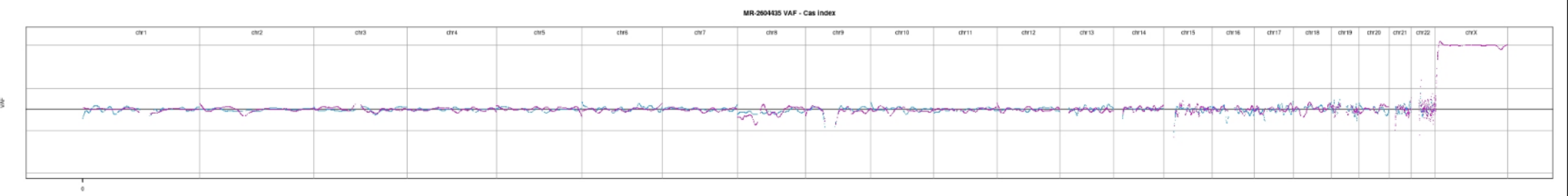
Garçon de 4 ans
trio parents

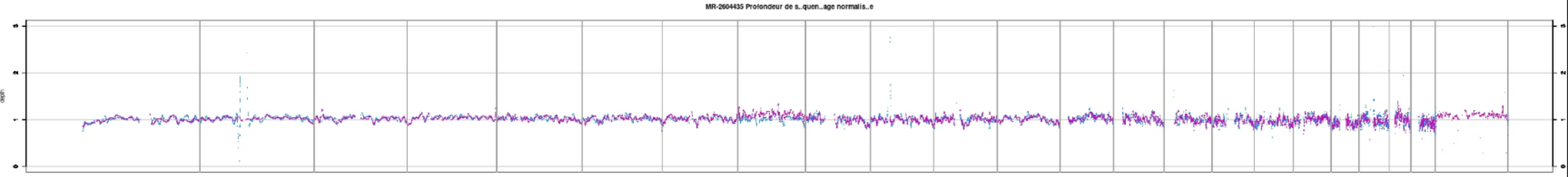


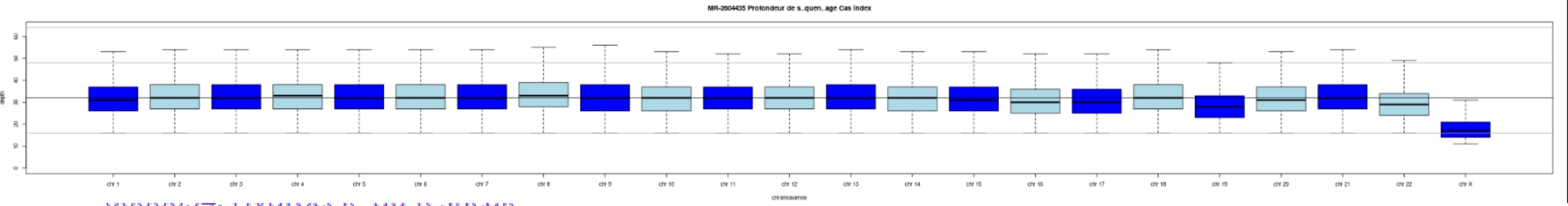
Avertissement : Un déséquilibre de la distribution des VAF du chr8 évoque une mosaïque chromosomique. Consultez la section Autres.


chr8 CI
BAF
0
20
40
60
80
100
0.0e+00
5.0e+07
1.0e+08
1.5e+08
P..re - 51 %
BAF
0
20
40
60
80
100
0.0e+00
5.0e+07
1.0e+08
1.5e+08
M..re - 49 %
BAF
0
20
40
60
80
100
0.0e+00
5.0e+07
1.0e+08
1.5e+08


IGV
hg38
chr8
chr8:1-145,138,636
145 mb
Cursor Guide
Center Line
Track Labels
Save SVG
10 mb
20 mb
30 mb
40 mb
50 mb
60 mb
70 mb
80 mb
90 mb
100 mb
110 mb
120 mb
130 mb
140 mb
LIB00093235_S10 Cas index
LIB00093233_S8 Père
LIB00093232_S7 Mère
Gains common
Gains cohort (n=1860)
Gains log2(CN) Cas index
BAF Cas index
Losses log2(CN) Cas Index
Losses cohort (n=1860)
Losses common







0001869: Plis plantaires profonds

Syndrome de trisomie 8 en mosaïque

Contribuer

Définition

Anomalie autosomique rare définie par la présence de trois copies du chromosome 8 dans certaines cellules de l'organisme, caractérisée cliniquement par une dysmorphie faciale, des plis palmaires et plantaires généralement profonds, une légère déficience intellectuelle et des anomalies articulaires, urinaires, cardiaques et squelettiques.

Symptômes renseignés

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0000034: Hydrocèle du testicule
0001869: Plis plantaires profonds

Trisomie 8 partielle ou complète ?
Iso8p, anneau, dérivé… ?
en mosaïque

→ VI variation incertaine (pas VSI…)
→ Caryotype et FISH nécessaires

Variant de signification incertaine (VSI) :

- **Situations très différentes**
- **Rendre les VSI d'intérêt, avec explorations à proposer +++**
- **Discussion en RICB**

Pour aller plus loin :

Rétrophénotypage
Genematcher/Auramatcher/Collaboration
Épisignature
étude ARN, RNAseq
Caryotype/FISH
Bionano, Nanopore
Explorations fonctionnelles (contacter auteurs ou équipe de recherche++)
Minigène
Dosage
Imagerie
…

Genet Med. 2025 Jun;27(6):101400. doi: 10.1016/j.gim.2025.101400. Epub 2025 Feb 28.

Distinct rates of VUS reclassification are observed when subclassifying VUS by evidence level

Gwendolyn Bennett [1], Izabela Karbassi [1], Wenjie Chen [2], Steven M Harrison [3], Matthew S Lebo [4], Linyan Meng [5], Narasimhan Nagan [2], Robert Rigobello [6], Heidi L Rehm [7]

Affiliations + expand

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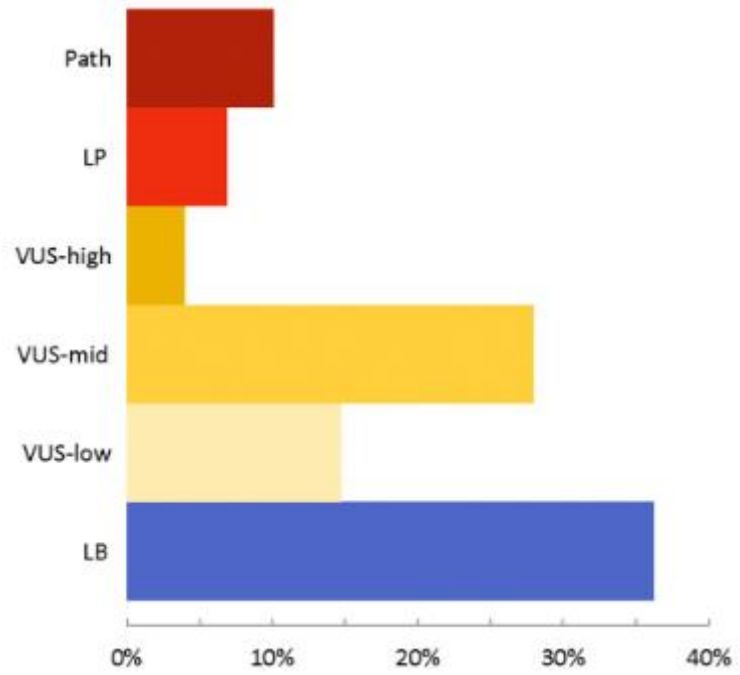

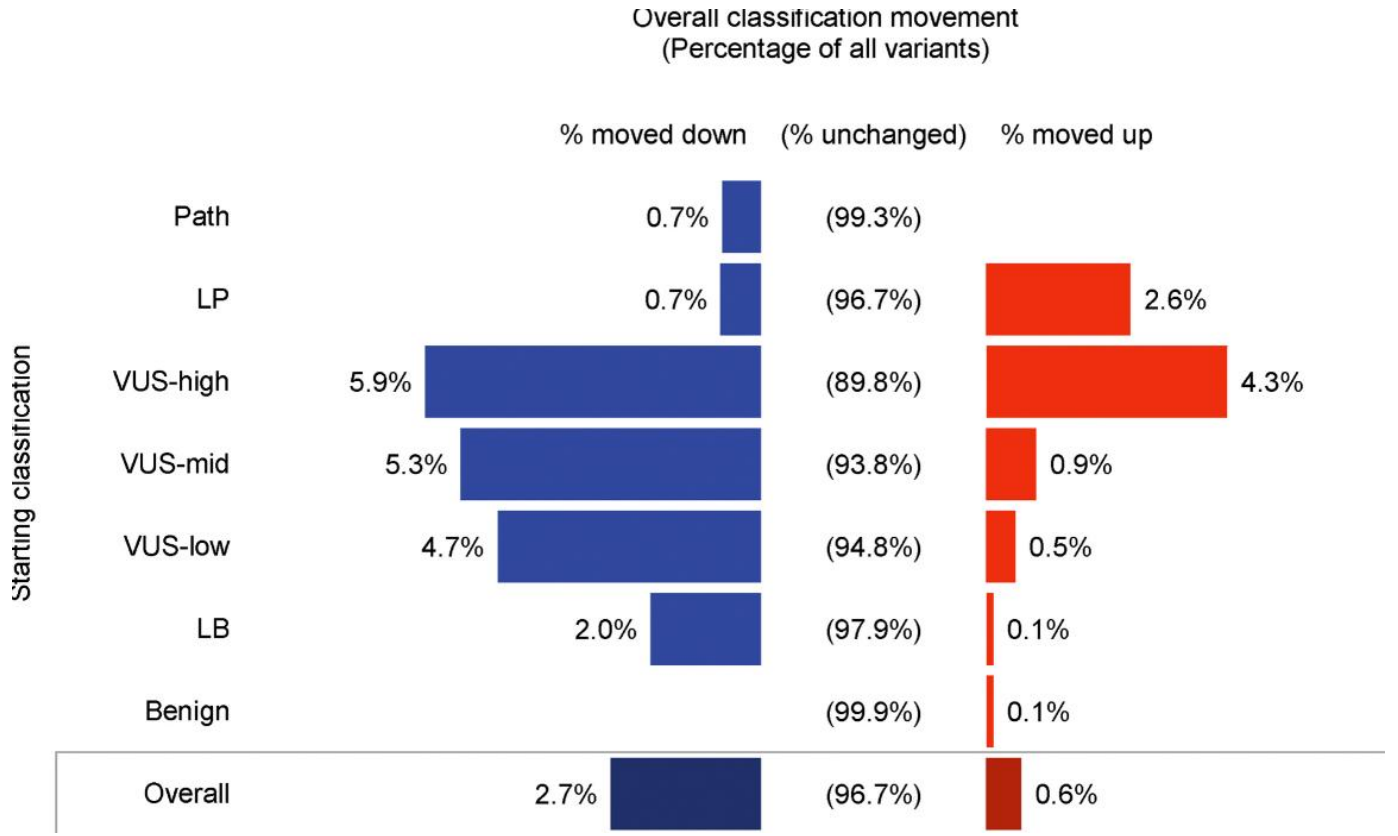

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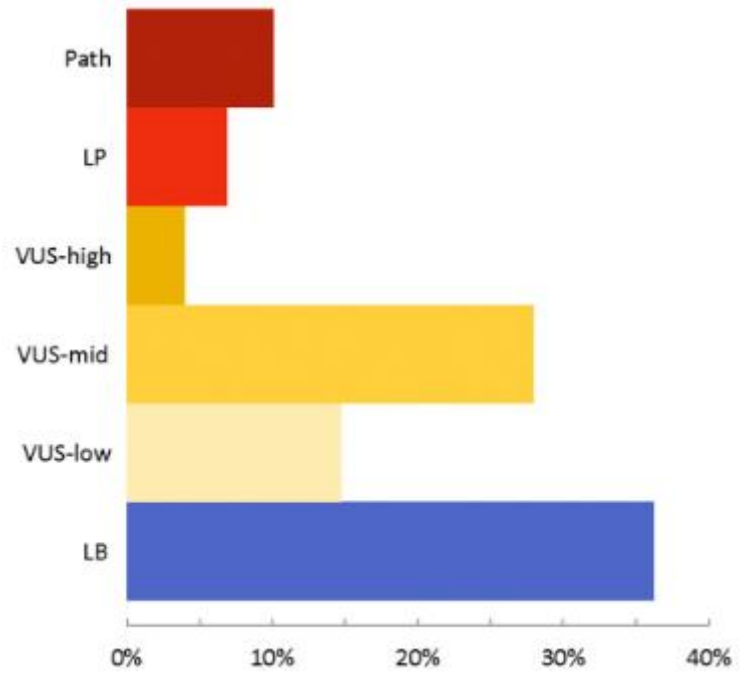

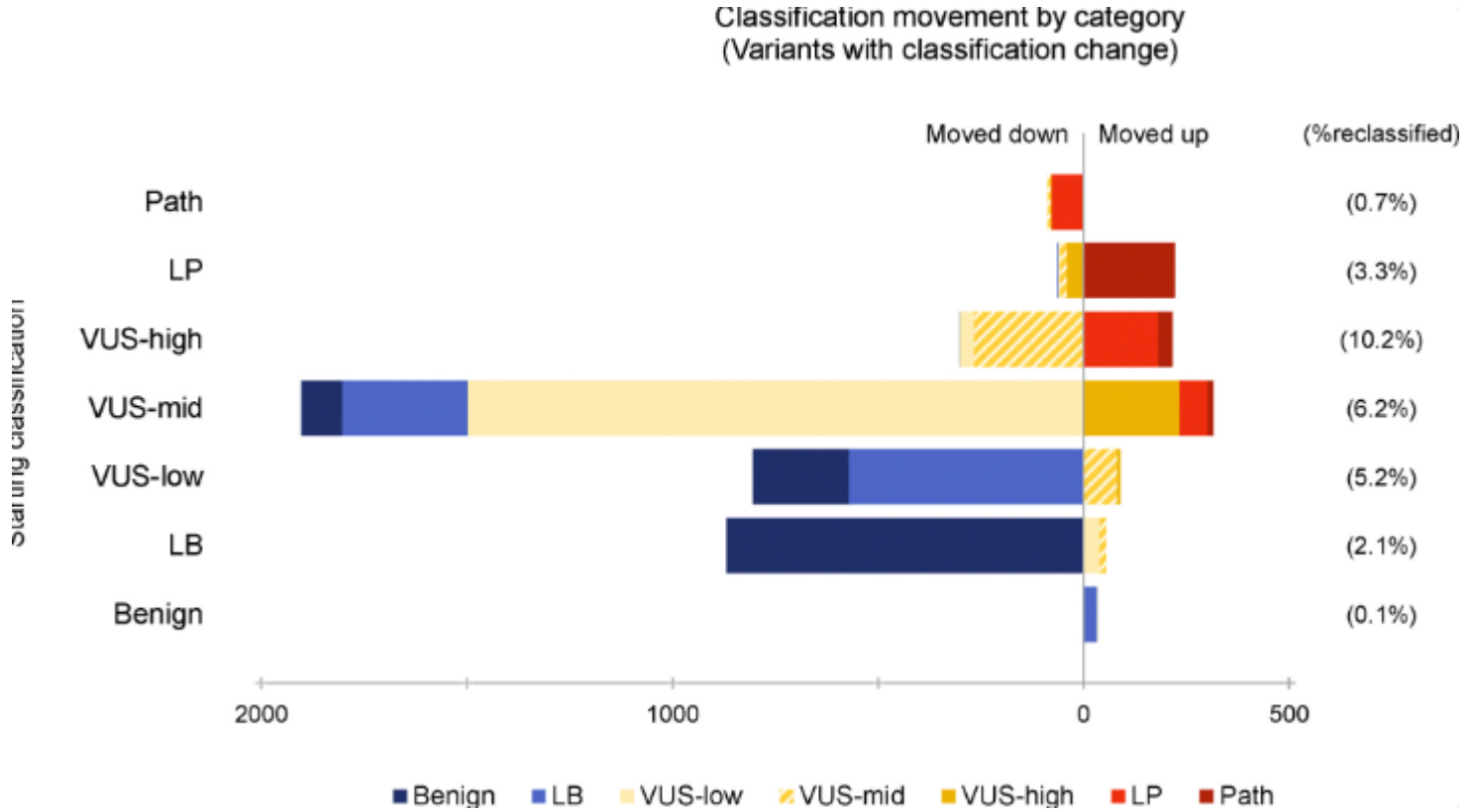

ACMG/AMP v4 prévu prochainement ?

Points	Classification
≥ 10	Pathogenic
6 to 9	Likely Pathogenic
0 to 5	Uncertain Significance
-3 to -1	Likely Benign
≤ -4	Benign

Remerciements

- **Service de Génétique Médicale, CHU Montpellier**

Pr. Geneviève, Dr. Willems, Dr. Rouxel, Dr. Ganne, Dr. Wells, Dr. Deiller, Dr. Ruault, Dr. Puechberty, Dr. Gatinois, Dr. Yauy

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Dr. Aubert Mucca, Dr. Ziegler, Dr. Patat, Dr. Weber, Dr. Chesneau, Dr. Chelloug, Dr. Dewulf, Dr. Chassaing, Dr. Dupin-Deguine, Dr. Guerry

- **Service de Génétique Médicale, CH Toulon**

Dr. Grelet, Dr. Riccardi, Dr. Dupuy

- **Equipe bioinformatique**
- **Biologistes Auragen**
- **Consortium AURAGEN**
- **Centre experts**

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