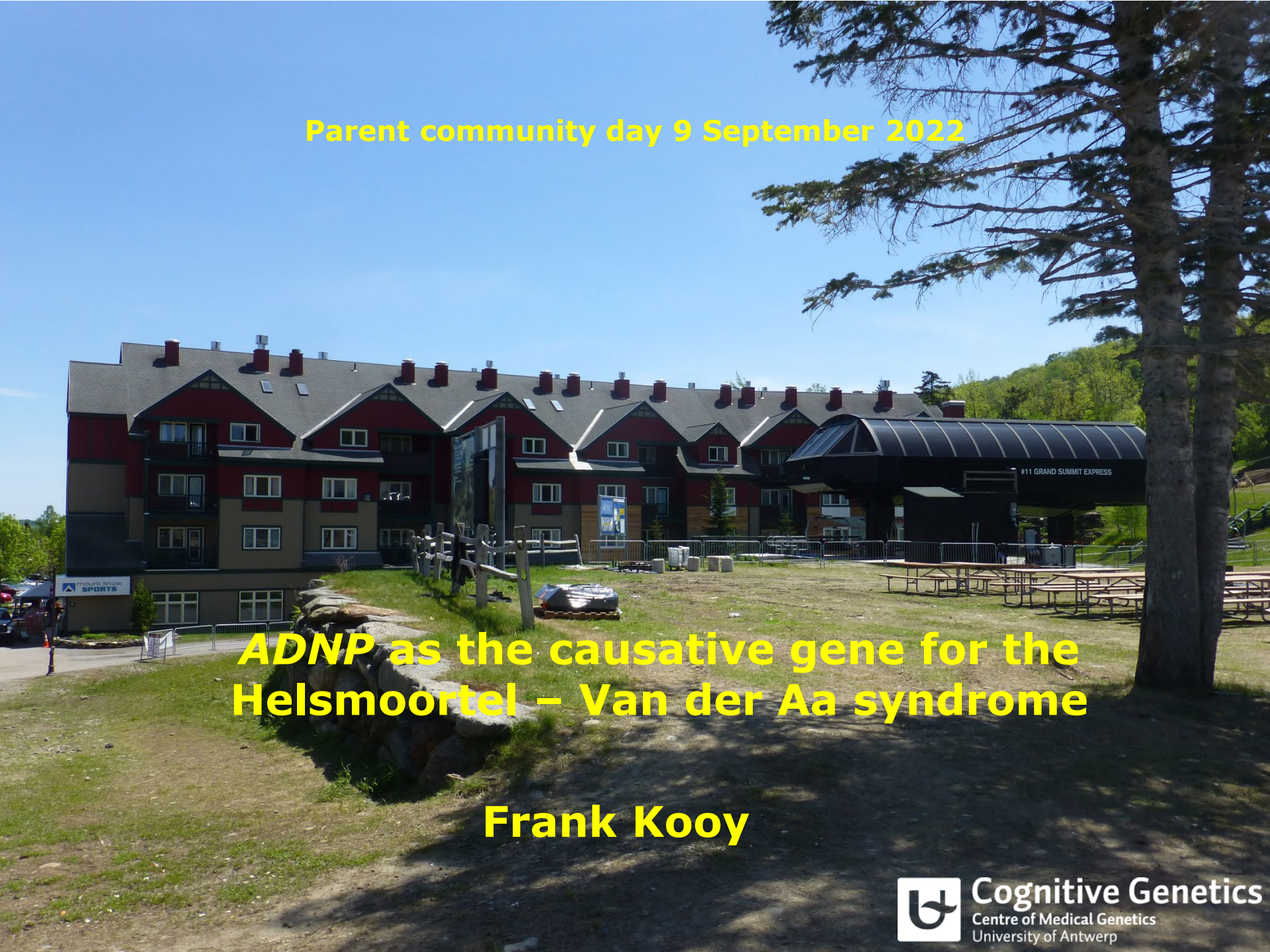


Parent community day 9 September 2022

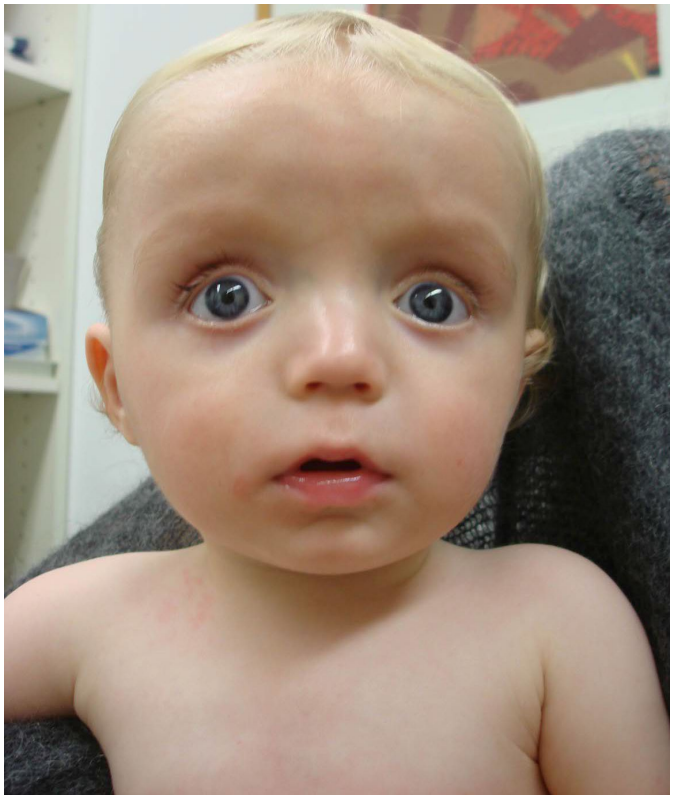
ADNP as the causative gene for the Helsmoortel – Van der Aa syndrome

Frank Kooy

Cognitive Genetics
Centre of Medical Genetics
University of Antwerp

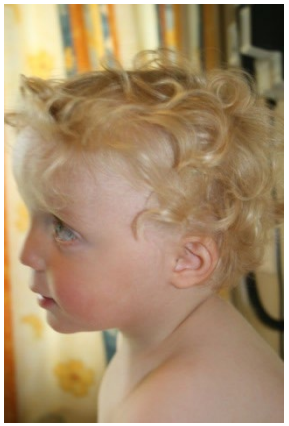
Young boy

- Global developmental delay
- Failure to thrive
- Autism Spectrum Disorder
- Cardiac: atrial septal defect
- White matter lesions
- Facial Dysmorphism

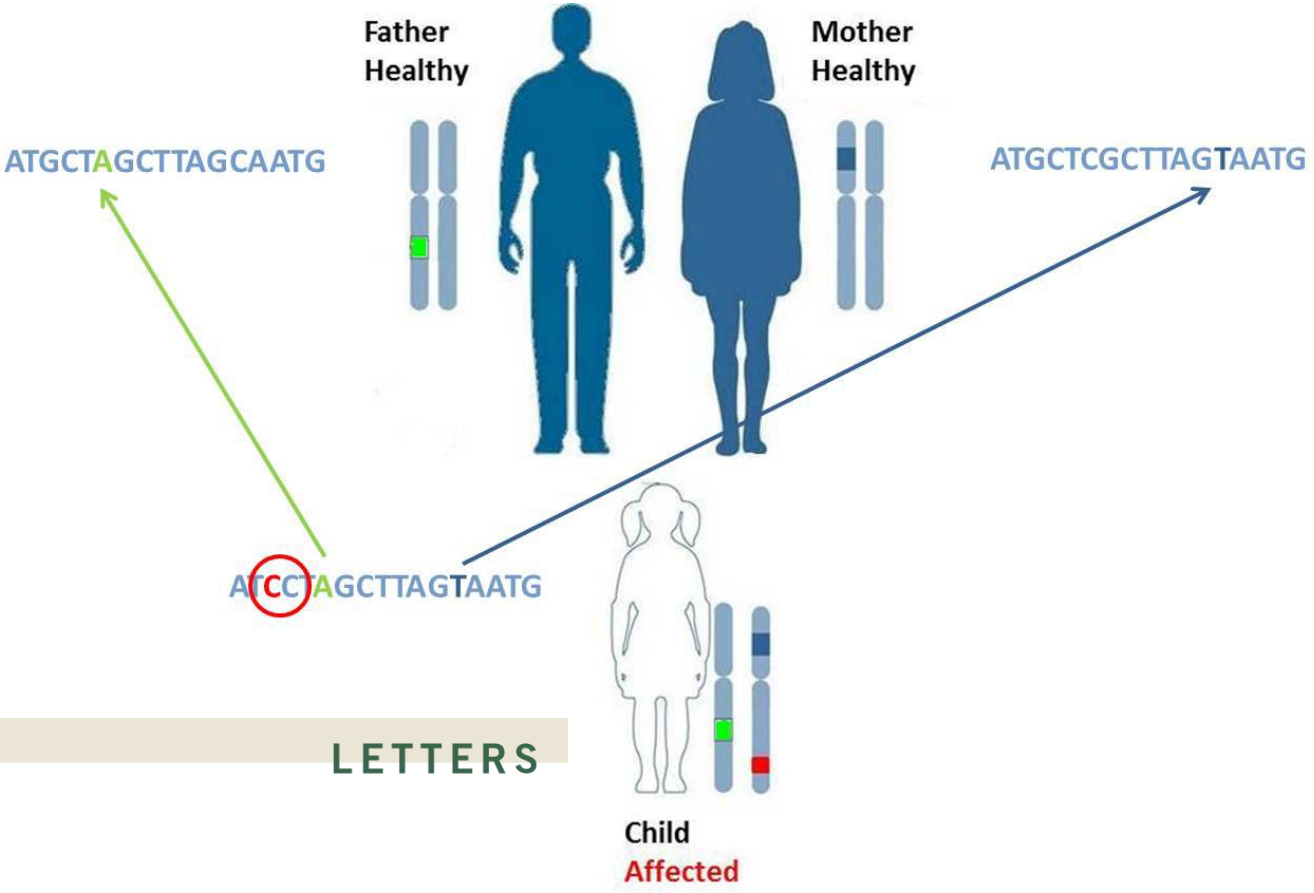


Diagnostic work up

- Karyotype: normal 46, XY
- SNP array: no abnormalities detected
- Differential diagnosis: Noonan spectrum disease, but targeted screening of relevant *PTPN11, SOS1, RAF1, KRAS* genes revealed no mutations



Next Generation Sequencing
Trio approach



LETTERS

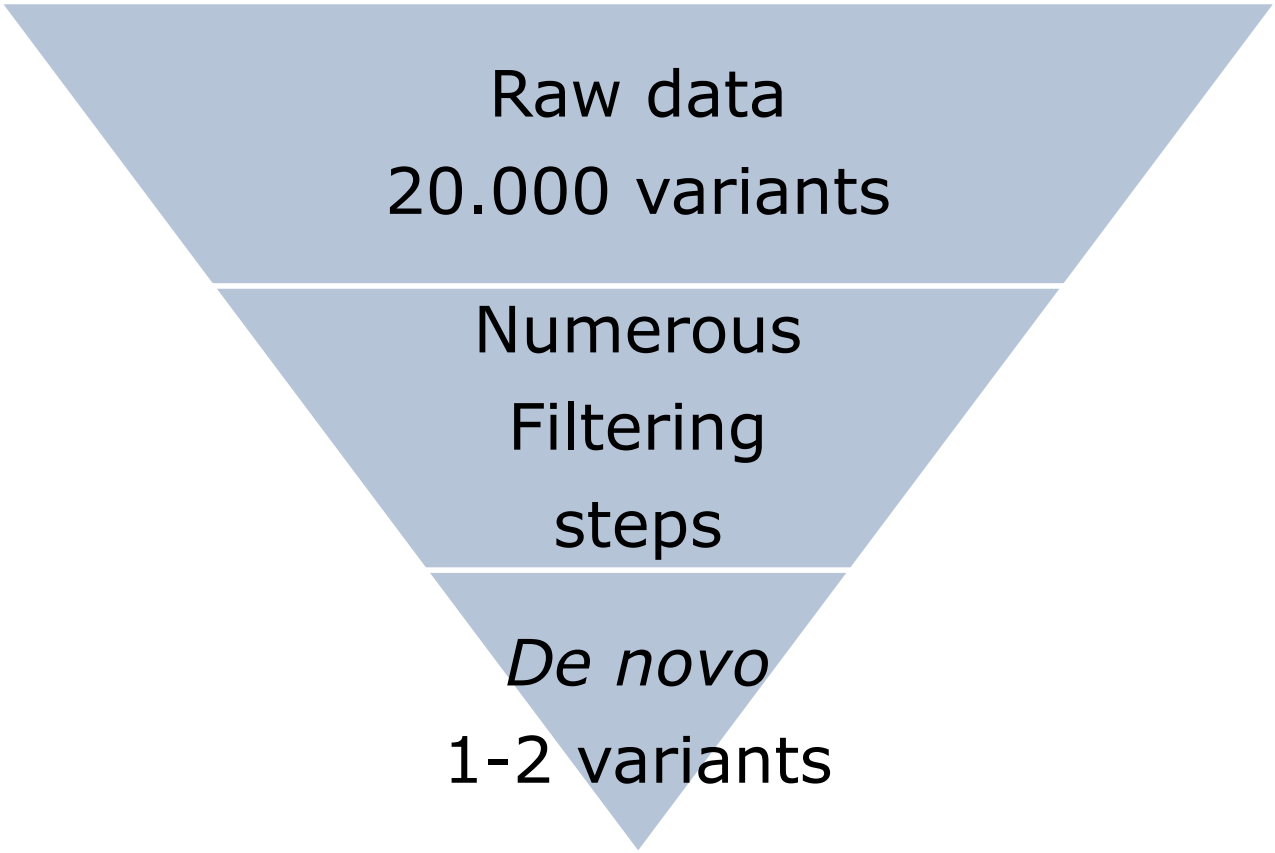
nature genetics

A *de novo* paradigm for mental retardation

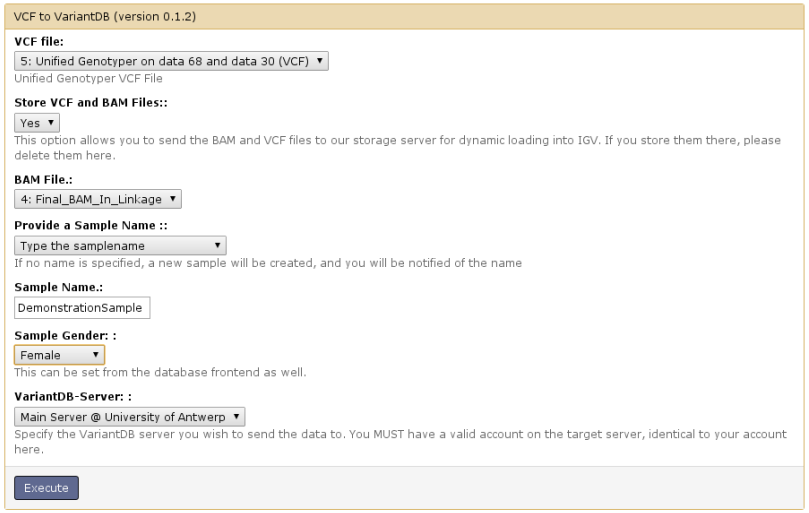
Lisenka E L M Vissers[1,2], Joep de Ligt[1,2], Christian Gilissen[1], Irene Janssen[1], Marloes Steehouwer[1], Petra de Vries[1], Bart van Lier[1], Peer Arts[1], Nienke Wieskamp[1], Marisol del Rosario[1], Bregje W M van Bon[1], Alexander Hoischen[1], Bert B A de Vries[1], Han G Brunner[1,3] & Joris A Veltman[1,3]

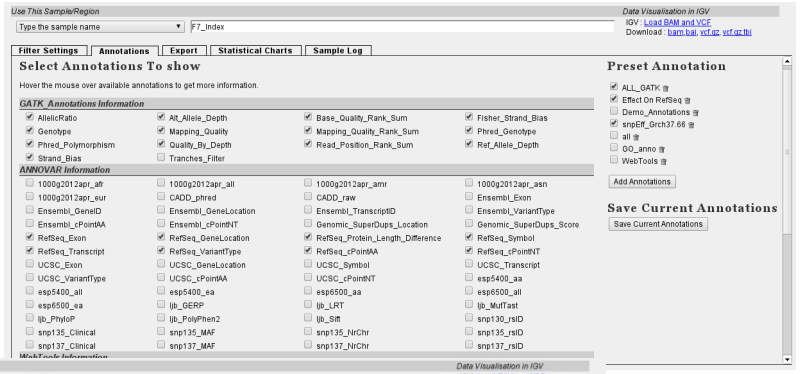
Trio approach

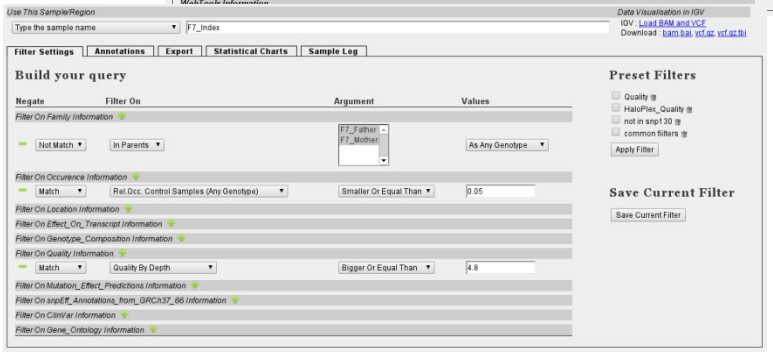
Variant calling



VariantDB
Web-based interface







What it does

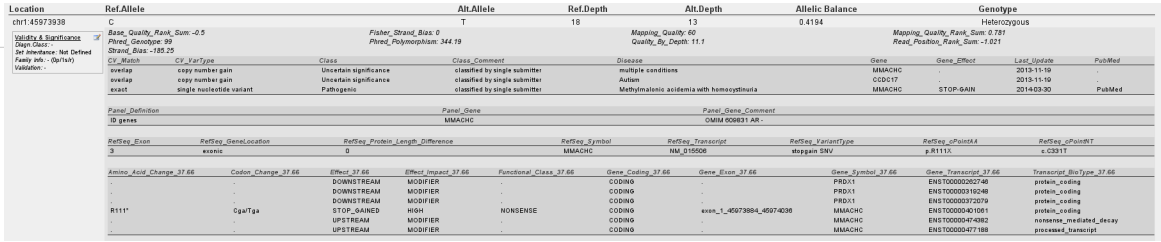
This tools sends the results from the GATK unified genotyper to a VariantDB server. From there, variants can be compared between samples, filtered on various annotations etc. To add servers, specify them in the tool configuration XML file.

Input file

VCF file from the GATK Unified Genotyper.

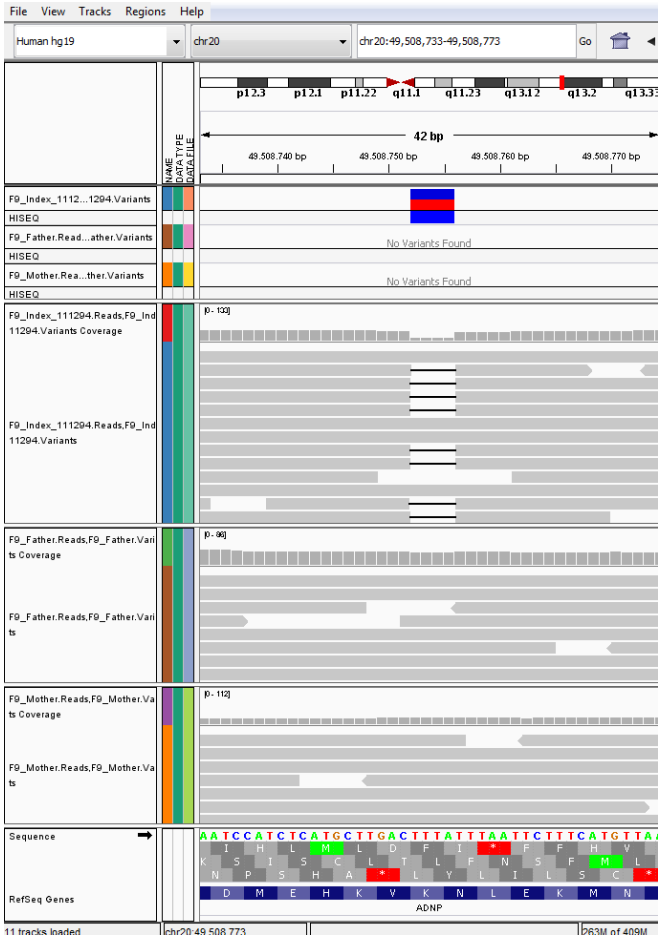
Outputs

Text file with some results from the vcf-parser.

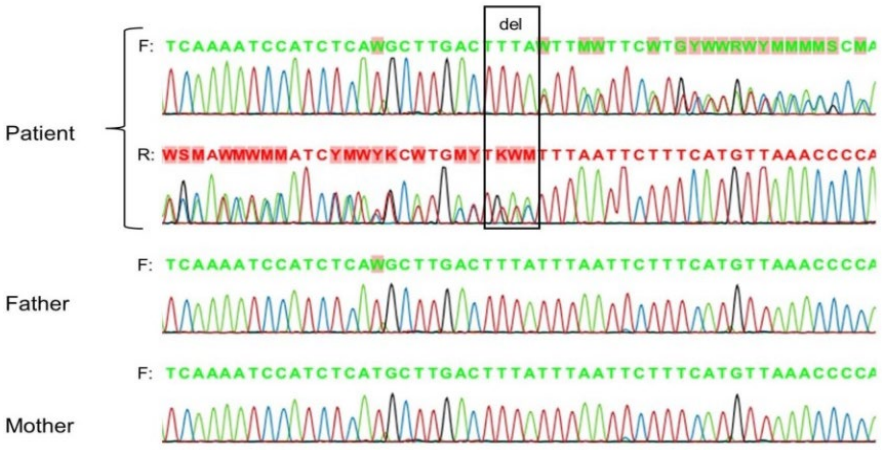


Vandeweyer et al., submitted

NGS analysis



NGS analysis:
a single de novo mutation



- 4bp del in *ADNP*
- Causes frameshift introducing stop codon
- Mutation not control databases, e.g.,ESP, 1000g, dbSNP

ADNP gene

Activity Dependent Neuroprotective Protein

- Expressed in brain
- Zinc fingers/homeobox domain: potential transcription factor
- Involved in neurogenesis
- Involved in heart development
- Homozygous KO mice are embryonically lethal
- Heterozygous KO mice have cognitive & behavioral problems

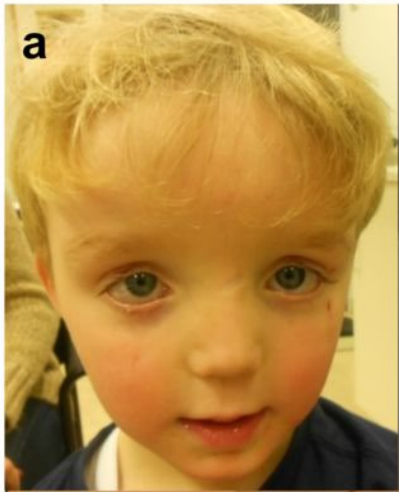
Other mutations

Table 2. Recurrent disruptive mutations in ID and ASD

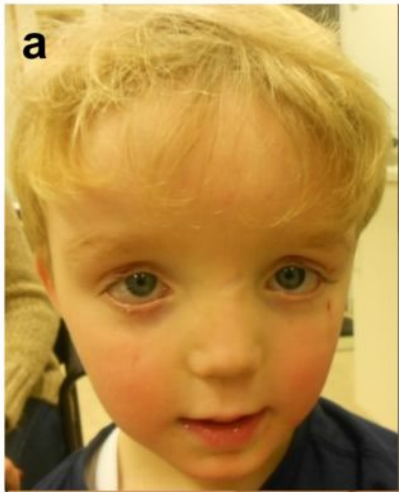
Gene[a,b]	ID cases	ASD cases	Summary[c,d,e]	ESP samples	
				Variants	Frequency
CHD8	–	9/2446	2 (O), 7 (O*) [+3 (N*)]	0	0/6503
SCN2A	3/151	2/593	1 (L), 2 (R), 2 (S) [+1 (N*)]	1	7/6503
SYNGAP1	3/151	–	1 (L), 2 (R)	1	207/6503[f]
GRIN2B	–	3/2446	1 (O), 2 (O*)	0	0/6503
DYRK1A	–	3/2446	1 (I), 1 (O), 1 (O*)	0	0/6503
ZNF292	1/151	1/593	1 (L), 1 (N)	1	2/6503
POGZ	–	2/593	1 (I), 1 (N)	1	1/6503
KATNAL2	–	2/593	1 (O), 1 (S)	1	1/6503
TBR1	–	2/2446	1 (O), 1 (O*)	0	0/6503
CTNNB1	1/151	1/2446	1 (L), 1 (O*), [+1 (L*)]	0	0/6503
SETBP1	1/151	1/593	1 (O), 1 (R)	3	58/6503[f]
ADNP	–	2/2446	1 (O), 1 (O*)	1	1/6500
LRP2	1/151	1/593	1 (I), 1 (L)	6	53/6500
ARID1B	–	2/2446	1 (O), 1 (O*)	5	314/6500

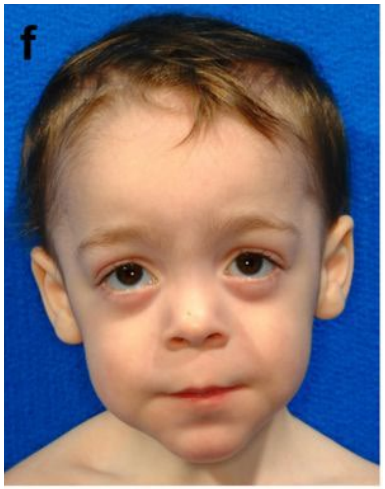
- 1 patient in exome study - O'Roak ea, Nature 2012
- 1 patient in MIPS screening - O'Roak ea, Science 2012
- 1 in ESP non-neurological control cohort

ADNP mutation

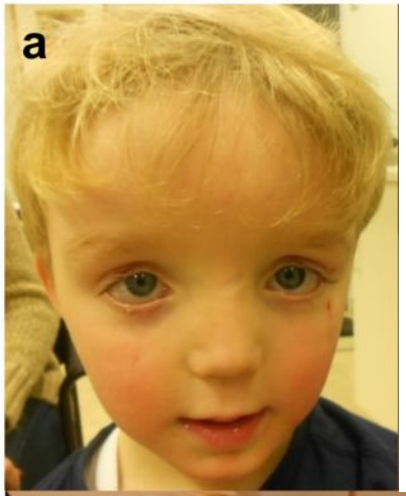


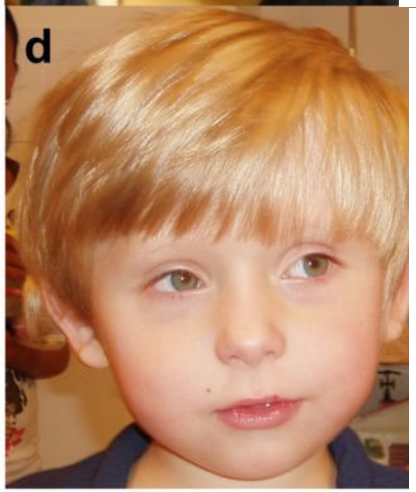
ADNP mutation

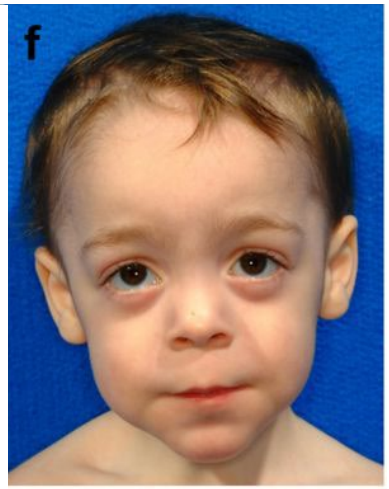




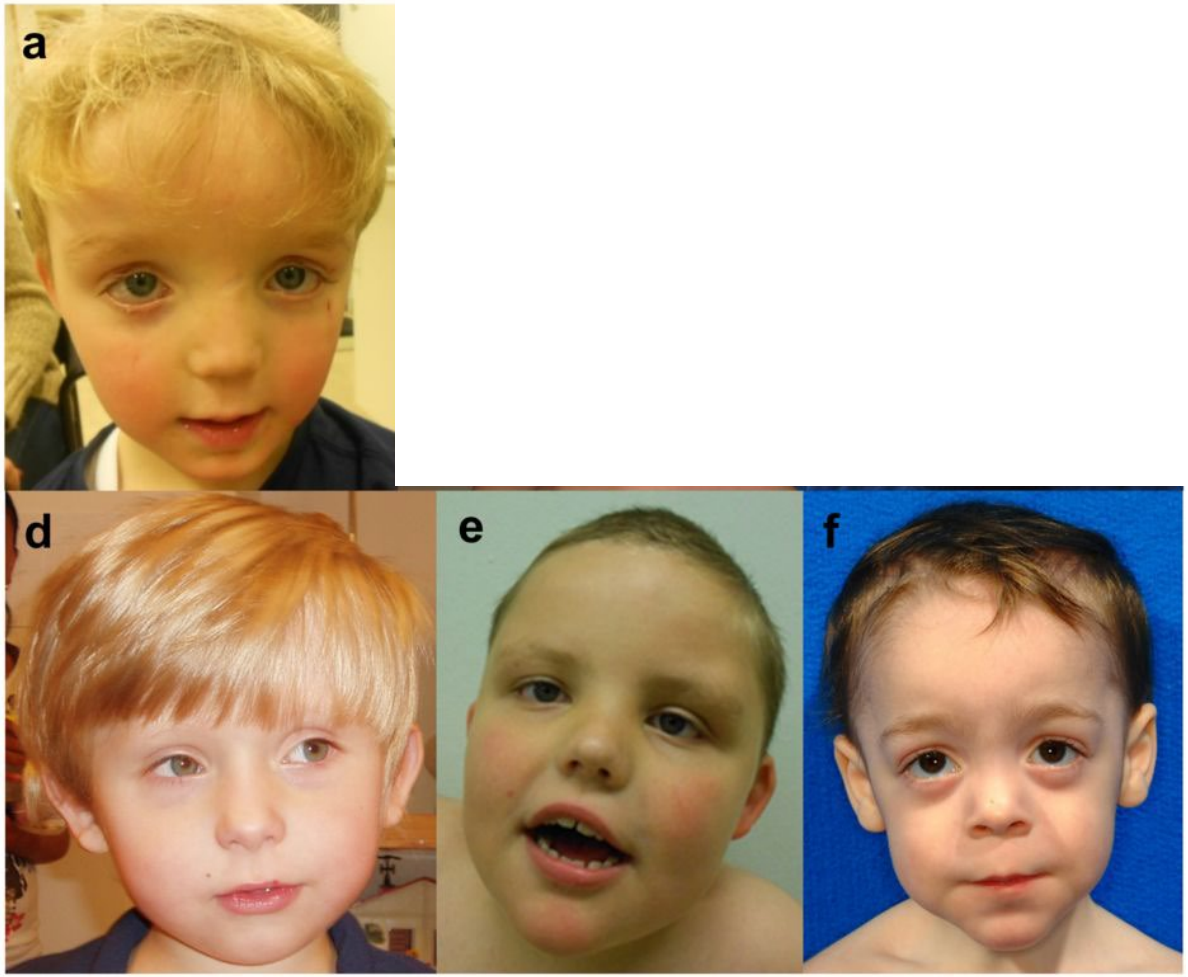
ADNP mutation



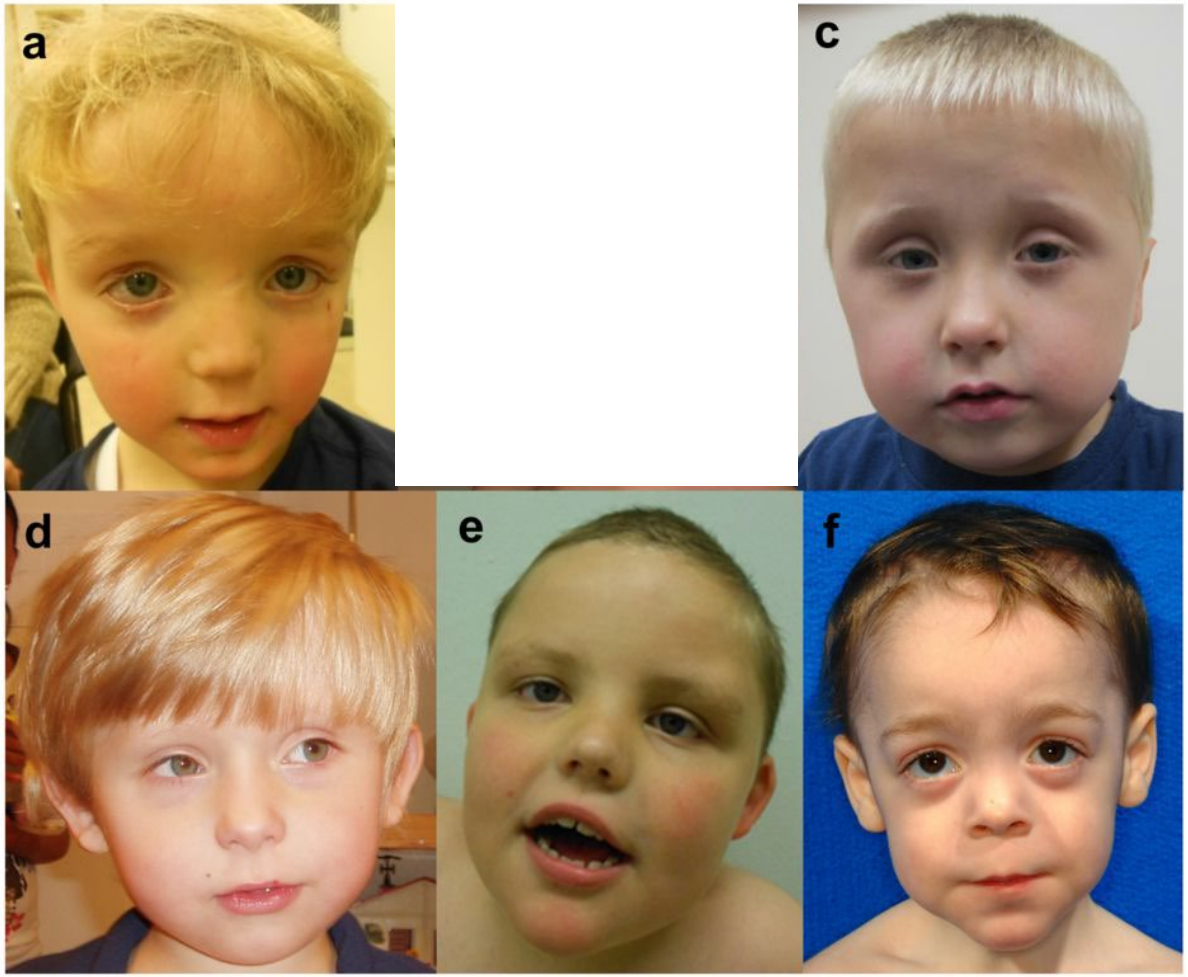




ADNP mutation



ADNP mutation

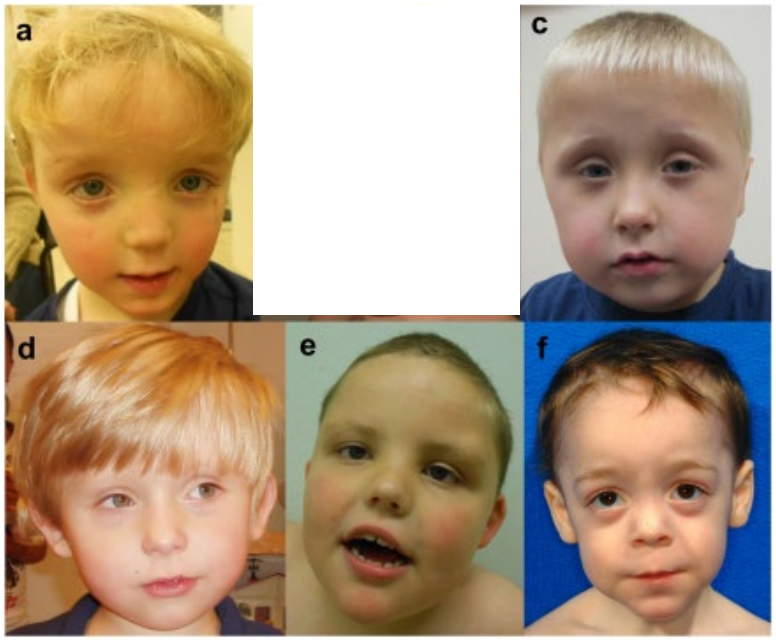


Ten patients with truncating mutations in *ADNP*

Patient	Patient ID	Origin	Screening method	Cohort composition	Cohort size	mutation in genomic DNA (chr20)	mutation in cDNA (NM_015339.2)	Protein	Mutation Type	Inheritance
1	111294	Antwerp	WES	Moderate to severe ID and/or autism + dysmorphic features	10	g.49508752_49508755 delTTTA	c.2496_2499delTAAA	p.Asp832Lysfs*80	Frameshift	*de novo*
2	11-08612	Nijmegen	WES	Non-syndromic severe ID	100	g.49510040G>T	c.1211C>A	p.Ser404*	Nonsense	*de novo*
3	12130.p1	Seattle	WES[2,16]	ASD from the Simon Simplex Collection	189	g.49510028_49510029 delTT	c.1222_1223delAA	p.Lys408Valfs*31	Frameshift	*de novo*
4	1050237	Westmead	WES	Non-syndromic severe ID	95	g.49509086_49509098 delATTTGCTCGTAAG	c.2153_2165delCTTAC GAGCAAAT	p.Thr718Glyfs*12	Frameshift	*de novo*
5	3061-08D	Stockholm	WES	Moderate to severe ID and/or autism + dysmorphic features	45	g.49509094G>C	c.2157C>G	p.Tyr719*	Nonsense	*de novo*
6	122793	Antwerp	HRM	Autism	148	g.49508757_49508760 delTTAA	c.2491_2494delTTAA	p.Lys831Ilefs*81	Frameshift	*de novo*
7	07-06960	Nijmegen	MIPS	ID and/or autism	2743	g.49508443delG	c.2808delC	P.Tyr936*	Frameshift	*de novo*
8	2376	Troina	MIPS	ID and/or autism	Idem as patient 7	g.49508757_49508760 delTTAA	c.2491_2494delTTAA	p.Lys831Ilefs*81	Frameshift	*de novo*
9	2533	Troina	MIPS	ID and/or autism	Idem as patient 7	g.49509321G>A	c.1930C>T	p.644Arg*	Nonsense	parents not available
10	13545.p1	Seattle	MIPS[16]	ASD from the Simon Simplex Collection	2446	g.49509094_49509095 insT	c.2156_2157insA	p.Tyr719*	Frameshift	*de novo*

Dysmorphic features

Phenotype	Frequency
Prominent forehead	5/8
High hairline	7/8
Eversion/notch eyelid	3/7
Hypertelorism	1/8
Broad nasal bridge	6/8
Short nose	2/8
Thin upper lip	6/7



Clinical characteristics

Phenotype	Frequency
Autism Spectrum Disorder (ASD)	**10/10**
Intellectual Disability (ID)	**10/10**
Developmental delay (motor)	**9/10**
Developmental delay (speech)	8/9
ADHD	2/9
Hypotonia	7/9
Growth retardation / Short stature	5/8
Feeding problems	5/8
Recurrent infections	5/8
Congenital heart defect	3/8
Hyperlaxity	6/8
Obesity	4/7
Hypermetropia	6/6
Seizures	2/7
Behavior	5/7
Insensitivity to pain	2/5
MRI brain abnormality	5/9
Hand abnormalities	6/8
Constipation	2/6

Statistics

- The frequency of truncating *de novo* mutations in *ADNP* is significantly higher (p: 0.001852, odds ratio 13.24668, one-sided Fisher's exact test) in patients compared to the ESP cohort and additional controls from the Simons Siblings.
- The probability of detecting 8 or more *de novo* truncating events in *ADNP* within our cohort by chance was estimated to be $p = 2.65e^{-18}$ (binomial test) under a *de novo* rate of 1.2 non-synonymous coding variants per individual according to a probabilistic model of a locus specific enrichment for truncating variation [O'Roak et al., 2012].

De novo mutations in *ADNP* cause new autism syndrome

Autism spectrum disorder
Intellectual Disability
Facial dysmorrphology
Congenital malformations

may explain etiology of
0.17% of ASD patients

LETTERS

nature genetics

A SWI/SNF-related autism syndrome caused by *de novo* mutations in *ADNP*

Céline Helsmoortel[1], Anneke T Vulto-van Silfhout[2,16], Bradley P Coe[3,4,16], Geert Vandeweyer[1,5], Liesbeth Rooms[1], Jenneke van den Ende[6], Janneke H M Schuurs-Hoeijmakers[2], Carlo L Marcelis[2], Marjolein H Willemsen[2], Lisenka E L M Vissers[2], Helger G Yntema[2], Madhura Bakshi[7], Meredith Wilson[8], Kali T Witherspoon[3,4], Helena Malmgren[9], Ann Nordgren[9], Göran Annerén[10], Marco Fichera[11,12], Paolo Bosco[13], Corrado Romano[14], Bert B A de Vries[2,15], Tjitske Kleefstra[2,15], R Frank Kooy[1], Evan E Eichler[3,4] & Nathalie Van der Aa[1,6]

Acknowledgements

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