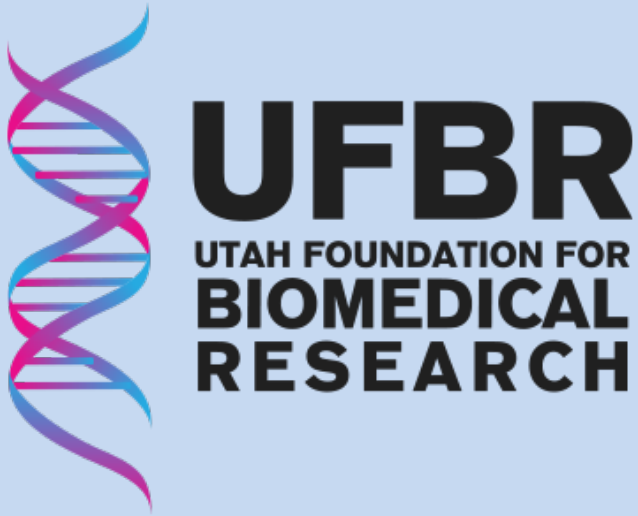
Human Genetics and Rare Diseases

Gholson J. Lyon, M.D. Ph.D.



"All science can do is to show that some things are very likely, others unlikely."

– C.H. Waddington
Tools for Thought, 1977

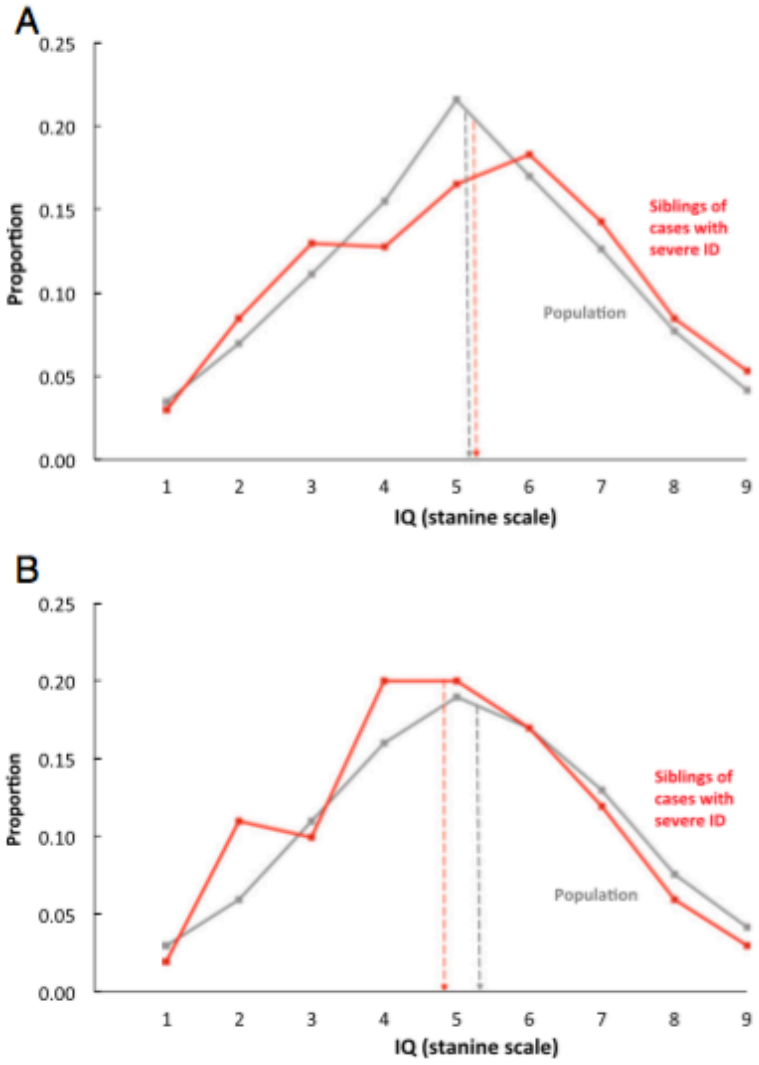


Fig. 3. Severe ID is not familial and thus not affected by the same genetic factors as mild ID or IQ in the normal range. Siblings of persons with severe ID have IQs indistinguishable from the rest of the population. (*A*) Swedish results: distribution of IQ scores for individuals who have a sibling diagnosed as having severe ID (mean = 5.17, SD = 2.06, n = 400 pairs) and the entire sibling population distribution (mean = 5.10, SD = 1.95, n = 381,122 pairs). (*B*) Israeli results: distribution of IQ scores for individuals who have a sibling diagnosed as having severe ID (mean = 4.90, SD = 2.02, n = 297 pairs) and the entire sibling population distribution (mean = 5.49, SD = 1.94, n = 239,117 pairs). Note: individuals with severe ID are not included in the stanine IQ score distributions presented.

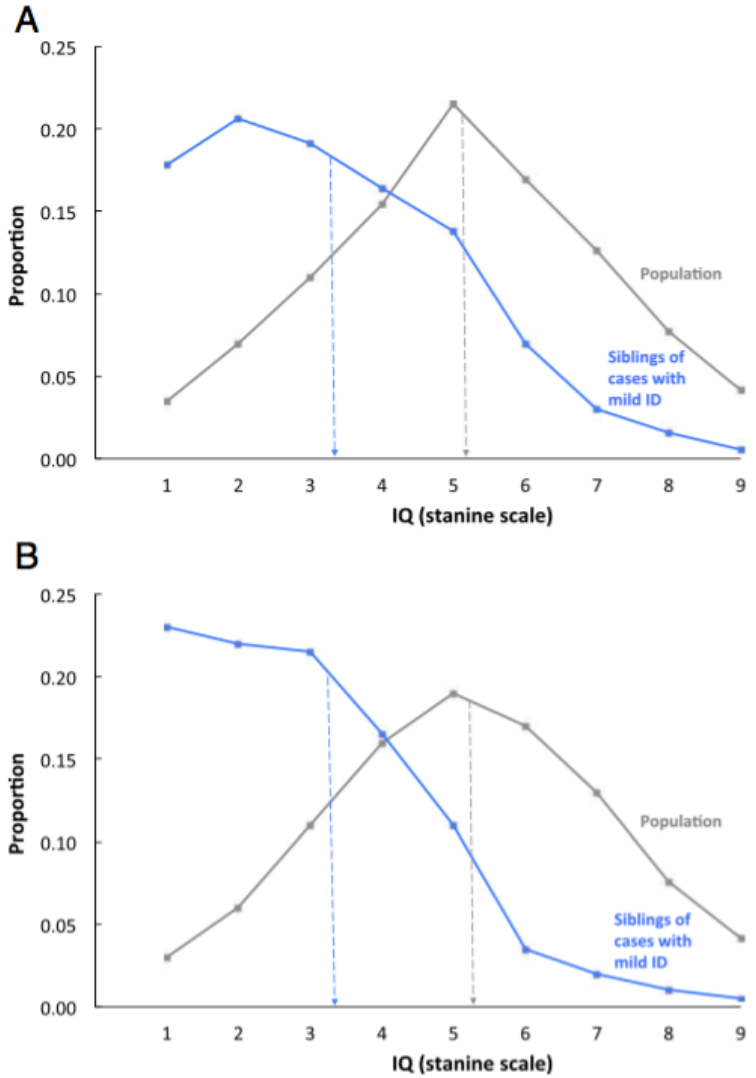


Fig. 1. Mild ID (lowest possible IQ stanine scale score of 1 equals lowest 3% IQ scores) is familial. Siblings of persons with mild ID have significantly and substantially lower IQs than the population. (*A*) Swedish results for male siblings of persons with IQ stanine score of 1 (mean = 3.31, SD = 1.80, n = 12,431 male pairs) and for the entire sibling population (mean = 5.10, SD = 1.95, n = 382,122 pairs). (*B*) Israeli results for male siblings of persons with IQ stanine score of 1 (mean = 3.36, SD = 2.46, n = 6,800 male pairs) and for the entire sibling population (mean = 5.49, SD = 1.94, n = 239,117 pairs). Note: individuals with severe ID are not included in the stanine IQ score distributions presented.

Discontinuity in the genetic and environmental causes of the intellectual disability spectrum

Abraham Reichenberg[a,b,1], Martin Cederlöf[c], Andrew McMillan[d], Maciej Trzaskowski[d], Ori Kapara[e], Eyal Fruchter[f], Karen Ginat[f], Michael Davidson[e], Mark Weiser[e,f], Henrik Larsson[c], Robert Plomin[d], and Paul Lichtenstein[c]

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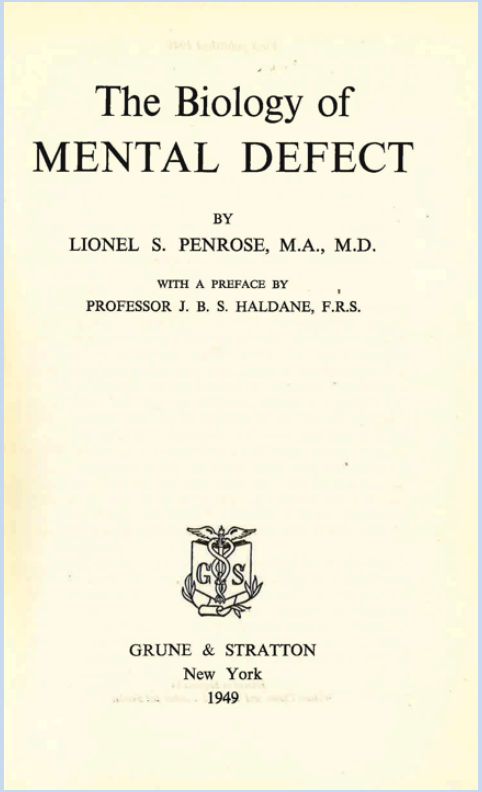
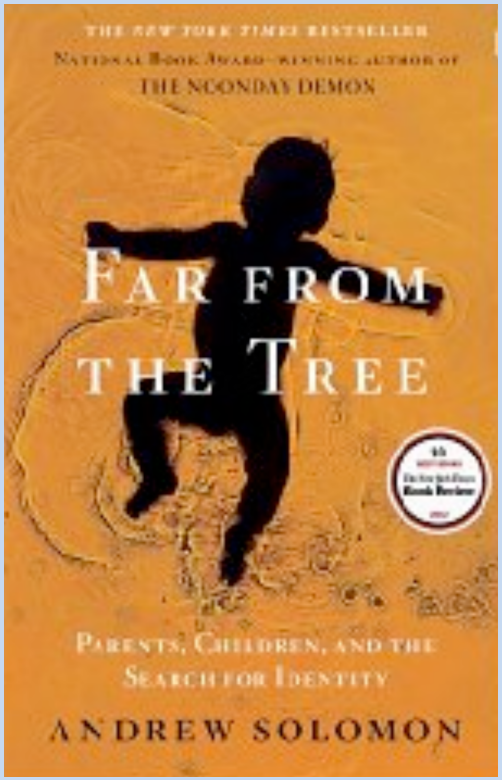
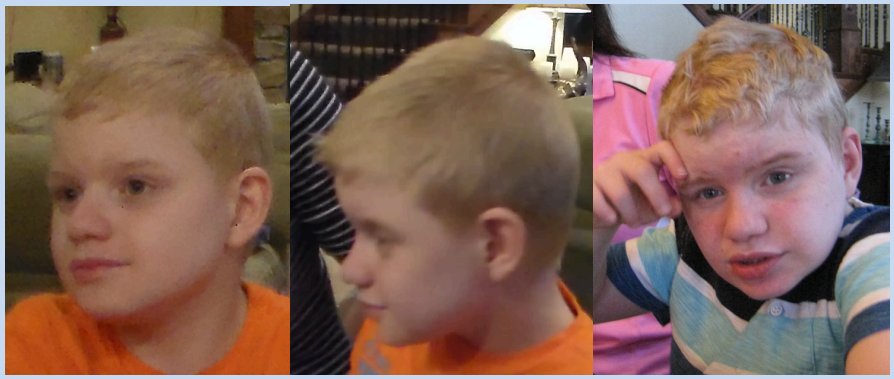
Edited by Daniel J. Benjamin, University of Southern California, Los Angeles, CA, and accepted by the Editorial Board November 13, 2015 (received for review April 24, 2015)



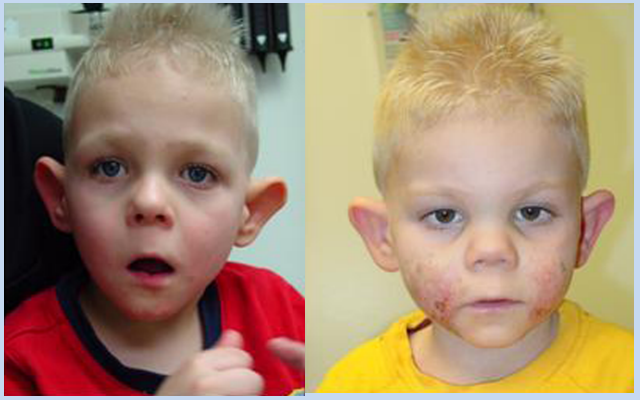


NAA10, NAA15, NAA50
“Ogden syndrome”

SCN8A syndrome

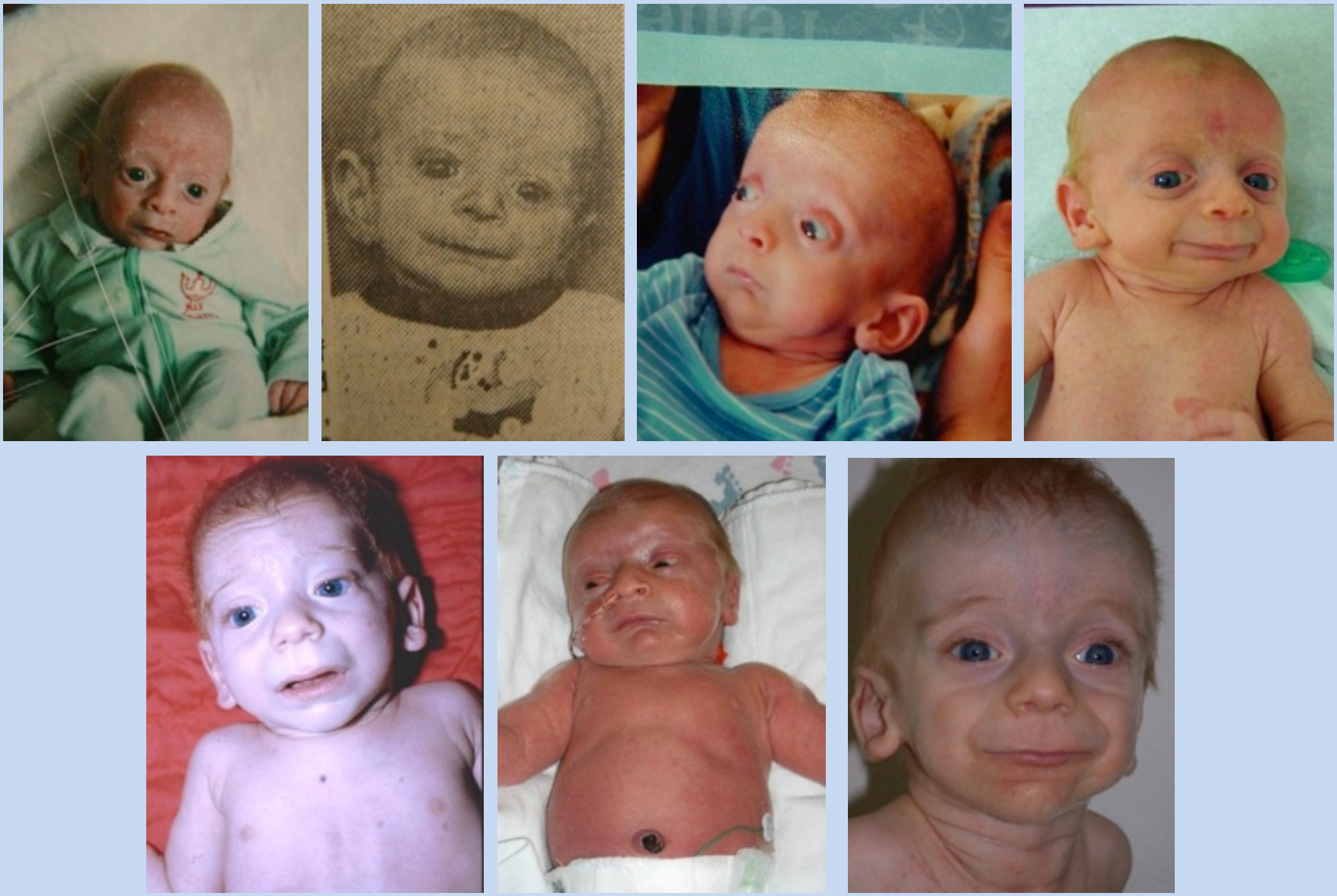


ANKRD11
“KBG syndrome”

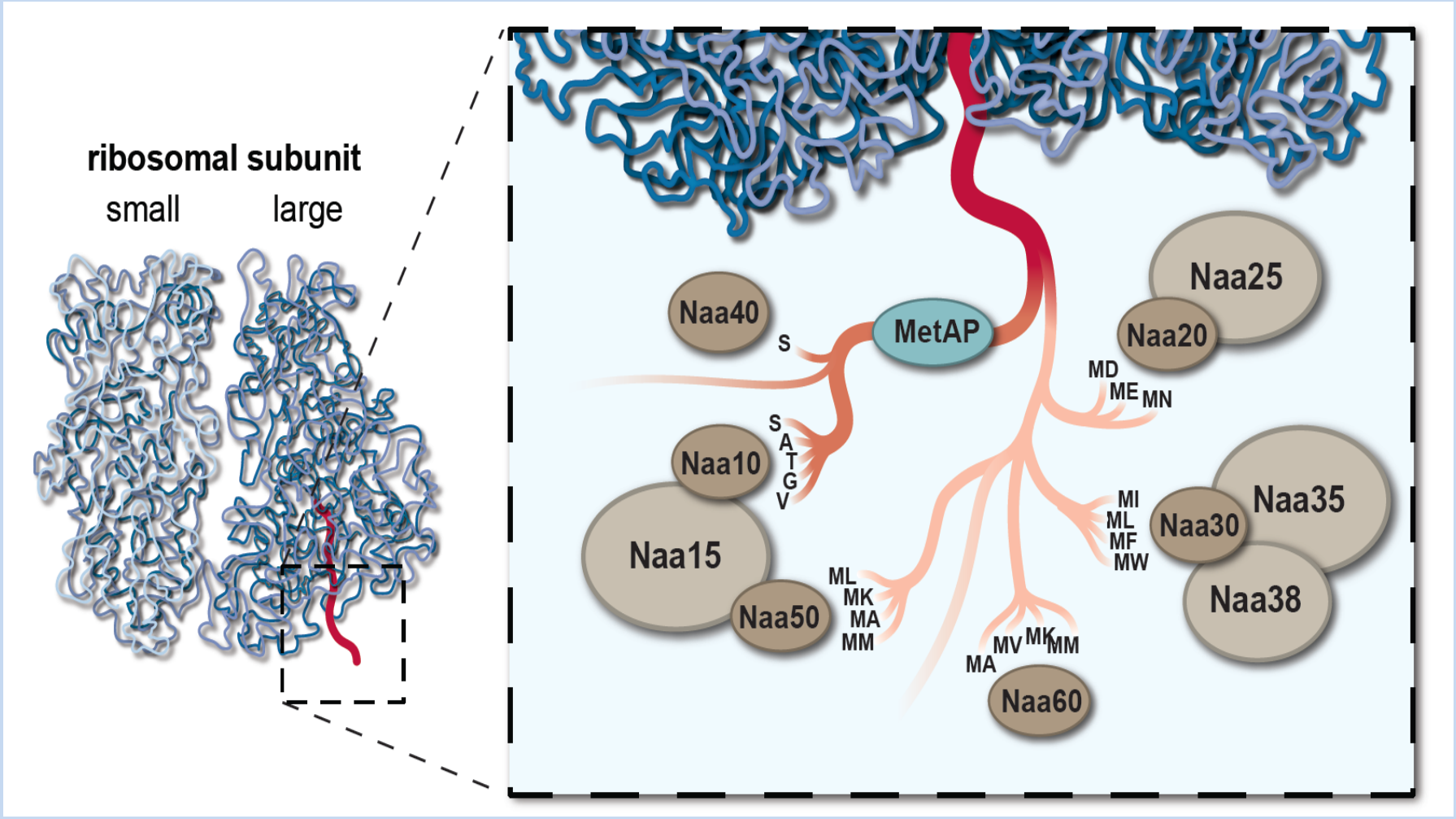


TAF1 syndrome

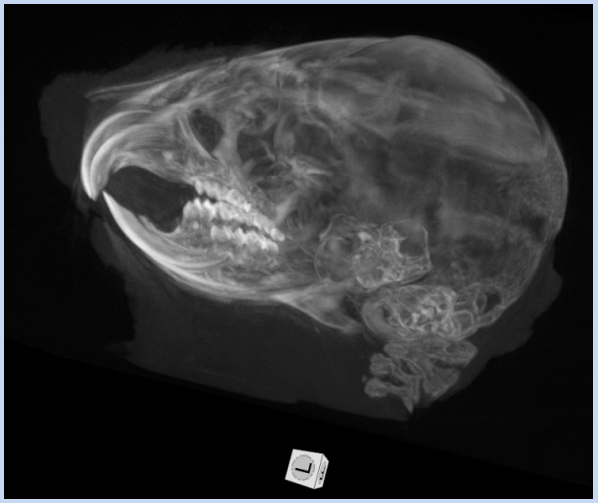
Vignette #1. Ogden Syndrome

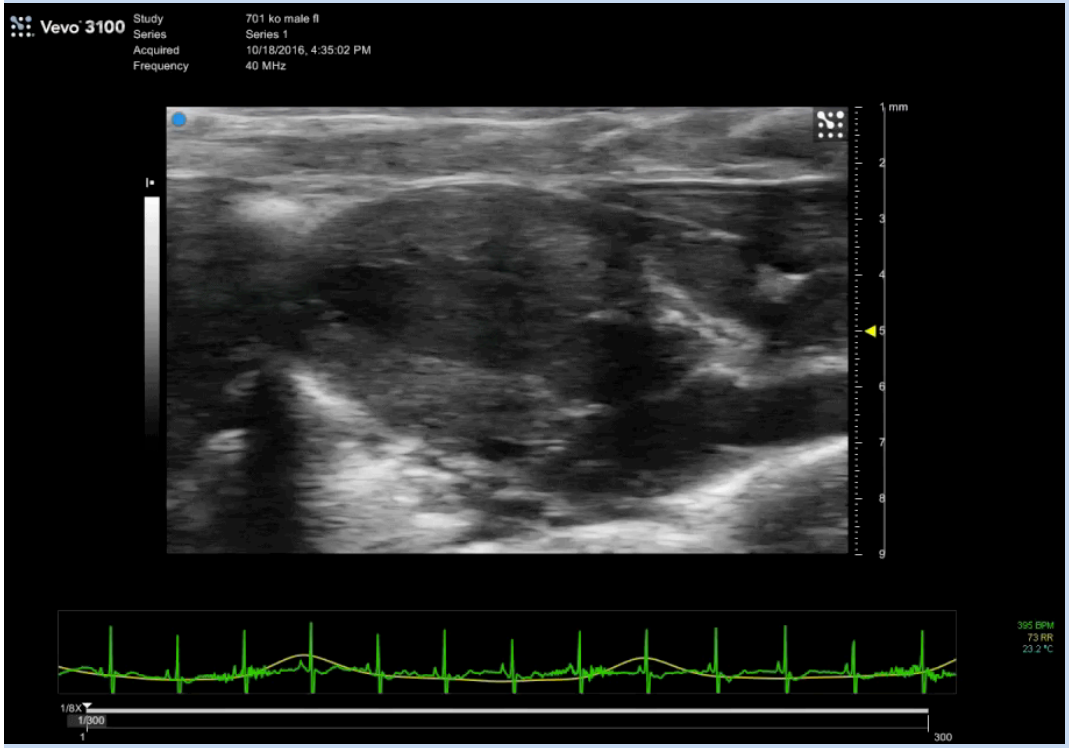


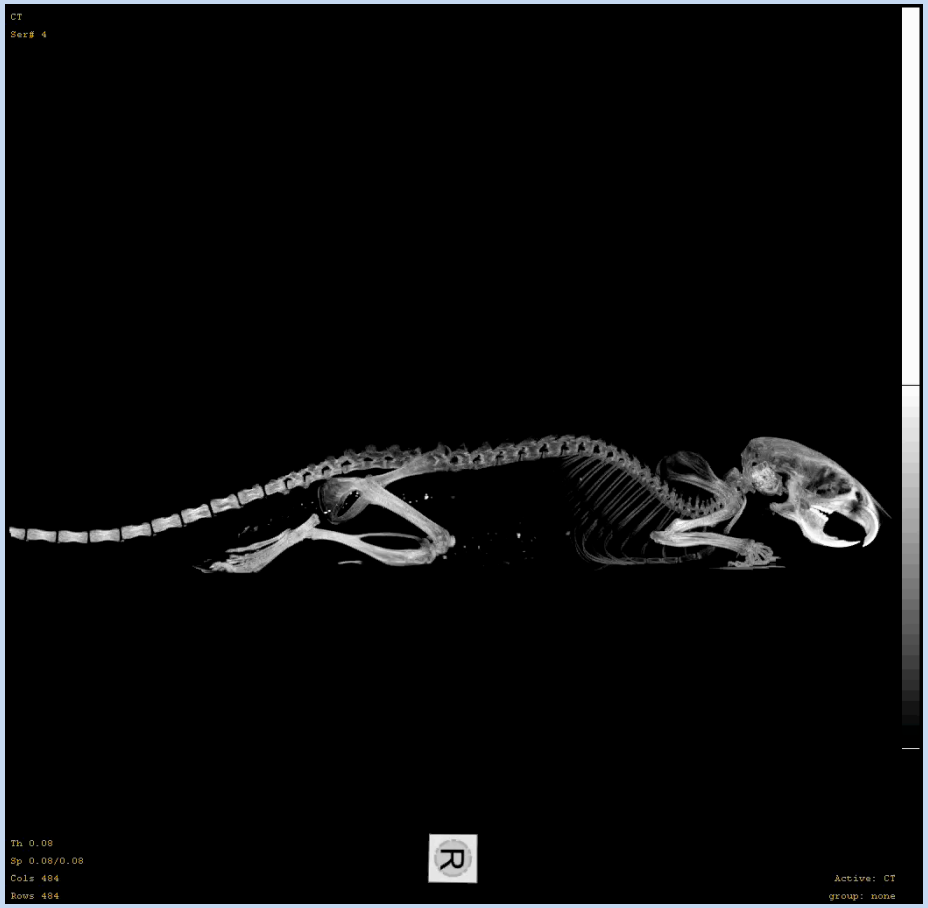
The American Journal of Human Genetics *89*, 1–16, July 15, 2011


ribosomal subunit
small
large
Naa40
S
MetAP
Naa25
Naa20
MD
ME
MN
S
A
T
G
V
Naa10
Naa15
Naa50
ML
MK
MA
MM
MI
ML
MF
MW
Naa30
Naa35
Naa38
MA
MV
MK
MM
Naa60

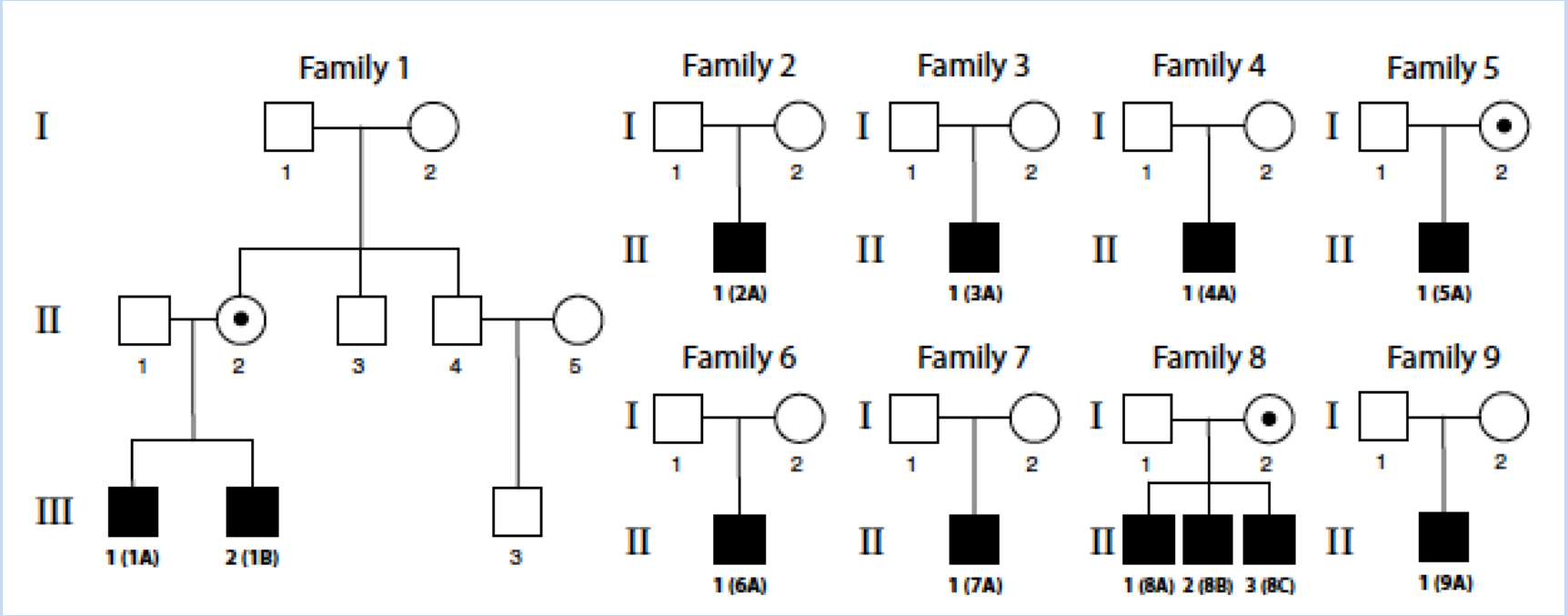
In-house Friday December 16th!

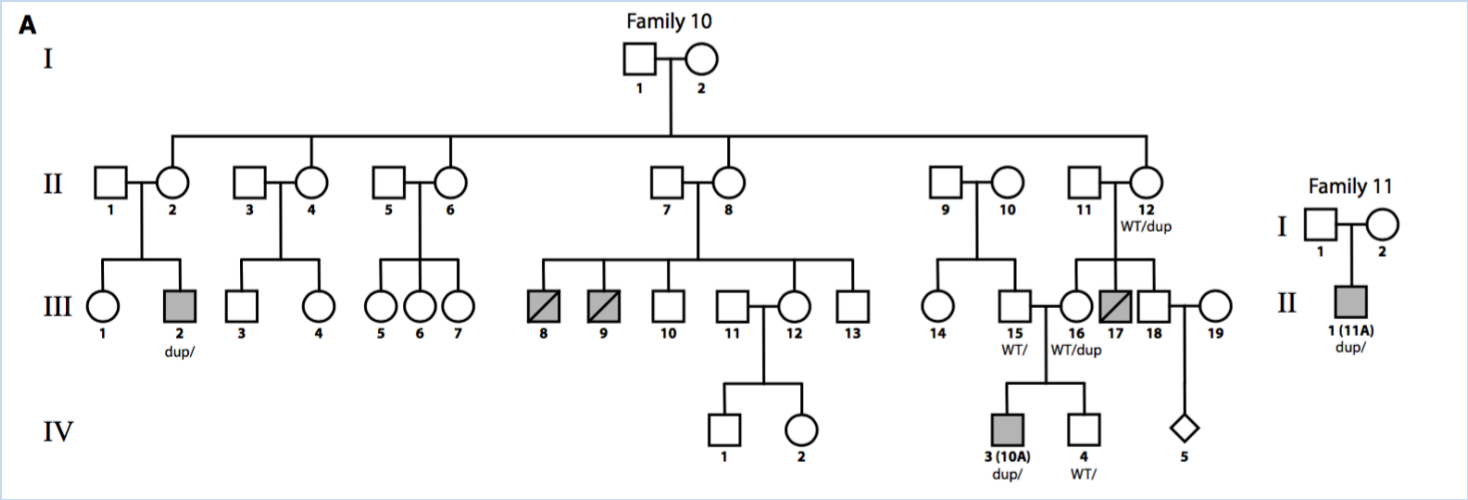




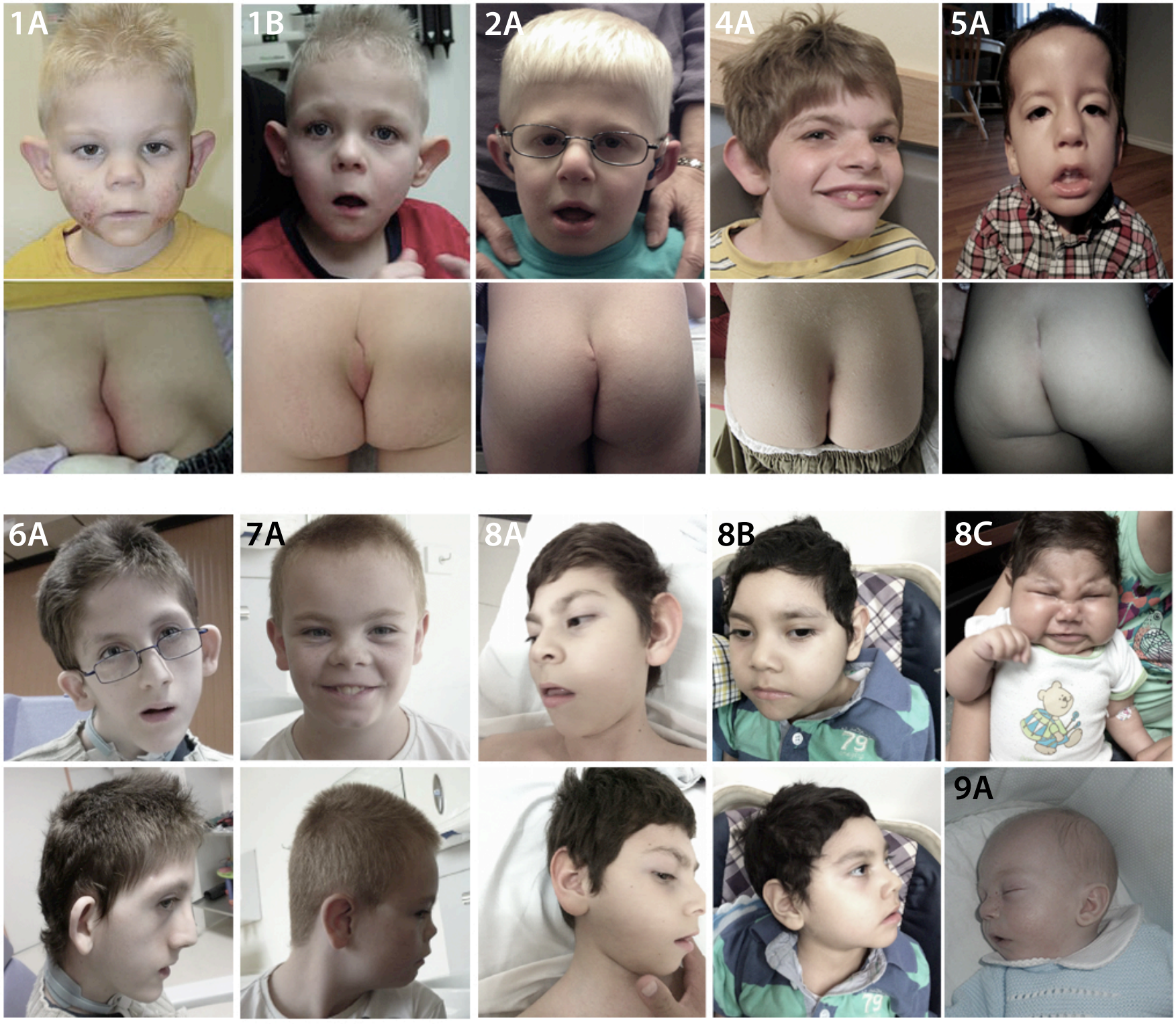


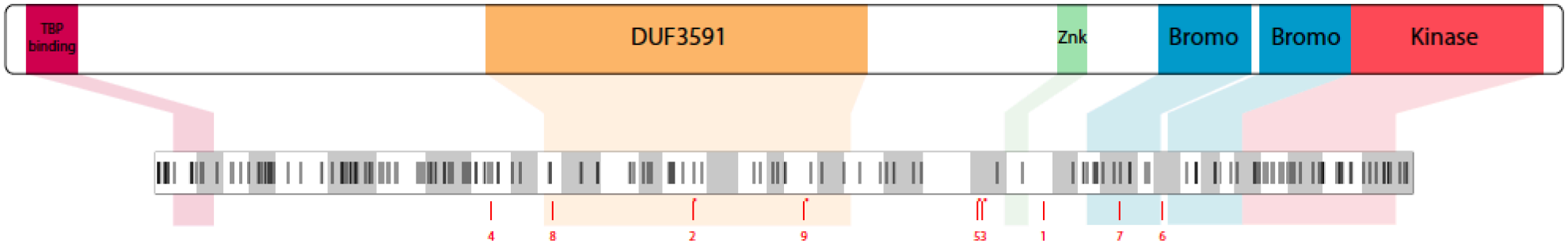
Vignette # 2: TAF1 Syndrome





The American Journal of Human Genetics *97*, 922–932, December 3, 2015

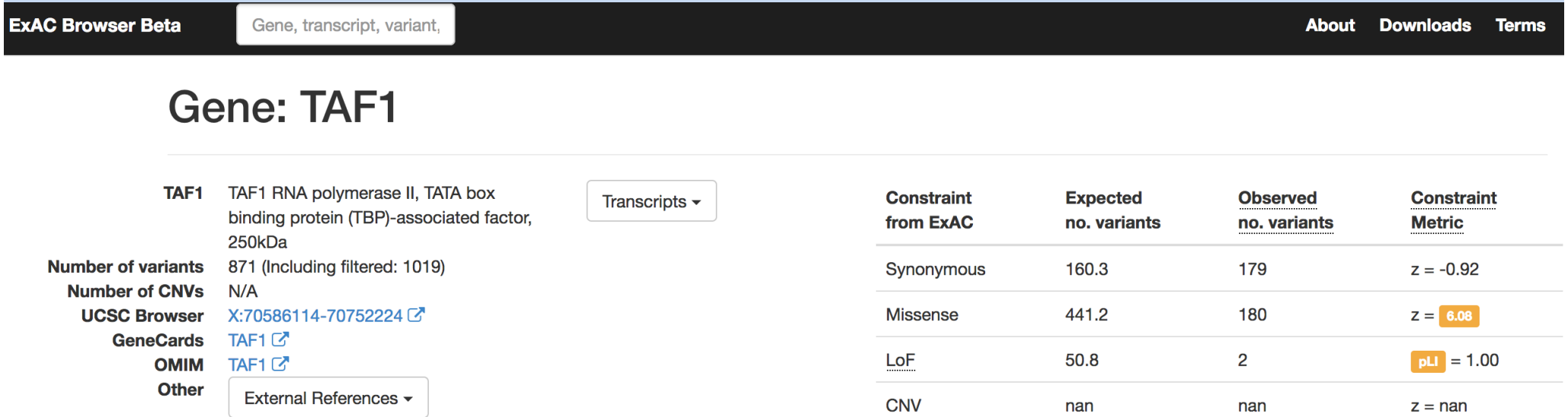

1A
1B
2A
4A
5A
6A
7A
8A
8B
8C
9A



ExAC Browser (Beta) | Exome Aggregation Consortium

Search for a gene or variant or region

Examples - Gene: PCSK9, Transcript: ENST00000407236, Variant: 22-46615880-T-C, Multi-allelic variant: rs1800234, Region: 22:46615715-46615880



LOF in females only

A clinician's plea

Judith G. Hall

Department of Pediatrics and Medical Genetics, University of British Columbia, Vancouver, British Columbia V6H 3V4, Canada. e-mail: jhall@cw.bc.ca

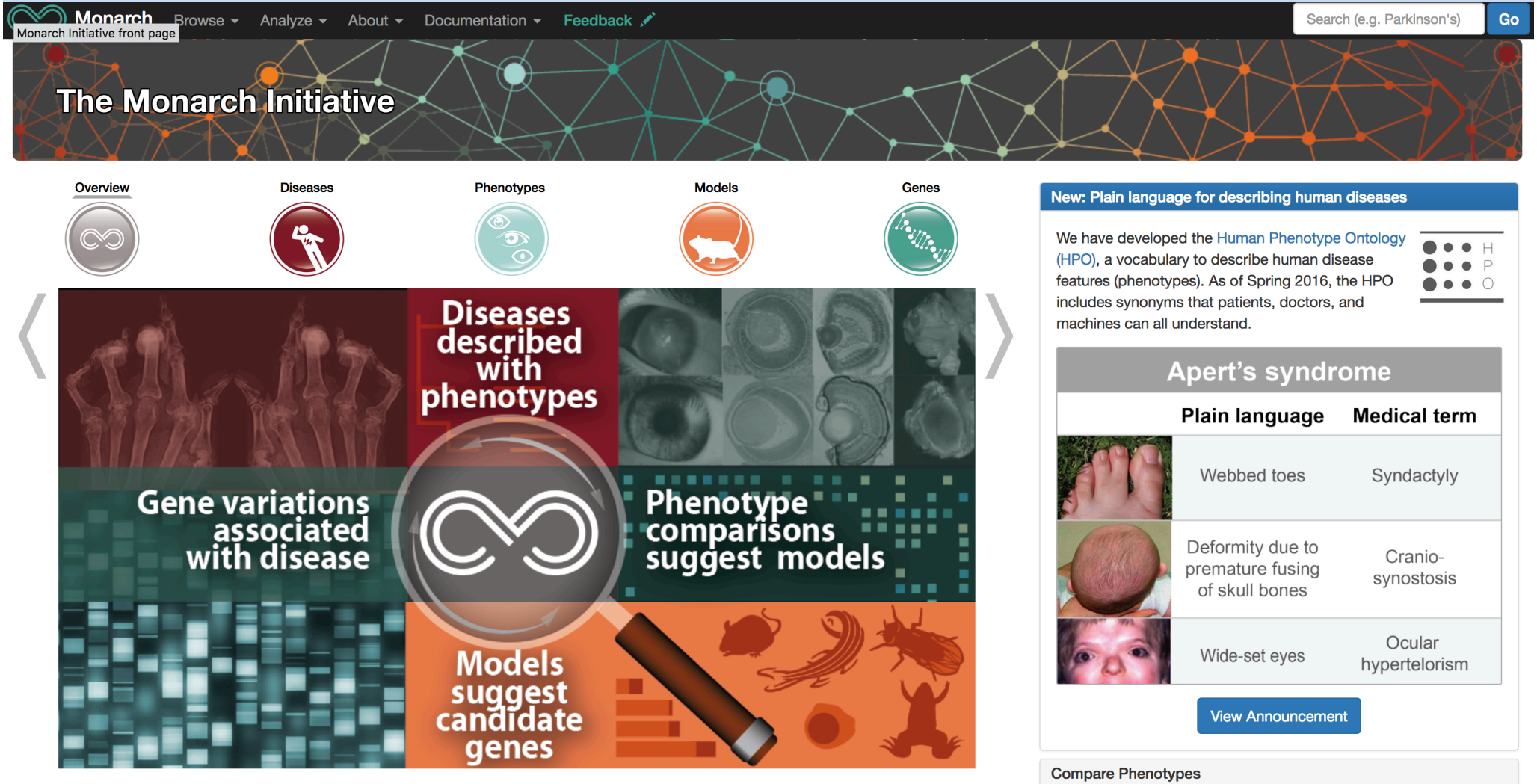
For the detection of human gene mutations to have practical application, clear clinical descriptions of the affected individuals (as well as those clinically affected in whom mutations are not found) should be part of the publication.

Nature Genetics, April 2003

Proband	1A	1B	2A	3A	4A	5A	6A	7A	8A	8B	8C	9A	10A	11A
Sex	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Age	15	13	5	6	9	3		11	9	4	1	3	16	8
Postnatal Growth Retardation; HP:0008897	+	+	+	+	+	+			+	+	+	+		+
Delayed Gross Motor Development; HP:0002194	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Delayed Speech and Language Development; HP:0000750	+	+	+	+	+	+	+	+	+	+	+		+	+
Oral-pharyngeal Dysphagia; HP:0200136	+	+	+	+		+			+	+	+		+	
Prominent Supraorbital Ridges; HP:0000336	+	+		+			+		+	+	+	+	+	+
Downslanted Palpebral Fissures; HP:0000494	+	+	+		+	+	+		+	+	+		+	
Sagging Cheeks;	+	+				+			+	+	+	+	+	+
Long Philtrum; HP:0000343	+	+	+	+	+	+		+	+	+	+	+		
Low-set Ears; HP:0000369	+	+	+	+	+	+	+		+	+	+	+		+
Protruding Ear; HP:0000411	+	+		+	+	+	+		+	+	+			+
Long Face; HP:0000276	+	+	+			+	+		+	+	+	+	+	+
High palate; HP:0000218				+		+	+		+	+	+	+	+	+
Pointed Chin; HP:0000307	+	+	+		+	+	+		+	+	+		+	+
Anteverted nares; HP:0000463			+	+	+	+		+	+	+	+	+		+
Hearing Impairment; HP:0000365	+	+	+	+		+			+	+	+			
Chromic Otitis Media; HP:0000389	+	+	+		+	+		+	+	+	+			
Strabismus; HP:0000486	+	+	+	+		+	+		+			+	+	
Microcephaly; HP:0000252	+	+	+	+	+			+	+	+	+	+		
Hypoplasia of the Corpus Callosum; HP:0002079	+	+	+		+	+	+		+	+	+	+		
Generalized hypotonia; HP:0001290	+	+	+	+	+	+	+		+	+	+	+		+
Unusual Gluteal Crease with Sacral Caudal Remnant/ Sacral dimple (abnormal sacral segmentation HP:0008468) (prominent protruding coccyx HP:0008472)	+	+	+	+	+	+		+	+	+	+	+		
Joint Hypermobility; HP:0001382	+	+		+		+			+	+	+	+		
Autistic Behaviors; HP:0000729	+	+	+				+	+	+	+	+		+	+
Intellectual Disability; HP:0001249	+	+	+	+	+		+	+	+	+	+	+	+	+

Nucleic Acids Research, 2016 1–12
doi: 10.1093/nar/gkw1039

The human phenotype ontology in 2017



Vignette #3: KBG Syndrome

COLD SPRING HARBOR
Molecular Case Studies

RESEARCH REPORT

KBG syndrome involving a single-nucleotide duplication in *ANKRD11*

Robert Kleyner,[1,9] Janet Malcolmson,[1,2,9] David Tegay,[1] Kenneth Ward,[3] Annette Maughan,[4] Glenn Maughan,[5] Lesa Nelson,[3] Kai Wang,[6,7,8] Reid Robison,[8] and Gholson J. Lyon[1,8]

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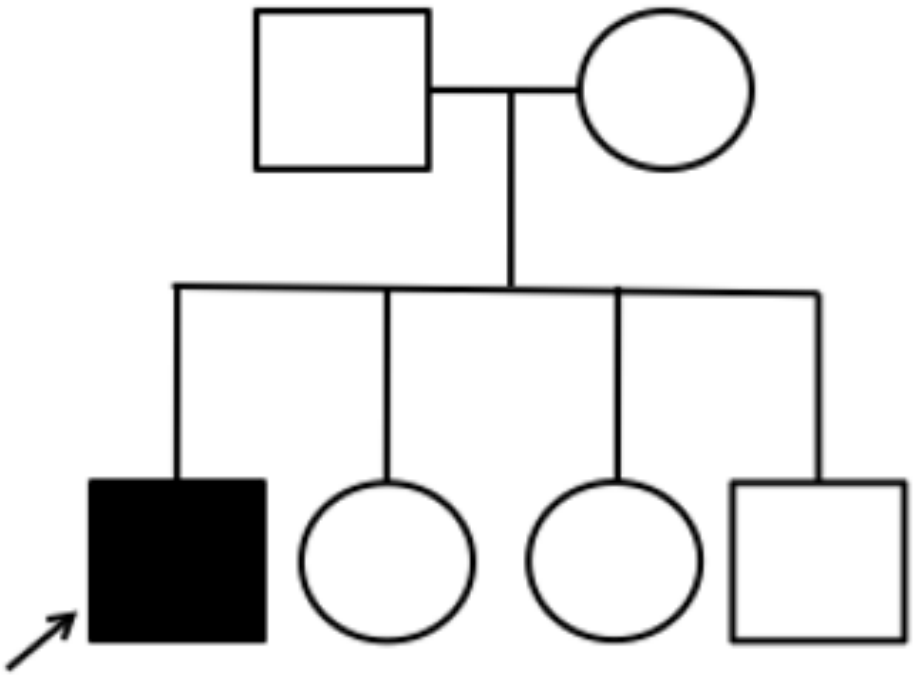
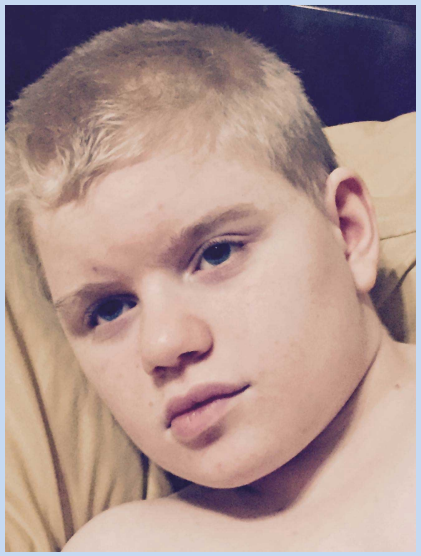
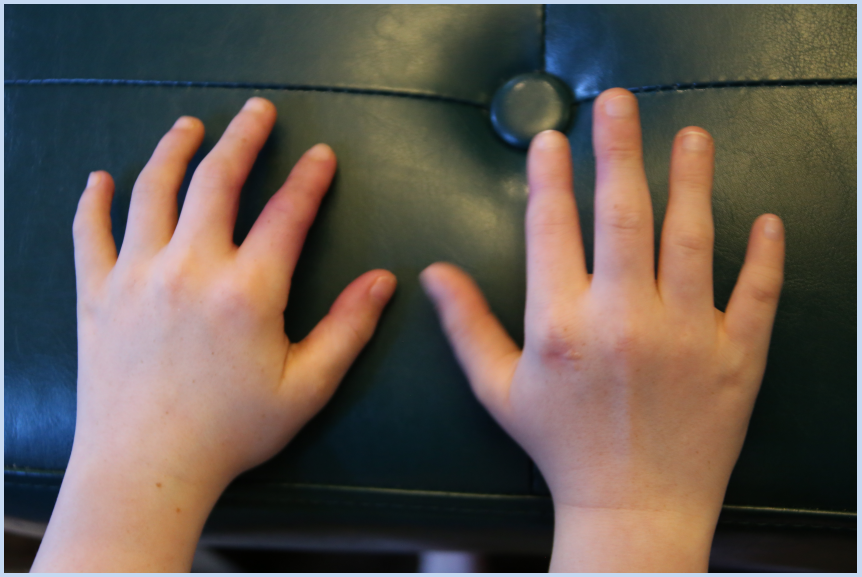






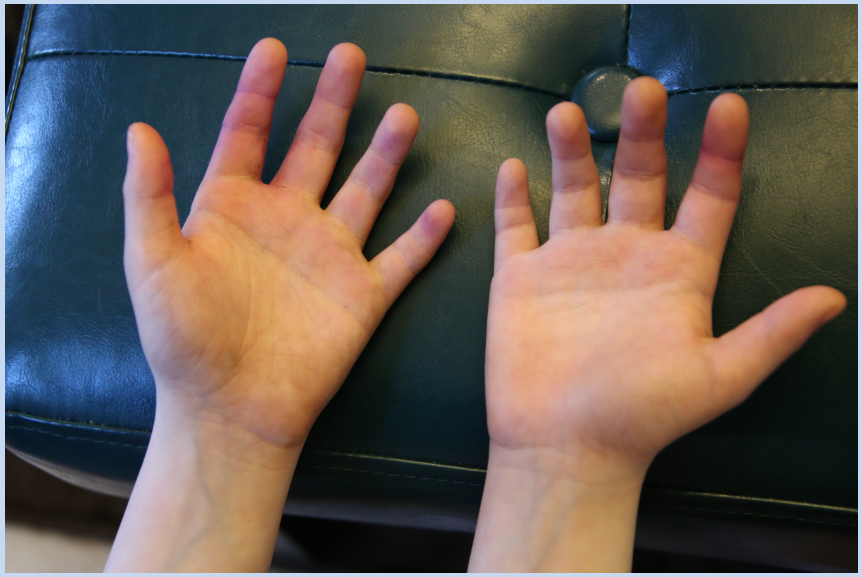
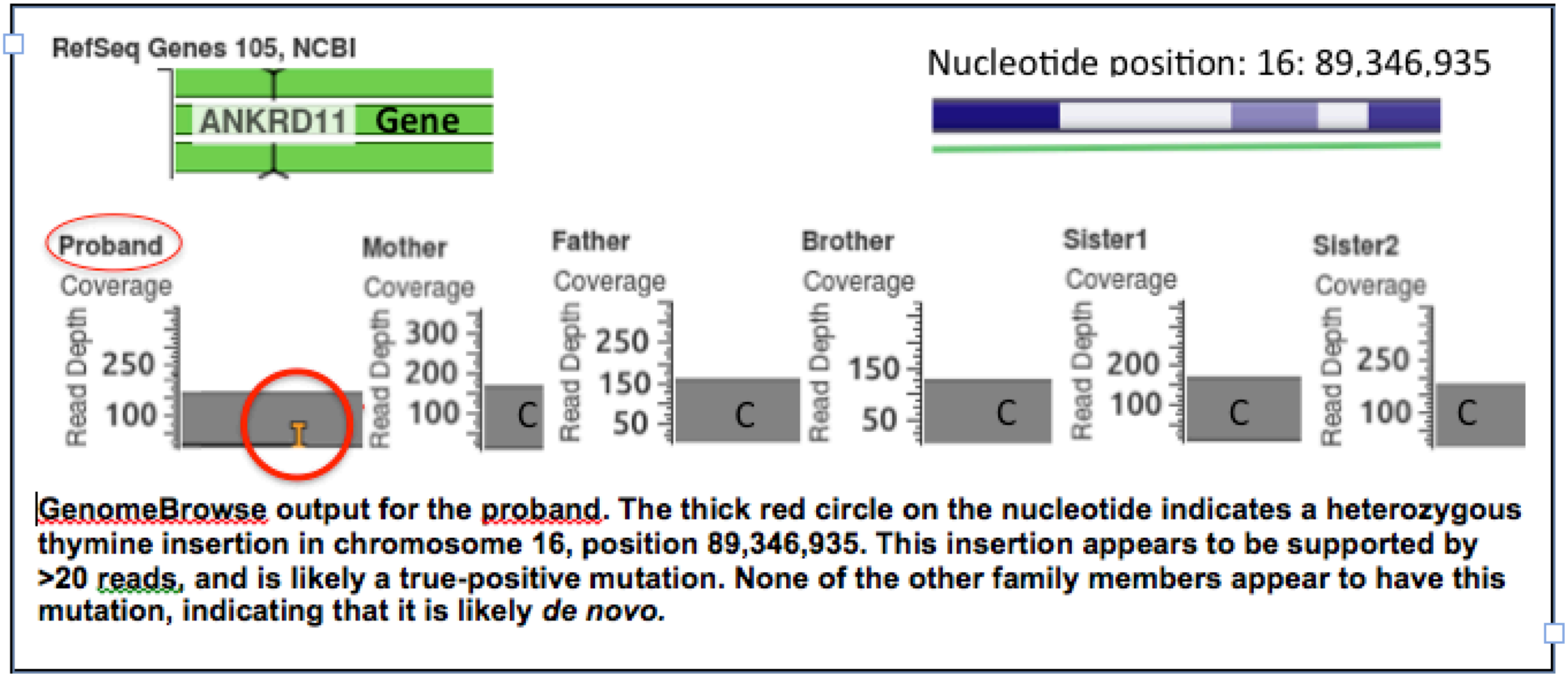
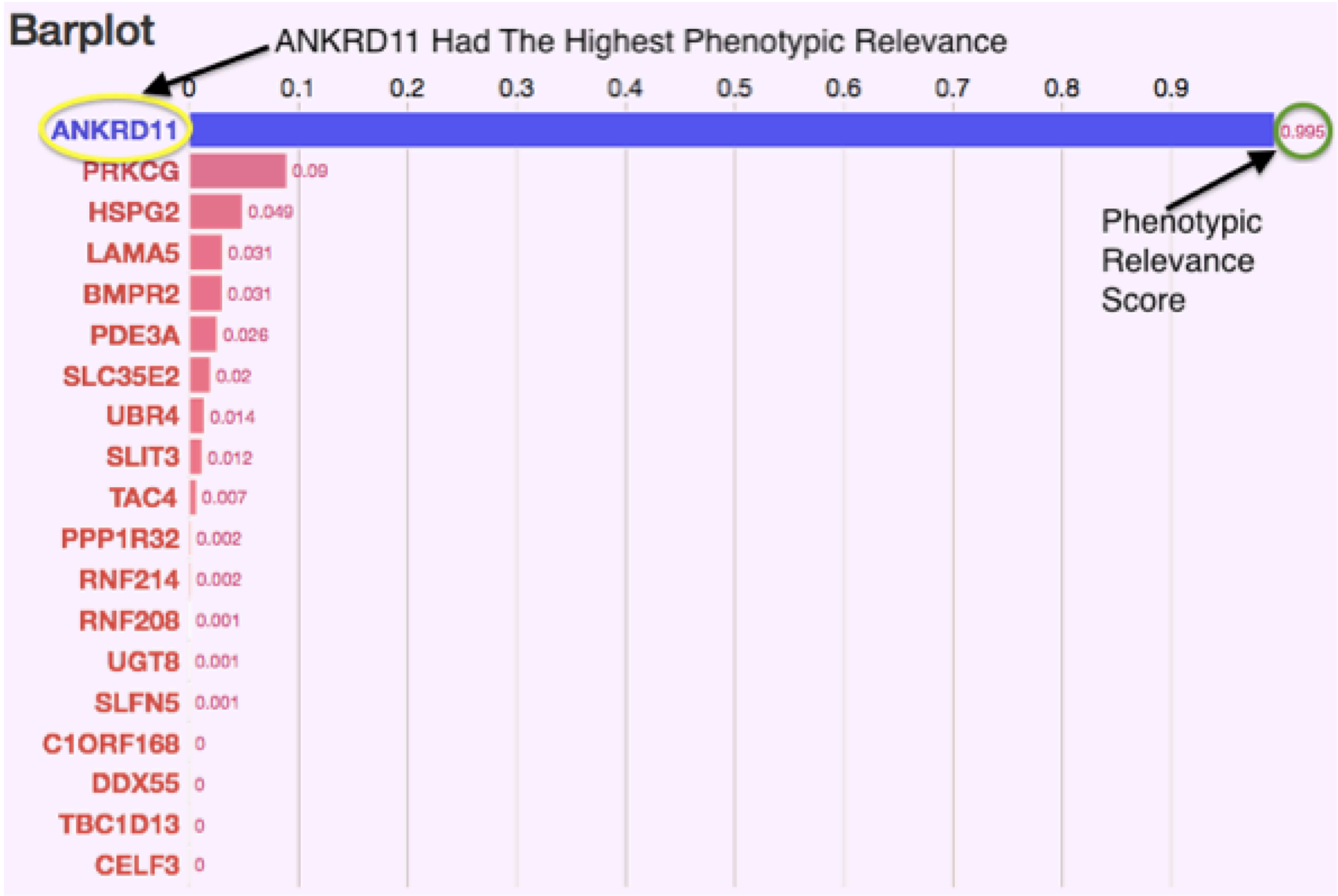


Table 1. Summary of the Clinical Features in this proband

Features (Human Phenotype Ontology Nos.)	Proband
FACIAL DYSMORPHISM	
Large fontanelle (HP:0000239)	+
Rounded Face (HP:0000311)	+
Bushy Eyebrows (HP:0000574)	+
Broad Nasal Tip (HP:0000455)	+
Short Philtrum (HP:0000322)	+
Full/Thick Lips (HP:0012471)	+
Cupid Bow Upper Lip (HP:0002263)	+
Macrodontia of Upper Central Incisors (HP:0000675)	+
Prognathism (HP:0000303)	+
DEVELOPMENTAL/INTELLECTUAL DISABILITY	
Intellectual Disability (HP:0001249)	+
Developmental Regression	+
Developmental Delay Prior to Regression?	+
Absent Speech (HP:0001344)	+
SKELETAL	
Clinodactyly of the 5th finger (HP:0004209)	+
Brachydactyly (HP:0009803)	+
Bilateral single transverse palmar creases (HP:0007598)	+
Short toes (HP:0001831)	+
Pes planus (HP:0001763)	+
NEUROLOGICAL	
Epilepsy Mixed (T/C, Atonic, Complex, Partial, Tonic, Gelastic) (HP:0001250)	+
GROWTH	
Currently short stature (HP:0004322)	+
BEHAVIORAL	
Autistic behavior (HP:0000729)	+
CONGENITAL BIRTH DEFECTS	
Congenital Heart Defect	-
Surgeries: ear tubes, broken jaw	+
Cryptorchidism	-
Palatal Defects	-
MISCELLANEOUS	
Low CSF 5-methyltetrahydrofolate (HP:0012446)	+
Hearing Loss	-



GenomeBrowse output for the proband. The thick red circle on the nucleotide indicates a heterozygous thymine insertion in chromosome 16, position 89,346,935. This insertion appears to be supported by >20 reads, and is likely a true-positive mutation. None of the other family members appear to have this mutation, indicating that it is likely *de novo*.



Phenolyzer output for the second individual. The bar graph indicates that a mutation in *ANKRD11* relates most to the phenotype, as it was calculated to have the highest Phenotypic relevance score.

ANKRD11 Gene relevance score: 1.000 variant score 0.950 total score: 0.975

Location & Effect

ANKRD11:uc002fnb.1:exon6:c.5886_5887insA:p.G1963fs (chr16:g.89346934->T)

FS_INSERTION

Deleteriousness Scores

Pathogenicity:

FS_INSERTION

Path score: 0.950

Frequency

No frequency data found

Variant read depth: 90

Relevant Phenotypes

- KBG syndrome [MIM:148050; gene: MIM:611192], autosomal dominant
- Orphanet: 16q24.3 microdeletion syndrome

PhenIX output. The mutation in *ANKRD11* was found to be the most likely contributing mutation. The mutation was found to be a deleterious frameshift insertion. The mutation is associated with KBG syndrome, which has a similar presentation to the individual's condition.

Report ID: 38835
Proband (M): proband_K10034 (222907)
Unaffected Sibling (M): brother_unaffectedd-K10034 (222906)
Unaffected Mother: mother- K10034 (222905)
Unaffected Father: father_K10034 (222904)
Indel mode: Indels Scored
Background: 1000 Genomes Project
VAAST Release: 3.0.3.6

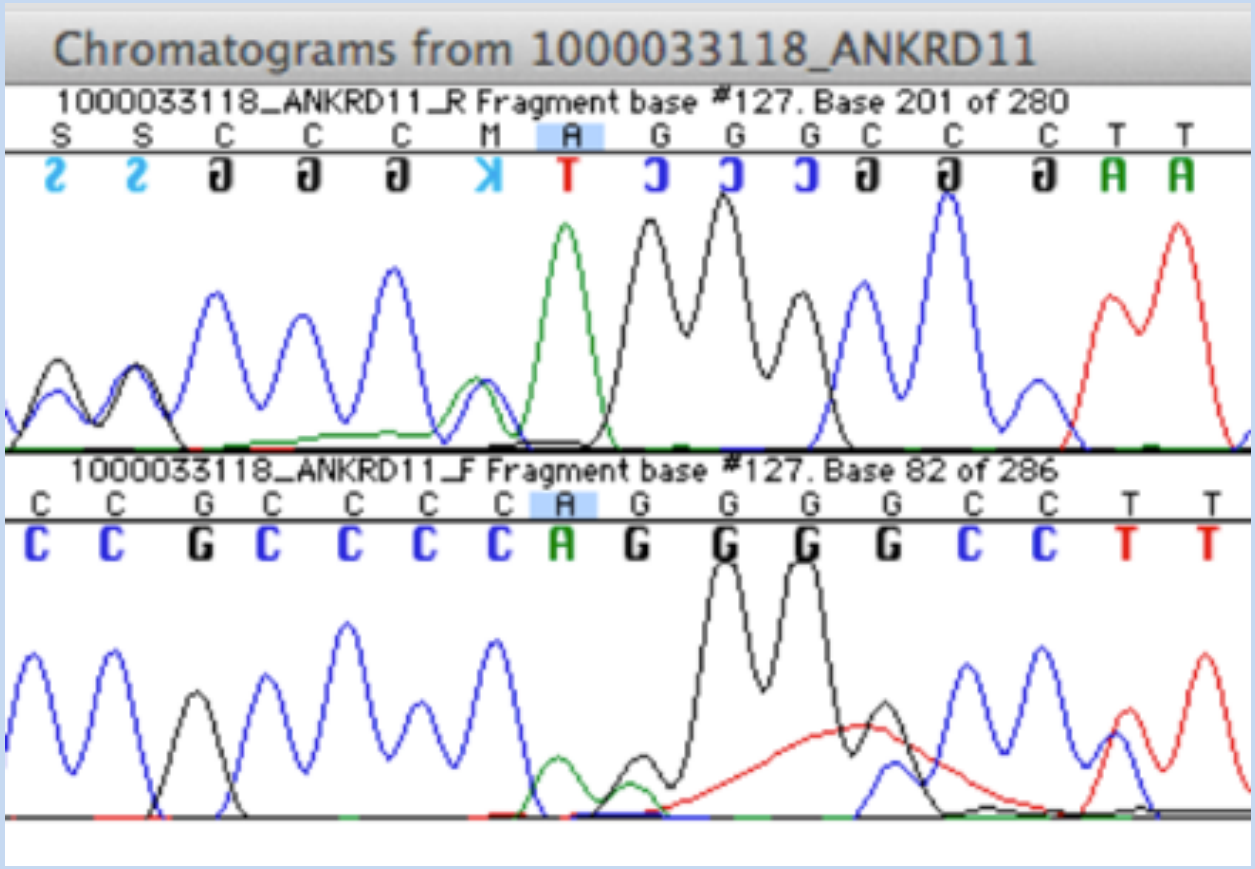
VAAST Quad Report

Recessive | X-Linked | De Novo | Reset Filters | VAAST Viewer | Export Report

Filtering Protocols
Apply Protocol
Gene Symbol
Panel
Chromosome
Filter By
Require
Exclude
Exclude Gene Sets

1KG Frequency: between 0.00% and 5.00%
Omicia Score: 0.7-1
Consequence: nonsynomous
Exclude: No-call, Intronic, Intergenic, Non-coding Genes

Review Priority	Gene	Position dbSNP	Change	Effect	Zygosity	Mother Zygosity	Father Zygosity	Sibling Zygosity	Quality GQ Coverage	1KG AF EVS AF ExAC AF	VVP CADD	Omicia Score	Evidence	VAAST Rank	VAAST V-Score	VAAST G-Score
●●●	ABCA12	chr2 215802232	A → C c.7542+2T>G	splice donor splice site impact	●○				36 65 20 : 17 : 3		60 27	0.903		254	16.25	16.25 5.90e-1
●●●	ABCE1	chr4 146030287	GC → G c.292delC p.Pro98LeufsTer11	frameshift	●○				114 99 40 : 30 : 10		49 -	0.800	COSMIC	137	16.25	16.25 1.67e-1
●●●	ACCSL	chr11 44069987	AC → A c.402delC p.Leu135TyrfsTer50	frameshift	●○				63 99 30 : 23 : 7		56 -	0.800	COSMIC	91	16.25	16.25 9.62e-2
●●●	ADAMTS17	chr15 100881255	CG → C c.438delC p.Ala147ProfsTer16	frameshift splice site impact	●○				93 99 23 : 15 : 8		62 -	0.800		278	16.25	16.25 8.55e-1
●●●	ALPK3	chr15 85403135	G → C c.4699+1G>C	splice donor splice site impact	●○				174 64 12 : 5 : 7		55 28	0.904		189	16.25	16.25 2.81e-1
●●●	AMOTL2	chr3 134086523	C → CG c.856_857insC p.Ser286ThrfsTer44	frameshift	●○				63 99 24 : 17 : 7		57 -	0.800		122	16.25	16.25 1.43e-1
●●●	ANKFY1	chr17 4120276	GC → G c.584+1delG	splice donor	●○				125 99 37 : 27 : 10		59 -	0.800		219	16.25	16.25 3.98e-1
●●●	ANKRD11	chr16 89346934	C → CT c.6015dupA p.Gly2006ArgfsTer26	frameshift splice site impact	●○				590 99 89 : 47 : 42		56 -	0.800		269	16.25	16.25 7.20e-1



De novo single base insertion of adenine (A) at position 6015 in exon 10 of *ANKRD11* (c.6015dupA , p.Gly2006Argfs*26)

ExAC Browser (Beta) | Exome Aggregation Consortium

Search for a gene or variant or region

Examples - Gene: PCSK9, Transcript: ENST00000407236, Variant: 22-46615880-T-C, Multi-allelic variant: rs1800234, Region: 22:46615715-46615880

Gene: ANKRD11

ANKRD11 ankyrin repeat domain 11
Number of variants 2145 (Including filtered: 2412)
UCSC Browser 16:89334038-89556969
GeneCards ANKRD11
OMIM ANKRD11
Other External References

Transcripts

Constraint from ExAC	Expected no. variants	Observed no. variants	Constraint Metric
Synonymous	678.2	684	z = -0.14
Missense	1174.5	981	z = 2.76
LoF	56.0	3	pLI = 1.00

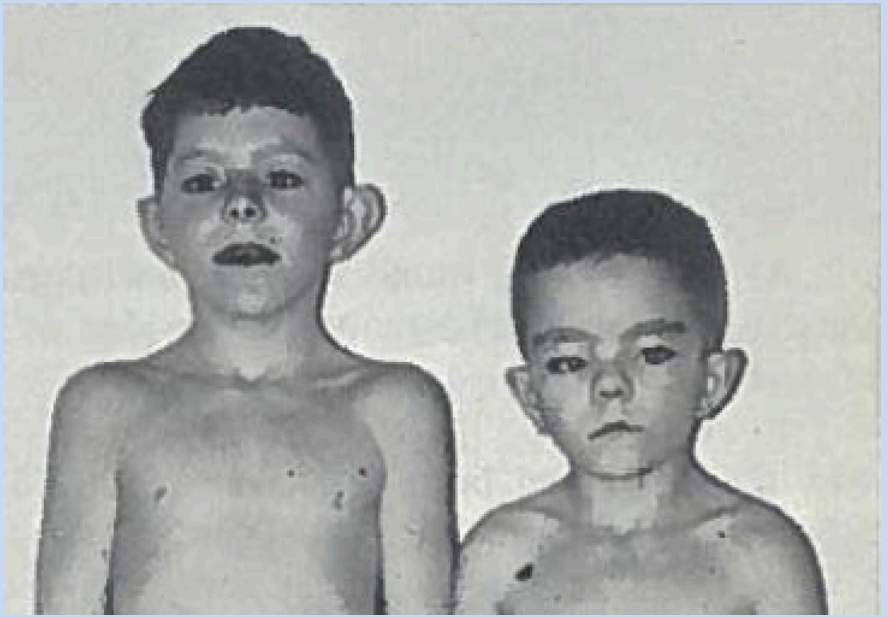
Variant	Chrom	Position	Consequence	Filter	Annotation	Flags	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
16:89350258 G / A	16	89350258	p.Arg898Ter	PASS	stop gained		1	120910	0	0.000008271
16:89349727 C / A	16	89349727	p.Glu1075Ter	PASS	stop gained		1	121398	0	0.000008237
16:89341551 G / A	16	89341551	p.Gln2507Ter	PASS	stop gained		1	93836	0	0.00001066

p.Gly2006Argfs*26

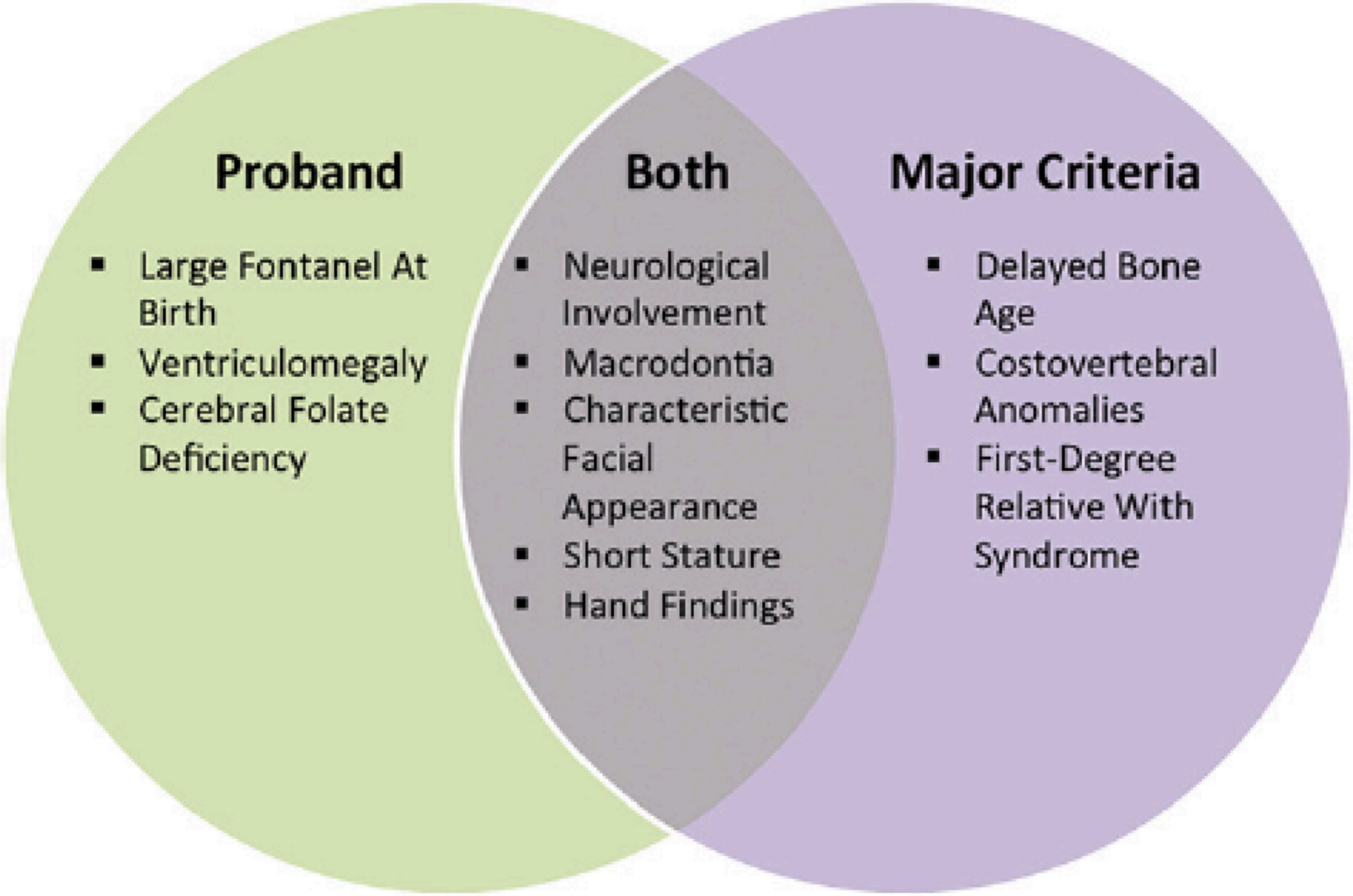
The KBG Syndrome– A Syndrome of Short Stature, Characteristic Facies, Mental Retardation, Macrodontia and Skeletal Anomalies*

Jürgen Herrmann, M.D., Philip D. Pallister, M.D.,
William Tiddy, D.D.S. and John M. Opitz, M.D.

A "new" malformation/retardation syndrome is described in 7 patients from 3 unrelated families. Affected individuals presented with mild mental retardation, shortness of stature, characteristic facial appearance, macrodontia and multiple other anomalies primarily of the skeleton. Using the patients' initials, the condition has been designated the KBG syndrome. It is caused by an autosomal dominant mutant gene.



Published in 1975



Somewhat low level of 5-methyltetrahydrofolate (5-MTHF) in his cerebrospinal fluid (CSF)(32 nmol/L, where the reference range is 40–128 nmol/L).

KBG Foundation

Research | Community | Cure

HOME | WHAT IS KBG? | RESEARCH | ABOUT THE FOUNDATION | PARTNERS

Like 1 Tweet G+1 0

NEW RESEARCH

BUILD COMMUNITY

FIND A CURE

WHAT IS KBG SYNDROME?

Do I have KBG?

Wondering if you or someone you love has KBG Syndrome? Learn more about the signs, symptoms and treatments.

In 1975, the first cases of KBG Syndrome were identified. Since that time, the underlying genetic cause has been identified and more and more patients are being diagnosed every year. With 60 documented cases worldwide, we wonder: who are we missing? Add your name to the research list and let's step up the search for a cure!

SIGN UP NOW!

VISITOR POSTS

Tracy Kuznik
November 2, 2015 at 9:22am

Hello! I'm very excited to have found this group. Our 3 year old daughter was recently diagnosed with KBG syndrome. We are currently living in Jacksonville, North Carolina. Our daughter doesn't appear to have most of the physical traits. She does have nystagmus, global developmental delay and feeding issues (purées).

Like · Comment 2 Likes 5 Comments

2 people like this. Chronological

KBG Foundation Hi Tracy! Welcome to the family, happy to have you, sorry you are here. We will make waves though and get the help our children deserve! Our son has few of the KBG traits as well, he has an insertion in the gene and not a deletion so his symptoms aren't going to be standard.

Like · Reply · 1 · November 2, 2015 at 11:19am

SIMONS VIP CONNECT

VARIATION IN INDIVIDUALS PROJECT

Announcing a New Online Community Resource!

For individuals with changes in genes related to developmental delay and features of autism (see the full list below!)

The **Simons Variations in Individuals Project (Simons VIP)**, funded by the Simons Foundation, has been a family support resource since 2010. Initially focusing on deletions and duplications of 16p11.2 and 1q21.1, the community has now expanded to include changes in 28 genes related to developmental delay and features of autism. As whole exome/genome sequencing becomes more frequently used in the evaluation of children with delays, this website community will provide support, resources and research opportunities to families found to have changes in the genes below:

ADNP	***BAF35***	***DST***	***MED13L***
ANKRD11	***BAF53b***	***DYRK1A***	***PTEN***
ARID1B	***BCL11A***	***FOXP1***	***REST***
ASXL3	***CHD2***	***GRIN2B***	***SCN2A***
BAF105	***CHD8***	***KDM6B***	***SMARCC1***
BAF180	***CTNNB1***	***KMT2E***	***SMARCC2***
BAF190	***CUL3***	***MBD5***	***SYNGAP1***

Developmental Cell
Article

Ankrd11 Is a Chromatin Regulator Involved in Autism that Is Essential for Neural Development

Denis Gallagher,[1,3,10] Anastassia Voronova,[1,10] Mark A. Zander,[1] Gonzalo I. Cancino,[1] Alexa Bramall,[1] Matthew P. Krause,[1] Clemer Abad,[4] Mustafa Tekin,[4] Paul M. Neilsen,[5] David F. Callen,[6] Stephen W. Scherer,[2,7] Gordon M. Keller,[3,8] David R. Kaplan,[1,7,*] Katherina Walz,[4] and Freda D. Miller[1,3,7,9,*]

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[6]Centre for Personalised Cancer Medicine, University of Adelaide, Adelaide SA 5000, Australia
[7]Department of Molecular Genetics
[8]Department of Medical Biophysics
[9]Department of Physiology
University of Toronto, Toronto, ON M5G 1X5, Canada
[10]Co-first author
*Correspondence: dkaplan@sickkids.ca (D.R.K.), fredam@sickkids.ca (F.D.M.)
http://dx.doi.org/10.1016/j.devcel.2014.11.031

Vignette #3: SCN8A Syndrome

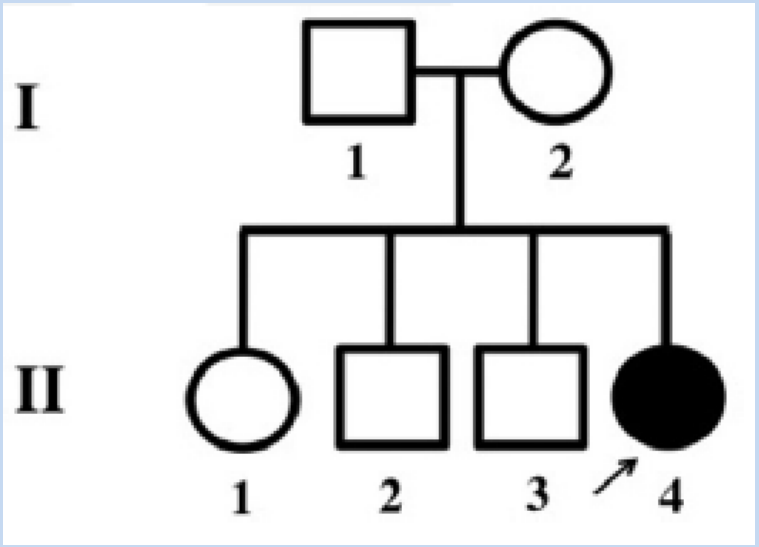
COLD SPRING HARBOR
Molecular Case Studies

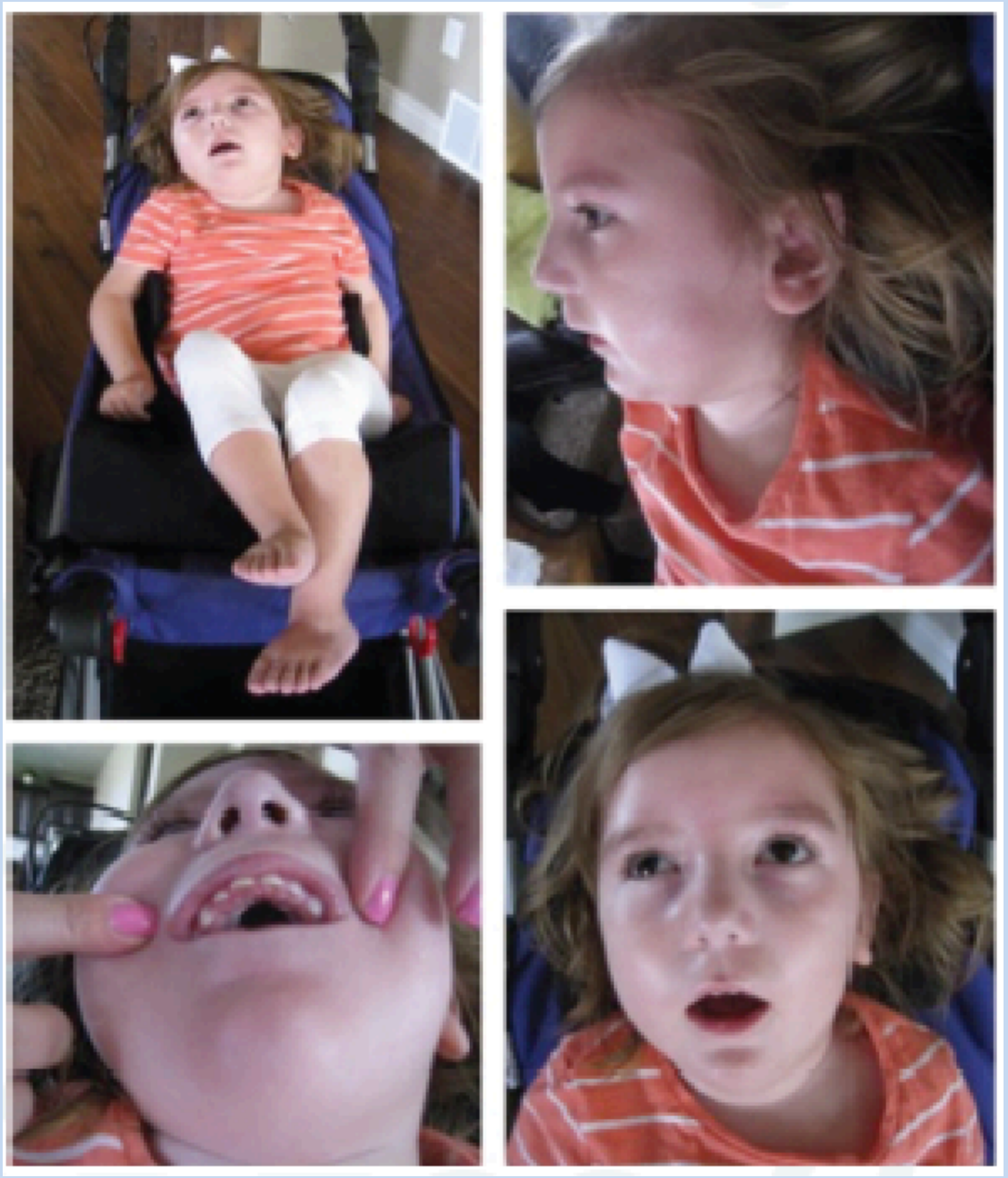
RESEARCH REPORT

SCN8A mutation in a child presenting with seizures and developmental delays

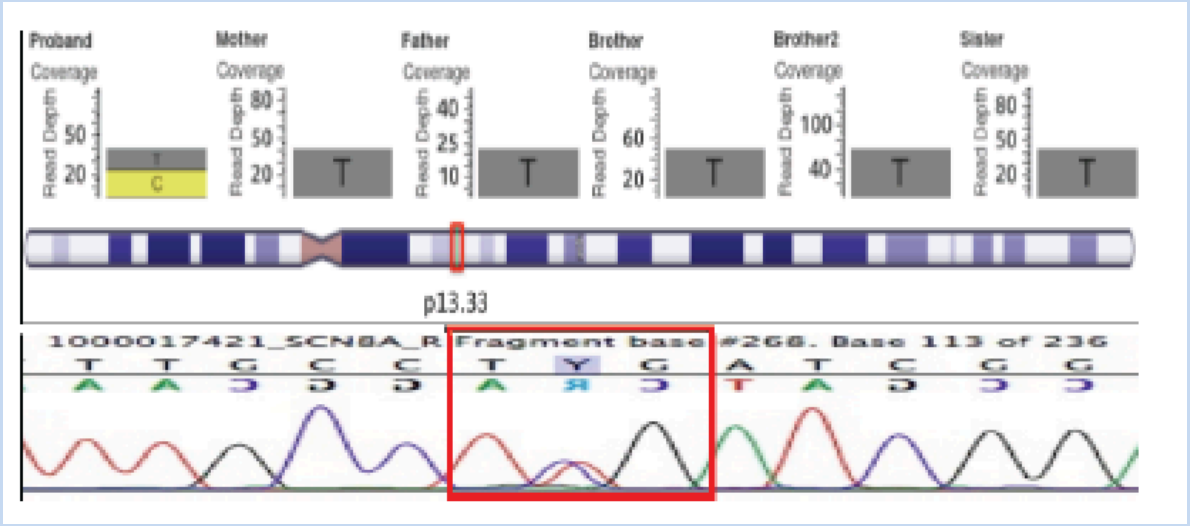
Janet Malcolmson,[1,2,8] Robert Kleyner,[1,8] David Tegay,[1] Whit Adams,[3] Kenneth Ward,[4] Justine Coppinger,[4] Lesa Nelson,[4] Miriam H. Meisler,[5] Kai Wang,[3,6,7] Reid Robison,[3] and Gholson J. Lyon[1,3]

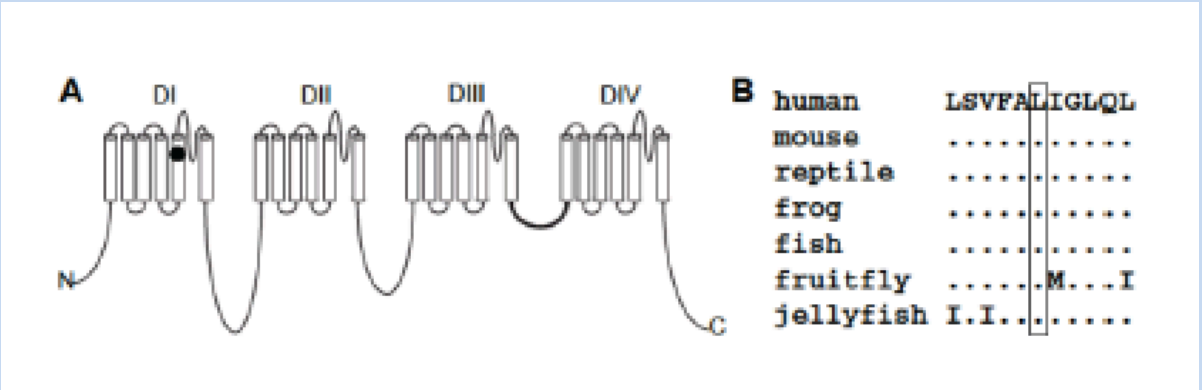
[1]Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA; [2]Genetic Counseling Graduate Program, Long Island University (LIU), Brookville, New York 11548, USA; [3]Utah Foundation for Biomedical Research, Salt Lake City, Utah 84107, USA; [4]Affiliated Genetics, Salt Lake City, Utah 84109, USA; [5]Department of Human Genetics, University of Michigan, Ann Arbor, Michigan 48109-5618, USA; [6]Zilkha Neurogenetic Institute, University of Southern California, Los Angeles, California 90089, USA; [7]Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA


I
1
2
II
1
2
3
4



Features (Human Phenotype Ontology Nos.)	Proband
EPILEPSY	
Epileptic encephalopathy (HP:0200134)	+
Generalized tonic seizures (HP:0010818)	+
EEG abnormality (HP:0002353)	+
DEVELOPMENTAL/INTELLECTUAL DISABILITY	
Global developmental delay (HP:0001263)	+
Developmental stagnation at onset of seizures (HP:0006834)	+
Developmental regression (HP:0002376)	+
Absent speech (HP:0001344)	+
Intellectual disability, severe (HP:0010864)	+
Motor delay (HP:0001270)	+
NEUROLOGICAL	
Generalized hypotonia (HP:0001290)	+
Appendicular hypotonia (HP:0012389)	+
Infantile axial hypotonia (HP:0009062)	+
Neck muscle weakness (HP:0000467)	+
Rigidity (HP:0002063)	+
Spasticity (HP:0001257)	+
GROWTH/FEEDING	
Failure to thrive in infancy (HP:0001531)	+
Gastrostomy tube feeding in infancy (HP:0011471)	+
Gastroesophageal reflux (HP:0002020)	+
Dysphagia (HP:0002015)	+
RESPIRATORY	
Respiratory difficulties (HP:0002880)	+
Hypoxemia (HP:0012418)	+
Abnormality of the tonsils (HP:0100765)	+
Obstructive sleep apnea (HP:0002870)	+
DYSMORPHISM	
Brachycephaly (HP:0000248)	+
Broad forehead (HP:0000337)	+
Broad Nasal Root or Bridge (HP:0000431)	+
Hypoplastic Alae Nasi (HP:0000430)	+
Full cheeks (HP:0000293)	+
Gingival Hyperplasia (HP:0000212)	+
Micrognathia (Mild) (HP:0000347)	+
Hypotonic Facies	+
NEUROLOGICAL	
Exaggerated startle response (HP:0002267)	+
Action tremor (HP:0002345)	+
Blepharospasm (HP:0000643)	+
Bulbar palsy (HP:0001283)	+
Nystagmus (HP:0000639)	+
MISCELLANEOUS	
Hyperreexia (HP:0001347)	+
No social interaction (HP:0008763)	+





Chr:position GRCh37(hg19)	HGVS cDNA	HGVS protein	Type of variant	Predicted effect	Genotype	Parent of origin
12:52,093,447	c.800T>C	p.Leu267Ser	Substitution	Missense	Heterozygous	De novo

HGVS, Human Genome Variation Society.

Gene: SCN8A

SCN8A sodium channel, voltage gated, type VIII, alpha subunit
Number of variants 965 (Including filtered: 1081)
Number of CNVs 1 (Including filtered: 10)
UCSC Browser 12:51984050-52206648
GeneCards SCN8A
OMIM SCN8A
Other External References

Transcripts

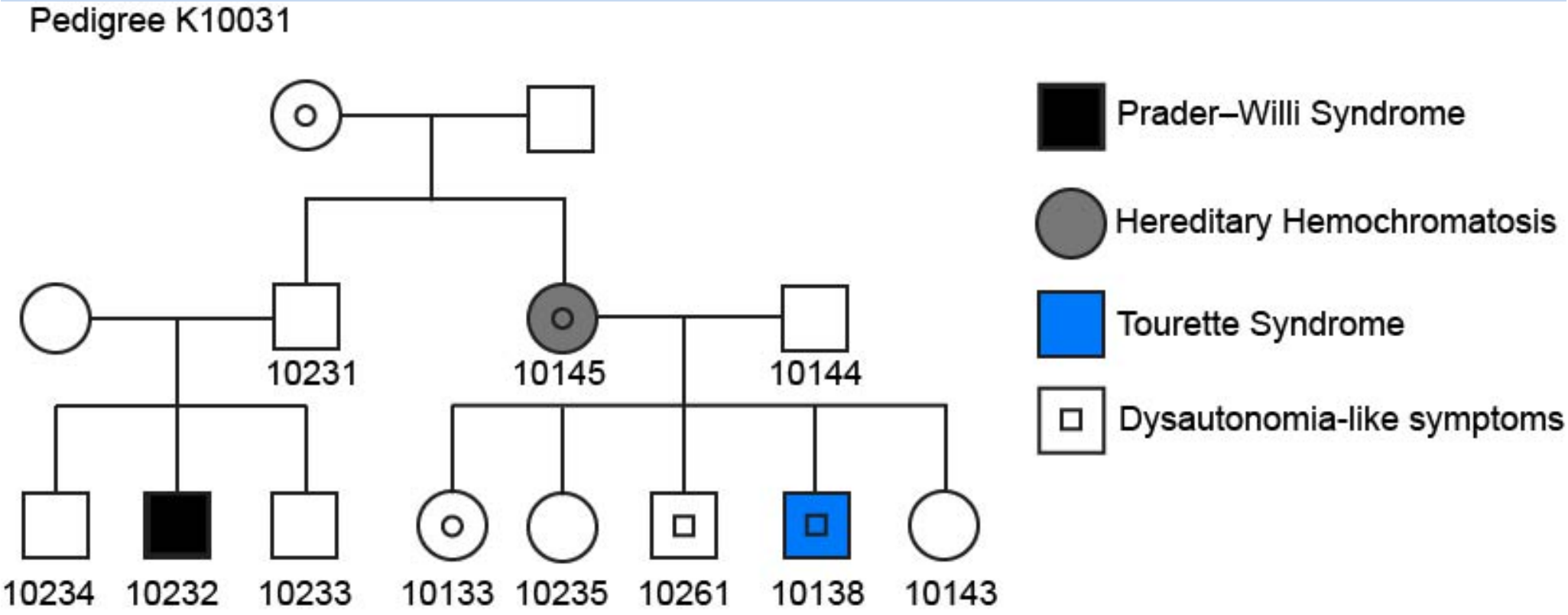
Constraint from ExAC	Expected no. variants	Observed no. variants	Constraint Metric
Synonymous	263.8	270	z = -0.24
Missense	646.6	246	z = 7.71
LoF	54.4	4	pLI = 1.00
CNV	9.8	1	z = 1.38

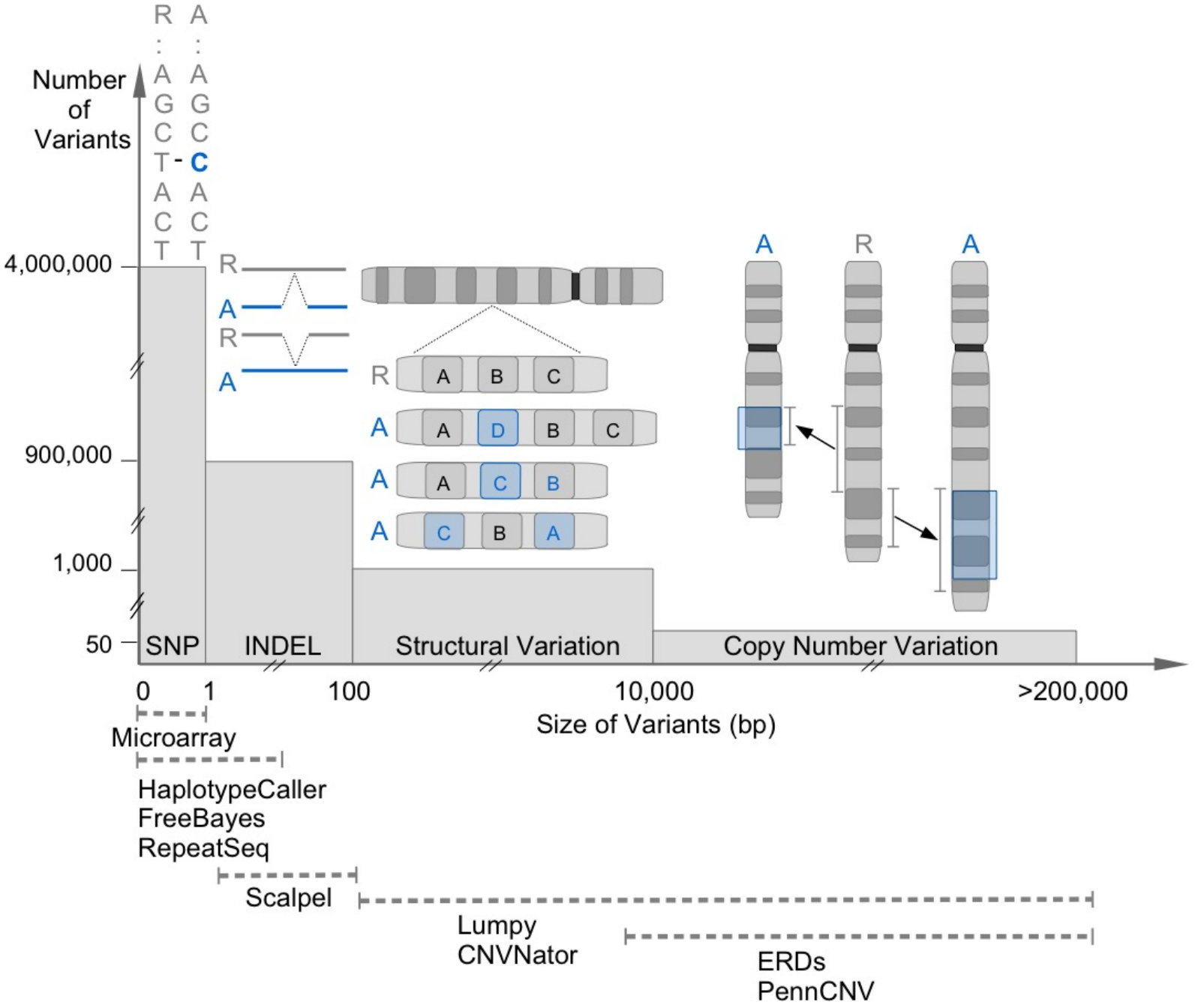
Variant	Chrom	Position	Consequence	Filter	Annotation	Flags	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
12:52115693 G / A	12	52115693	c.1998+1G>A	PASS	splice donor		1	114174	0	0.000008759
12:52174555 G / GGTAA	12	52174555		PASS	frameshift	LC LoF	1	119876	0	0.000008342
12:52184181 C / A	12	52184181	c.4420-1C>A	PASS	splice acceptor	LC LoF	1	103188	0	0.000009691
12:52188298 G / A	12	52188298	p.Trp1556Ter	PASS	stop gained		1	120666	0	0.000008287
12:52200119 C / T	12	52200119	p.Arg1617Ter	PASS	stop gained		1	110430	0	0.000009056

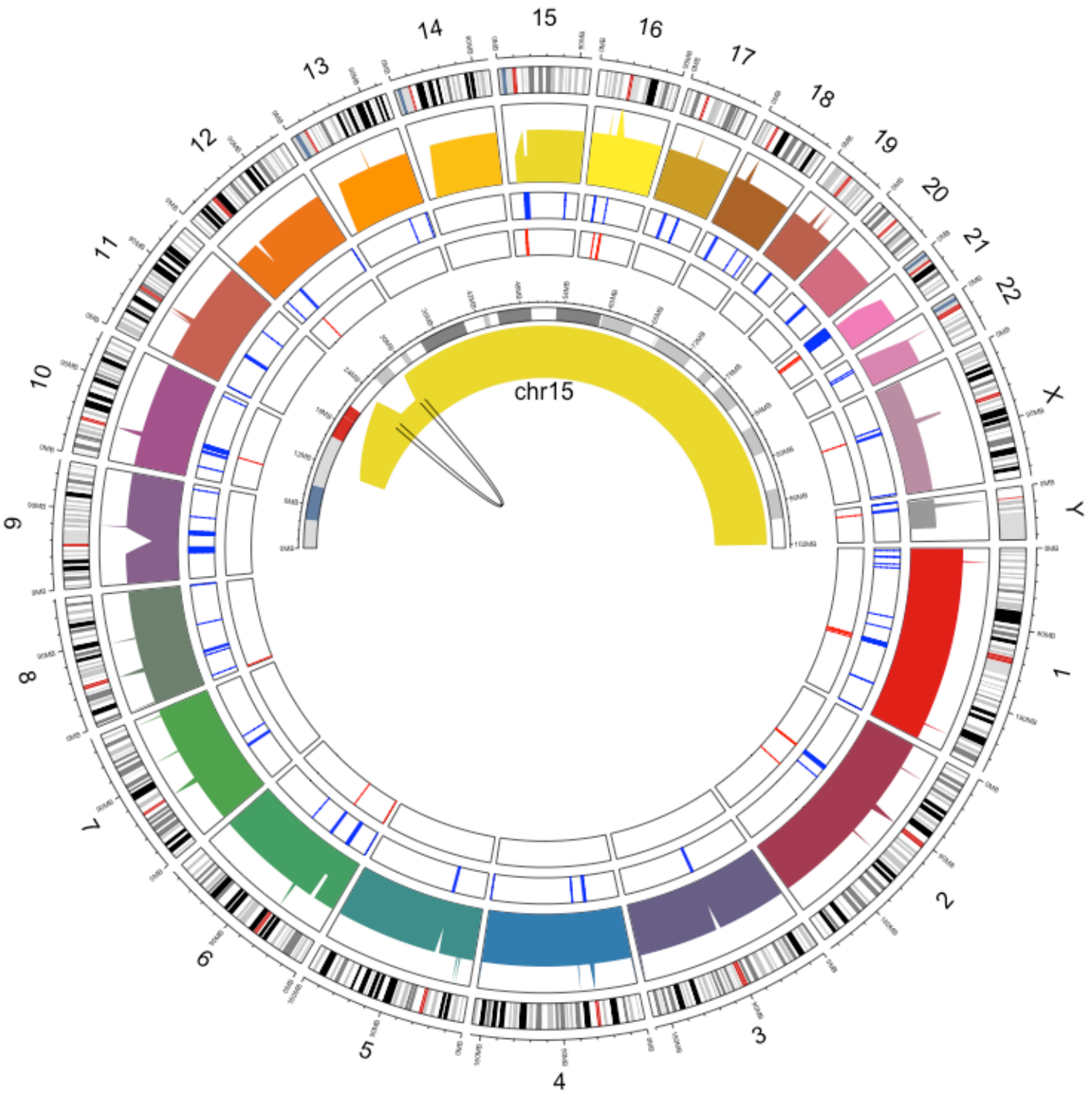
Vignette #4: Complex pedigrees

Whole genome sequencing of one complex pedigree illustrates challenges with genomic medicine

Han Fang[1,2,3#], Yiyang Wu[1,2#], Hui Yang[8,9], Margaret Yoon[1], Laura T. Jiménez-Barrón[1,4], David Mittelman[5], Reid Robison[6], Kai Wang[8,10,11],Gholson J. Lyon[1,2,7§]




R : A G C T A C T
A : A G C - A C T
Number of Variants
4,000,000
900,000
1,000
50
SNP
INDEL
Structural Variation
Copy Number Variation
0
1
100
10,000
>200,000
Size of Variants (bp)
R
A
R
A
A B C
A A D B C
A A C B
A C B A
A R A
Microarray
HaplotypeCaller
FreeBayes
RepeatSeq
Scalpel
Lumpy
CNVNator
ERDs
PennCNV


chr15
1
2
3
4
5
6
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10
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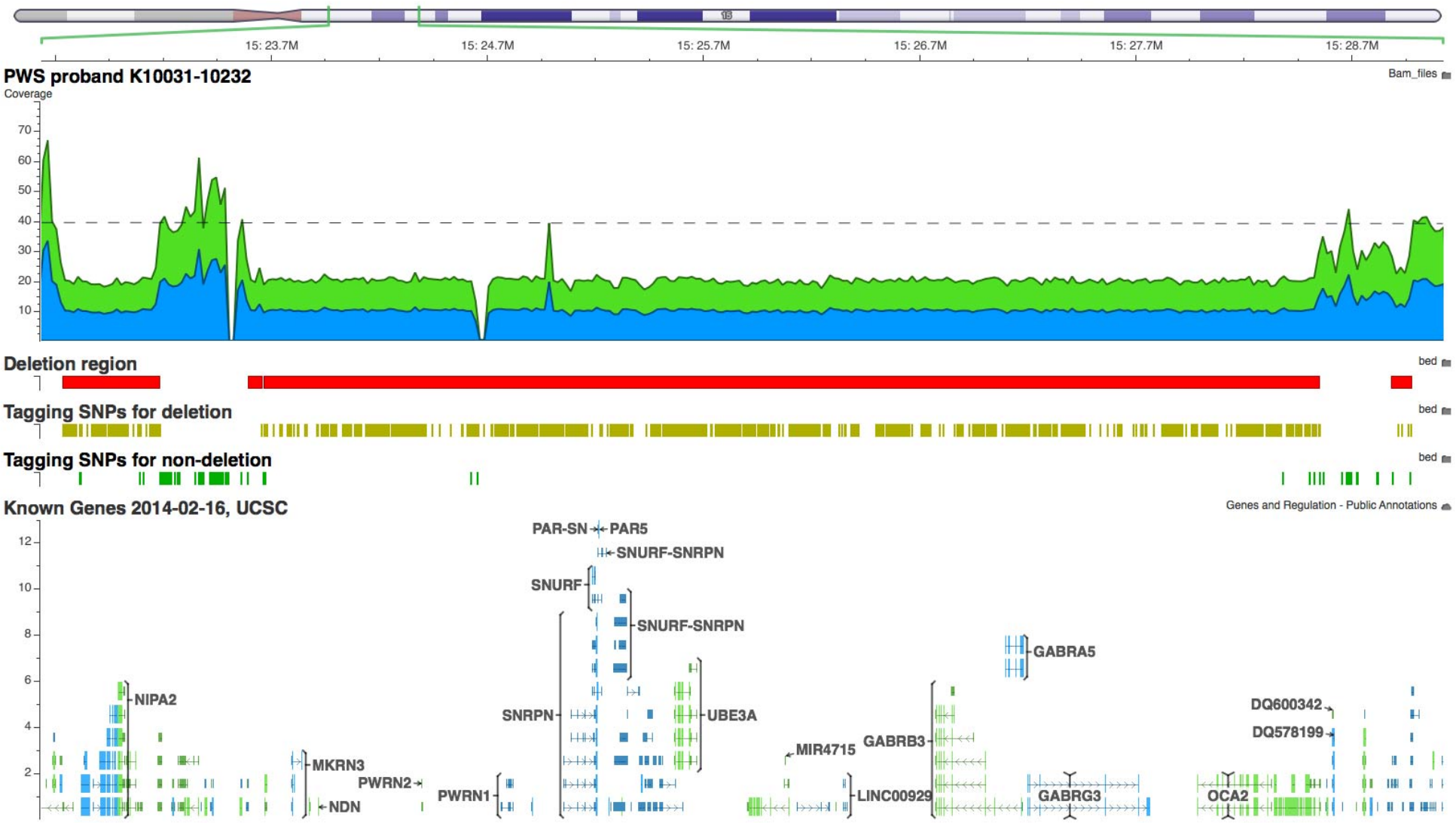
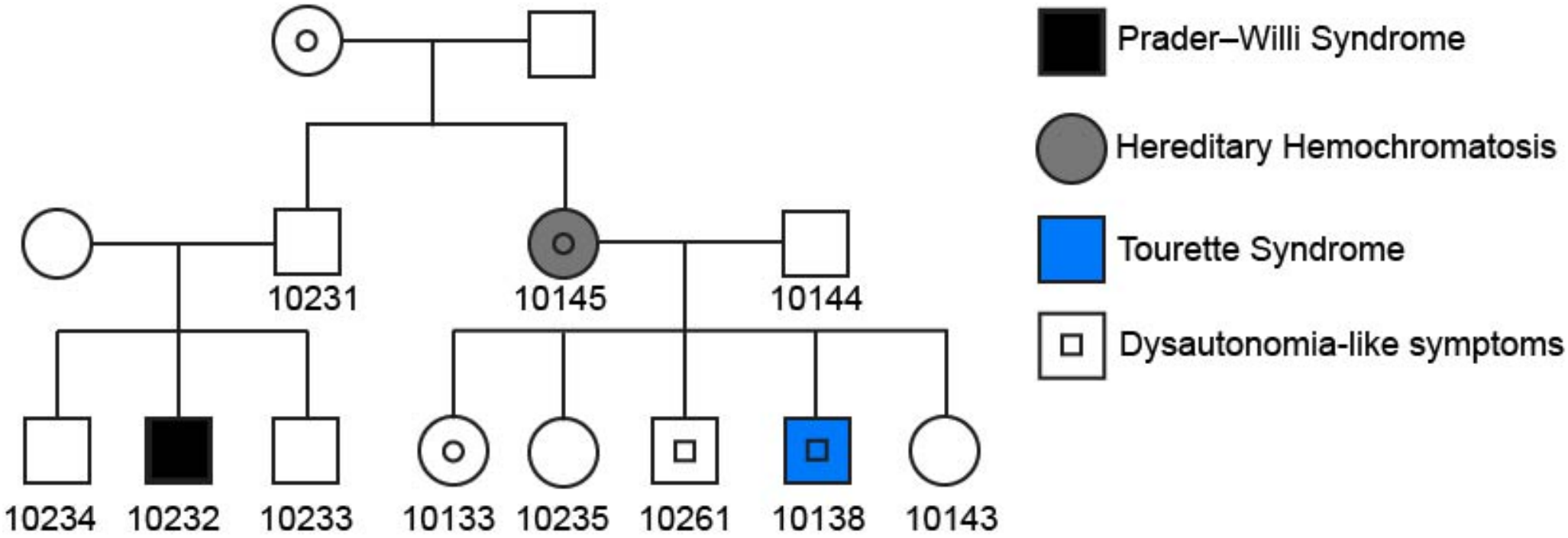
18
19
20
21
22
X
Y


15
15: 23.7M
15: 24.7M
15: 25.7M
15: 26.7M
15: 27.7M
15: 28.7M
PWS proband K10031-10232
Bam_files
Coverage
70
60
50
40
30
20
10
Deletion region
bed
Tagging SNPs for deletion
bed
Tagging SNPs for non-deletion
bed
Known Genes 2014-02-16, UCSC
Genes and Regulation - Public Annotations
12
10
8
6
4
2
PAR-SN
PAR5
SNURF-SNRPN
SNURF
SNURF-SNRPN
GABRA5
NIPA2
SNRPN
UBE3A
DQ600342
DQ578199
MIR4715
GABRB3
MKRN3
PWRN2
PWRN1
LINC00929
GABRG3
OCA2
NDN

Gene	Genomic coordinates	Change & variant type	Zygosity & Carriers	AAF	Relevant diseases & Inheritance
HFE	chr6: 26093141	G>A missense	hom: 10145, 10231 het: 10232, 10233, 10133, 10235, 10138, 10143	0.007%	hereditary hemochromatosis - AR)

Pedigree K10031



Vignette #5: Whole Genome Sequencing for autism families

COLD SPRING HARBOR
Molecular Case Studies

RESEARCH ARTICLE

Genome-wide variant analysis of simplex autism families with an integrative clinical-bioinformatics pipeline

Laura T. Jiménez-Barrón,[1,2] Jason A. O'Rawe,[1,3] Yiyang Wu,[1,3] Margaret Yoon,[1] Han Fang,[1] Ivan Iossifov,[4,5] and Gholson J. Lyon[1,3,6]

[1]Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA; [2]Centro de Ciencias Genómicas, Universidad Nacional Autónoma de México, Cuernavaca, Morelos 62210, Mexico; [3]Graduate Genetics Program, Stony Brook University, Stony Brook, New York 11794, USA; [4]Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA; [5]New York Genome Center, New York, New York 10013, USA; [6]Utah Foundation for Biomedical Research, Salt Lake City, Utah 84107, USA

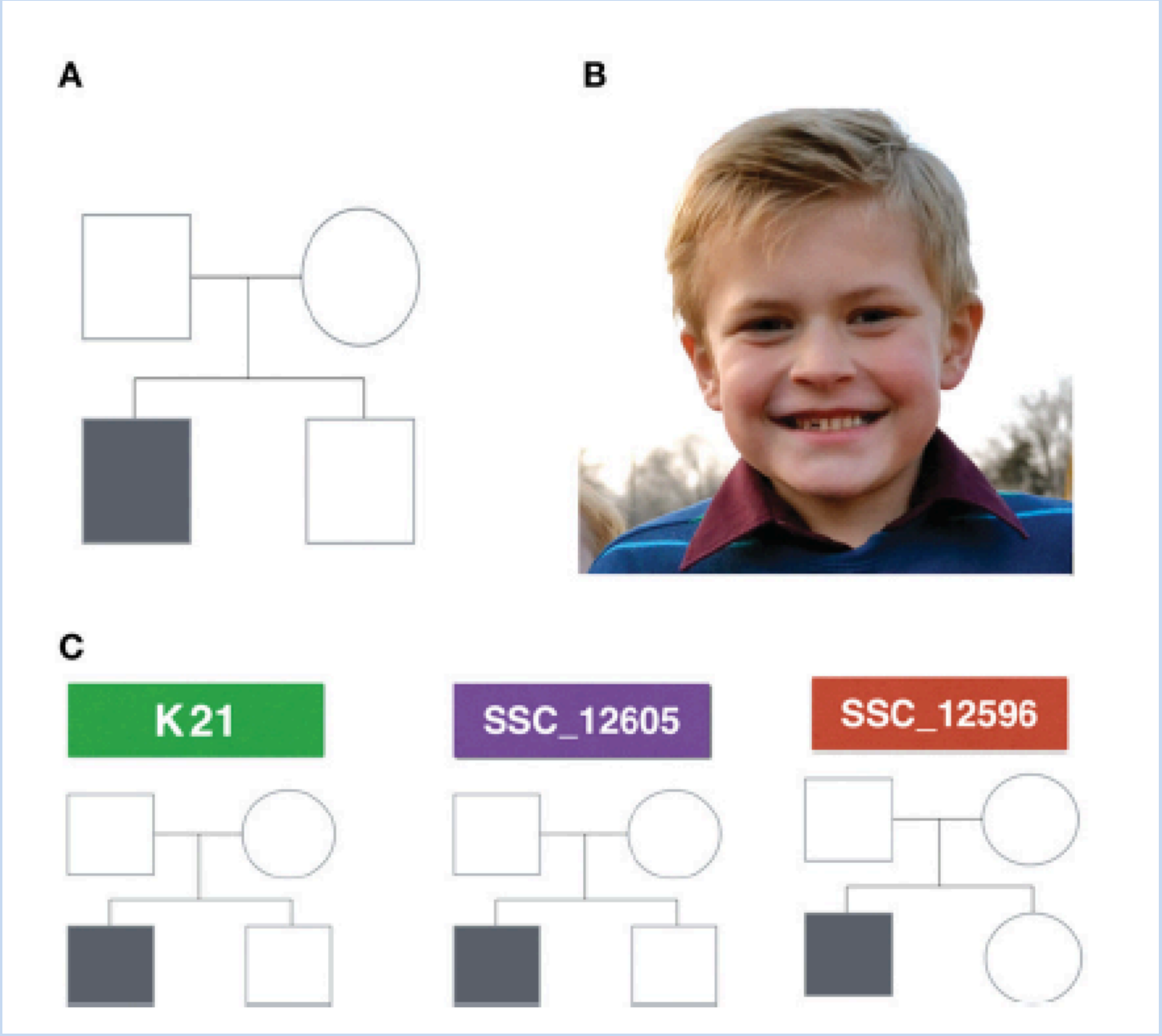

A
B
C
K21
SSC_12605
SSC_12596

Table 1. Body measurements and IQ test scores

Test	SSC_12596	SSC_2605
Diagnostic classification ADI-R	Autism	Autism
Diagnostic classification ADOS algorithm	Autism	Autism
ADOS module	1—no words	4
Certainty of ASD diagnosis	15	15
Verbal IQ	32	136
Nonverbal IQ	89	108
Full-scale IQ	61	120
ABC total score	53	34
Stereotyped behavior	7	1
Self-injurious	2	1
Compulsive behavior	6	13
Ritualistic behavior	6	4
Sameness behavior	11	10
Restricted behavior	8	7
Pregnancy optimality	0	4

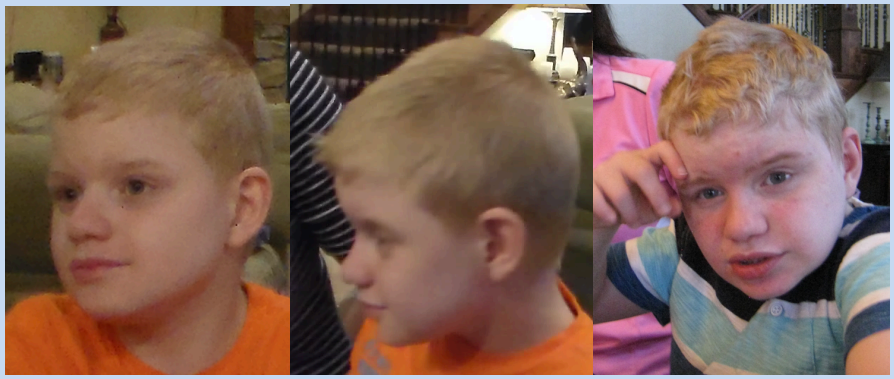
Table 4. Final set of single-nucleotide variants

Model	Ref → Alt/ effect	Location hg19	Affected gene	Algorithms that called the variant	Pedigree ID	ExAC allele frequency	CADD score
De novo	Sub (C → T) missense	Chr1: 209823359	*LAMB3*	FB, MA, GATK	SSC_12605	0	22.7
De novo	Sub (G → A) nonsense	Chr17: 4458481	*MYBBP1A*	FB, MA, GATK	K21	1/74014 = 0.00001351	40

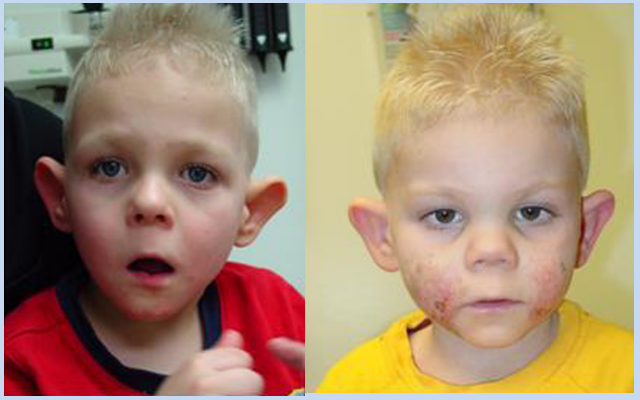
ExAC, Exome Aggregation Consortium; CADD, combined annotation dependent depletion; FB, FreeBayes; MA, multinomial analyzer; GATK, Genome Analysis Toolkit.

NAA10, NAA15, NAA50
“Ogden syndrome”

SCN8A syndrome



ANKRD11
“KBG syndrome”



TAF1 syndrome

The Biology of MENTAL DEFECT

BY

LIONEL S. PENROSE, M.A., M.D.

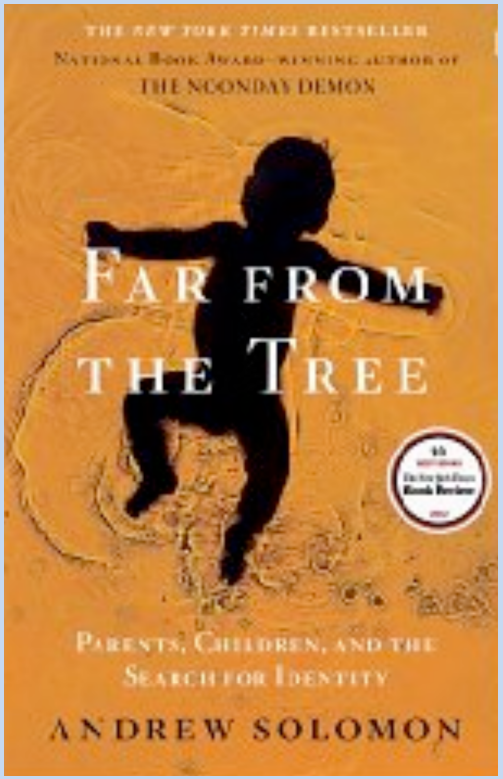
WITH A PREFACE BY

PROFESSOR J. B. S. HALDANE, F.R.S.

GRUNE & STRATTON

New York

1949

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Alexandra Solowinska

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Laura Jimenez
Janet Malcolmson
Margaret Yoon
Robert Kleyner
Ahmed Ismali
Alison Sebold
Taylor Marmorale
Jake Weiser
Syndi Barish
Prashant Kota

Collaborators

Scott Lyons
Keith Rivera
Darryl Pappin
Leyi Li (transgenics)
Denise Cahn (Histology)

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Omicia
Seven Bridges
XDP Foundation

our study families and many others