Childhood-onset Neuropsychiatric Disorders

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

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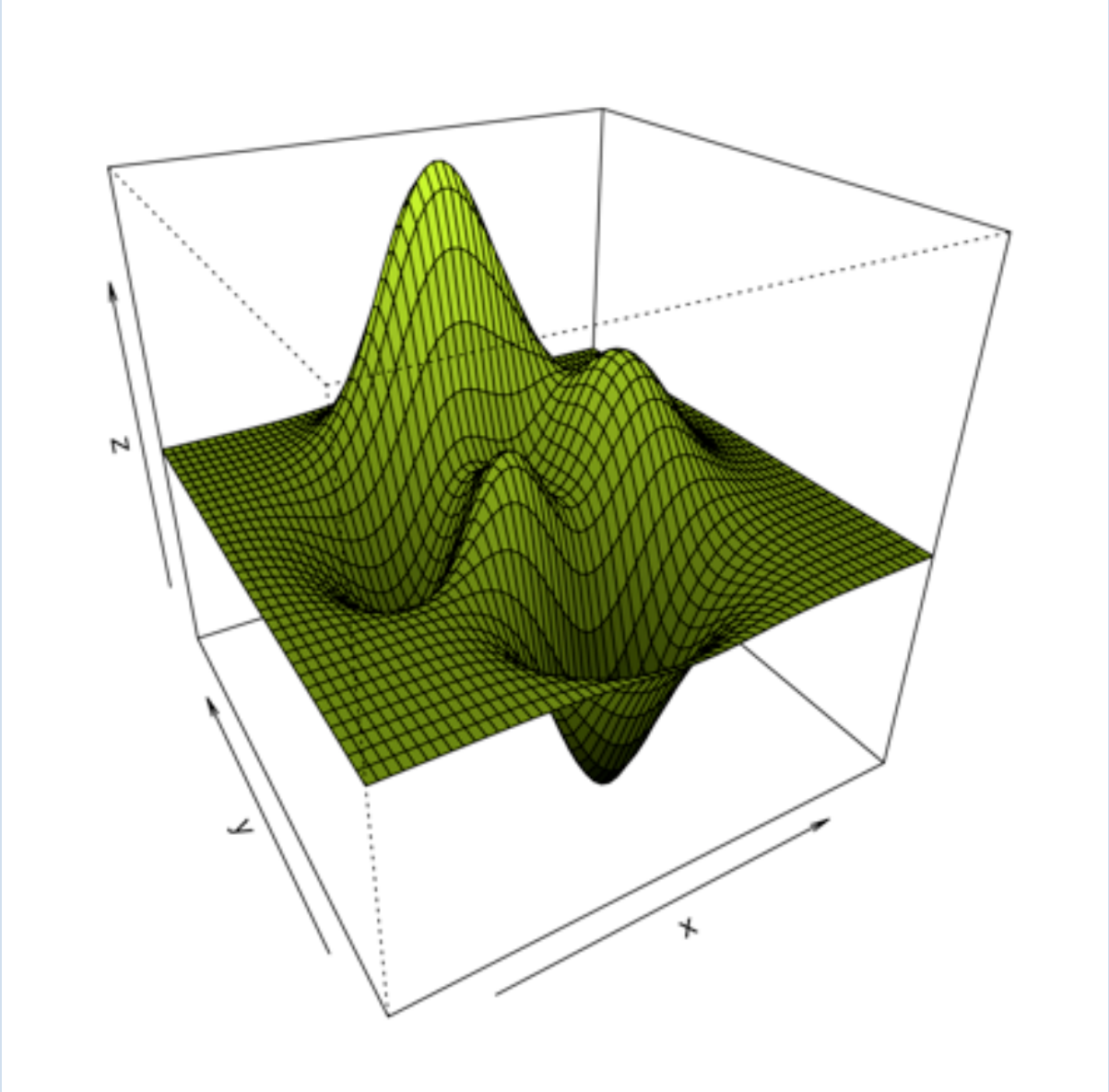
our study families

Take Home Message

Genotype ≠ Phenotype

Environment matters
Ancestry matters
Genomic background matters
Longitudinal course matters
Multiple Genomes per person: somatic mosaicism.

You are well-positioned to investigate this complexity here in the Faroe Islands.



A conceptual model of canalization. The *y* plane represents a phenotypic spectrum, the *x* plane represents the canalized progression of development through time, and the *z* plane represents environmental fluctuations.

Contents lists available at SciVerse ScienceDirect

Applied & Translational Genomics

journal homepage: www.elsevier.com/locate/atg

Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape

Gholson J. Lyon [a,b,*], Jeremy P. Segal [c,**]

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http://genomemedicine.com/content/5/3/28

Genome Medicine

RESEARCH Open Access

Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing

Jason O'Rawe[1,2], Tao Jiang[3], Guangqing Sun[3], Yiyang Wu[1,2], Wei Wang[4], Jingchu Hu[3], Paul Bodily[5], Lifeng Tian[6], Hakon Hakonarson[6], W Evan Johnson[7], Zhi Wei[4], Kai Wang[8,9*] and Gholson J Lyon[1,2,9*]

The role of thyroid hormone in cretinism, which is caused by lack of iodine during maternal pregnancy, so this is an environmentally triggered disease.

Isolation and Characterization of the Mouse Gene for the Type 3 Iodothyronine Deiodinase*

ARTURO HERNÁNDEZ†, GHOLSON J. LYON‡, MARK J. SCHNEIDER, AND DONALD L. ST. GERMAIN

Departments of Medicine and Physiology, Dartmouth Medical School, Lebanon, New Hampshire 03756

Postraumatic Stress Disorder and Reactive Attachment Disorder: Outcome in An Adolescent

Presenter: Gholson J. Lyon, M.D., Ph.D.
Discussants: Barbara Coffey, M.D., M.S. and Raul Silva, M.D.

NYU Child Study Center
New York, New York

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 18, Number 6, 2008

Pp. 641–646
DOI: 10.1089/cap.2008.1863

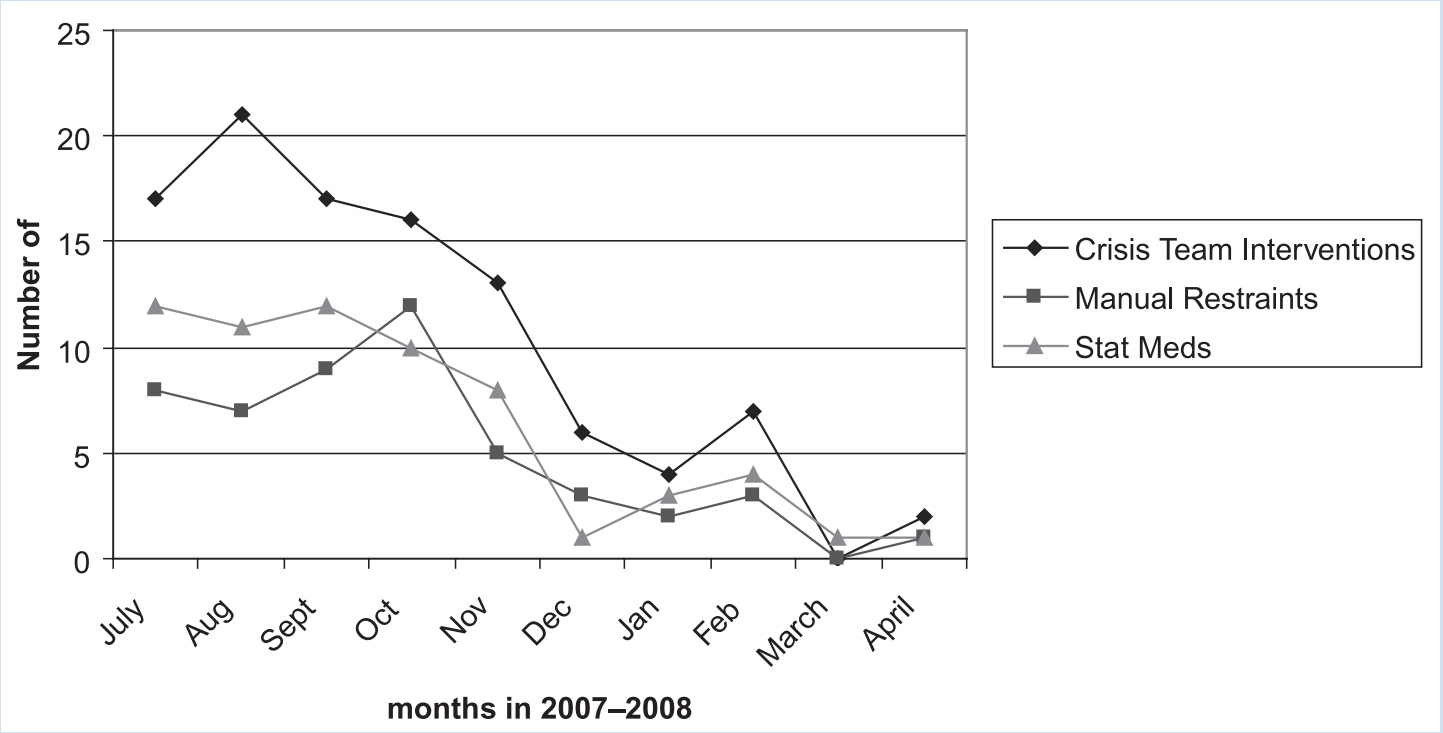


FIG. 1. Number of incidents including crisis team interventions (calls overhead for assistance), manual restraints, and urgent medications (by mouth or intramuscular) for each month during the course of this patient's hospitalization.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 19, Number 4, 2009

Pp. 469–474
DOI: 10.1089/cap.2009.19402

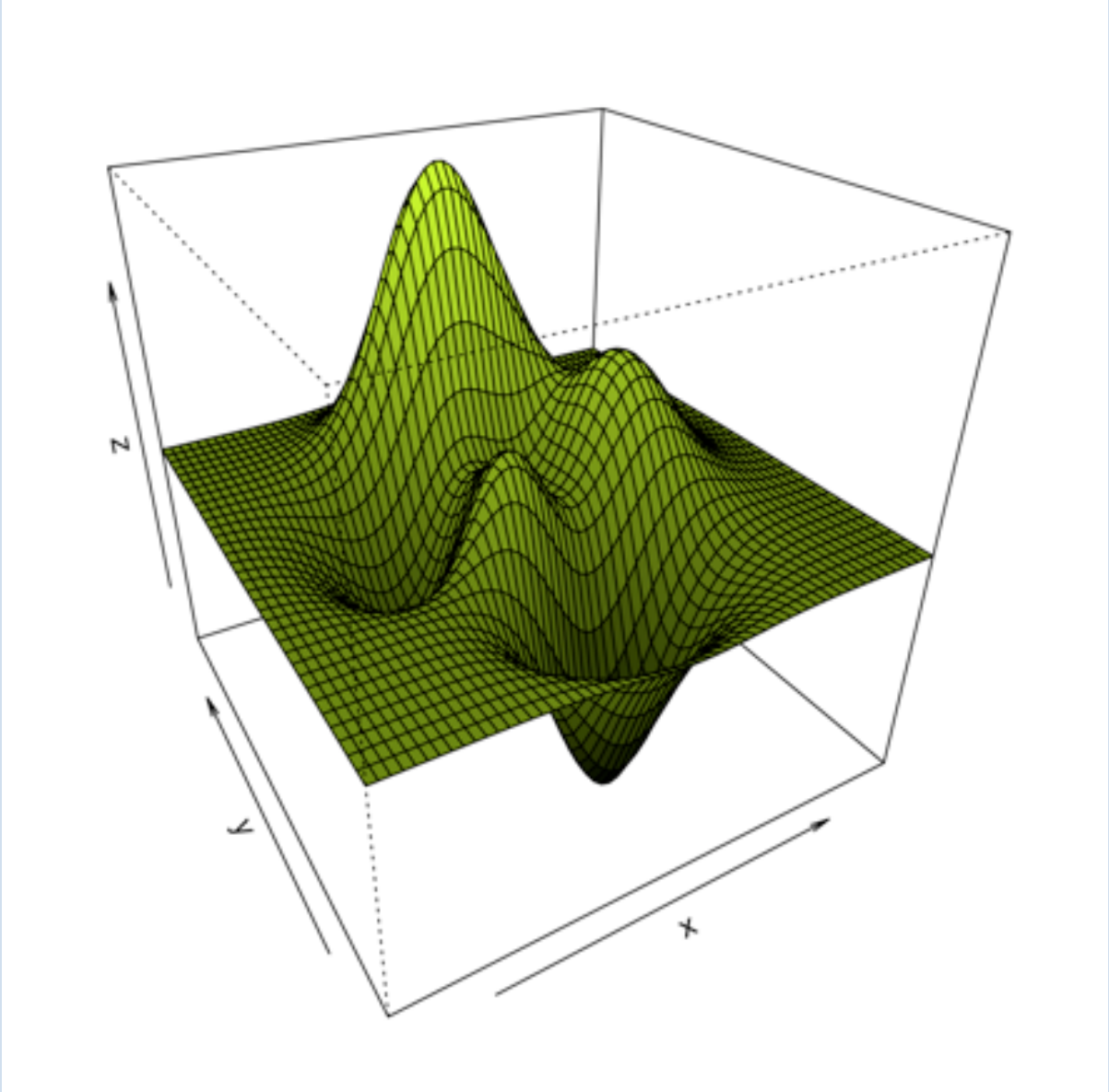
Advanced Pediatric Psychopharmacology

Complex Tics and Complex Management in a Case of Severe Tourette's Disorder (TD) in an Adolescent

Presenter: Gholson J. Lyon, M.D., Ph.D.[1]
Discussant: Barbara J. Coffey, M.D., M.S.[2]

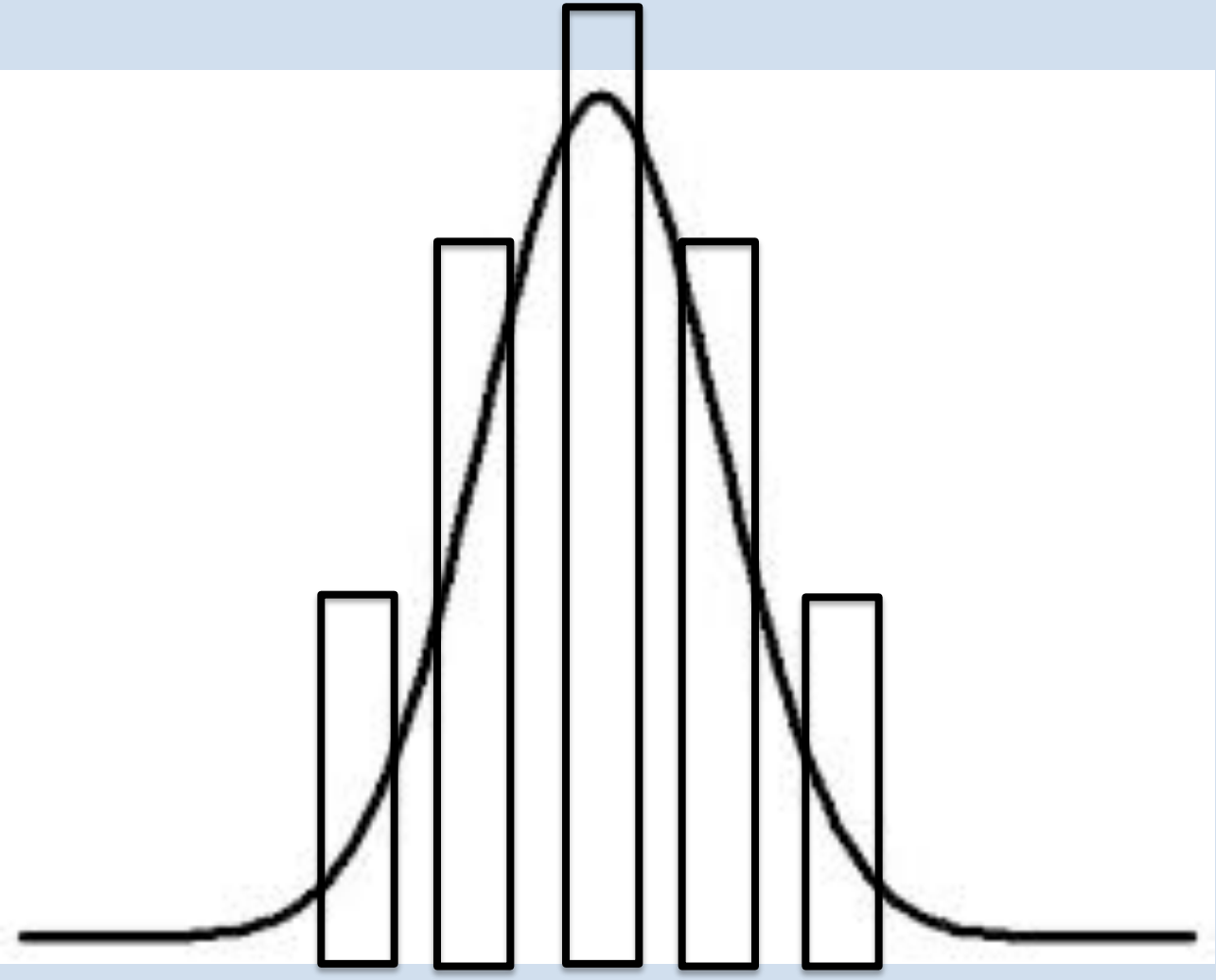
Multi-Axial Diagnoses

Axis I:	Tourette's Disorder, severe to marked. Obsessive-compulsive disorder, sub-threshold. Generalized anxiety disorder. Major depressive episode, secondary to risperidone and tetrabenazine, past.
Axis II:	Deferred.
Axis III:	Seizure disorder, not otherwise specified. Concussion twice within the past two years. Fractured arm, past.
Axis IV:	Level of psychosocial stressors: Severe: Hospitalized for tics and unable to attend the school in the past year.
Axis V:	Current Global Assessment of Functioning (GAF) Score: 40. Most severe lifetime GAF: 40.



A conceptual model of canalization. The *y* plane represents a phenotypic spectrum, the *x* plane represents the canalized progression of development through time, and the *z* plane represents environmental fluctuations.

Categorical Thinking Misses Complexity



Expression Issues

- We do not really know the expression of pretty much ALL mutations in **humans**, as we have not systematically sequenced or karyotyped any genetic alteration in **Thousands to Millions** of **randomly** selected people, nor categorized into ethnic classes, i.e. clans.

Genetics inMedicine | BRIEF REPORT

Open

Estimates of penetrance for recurrent pathogenic copy-number variations

Volume 15 | Number 6 | June 2013 | GENETICS in MEDICINE

Jill A. Rosenfeld, MS[1], Bradley P. Coe, PhD[2], Evan E. Eichler, PhD[2,3], Howard Cuckle, DPhil[4] and Lisa G. Shaffer, PhD[1,5]

Table 1 Penetrance estimates with case and control frequencies for recurrent CNVs

Region (gene within region)	Copy number	Coordinates (hg18)	Frequency, postnatal aCGH cases	Frequency, controls	*P* value (Fisher exact one-tailed test)	Frequency of *de novo* occurrence in cases	Penetrance estimate, % (95% CI)
Proximal 1q21.1 (*RBM8A*)	Duplication	chr1: 144.0–144.5 Mb	85/48,637 (0.17%)	10/22,246 (0.04%)	<<0.0001	0/13 (0%)	17.3 (10.8–27.4)
Distal 1q21.1 (*GJA5*)	Deletion	chr1: 145.0–146.35 Mb	97/33,226 (0.29%)	6/22,246 (0.03%)	<<0.0001	7/39 (17.9%)	36.9 (23.0–55.0)
Distal 1q21.1 (*GJA5*)	Duplication	chr1: 145.0–146.35 Mb	68/33,226 (0.20%)	6/22,246 (0.03%)	<<0.0001	5/30 (16.7%)	29.1 (16.9–46.8)
15q11.2 (*NIPA1*)	Deletion	chr15: 20.3–20.8 Mb	203/25,113 (0.81%)	84/22,246 (0.38%)	<<0.0001	0/27 (0%)	10.4 (8.45–12.7)
16p13.11 (*MYH11*)	Deletion	chr16: 14.9–16.4 Mb	50/33,226 (0.15%)	12/22,246 (0.05%)	<0.0005	5/23 (21.7%)	13.1 (7.91–21.3)
16p12.1 (*CDR2*)	Deletion	chr16: 21.85–22.4 Mb	62/33,226 (0.19%)	16/22,246 (0.07%)	<0.0002	1/28 (3.6%)	12.3 (7.91–18.8)
Distal 16p11.2 (*SH2B1*)	Deletion	chr16: 28.65–29.0 Mb	46/33,226 (0.14%)	1/22,246 (0.005%)	<<0.0001	7/21 (33.3%)	62.4 (26.8–94.4)
Distal 16p11.2 (*SH2B1*)	Duplication	chr16: 28.65–29.0 Mb	35/33,226 (0.11%)	10/22,246 (0.04%)	<0.01	1/8 (12.5%)	11.2 (6.26–19.8)
Proximal 16p11.2 (*TBX6*)	Deletion	chr16: 29.5–30.15 Mb	146/33,226 (0.44%)	6/22,246 (0.03%)	<<0.0001	33/47 (70.2%)[a]	46.8 (31.5–64.2)
Proximal 16p11.2 (*TBX6*)	Duplication	chr16: 29.5–30.15 Mb	93/33,226 (0.28%)	9/22,246 (0.04%)	<<0.0001	7/30 (23.3%)	27.2 (17.4–40.7)
17q12 (*HNF1B*)	Deletion	chr17: 31.8–33.3 Mb	29/33,226 (0.09%)	2/22,246 (0.01%)	<0.0001	5/9 (55.6%)	34.4 (13.7–70.0)
17q12 (*HNF1B*)	Duplication	chr17: 31.8–33.3 Mb	37/33,226 (0.11%)	5/22,246 (0.02%)	<0.0001	2/9 (22.2%)	21.1 (10.6–39.5)
22q11.21 (*TBX1*)	Duplication	chr22: 17.2–19.9 Mb	136/48,637 (0.28%)	12/22,246 (0.05%)	<<0.0001	12/47 (25.5%)	21.9 (14.7–31.8)

aCGH, microarray-based comparative genomic hybridization; CI, confidence interval; CNV, copy-number variation; <<, much less than.

[a]Deletions of the proximal 16p11.2 region showed a maternal transmission bias (14/68 mothers identified to be carriers vs. 0/38 fathers; two-tailed $P = 0.0018$, Fisher exact test); no parental transmission bias was detected for any other CNV.

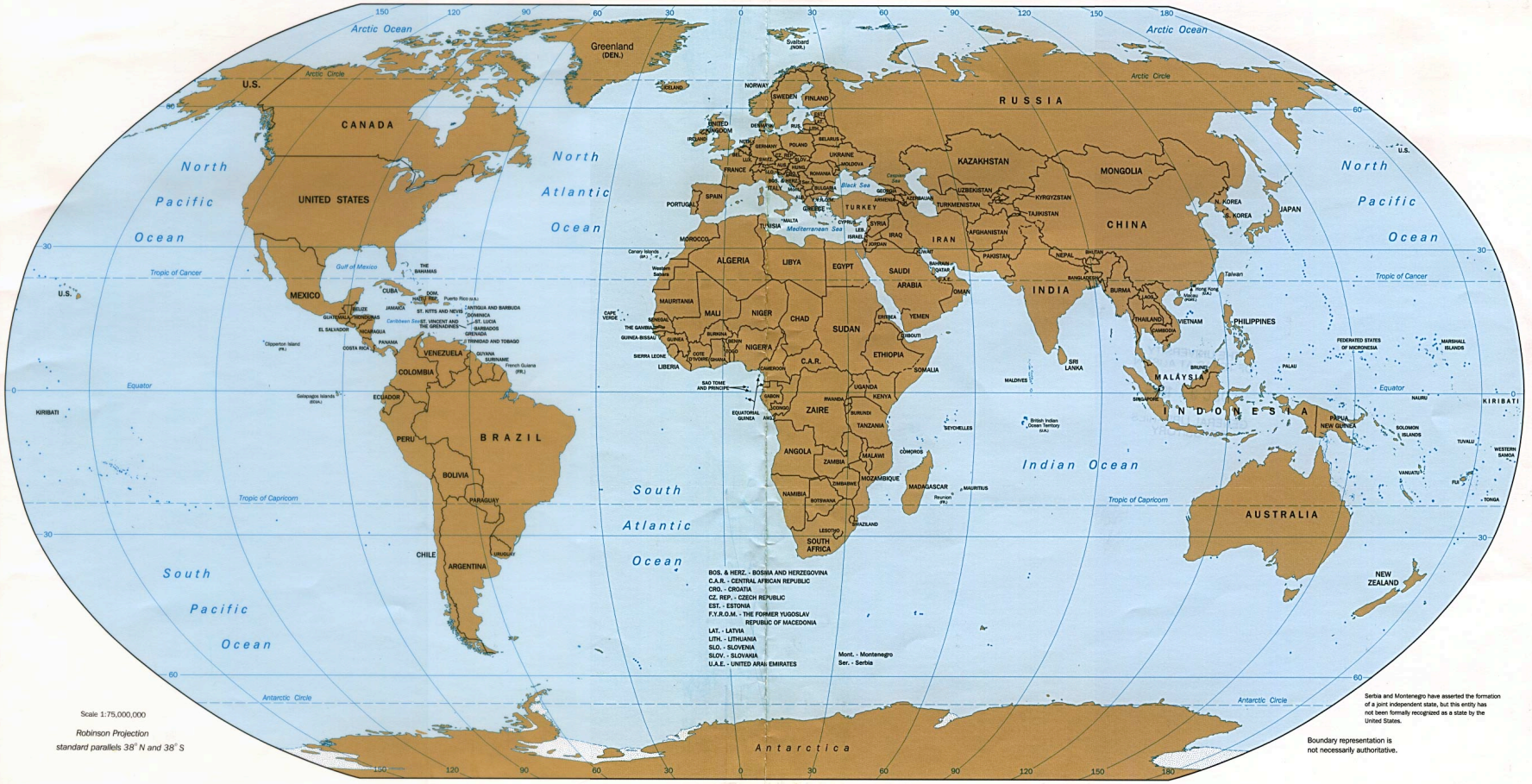
XLID-Causing Mutations and Associated Genes Challenged in Light of Data From Large-Scale Human Exome Sequencing

Amélie Piton,[1,2,4,*] Claire Redin,[1,2,4] and Jean-Louis Mandel[1,2,3,*]

"Nonetheless, the boundary between true mutations and rare non-disease-causing variants often remains elusive. The sequencing of a large number of control X chromosomes, required for avoiding false-positive results, was not systematically possible in the past".

"We propose that similar reassessment of reported mutations (and genes) with the use of data from large-scale human exome sequencing would be relevant for a wide range of other genetic diseases".

Political Map of the World



Scale 1:75,000,000

Robinson Projection
standard parallels 38° N and 38° S

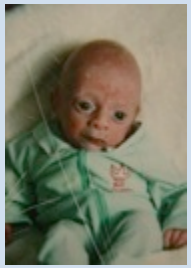
Serbia and Montenegro have asserted the formation of a joint independent state, but this entity has not been formally recognized as a state by the United States.

Boundary representation is not necessarily authoritative.

802373 (R00350) 4-95

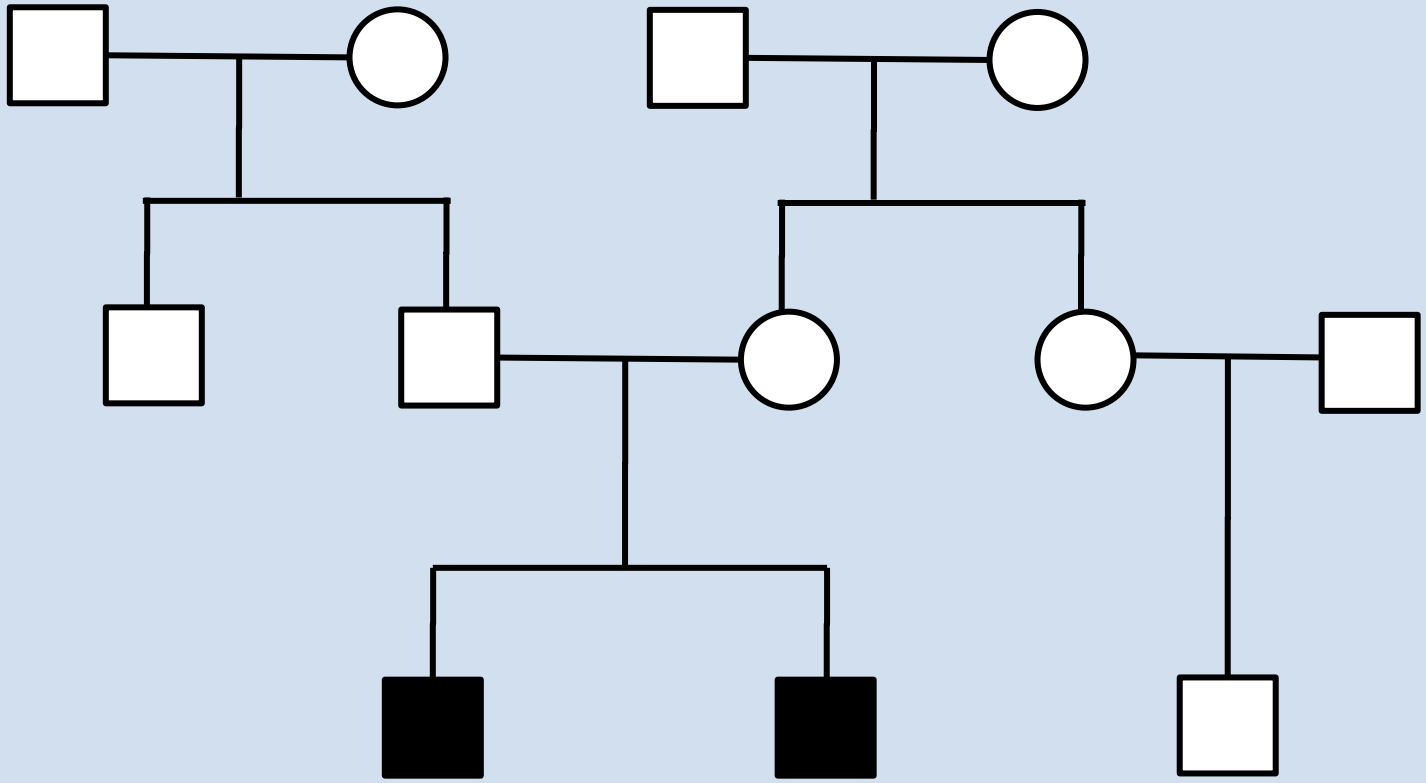
Utah, New York and Faroe Islands

Vignette #1: Variable expressivity in any disease, including in this one: Ogden Syndrome in Ogden, Utah.

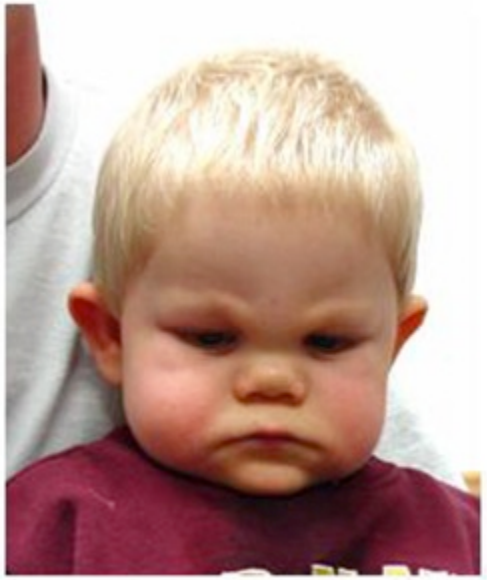


Am J Hum Genet. 2011 Jul 15;89(1):28-43.

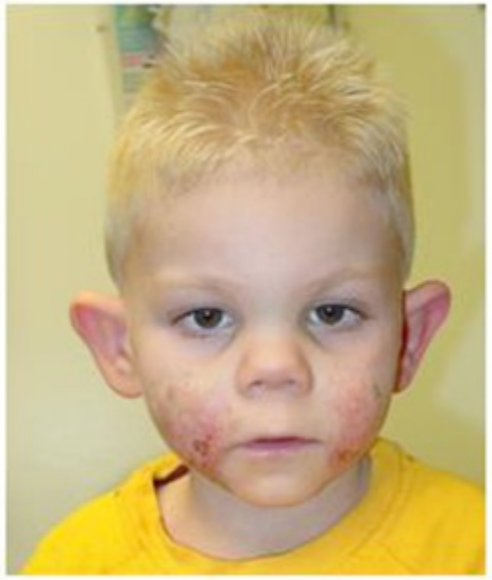
Vignette #2: Another family in Utah: New Syndrome with Intellectual Disability, “Autism”, “ADHD”



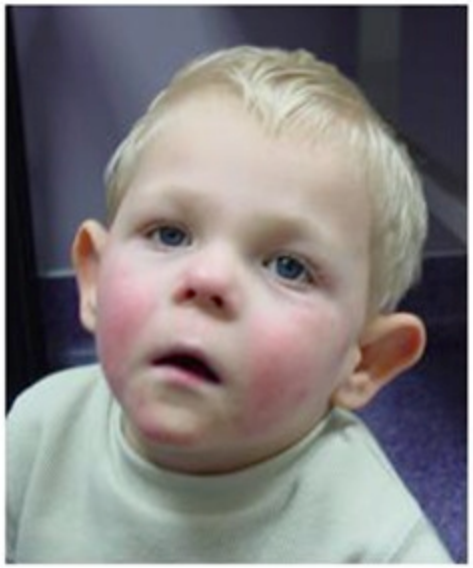
Likely X-linked or Autosomal Recessive, with X-linked being supported by extreme X-skewing in the mother



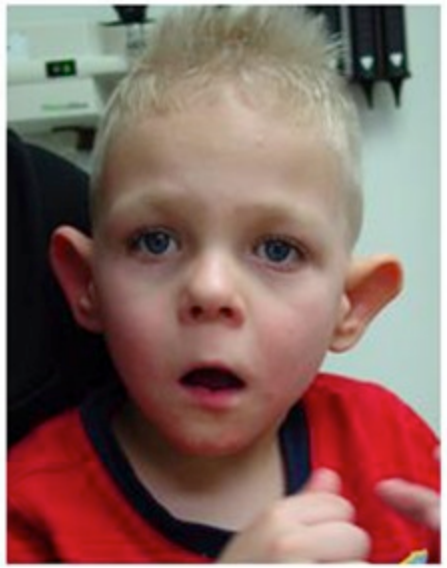
1.5 years old



3.5 years old



3 years old



5 years old

Dysmorphic
Mental Retardation
“autism”
“ADHD”
Hearing difficulties

Workup Ongoing for past 10 years

- Numerous genetic tests negative, including negative for Fragile X and MANY candidate genes.

- Whole genome sequencing was performed using :
  - Complete Genomics sequencing and analysis pipeline v2.0
  - Ilumina HiSeq 2000 sequencing platform.
    - Illumina reads were mapped to the hg19 reference genome using BWA v. 0.6.2-r126
    - Variant detection was performed using the GATK v. 2.4-9.
    - A second analytical pipeline was used to map reads to the hg19 reference genome using Novoalign, and variants were also detected using the FreeBayes caller.

Using only nuclear family:

55195 Variants were found to be *de-novo* in the two affected boys

122 were coding :

107 non-synonymous missense

4 splicing

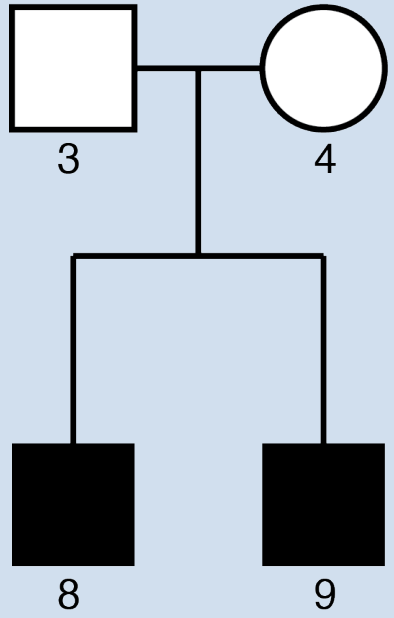
3 frame-shift deletions

3 frame-shift insertions

2 frame-shift substitutions

2 stop-gain

1 stop-loss



26514 Variants were found to conform to an X-linked disease model

28 were coding:

27 non-synonymous missense

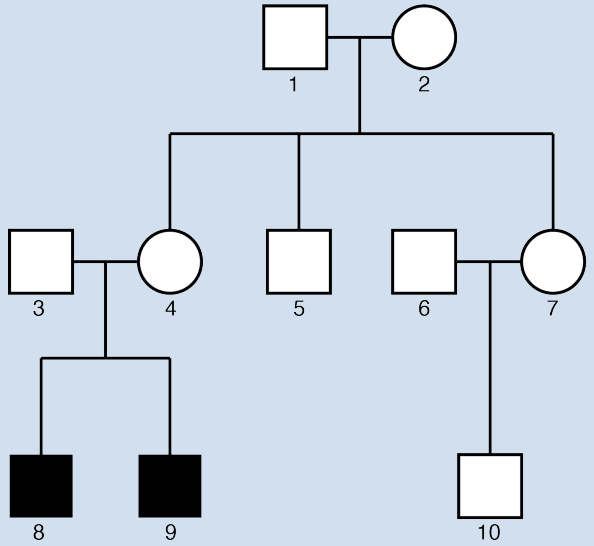
1 splicing

Using information from a greater portion of the family structure:

17726 Variants were found to be *de-novo* in the two affected boys

40 were coding :

- 32 non-synonymous missense
- 3 splicing
- 2 frame-shift deletions
- 1 stop-loss
- 1 frame-shift insertion
- 1 frame-shift substitution

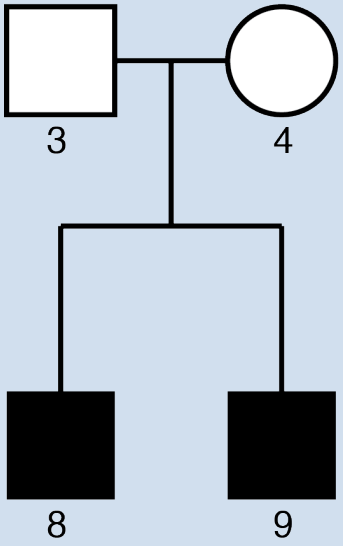


2824 Variants were found to conform to an X-linked disease model

4 were coding:

- 3 non-synonymous missense
- 1 splicing

- The numbers of mutations differ as expected between these two sets of analyses:
  - More mutations are filtered when a greater portion of the family is incorporated into the analysis.
  - This is likely due to false positive and false negative rates across sequencing and informatics platforms.



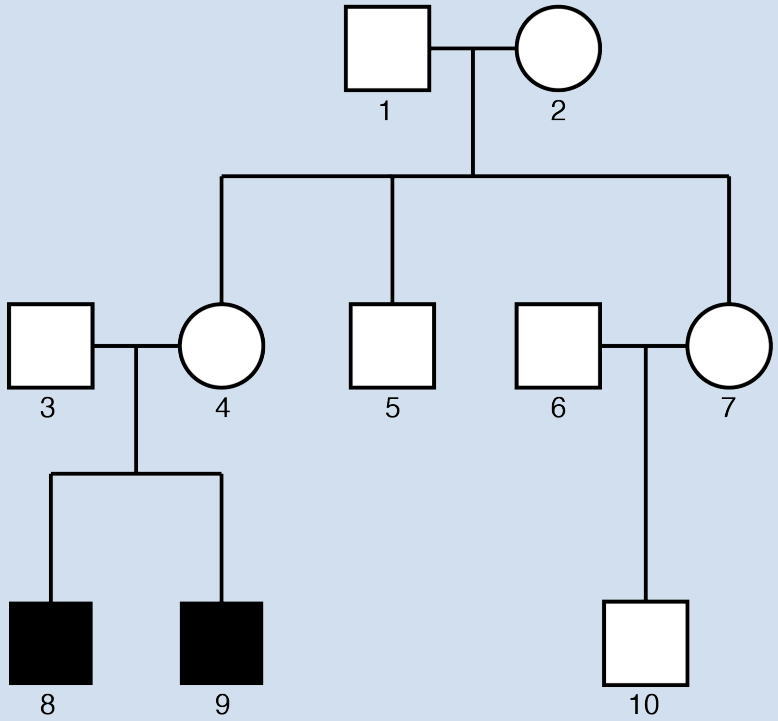
Using only nuclear family:

De-novo ranked genes:

RANK	Gene	p-value	p-value-ci	Score	Variants
1	PRAMEF4	0.00192	0.00144,0.00265	13.13	chr1:12939476;13.13;G->C;N->K;0,1
2	PRAMEF10	0.00318	0.00243,0.00417	20.77	chr1:12954852;20.77;T->C;H->R;3,2
3	LOC440563	0.00523	0.00416,0.00653	9.89	chr1:13183056;9.89;T->C;N->D;0,1

X-linked ranked genes:

RANK	Gene	p-value	p-value-ci	Score	Variants
1	ASB12	0.000898	0.000898,0.00119	18.7	chrX:63444792;18.70;C->A;G->C;0,1
2	TAF1	0.00153	0.00117,0.00214	14.59	chrX:70621541;14.59;T->C;I->T;0,1
3	ZNF41	0.002	0.0015,0.00275	12.9	chrX:47307978;12.90;G->T;D->E;0,1



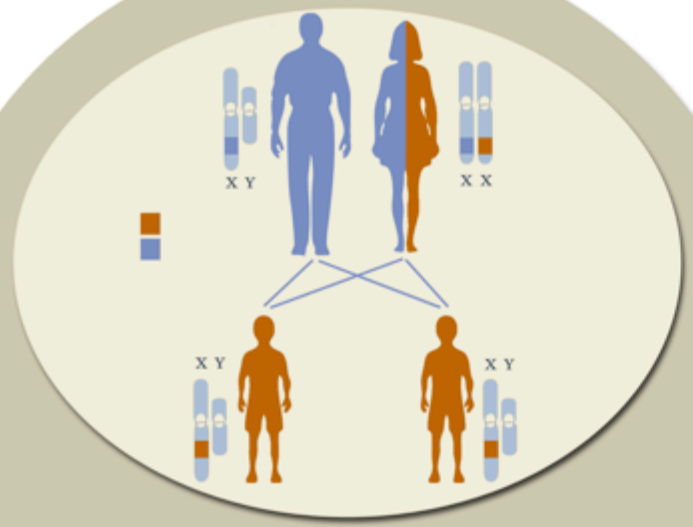
Using information from a greater portion of the family structure:

De-novo ranked genes:

RANK	Gene	p-value	p-value-ci	Score	Variants
1	PRAMEF10	0.00342	0.00262,0.00445	20.77	chr1:12954852;20.77;T->C;H->R;3,2

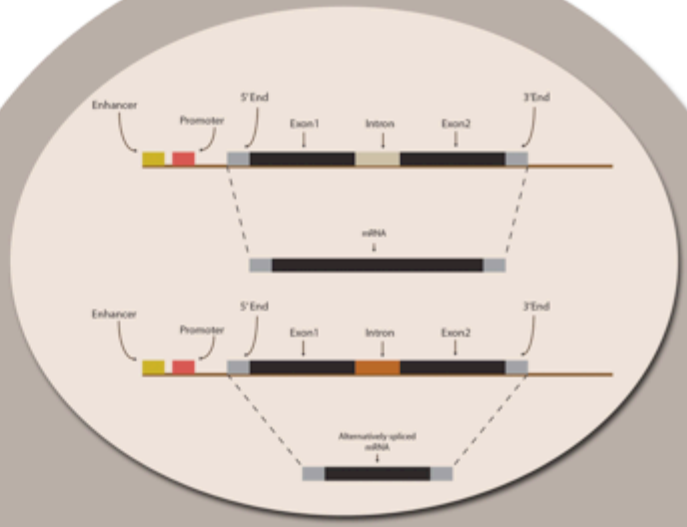
X-linked ranked genes:

RANK	Gene	p-value	p-value-ci	Score	Variants
1	TAF1	0.002	0.0015,0.00275	14.59	chrX:70621541;14.59;T->C;I->T;0,1



X-linked

Gene	Locus	Exon	Protein
ZNF41	X:47307978	5	p.Asp397Glu
ASB12	X:63444792	2	p.Gly247Cys
TAF1	X:70621541	25	p.Ile1337Thr



Non-coding

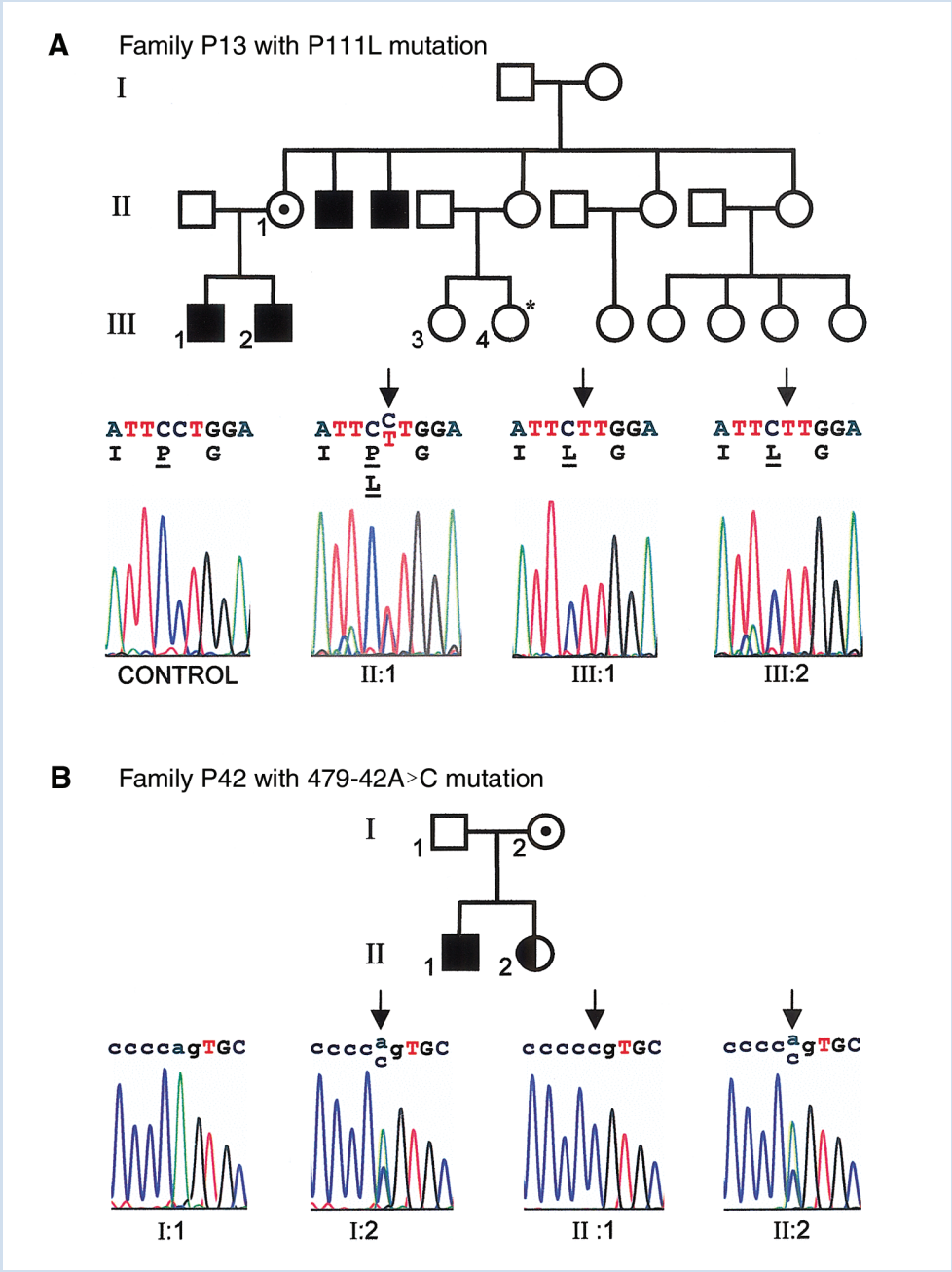
Gene	Locus	Exon	Protein
UTR3 AR	X:66945414	-------	-------
FAM155B (dist=271971)	X:68453113	-------	-------
MIR221 (dist=35606)	X:45569979	-------	-------
DMD-AS2 intronic	X:31284835	-------	-------
MID1 (dist=30252)	X:10383096	-------	-------

Mutations in the *ZNF41* Gene Are Associated with Cognitive Deficits: Identification of a New Candidate for X-Linked Mental Retardation

Sarah A. Shoichet,[1] Kirsten Hoffmann,[1] Corinna Menzel,[1] Udo Trautmann,[2] Bettina Moser,[1] Maria Hoeltzenbein,[1] Bernard Echenne,[3] Michael Partington,[4] Hans van Bokhoven,[5] Claude Moraine,[6] Jean-Pierre Fryns,[7] Jamel Chelly,[8] Hans-Dieter Rott,[2] Hans-Hilger Ropers,[1] and Vera M. Kalscheuer[1]

[1]Max-Planck-Institute for Molecular Genetics, Berlin; [2]Institute of Human Genetics, University of Erlangen-Nuremberg, Erlangen-Nuremberg; [3]Centre Hospitalier Universitaire de Montpellier, Hôpital Saint-Eloi, Montpellier, France, [4]Hunter Genetics and University of Newcastle, Waratah, Australia; [5]Department of Human Genetics, University Medical Centre, Nijmegen, The Netherlands; [6]Services de Génétique–INSERM U316, CHU Bretonneau, Tours, France; [7]Center for Human Genetics, Clinical Genetics Unit, Leuven, Belgium; and [8]Institut Cochin de Génétique Moleculaire, Centre National de la Recherche Scientifique/INSERM, CHU Cochin, Paris

Am. J. Hum. Genet. 73:1341–1354, 2003



The two brothers with the P111L mutations reported in the prior paper do have mental deficiency, hyperkinesia, no motor or neurologic sign except for the delay, and slight dysmorphic facial anomalies: large low-set ears, thin upper lip, slight downward palpebral slants, but no upturned nose, and a short philtrum. The mother was normal in appearance.

- Previously reported P111L change in the ZNF41 protein has now also been found in two "male controls" (EVS server, ESP6500), and furthermore, there are two rare, likely heterozygous ZNF41 frameshift mutations and one heterozygous stop-gained mutation reported in control individuals (ESP6500) (personal communication from Dr. Vera Kalscheuer).

XLID-Causing Mutations and Associated Genes Challenged in Light of Data From Large-Scale Human Exome Sequencing

Amélie Piton,[1,2,4,*] Claire Redin,[1,2,4] and Jean-Louis Mandel[1,2,3,*]

Vignette #3:

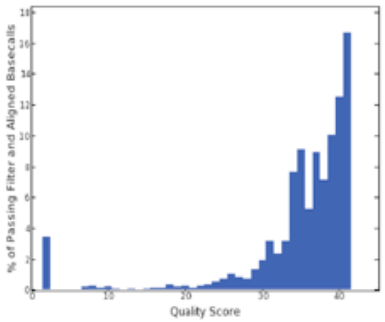
A third family in Utah, with a 40 year old Caucasian man with
very severe obsessive compulsive disorder, severe depression and intermittent psychoses, with symptoms that started around age 5.

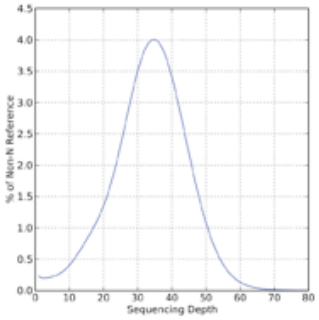
Sequencing and Analytics

Data Volume and Quality

	Yield (Gigabases)	% Bases ≥ Q30	% Bases Aligned
Passing Filter	113.10	87.10%	87.80%

	% Callable	% ≥ 5x depth	% ≥ 10x depth	% ≥ 20x depth	Mean depth(x)
Non-N Reference	93.28%	97.57%	96.22%	88.54%	33.35





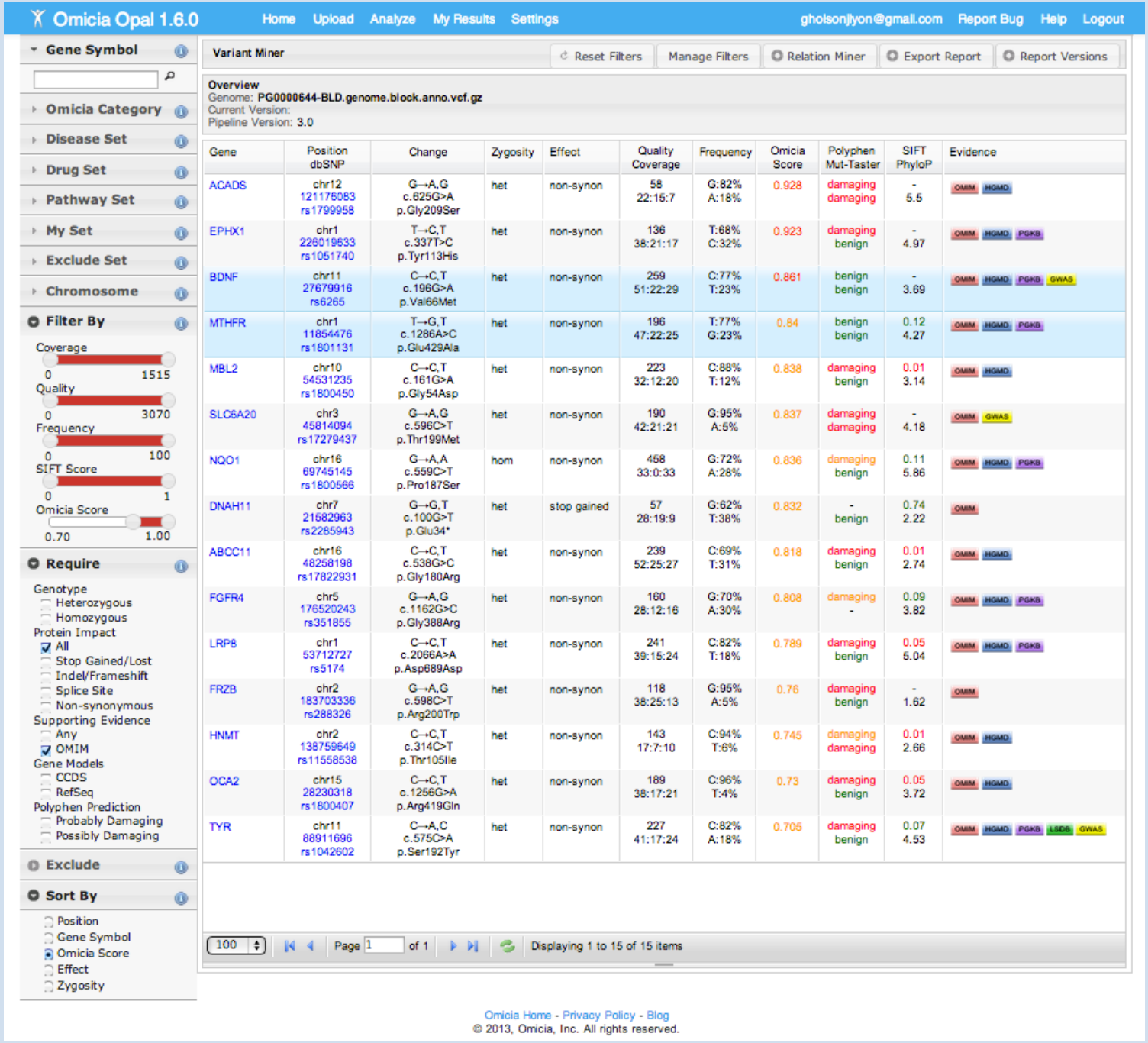
SNP Assessment

Total	Het/Hom	% in dbSNP	% in Genes	% in Coding
3,308,246	1.61	98.13%	45.47%	0.63%

Variant Statistics

	SNVs
Total Number	3,308,246
Number in Genes	1,504,121
Number in Coding Regions	20,879
Number in UTRs	24,946
Splice Site Region	2,917
Stop Gained	72
Stop Lost	16
Non-synonymous	9,884
Synonymous	10,907
Mature miRNA	36

From the Illumina Understand Your Genome Symposium October 2012


Omicia Opal 1.6.0
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Gene Symbol
Omicia Category
Disease Set
Drug Set
Pathway Set
My Set
Exclude Set
Chromosome
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Protein Impact
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Indel/Frameshift
Splice Site
Non-synonymous
Supporting Evidence
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CCDS
RefSeq
Polyphen Prediction
Probably Damaging
Possibly Damaging
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Omicia Score
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Zygosity
Variant Miner
Reset Filters
Manage Filters
Relation Miner
Export Report
Report Versions
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Pipeline Version: 3.0
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Position dbSNP
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Zygosity
Effect
Quality Coverage
Frequency
Omicia Score
Polyphen Mut-Taster
SIFT PhyloP
Evidence
ACADS chr12 121176083 rs1799958 G→A,G c.625G>A p.Gly209Ser het non-synon 58 22:15:7 G:82% A:18% 0.928 damaging damaging - 5.5 OMIM HGMD
EPHX1 chr1 226019633 rs1051740 T→C,T c.337T>C p.Tyr113His het non-synon 136 38:21:17 T:68% C:32% 0.923 damaging benign - 4.97 OMIM HGMD PGKB
BDNF chr11 27679916 rs6265 C→C,T c.196G>A p.Val66Met het non-synon 259 51:22:29 C:77% T:23% 0.861 benign benign - 3.69 OMIM HGMD PGKB GWAS
MTHFR chr1 11854476 rs1801131 T→G,T c.1286A>C p.Glu429Ala het non-synon 196 47:22:25 T:77% G:23% 0.84 benign benign 0.12 4.27 OMIM HGMD PGKB
MBL2 chr10 54531235 rs1800450 C→C,T c.161G>A p.Gly54Asp het non-synon 223 32:12:20 C:88% T:12% 0.838 damaging benign 0.01 3.14 OMIM HGMD
SLC6A20 chr3 45814094 rs17279437 G→A,G c.596C>T p.Thr199Met het non-synon 190 42:21:21 G:95% A:5% 0.837 damaging damaging - 4.18 OMIM GWAS
NQO1 chr16 69745145 rs1800566 G→A,A c.559C>T p.Pro187Ser hom non-synon 458 33:0:33 G:72% A:28% 0.836 damaging benign 0.11 5.86 OMIM HGMD PGKB
DNAH11 chr7 21582963 rs2285943 G→G,T c.100G>T p.Glu34* het stop gained 57 28:19:9 G:62% T:38% 0.832 - benign 0.74 2.22 OMIM
ABCC11 chr16 48258198 rs17822931 C→C,T c.538G>C p.Gly180Arg het non-synon 239 52:25:27 C:69% T:31% 0.818 damaging benign 0.01 2.74 OMIM HGMD
FGFR4 chr5 176520243 rs351855 G→A,G c.1162G>C p.Gly388Arg het non-synon 160 28:12:16 G:70% A:30% 0.808 damaging - 0.09 3.82 OMIM HGMD PGKB
LRP8 chr1 53712727 rs5174 C→C,T c.2066A>A p.Asp689Asp het non-synon 241 39:15:24 C:82% T:18% 0.789 damaging benign 0.05 5.04 OMIM HGMD PGKB
FRZB chr2 183703336 rs288326 G→A,G c.598C>T p.Arg200Trp het non-synon 118 38:25:13 G:95% A:5% 0.76 damaging benign - 1.62 OMIM
HNMT chr2 138759649 rs11558538 C→C,T c.314C>T p.Thr105Ile het non-synon 143 17:7:10 C:94% T:6% 0.745 damaging damaging 0.01 2.66 OMIM HGMD
OCA2 chr15 28230318 rs1800407 C→C,T c.1256G>A p.Arg419Gln het non-synon 189 38:17:21 C:96% T:4% 0.73 damaging benign 0.05 3.72 OMIM HGMD
TYR chr11 88911696 rs1042602 C→A,C c.575C>A p.Ser192Tyr het non-synon 227 41:17:24 C:82% A:18% 0.705 damaging benign 0.07 4.53 OMIM HGMD PGKB LSDB GWAS
100
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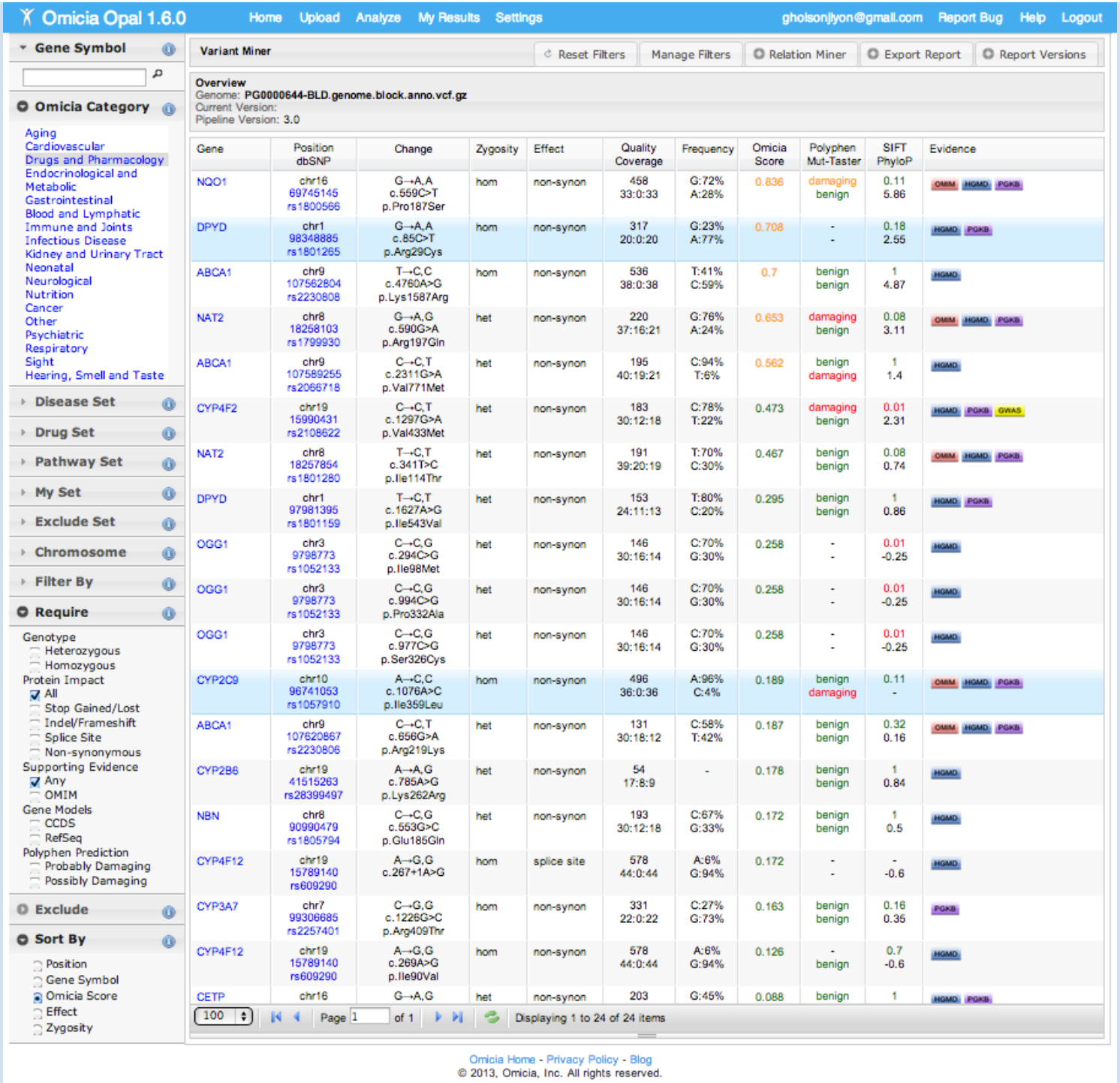
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Home Upload Analyze My Results Settings
gholsonjlyon@gmail.com Report Bug Help Logout
Gene Symbol
Omicia Category
Aging
Cardiovascular
Drugs and Pharmacology
Endocrinological and Metabolic
Gastrointestinal
Blood and Lymphatic
Immune and Joints
Infectious Disease
Kidney and Urinary Tract
Neonatal
Neurological
Nutrition
Cancer
Other
Psychiatric
Respiratory
Sight
Hearing, Smell and Taste
Disease Set
Drug Set
Pathway Set
My Set
Exclude Set
Chromosome
Filter By
Require
Genotype
Heterozygous
Homozygous
Protein Impact
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Indel/Frameshift
Splice Site
Non-synonymous
Supporting Evidence
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CCDS
RefSeq
Polyphen Prediction
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Possibly Damaging
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Variant Miner
Reset Filters
Manage Filters
Relation Miner
Export Report
Report Versions
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Zygosity
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Frequency
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Polyphen Mut-Taster
SIFT PhyloP
Evidence
NQO1 chr16 69745145 rs1800566 G→A,A c.559C>T p.Pro187Ser hom non-synon 458 33:0:33 G:72% A:28% 0.836 damaging benign 0.11 5.86 OMIM HGMD PGKB
DPYD chr1 98348885 rs1801265 G→A,A c.85C>T p.Arg29Cys hom non-synon 317 20:0:20 G:23% A:77% 0.708 - - 0.18 2.55 HGMD PGKB
ABCA1 chr9 107562804 rs2230808 T→C,C c.4760A>G p.Lys1587Arg hom non-synon 536 38:0:38 T:41% C:59% 0.7 benign benign 1 4.87 HGMD
NAT2 chr8 18258103 rs1799930 G→A,G c.590G>A p.Arg197Gln het non-synon 220 37:16:21 G:76% A:24% 0.653 damaging benign 0.08 3.11 OMIM HGMD PGKB
ABCA1 chr9 107589255 rs2066718 C→C,T c.2311G>A p.Val771Met het non-synon 195 40:19:21 C:94% T:6% 0.562 benign damaging 1 1.4 HGMD
CYP4F2 chr19 15990431 rs2108622 C→C,T c.1297G>A p.Val433Met het non-synon 183 30:12:18 C:78% T:22% 0.473 damaging benign 0.01 2.31 HGMD PGKB GWAS
NAT2 chr8 18257854 rs1801280 T→C,T c.341T>C p.Ile114Thr het non-synon 191 39:20:19 T:70% C:30% 0.467 benign benign 0.08 0.74 OMIM HGMD PGKB
DPYD chr1 97981395 rs1801159 T→C,T c.1627A>G p.Ile543Val het non-synon 153 24:11:13 T:80% C:20% 0.295 benign benign 1 0.86 HGMD PGKB
OGG1 chr3 9798773 rs1052133 C→C,G c.294C>G p.Ile98Met het non-synon 146 30:16:14 C:70% G:30% 0.258 - - 0.01 -0.25 HGMD
OGG1 chr3 9798773 rs1052133 C→C,G c.994C>G p.Pro332Ala het non-synon 146 30:16:14 C:70% G:30% 0.258 - - 0.01 -0.25 HGMD
OGG1 chr3 9798773 rs1052133 C→C,G c.977C>G p.Ser326Cys het non-synon 146 30:16:14 C:70% G:30% 0.258 - - 0.01 -0.25 HGMD
CYP2C9 chr10 96741053 rs1057910 A→C,C c.1076A>C p.Ile359Leu hom non-synon 496 36:0:36 A:96% C:4% 0.189 benign damaging 0.11 - OMIM HGMD PGKB
ABCA1 chr9 107620867 rs2230806 C→C,T c.656G>A p.Arg219Lys het non-synon 131 30:18:12 C:58% T:42% 0.187 benign benign 0.32 0.16 OMIM HGMD PGKB
CYP2B6 chr19 41515263 rs28399497 A→A,G c.785A>G p.Lys262Arg het non-synon 54 17:8:9 - 0.178 benign benign 1 0.84 HGMD
NBN chr8 90990479 rs1805794 C→C,G c.553G>C p.Glu185Gln het non-synon 193 30:12:18 C:67% G:33% 0.172 benign benign 1 0.5 HGMD
CYP4F12 chr19 15789140 rs609290 A→G,G c.267+1A>G hom splice site 578 44:0:44 A:6% G:94% 0.172 - - - -0.6 HGMD
CYP3A7 chr7 99306685 rs2257401 C→G,G c.1226G>C p.Arg409Thr hom non-synon 331 22:0:22 C:27% G:73% 0.163 benign benign 0.16 0.35 PGKB
CYP4F12 chr19 15789140 rs609290 A→G,G c.269A>G p.Ile90Val hom non-synon 578 44:0:44 A:6% G:94% 0.126 - benign 0.7 -0.6 HGMD
CETP chr16 G→A,G het non-synon 203 G:45% 0.088 benign 1 HGMD PGKB
100
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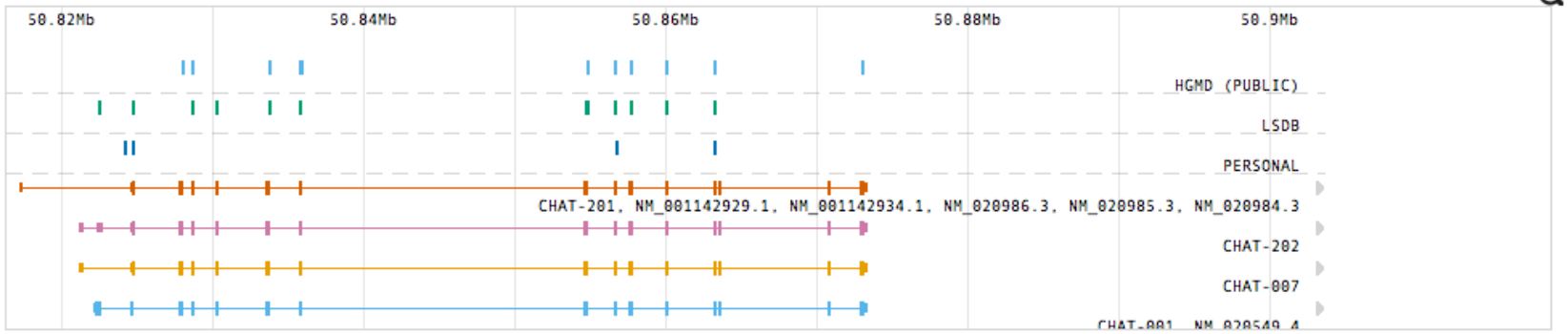
No rare variants with high biological effect as related to mental illness. One variant related to Refsum Disease (involving vision).

3 common SNVs in this person that have been implicated in the literature as predisposing to mental illness.

Gene name	Genomic coordinates	Amino acid change	Zygosity	Mutation type	Population Frequency	Clinical significance
MTHFR	chr1: 11854476	Glu>Ala	heterozygous	non-synon	T:77% G:23%	Susceptibility to psychoses, schizophrenia, occlusive vascular disease, neural tube defects, colon cancer, acute leukemia, and methylenetetra-hydrofolate reductase deficiency
BDNF	chr11: 27679916	Val>Met	heterozygous	non-synon	C:77% T:23%	Susceptibility to OCD, psychosis, and diminished response to exposure therapy
CHAT	chr10: 50824117	Asp>Asn	heterozygous	non-synon	G:85% A:15%	Susceptibility to schizophrenia and other psychopathological disorders.

Gene Summary for CHAT



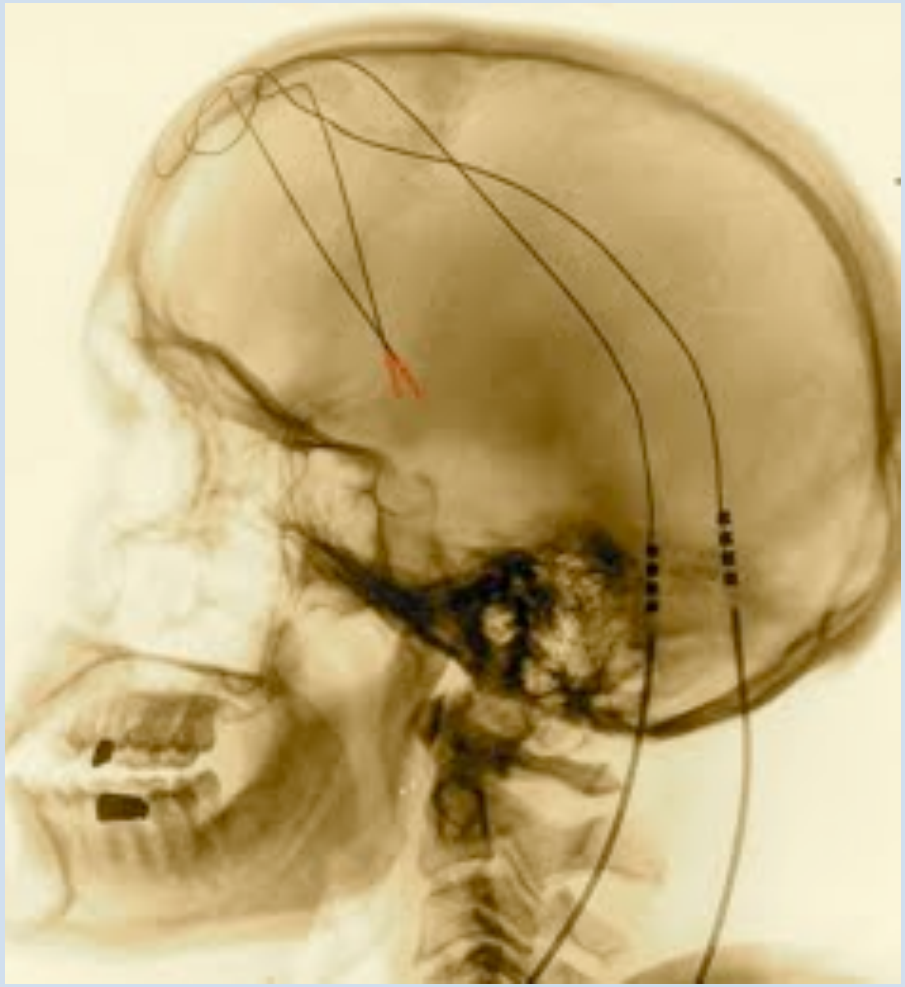
Gene Overview	
Symbol	CHAT
Name	choline O-acetyltransferase
Location	10q11.2
Summary	This gene encodes an enzyme which catalyzes the biosynthesis of the neurotransmitter acetylcholine. This gene product is a characteristic feature of cholinergic neurons, and changes in these neurons may explain some of the symptoms of Alzheimer's disease. Polymorphisms in this gene have been associated with Alzheimer's disease and mild cognitive impairment. Mutations in this gene are associated with congenital myasthenic syndrome associated with episodic apnea. Multiple transcript variants encoding different isoforms have been found for this gene, and some of these variants have been shown to encode more than one isoform. [provided by RefSeq, May 2010]

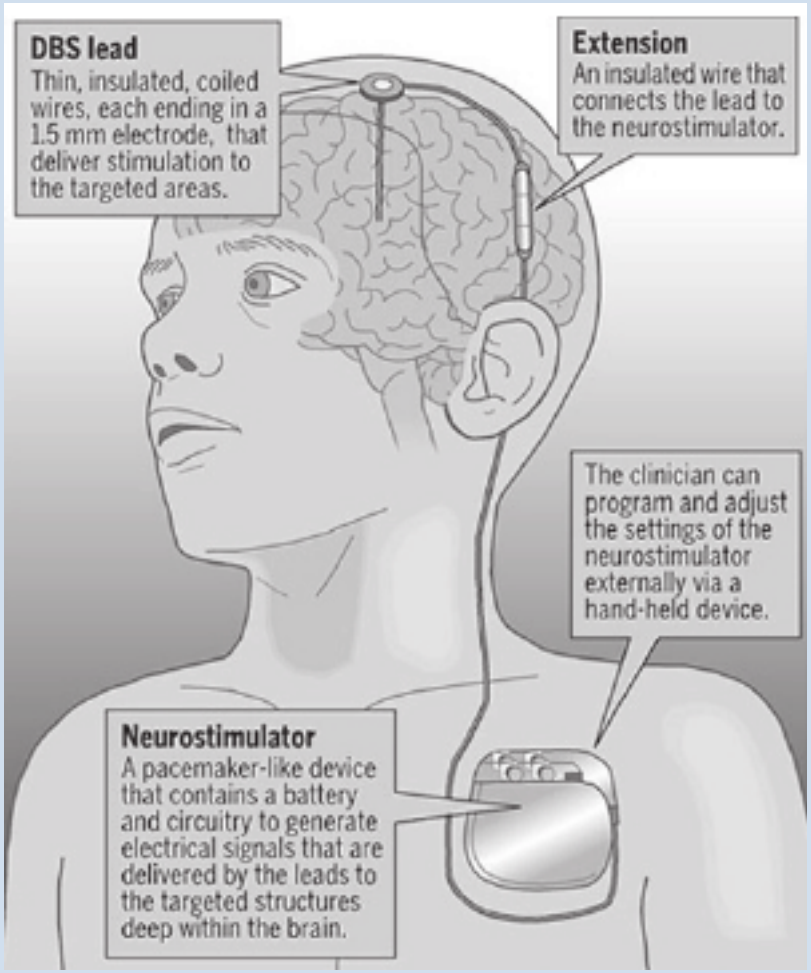
Relevant Reference Resources	
NCBI Gene	http://www.ncbi.nlm.nih.gov/gene/1103
GeneTests	http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/gene/CHAT
Ensembl	http://www.ensembl.org/human/Gene/Summary?g=ENSG00000070748
UCSC Gene Browser	http://genome.ucsc.edu/cgi-bin/hgTracks?org=human&db=hg19&singleSearch=knownCanonical&position=CHAT
Genetics Home Reference	http://ghr.nlm.nih.gov/gene/CHAT

Associated Disease Categories		
Category	**Disease**	**Citation**
DRUGS, CLINICAL PHARMACOLOGY AND ENVIRONMENT	Drug toxicity	Roden et al., 2002

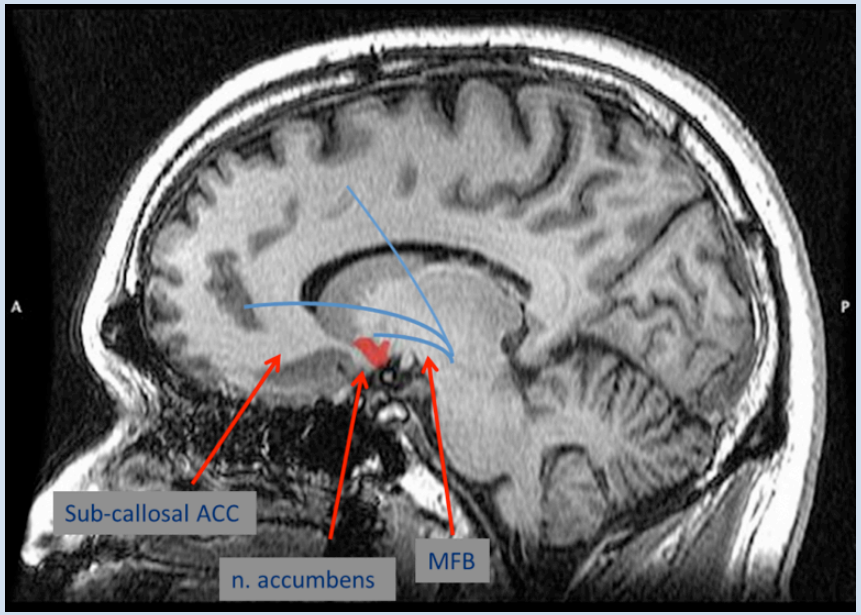
Associated Knowledge Sets		
Name	**Type**	**Description**
ODG - Alzheimers	disease	Omicia Disease Genes (ODG) Top 10 Neurological - Alzheimers
TruSight Exome	disease	Illumina's targeted rare genetic conditions exome test containing 2,761 genes covered in the HGMD database.
MitoGO	myset	
Longo - Phenomizer Fatty Acid Big	myset	A list of genes from phenomizer build from Patient Features HP:0004359. Long List ~3000 genes

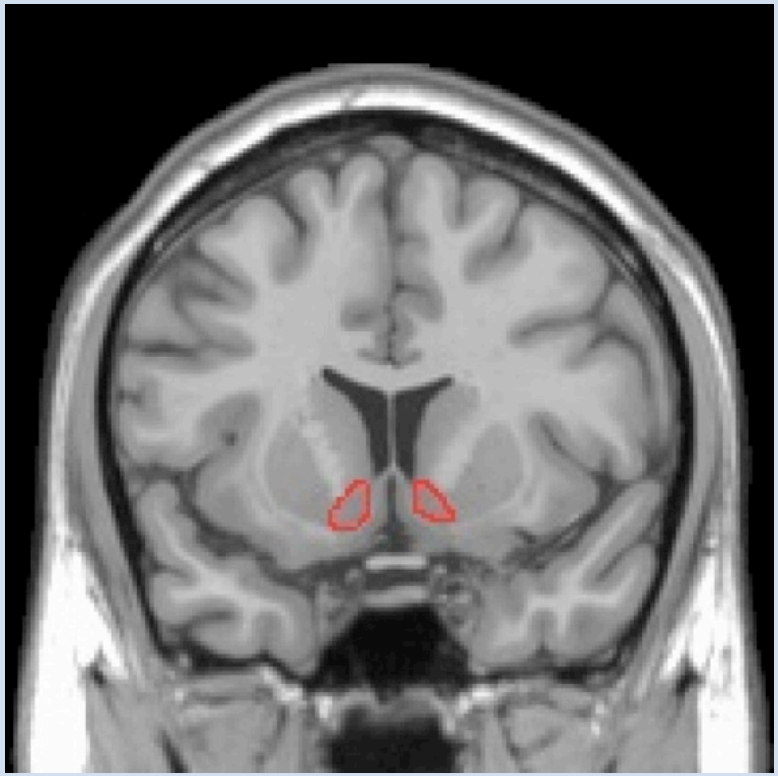
Personal Variants in this Gene						
Position	**Transcript**	**Transcript HGVS**	**Protein**	**Protein HGVS**	**Zyg**	**Effect**
50824117	NM_001142933.1	c.19G>A	NP_001136405	p.Asp7Asn	het	non-synon
50824619	NM_001142933.1	c.112G>A	NP_001136405	p.Ala38Thr	het	non-synon
50856652	NM_020549	c.1382G>A	NP_065574	p.Val461Met	hom	non-synon
50863147	NM_020549	c.1642T>C	NP_065574	p.His548His	hom	synonymous




DBS lead
Thin, insulated, coiled wires, each ending in a 1.5 mm electrode, that deliver stimulation to the targeted areas.
Extension
An insulated wire that connects the lead to the neurostimulator.
The clinician can program and adjust the settings of the neurostimulator externally via a hand-held device.
Neurostimulator
A pacemaker-like device that contains a battery and circuitry to generate electrical signals that are delivered by the leads to the targeted structures deep within the brain.

Nucleus accumbens





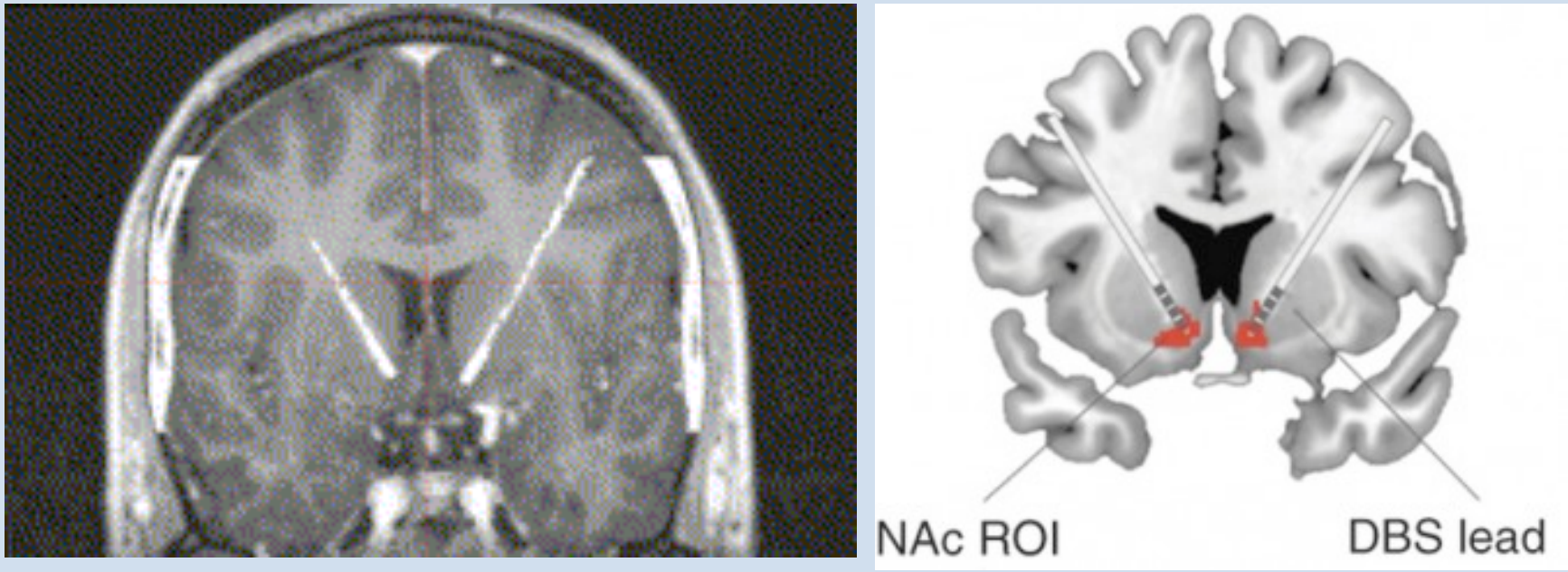
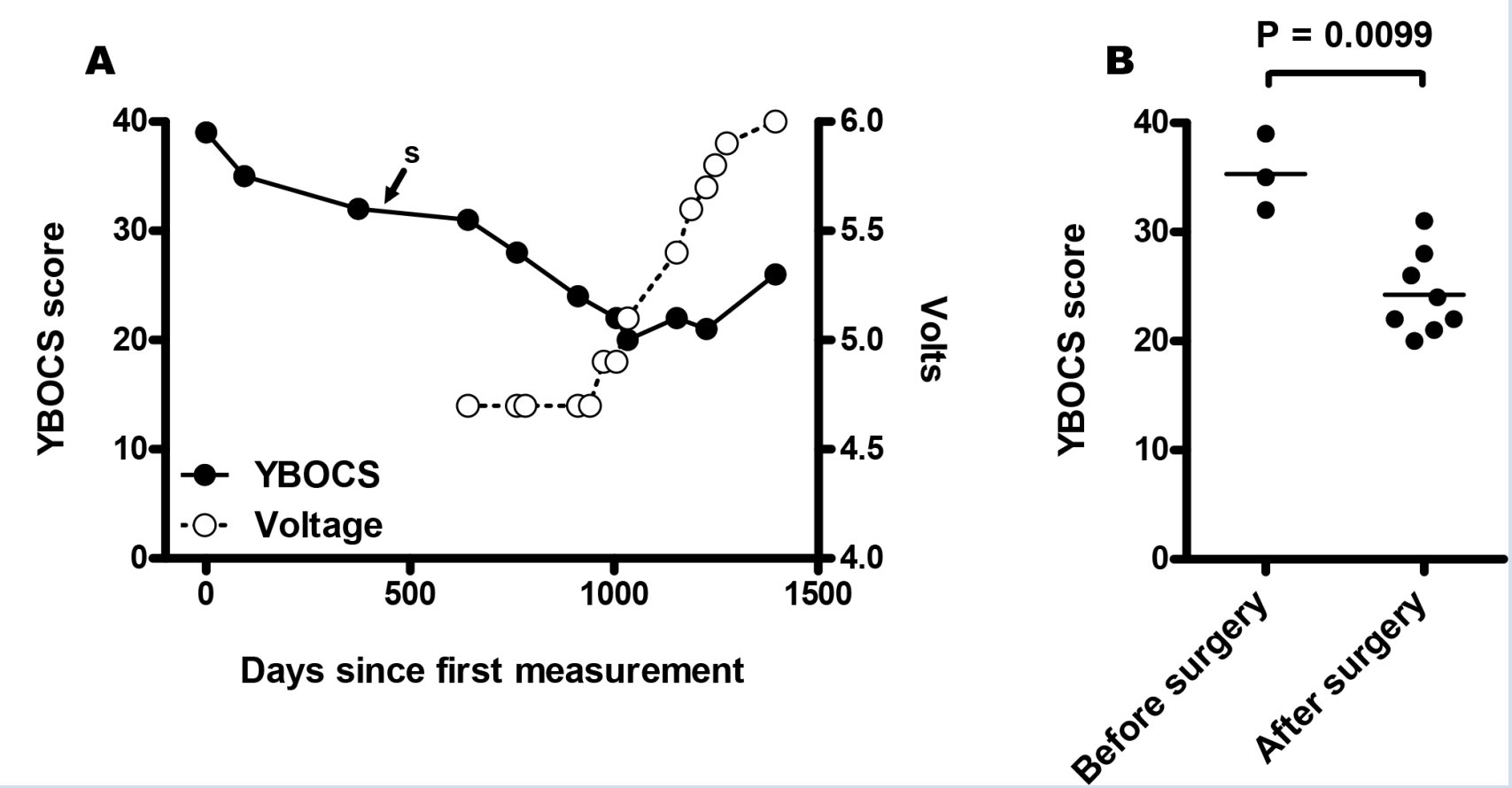


Fig. 1. Coronal section of the brain near the nucleus accumbens with the track of the electrodes on the left and right side.

2.5 year follow-up

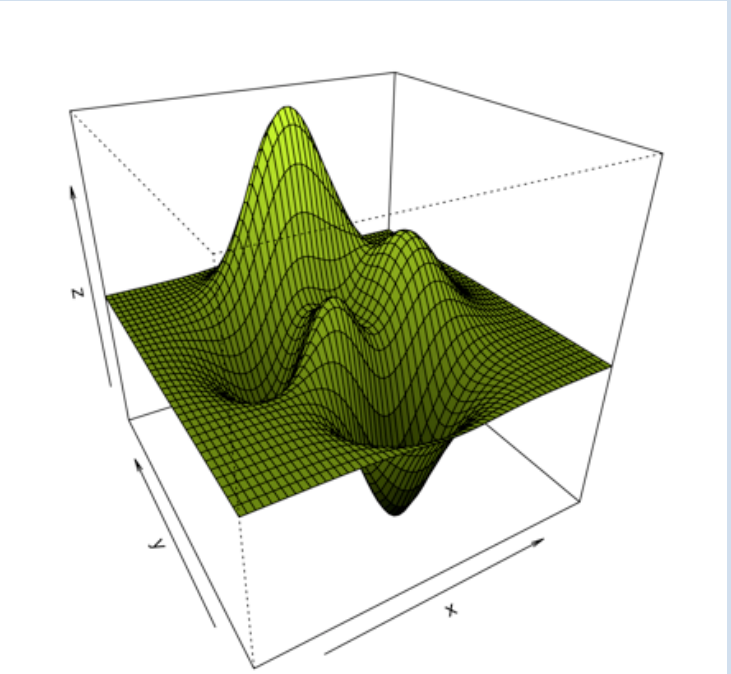


Global Assessment of Functioning (GAF) 0 to 100 scale

From 5 to 15 in 2008-2009

To

45 to 55 in 2013


z
y
x

Take Home Message

Genotype ≠ Phenotype

Environment matters!

Ancestry matters!

Genomic background matters!

Longitudinal course matters!

You are extremely well-positioned to study this in very good fashion here in the Faroe Islands.