Interesting cases

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Case 1

- male, 32 yrs
- Intellectual disability
- Behavioural problems
- Testicular atrophy
- Syncope
- Height 193 cm
- Long face
- Pituitary adenoma with hyperprolactinemia
- Sporadic case
  - **Chromosomes (klinefelter): normal**
  - **Now WES: ID panel + open exome**

Filtering ID panel

- Total variants: 122059
- Disease variants: 7694
- Default filter: 55
- De novo: 1

DNMT3A;Chr2(GRCh37):g.25463289T>C;NM_022552.4:c.2204A>G (p.(Tyr735Cys))

615879

TATTON-BROWN-RAHMAN SYNDROME; TBRS

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
2p23.3	Tatton-Brown-Rahman syndrome	615879	AD	3	DNMT3A	602769

Clinical Synopsis

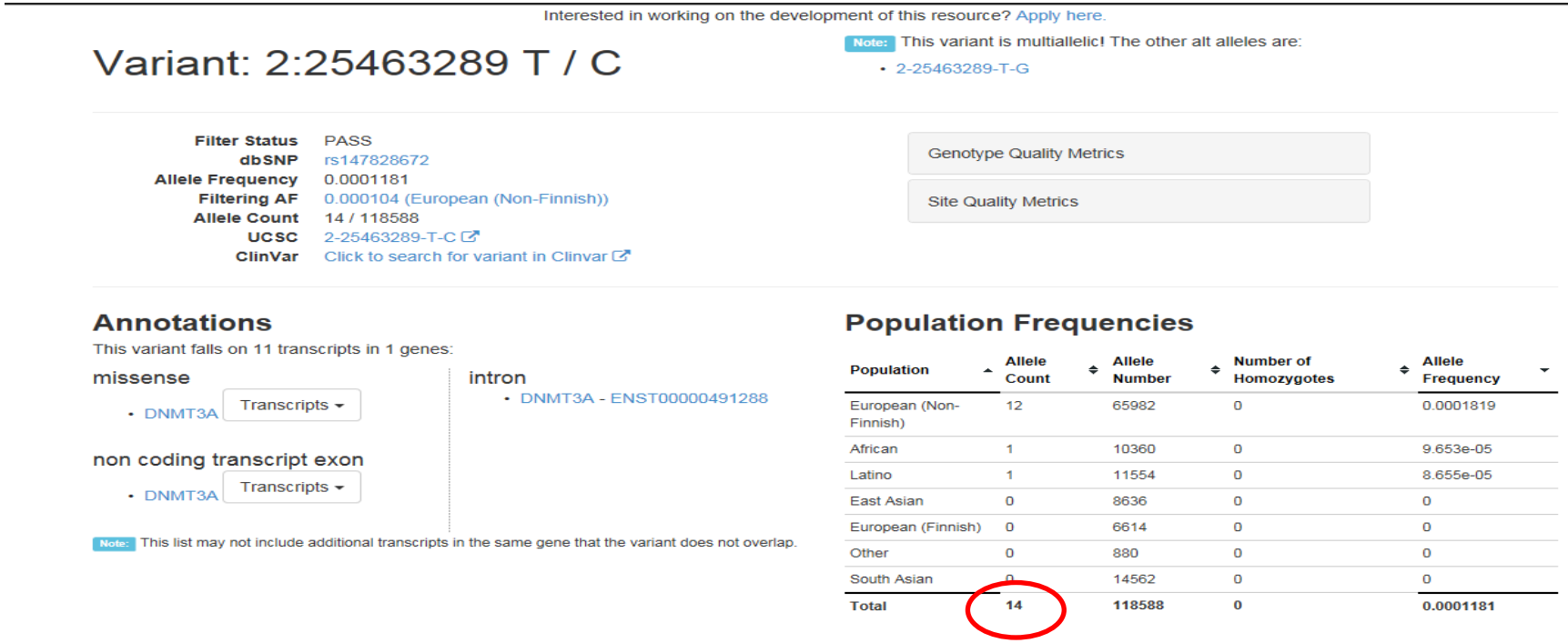
TEXT

A number sign (#) is used with this entry because Tatton-Brown-Rahman syndrome (TBRS) is caused by heterozygous mutation in the DNMT3A gene (602769) on chromosome 2p23.

Description

Tatton-Brown-Rahman syndrome is characterized by tall stature, a distinctive facial appearance, and intellectual disability (Tatton-Brown et al., 2014).

Pathogenic or tolerated?



Interested in working on the development of this resource? Apply here.

Variant: 2:25463289 T / C

Note: This variant is multiallelic! The other alt alleles are:

- 2-25463289-T-G

Filter Status	PASS
dbSNP	rs147828672
Allele Frequency	0.0001181
Filtering AF	0.000104 (European (Non-Finnish))
Allele Count	14 / 118588
UCSC	2-25463289-T-C
ClinVar	Click to search for variant in Clinvar

Genotype Quality Metrics

Site Quality Metrics

Annotations

This variant falls on 11 transcripts in 1 genes:

missense

- DNMT3A Transcripts

non coding transcript exon

- DNMT3A Transcripts

intron

- DNMT3A - ENST00000491288

Note: This list may not include additional transcripts in the same gene that the variant does not overlap.

Population Frequencies

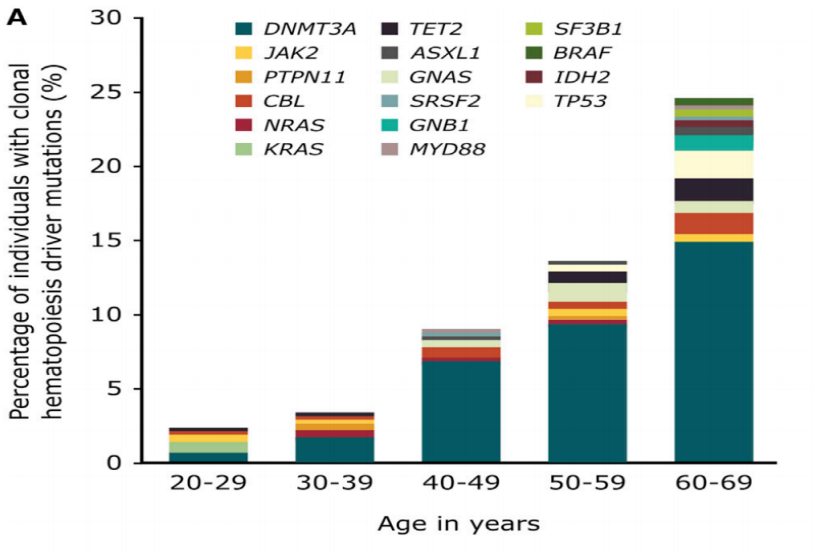
Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (Non-Finnish)	12	65982	0	0.0001819
African	1	10360	0	9.653e-05
Latino	1	11554	0	8.655e-05
East Asian	0	8636	0	0
European (Finnish)	0	6614	0	0
Other	0	880	0	0
South Asian	0	14562	0	0
Total	**14**	**118588**	**0**	**0.0001181**

http://exac.broadinstitute.org/variant/2-25463289-T-C

Contols are not heterozygous!

Ultra-sensitive Sequencing Identifies High Prevalence of Clonal Hematopoiesis-Associated Mutations throughout Adult Life

Rocio Acuna-Hidalgo,[1] Hilal Sengul,[1] Marloes Steehouwer,[1] Maartje van de Vorst,[2] Sita H. Vermeulen,[3] Lambertus A.L.M. Kiemeney,[3] Joris A. Veltman,[2,4] Christian Gilissen,[2] and Alexander Hoischen[1,5,*]



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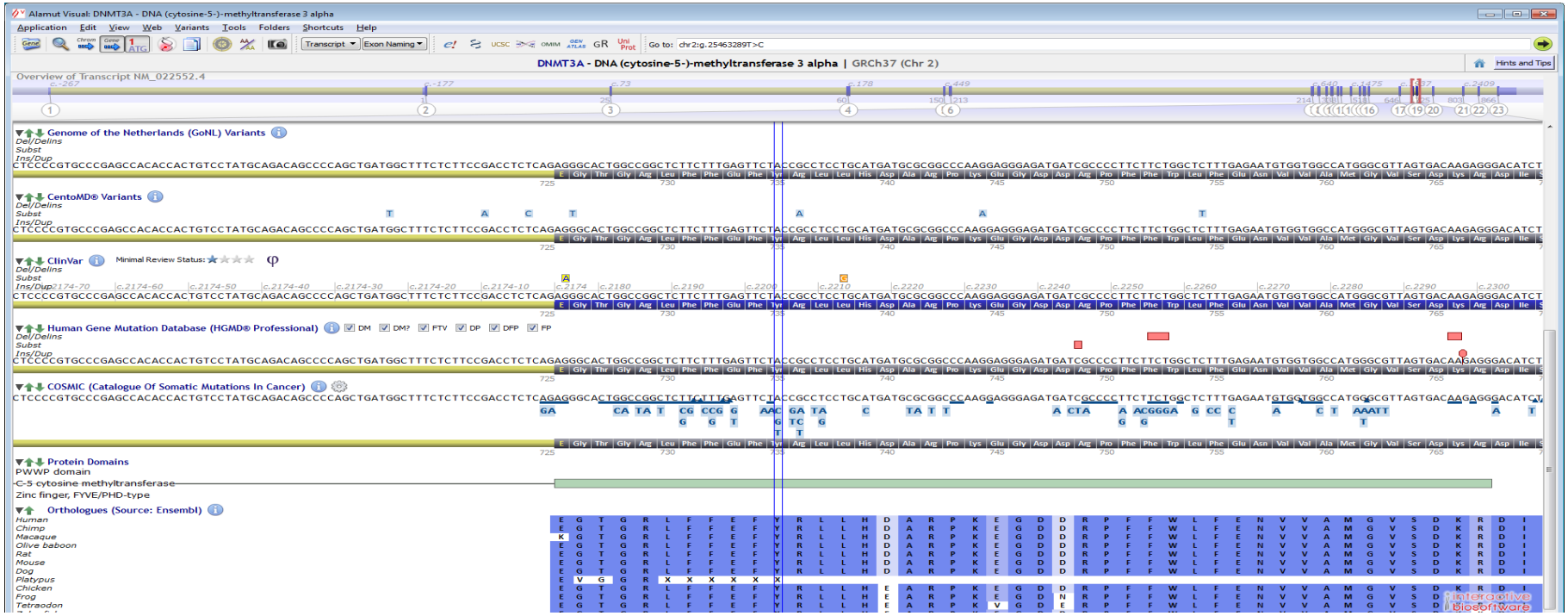
Causative for phenotype case 1



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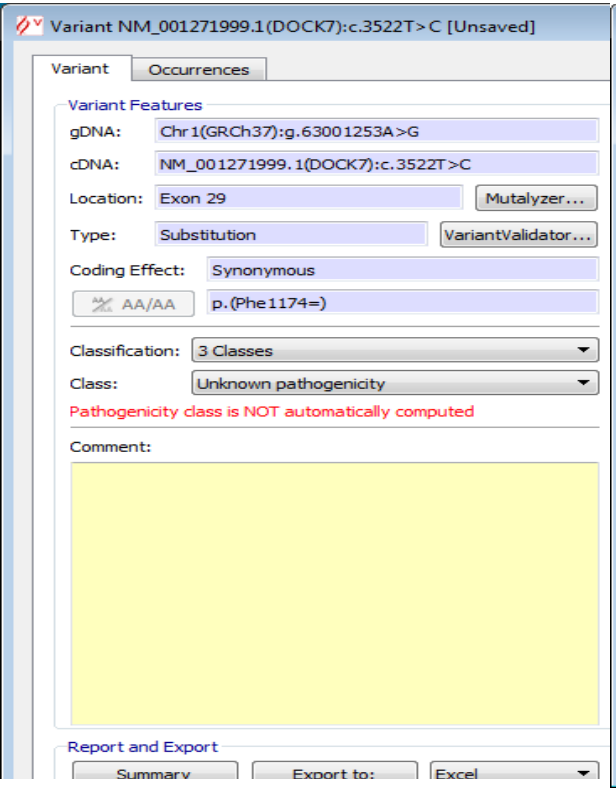
Case 2

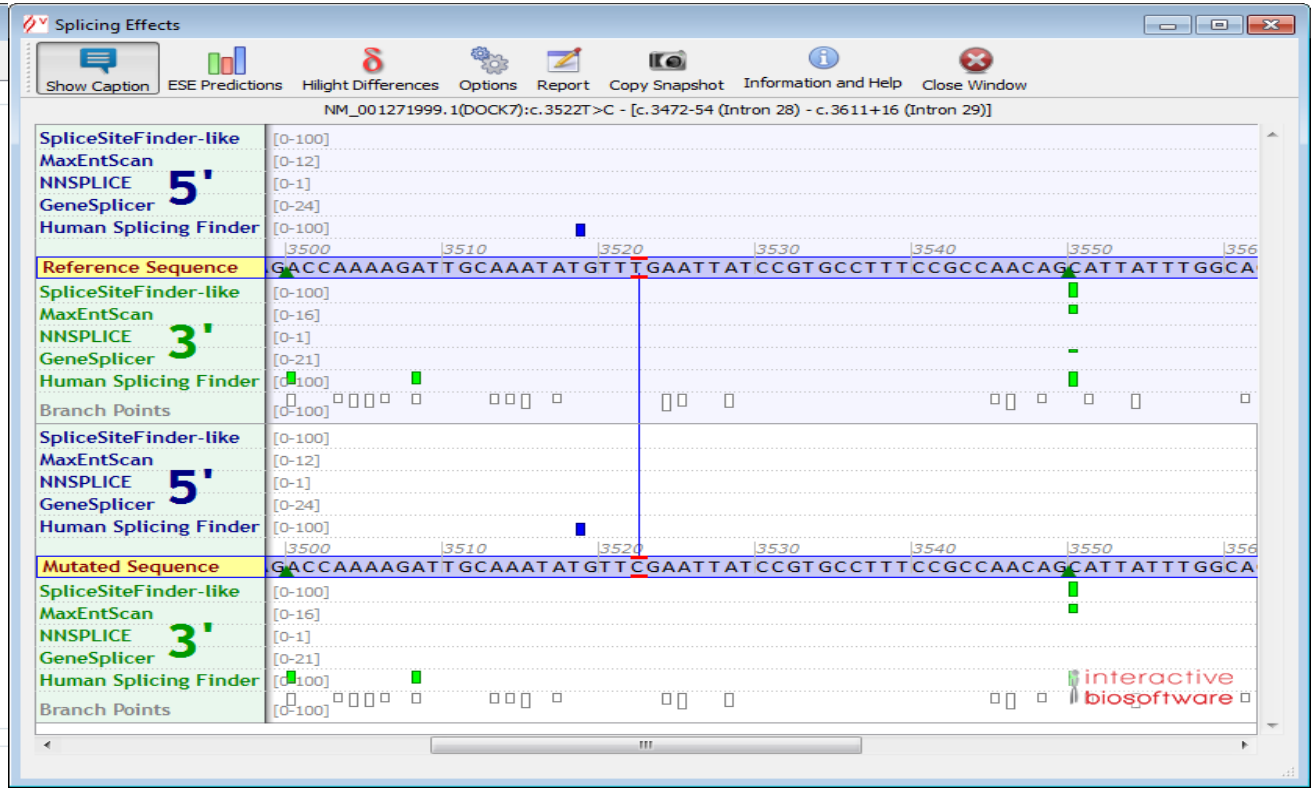
- Female, 31 yrs
- Intellectual disability
- Epilepsy
- Behavioural problems
- Autism
- Sister with epilepsy and normal IQ

***SCN1A*, *SCN2A*, *GABRG2*, *SLC2A1* (negative)**
Now WES: ID + epilepsy panels + open exome

	ID panel	Epilepsy panel
• Total variants:	138535	138535
• Disease variants:	9090	2005
• Default filter:	76	14
• De novo:	4	1

Silent change in DOCK7





	ID panel	Epilepsy panel
• Total variants:	138535	138535
• Disease variants:	9090	2005
• Default filter:	76	14
• De novo:	4	1

2 unique non-synonymous variants (1 mat CTSD, 1 pat PCDH19)

X-linked *paternal* variant in female

PCDH19;ChrX(GRCh37):g.99662889G>A;NM_001184880.1:c.707C>T (p.(Pro236Leu))

* 300460

PROTOCADHERIN 19; PCDH19

Alternative titles; symbols

KIAA1313

HGNC Approved Gene Symbol: PCDH19

Cytogenetic location: Xq22.1 ***Genomic coordinates (GRCh38): X:100,291,643-100,410,272*** (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
Xq22.1	Epileptic encephalopathy, early infantile, 9	300088	XL	3

A number sign (#) is used with this entry because early infantile epileptic encephalopathy-9 (EIEE9), also known as epilepsy and mental retardation restricted to females (EFMR), is caused by mutation in the gene encoding protocadherin-19 (PCDH19; 300460) on chromosome Xq22.

For a general phenotypic description and a discussion of genetic heterogeneity of EIEE, see EIEE1 (308350).

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Case 3

- Female, 14 yrs
- Intellectual disability
- Psychiatric problems (recurrent psychosis)
- Family history negative

BWS (pos), array (neg)
Now WES: ID panel + open exome

Filtering ID panel

- Total variants: 116356
- Disease variants: 6422
- Default filter: 51
- De novo: 3 (rec. genes, no 2nd, different phen.)

1 unique truncating variant (pat MAGEL2)

Truncating paternal mutation

MAGEL2;Chr15(GRCh37):g.23889655C>A;NM_019066.4:c.3235G>T (p.(Glu1079*))

ICD+

615547

SCHAAF-YANG SYNDROME; SHFYNG

Alternative titles; symbols

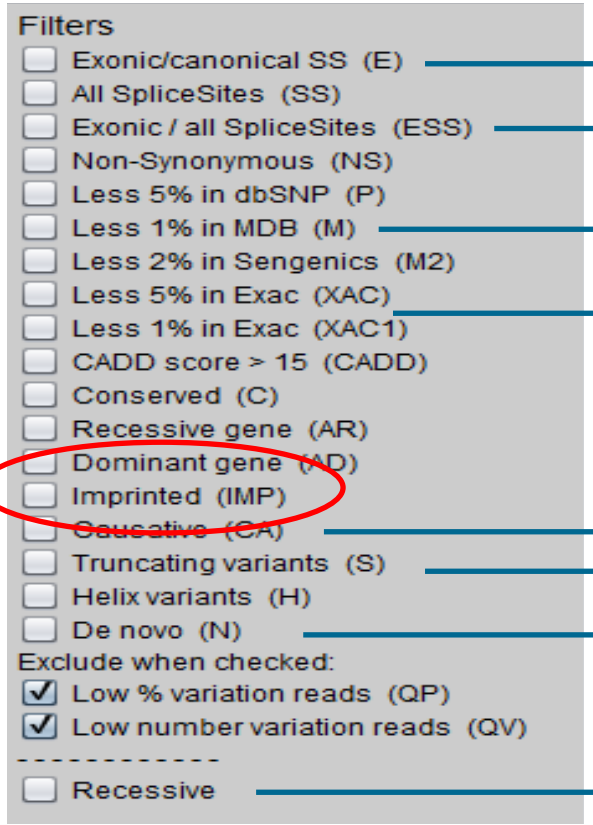
PRADER-WILLI-LIKE SYNDROME; PWLS

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
15q11.2	Schaaf-Yang syndrome	615547	AD	3	MAGEL2	605283

features. The severity of the disorder is highly variable: some patients may die in utero with fetal akinesia, whereas others can live with moderate disability. Individuals are affected only if the mutation occurs on the paternal allele, since MAGEL2 is a maternally imprinted gene (summary by Fountain et al., 2017)

Filter steps



Exon +/- 2 bp

Exon +8 /-20 bp

<1 % in house database frequency (~ 18.000 exomes)

<5 and < 1% EXAC database

HGMD and/or in house classification database

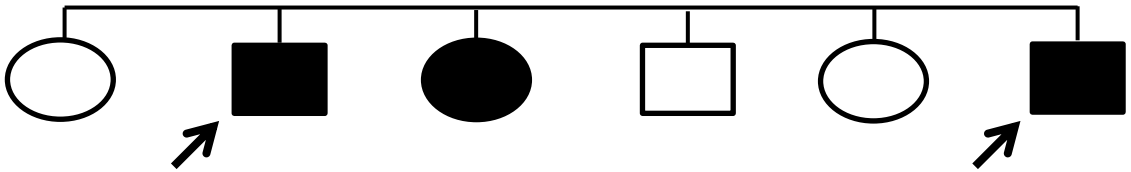
Nonsense / frameshift / startloss / canonical splice

De novo (trio)

Homozygous / two heterozygous (comp. het. in trio)

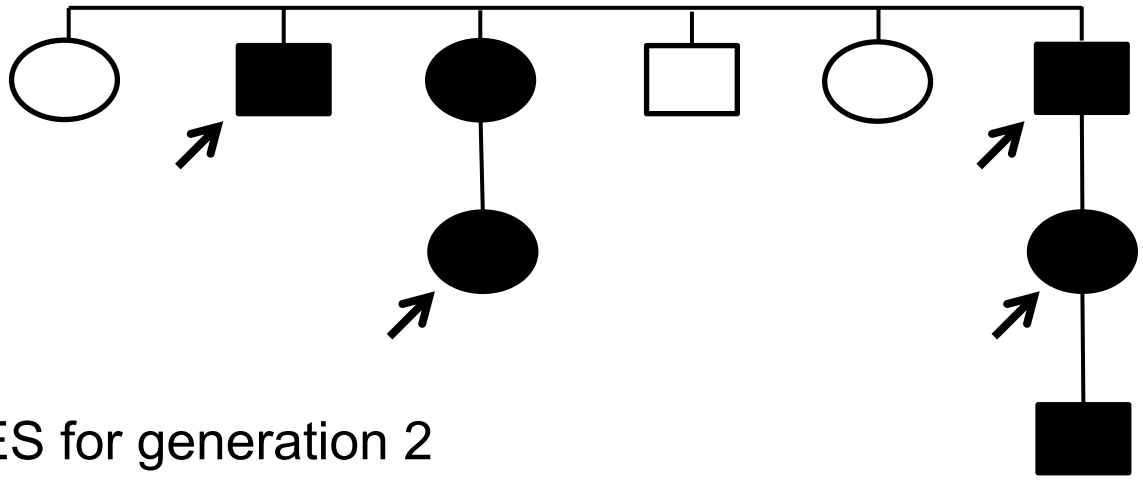
Case 4

- Family with Hereditary Sastic Paraplegia



Previous testing: 19 HSP genes (Sanger), WES for recessive HSP in 2013 (negative)

Extended family



- 2015: WES for generation 2
- overlap in variants between all 4
- dominant mode of inheritance

Filtering movement disorders panel

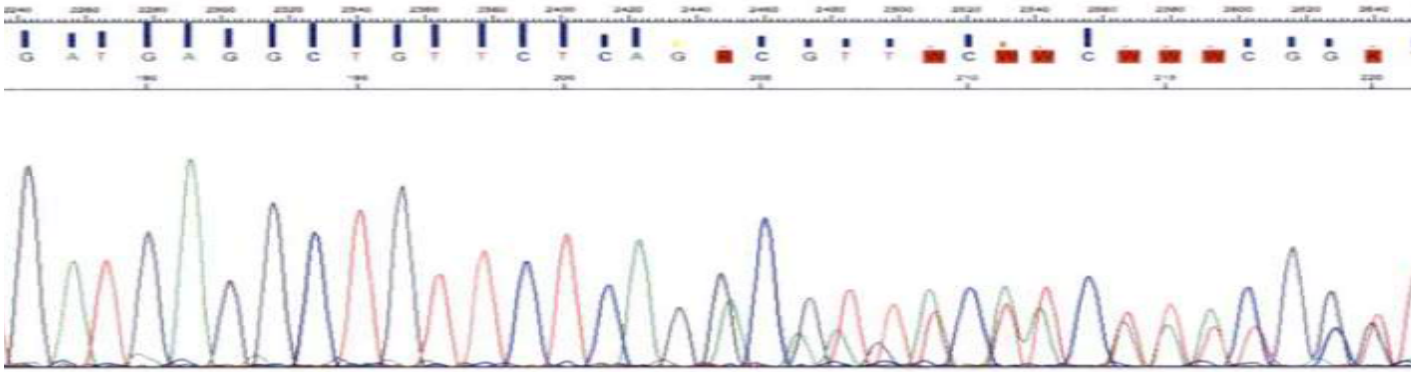
- Total variants: 90336
- Disease variants: 1060
- Default filter: 6
- Overlapping: 0

1 overlapping intronic variant in HSP gene

Intronic variant is not a great acceptor

SPAST; Chr2(GRCh37):g.32366949A>G; NM_014946.3:c.1494-24A>G (r.spl?)

Variant leads to skipping exon 13



Exon 13 skipped from mRNA (approx. 50% transcripts)

SPAST; Chr2(GRCh37):g.32366949A>G; NM_014946.3:c.1494-24A>G (r.1494_1536del (p.(Arg499fs))

Take home message

- Default filtersettings are very useful for selection and interpretation of clinically relevant variants

- Always keep in mind unexpected/rare biological phenomena

- Examples: high frequency in controls, sex specific phenotype, imprinting, intronic mutations…..

pseudodominance, UPD, noncoding genes, pseudogenes, etc

Acknowledgments

Helger Yntema

Erik-Jan Kamsteeg

Rolph Pfundt