Human Genetic Variation and the Genotype-Phenotype Problem

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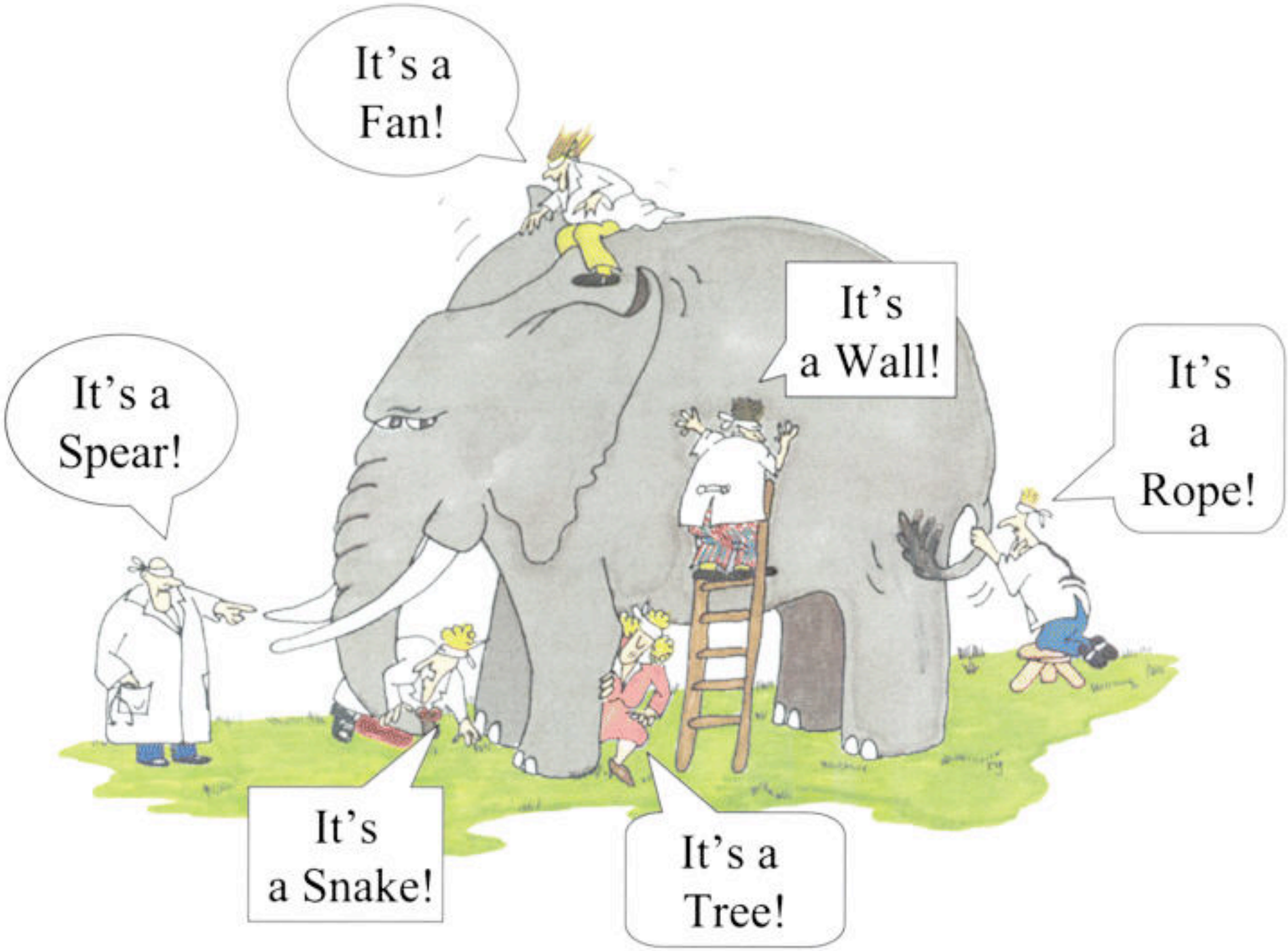
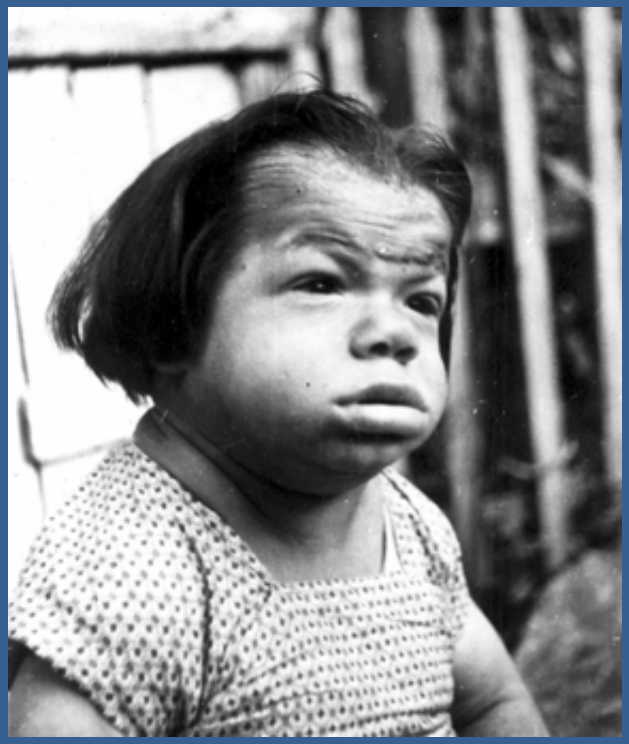
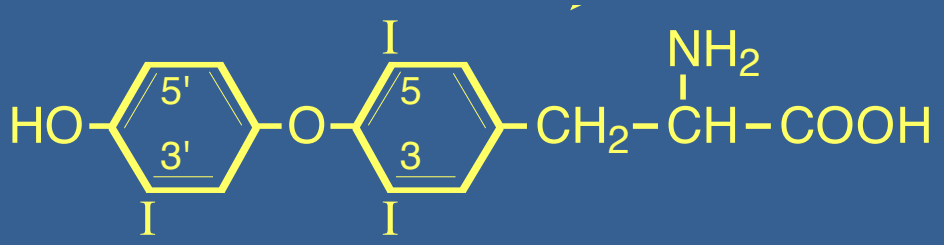
STANLEY INSTITUTE FOR COGNITIVE GENOMICS
COLD SPRING HARBOR LABORATORY

UFBR
UTAH FOUNDATION FOR BIOMEDICAL RESEARCH


It's a Fan!
It's a Spear!
It's a Wall!
It's a Rope!
It's a Snake!
It's a Tree!

Cretinism – lack of iodine in the diet, leading to thyroid hormone deficiency.





Thyroid Hormone

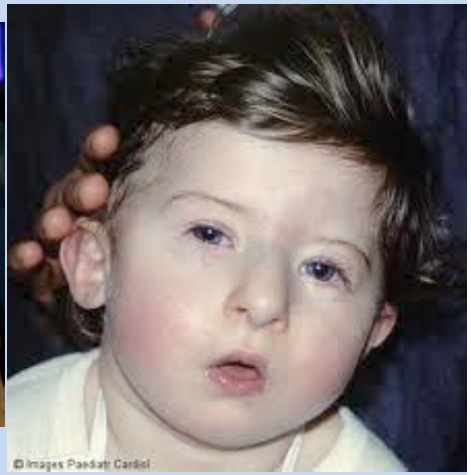
Down Syndrome

Down Syndrome

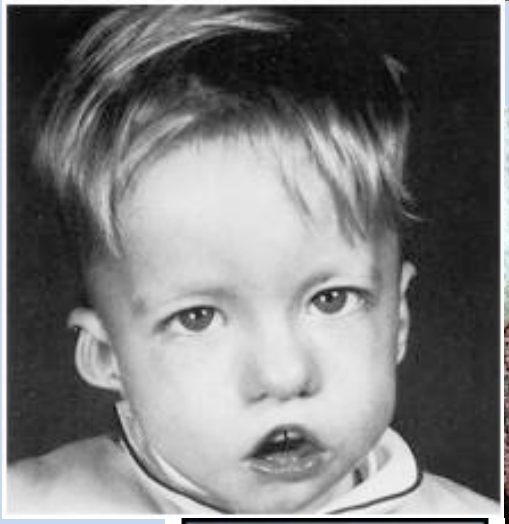
Christopher Joseph "Chris" Burke (born August 26, 1965) is an American actor and folk singer, who lives with Down syndrome, who has become best known for his character Charles "Corky" Thacher on the television series Life Goes On.

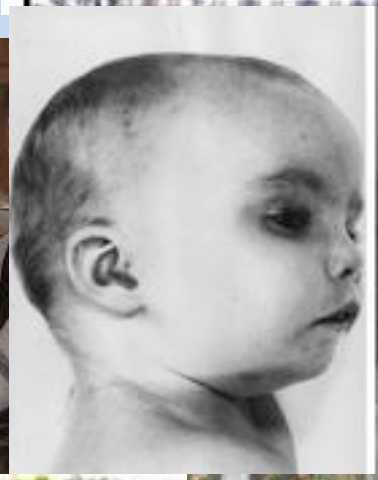
And there are people with Mosaic Down Syndrome, who are much less affected.

Velocardiofacial (22q11.2) Syndrome

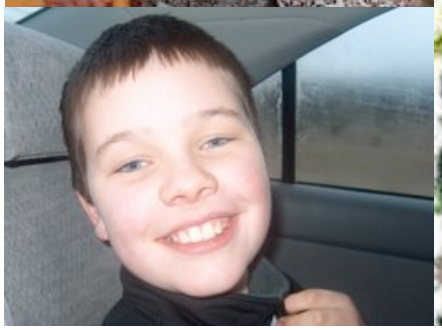





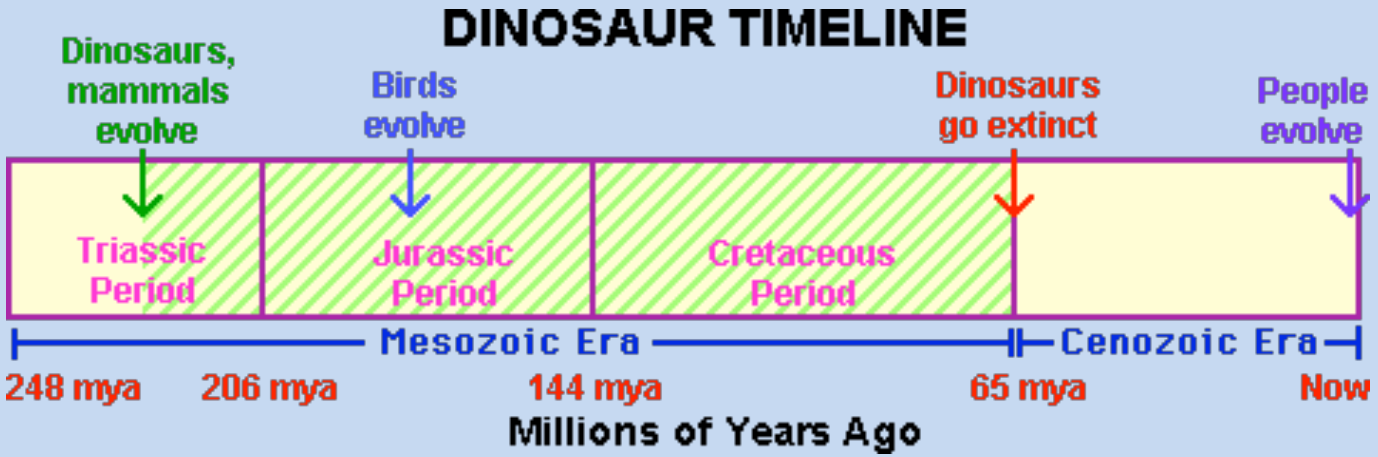


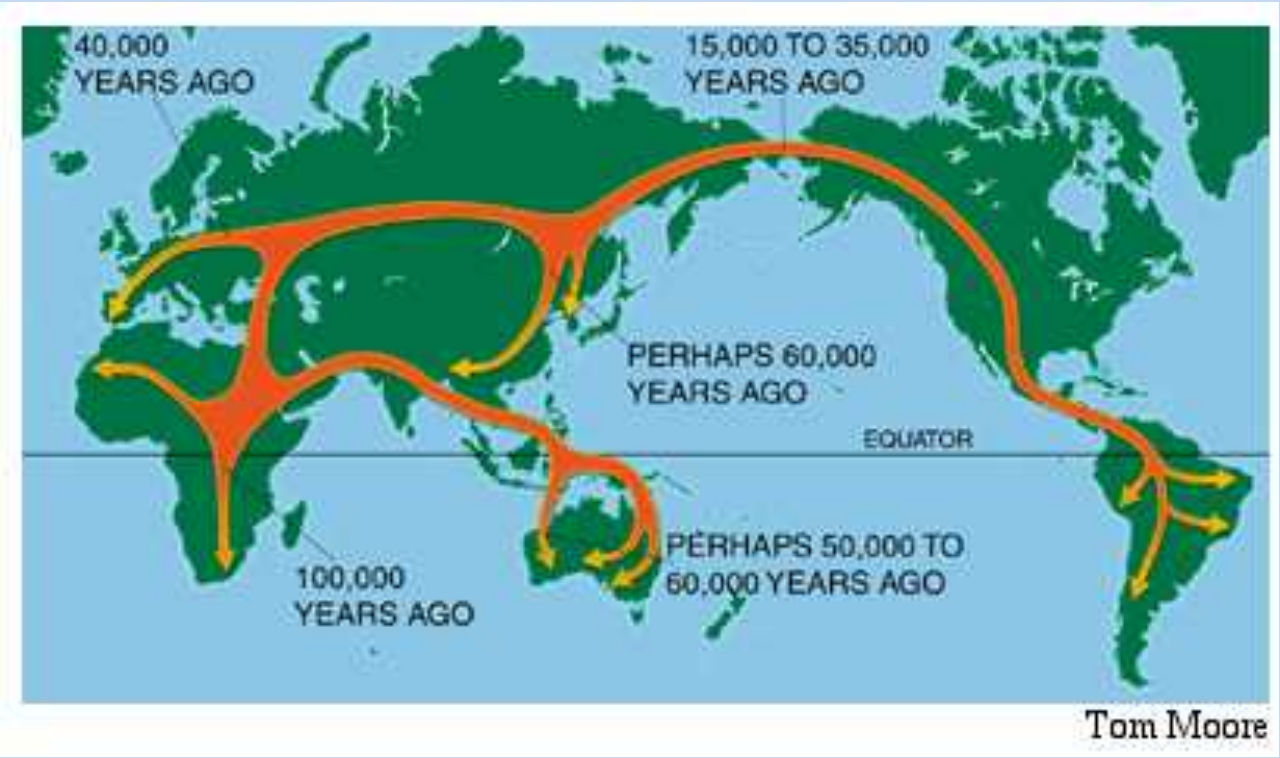


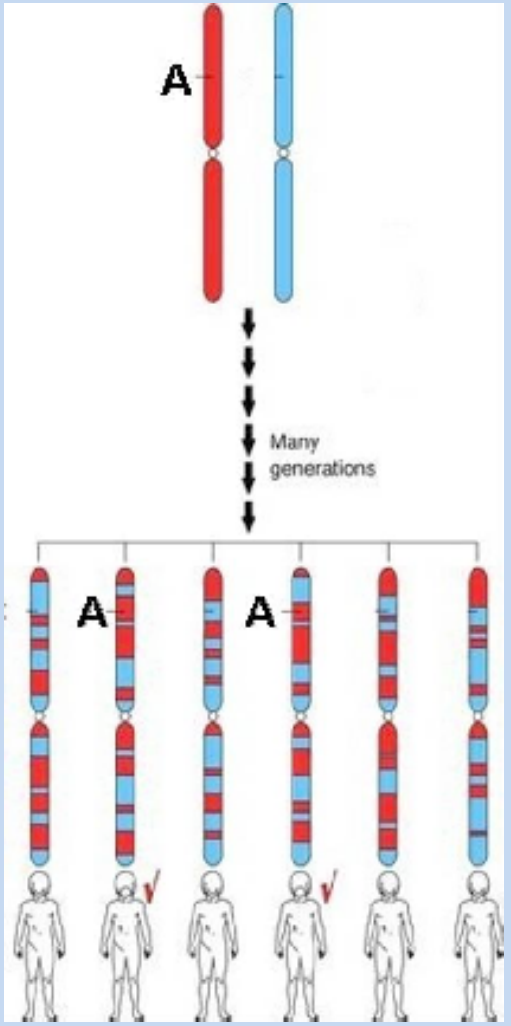





The Earth
is 4.5 Billion
Years Old


DINOSAUR TIMELINE
Dinosaurs, mammals evolve
Birds evolve
Dinosaurs go extinct
People evolve
Triassic Period
Jurassic Period
Cretaceous Period
Mesozoic Era
Cenozoic Era
248 mya
206 mya
144 mya
65 mya
Now
Millions of Years Ago

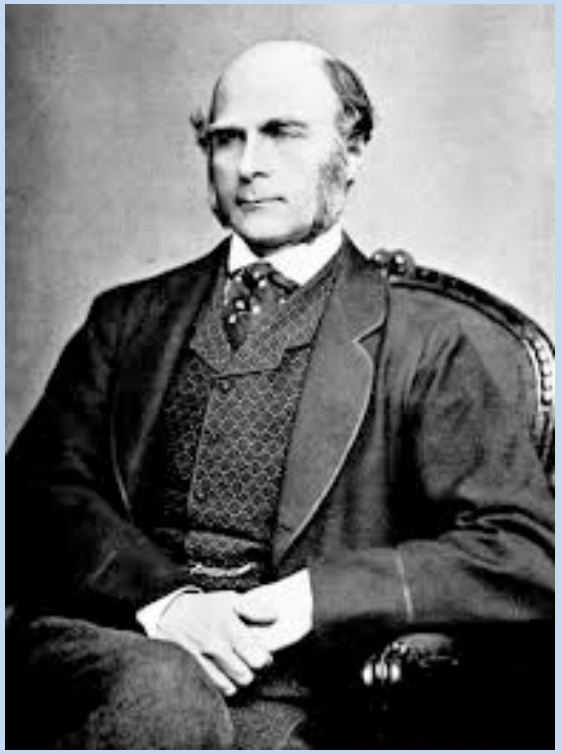




Population Stratification is from the migration patterns of haplotypes throughout human history

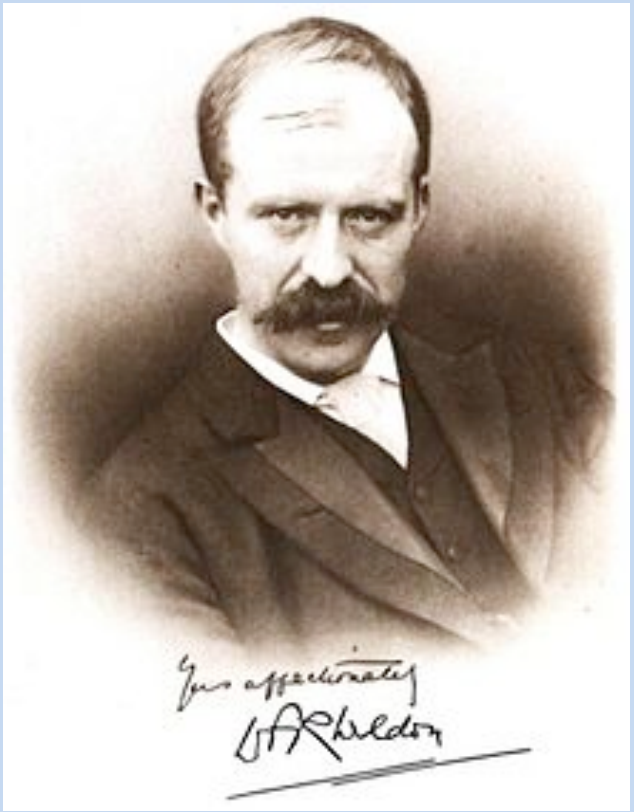
Charles Darwin
1809-1882

Gregor Mendel
1822-1884



Frances Galton
1822-1911

Karl Pearson
1857-1936

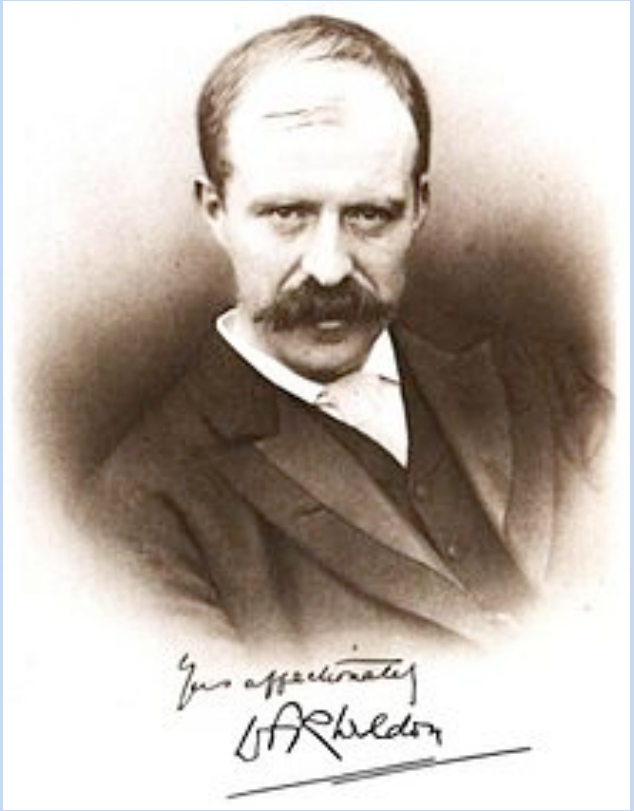


Walter Frank Raphael Weldon
1860-1906

William Bateson
1861-1926

Beyond our Kuhnian inheritance

A recent lecture by Prof Greg Radick questions our scientific inheritance, through textbook histories of genetics and Thomas Kuhn's legacy http://www.guardian.co.uk/science/the-h-word/2012/aug/28/thomas-kuhn



Walter Frank Raphael Weldon

Vs.

William Bateson

Forthcoming by Greg Radick. Scholarly edition of W. F. R. Weldon's Theory of Inheritance (1904-1905), coedited with Annie Jamieson.

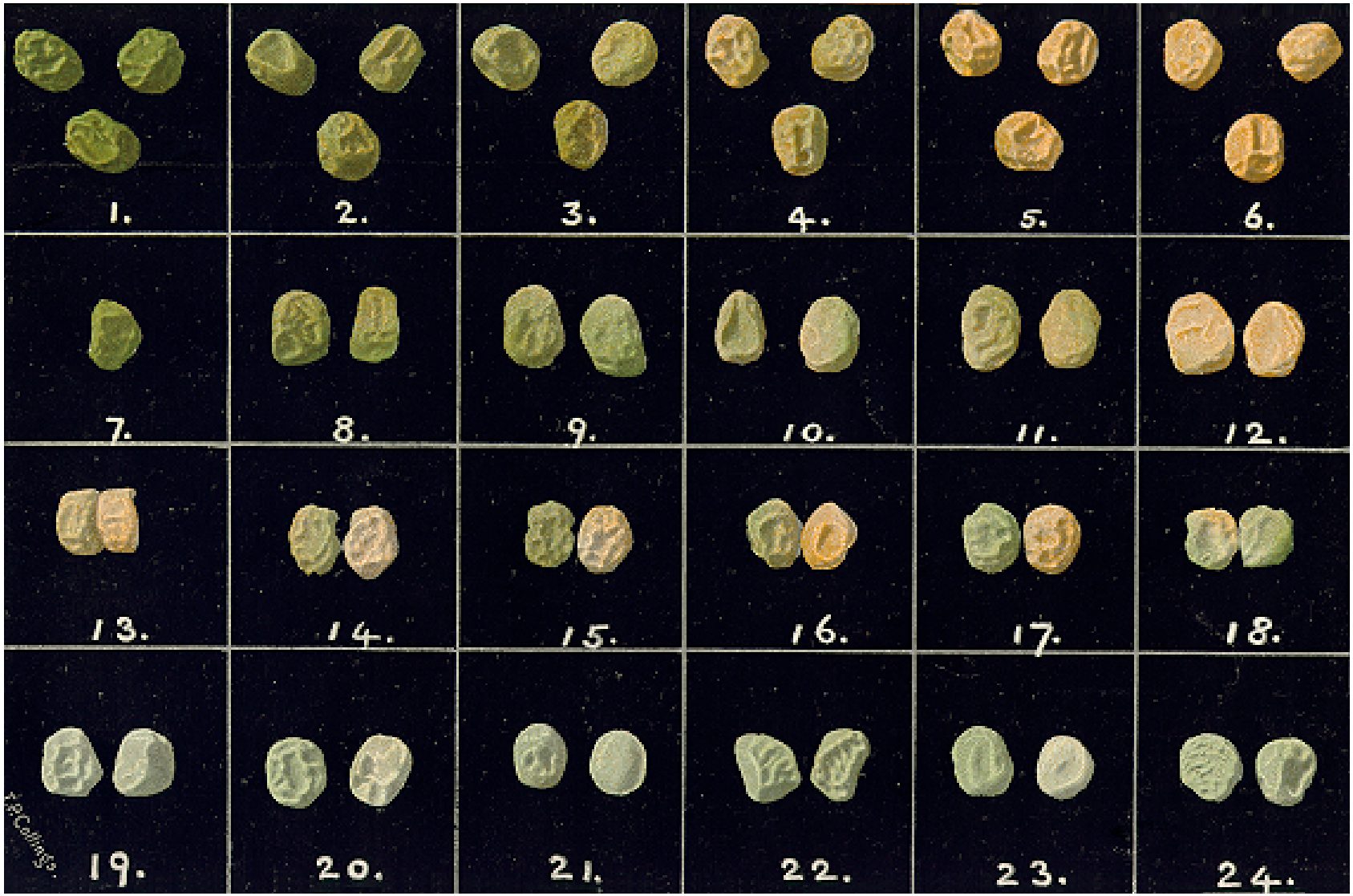


Plate I.

- *“The fundamental mistake which vitiates all work based upon Mendel’s method is the neglect of ancestry, and the attempt to regard the whole effect upon offspring, produced by a particular parent, as due to the existence in the parent of particular structural characters; while the contradictory results obtained by those who have observed the offspring of parents apparently identical in certain characters show clearly enough that not only the parents themselves, but their race, that is their ancestry, must be taken into account before the result of pairing them can be predicted” – Walter Frank Raphael Weldon (Weldon, 1902).*

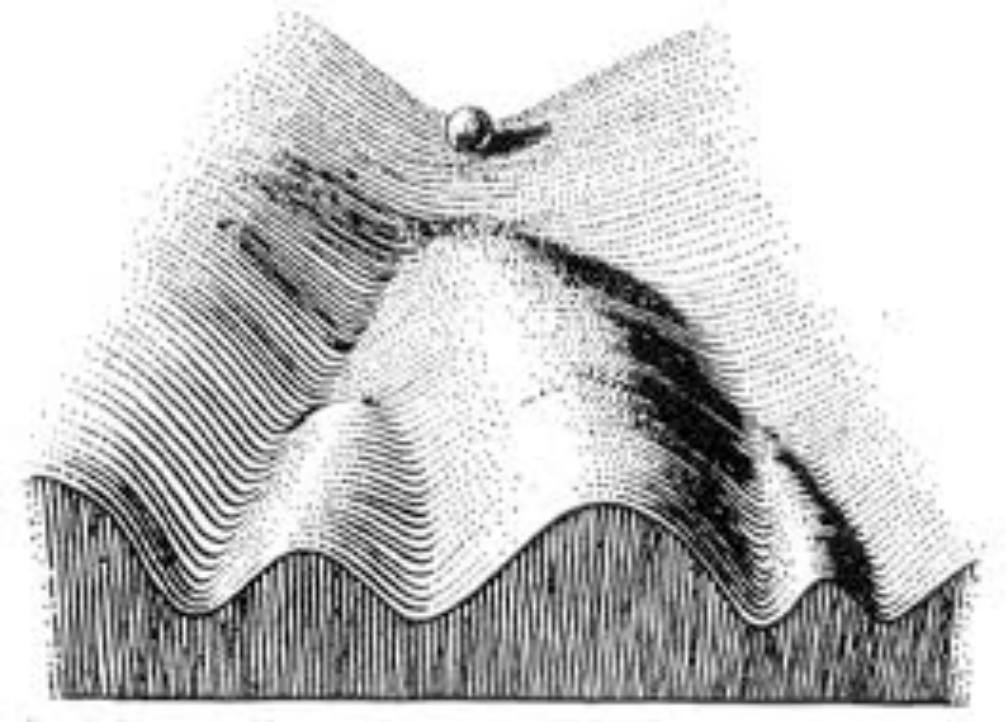

Walter Frank Raphael Weldon 1860–1906
A Memoir
Karl Pearson

“Biological Indeterminacy”

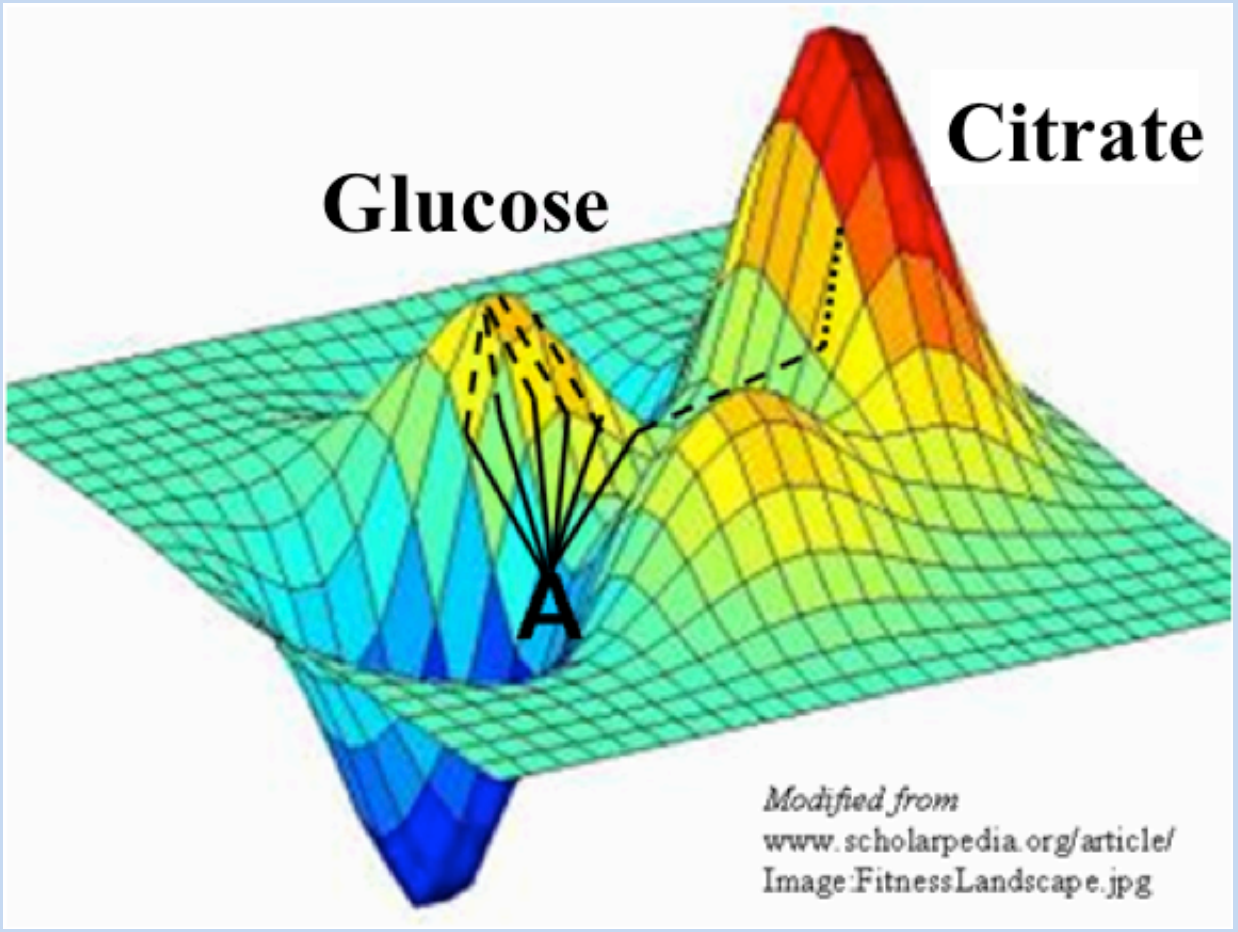
- Bateson became famous as the outspoken Mendelian antagonist of Walter Raphael Weldon, his former teacher, and Karl Pearson who led the biometric school of thinking. This concerned the debate over saltationism versus gradualism (Darwin had been a gradualist, but Bateson was a saltationist). Later, Ronald Fisher and J.B.S. Haldane showed that discrete mutations were compatible with gradual evolution: see the modern evolutionary synthesis.

Biological Indeterminacy. Greenspan RJ. Sci Eng Ethics. 2012 Jul 3

Biological Robustness.



The canalisation metaphor suggests that phenotypes are very robust to small perturbations, for which development does not exit the canal, and rapidly returns back down, with little effect on the final outcome of development. But perturbations whose magnitude exceeds a certain threshold will break out of the canal, moving the developmental process into uncharted territory. Strong robustness up to a limit, with little robustness beyond, is a pattern that could increase evolvability in a fluctuating environment.



E. coli adapting to low glucose conditions, in the context of media containing citrate. – Richard Lemski experiment

"Finally, novel functions often emerge in rudimentary forms that must be refined to exploit the ecological opportunities. This three-step process — in which potentiation makes a trait possible, actualization makes the trait manifest, and refinement makes it effective — is probably typical of many new functions." - Lemski

Genotype ≠ Phenotype

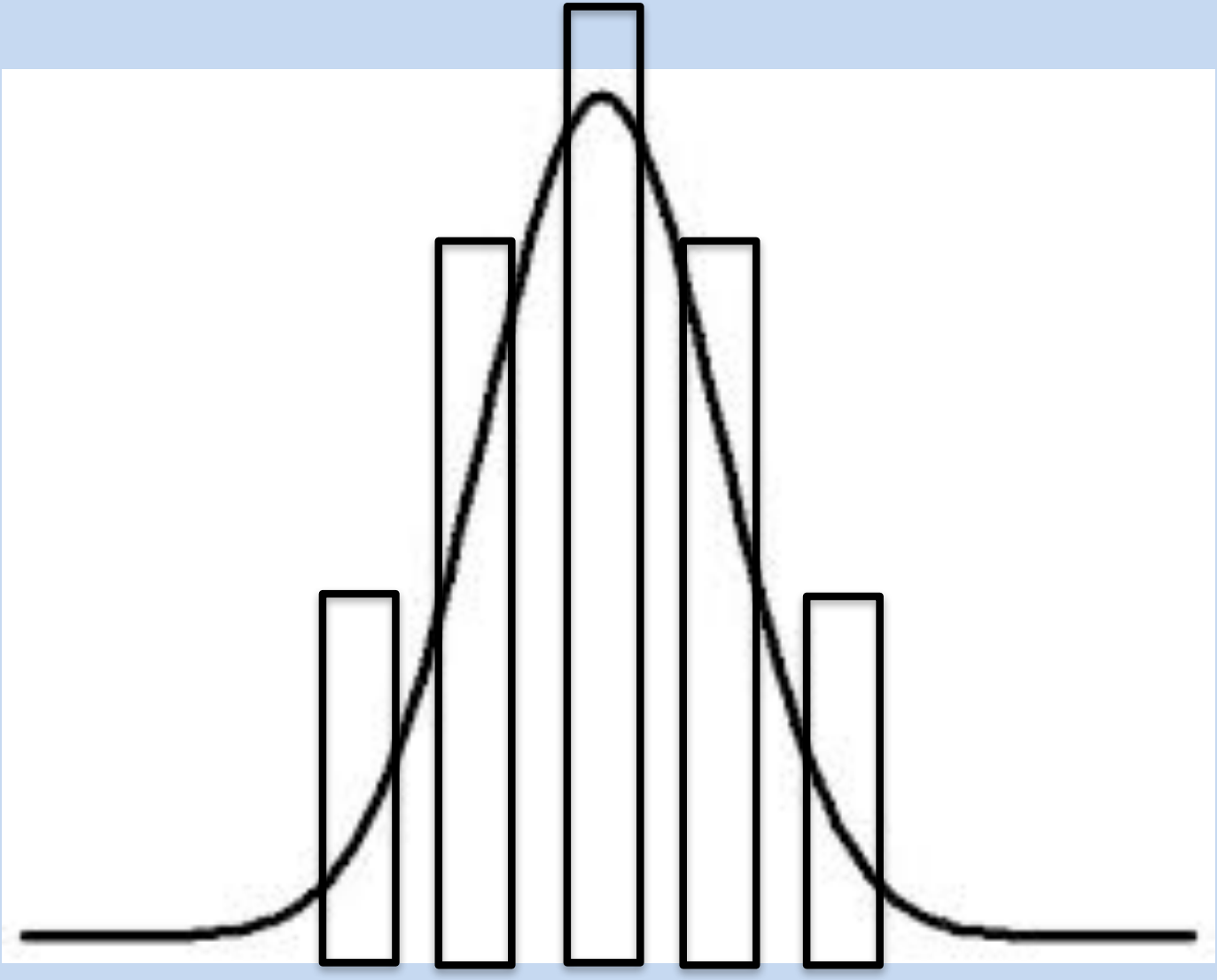
Environment matters!

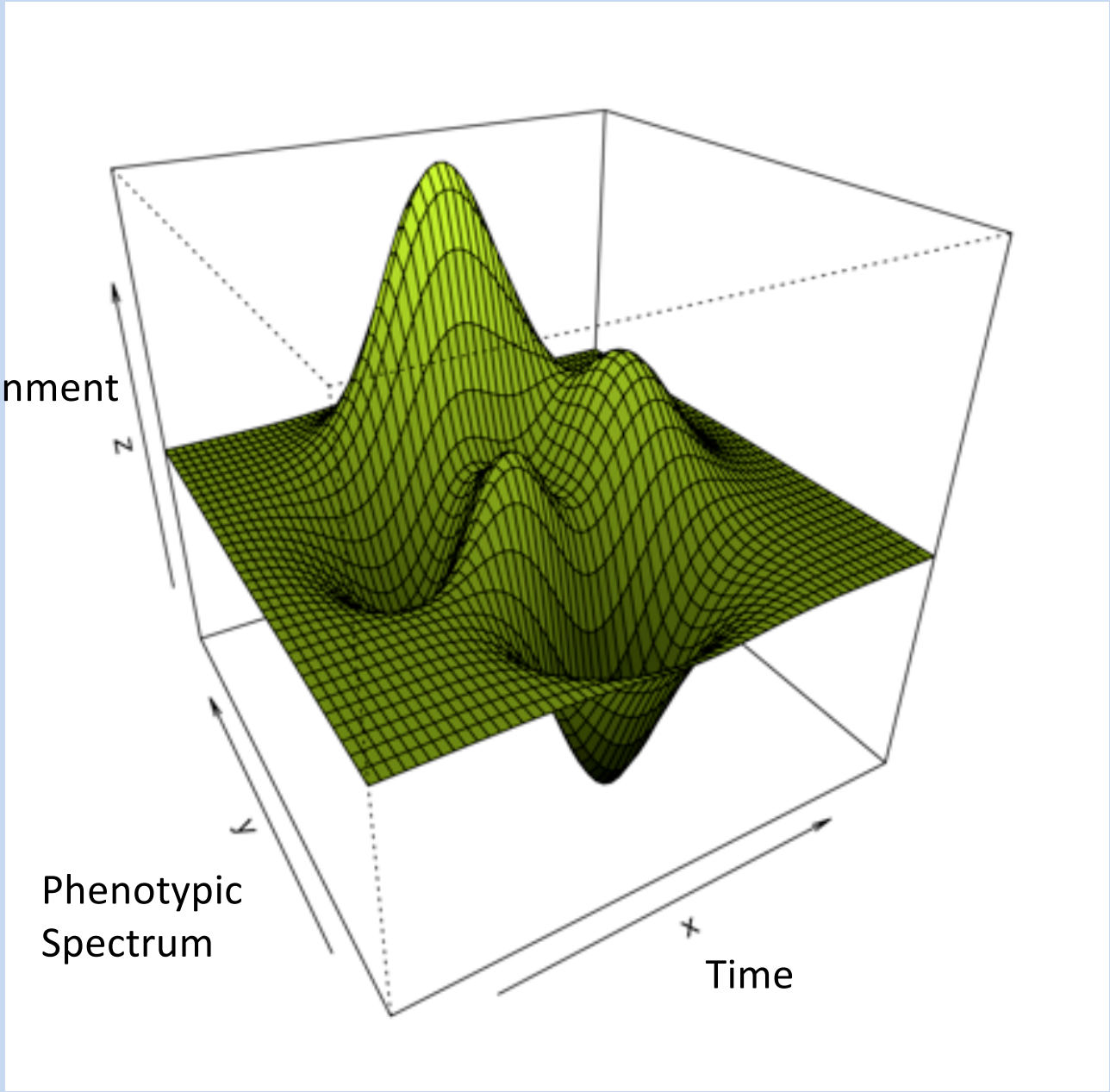
Ancestry matters!

Genomic background matters!

Longitudinal course matters!

Categorical Thinking Misses Complexity





A conceptual model of genotype-phenotype correlations. 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.

The Biology of MENTAL DEFECT

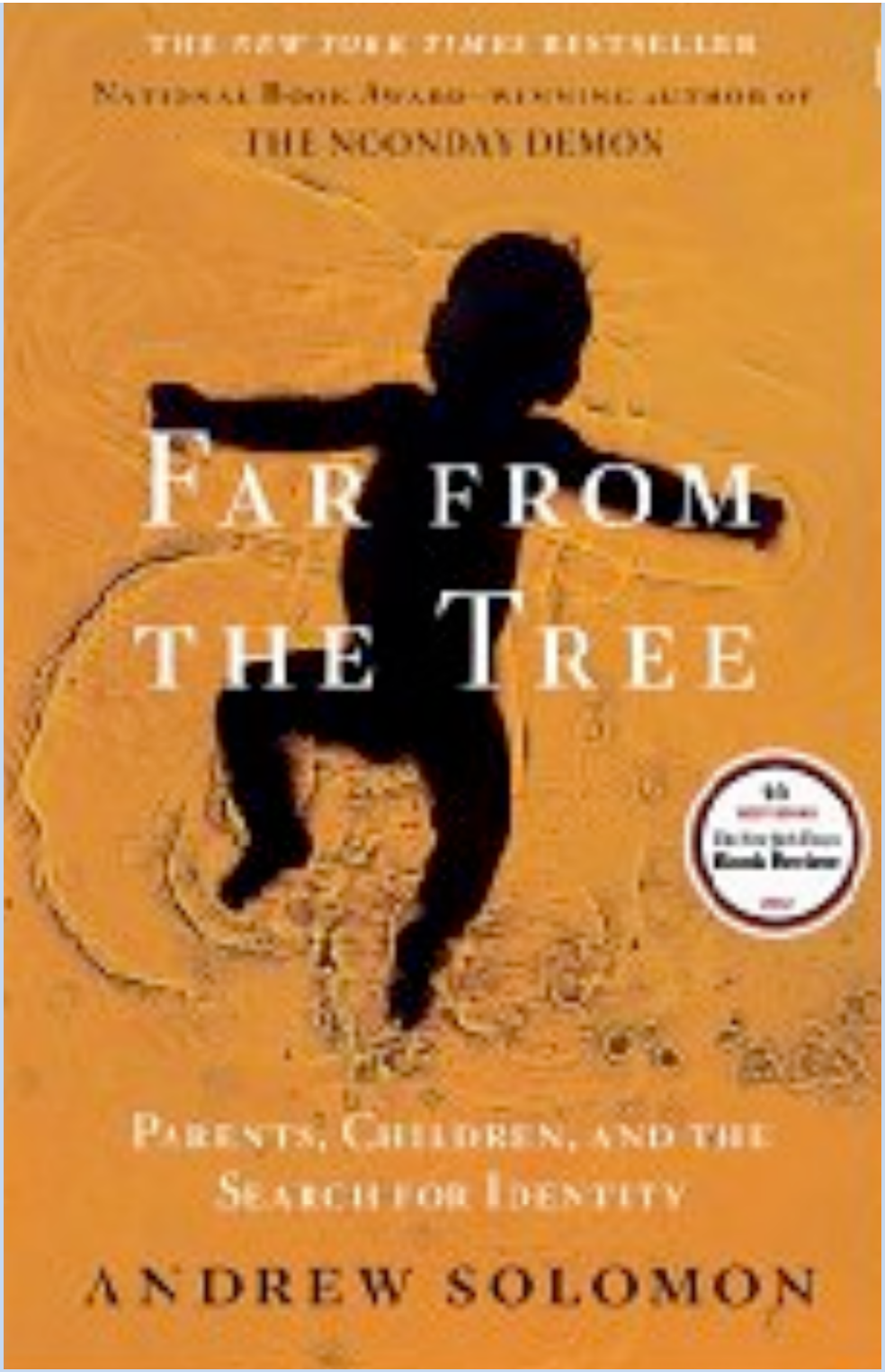
BY

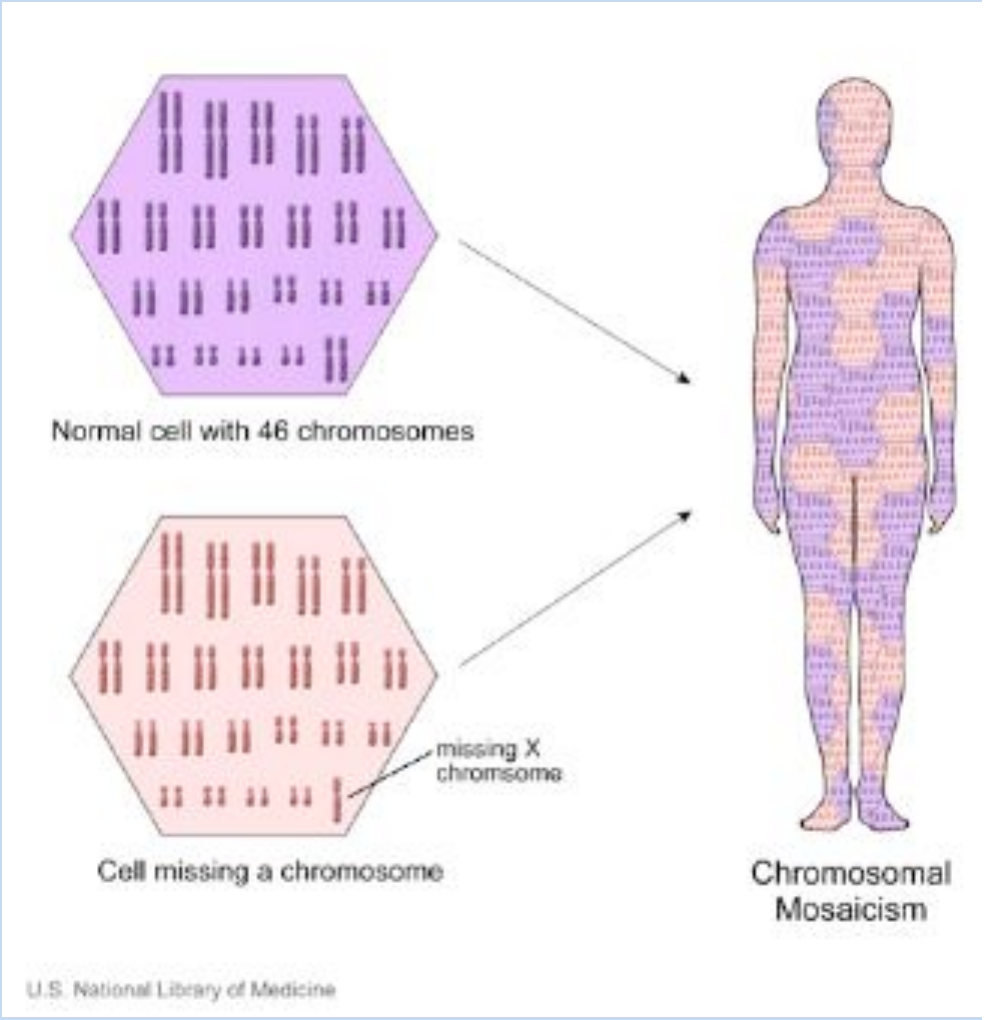
LIONEL S. PENROSE, M.A., M.D.

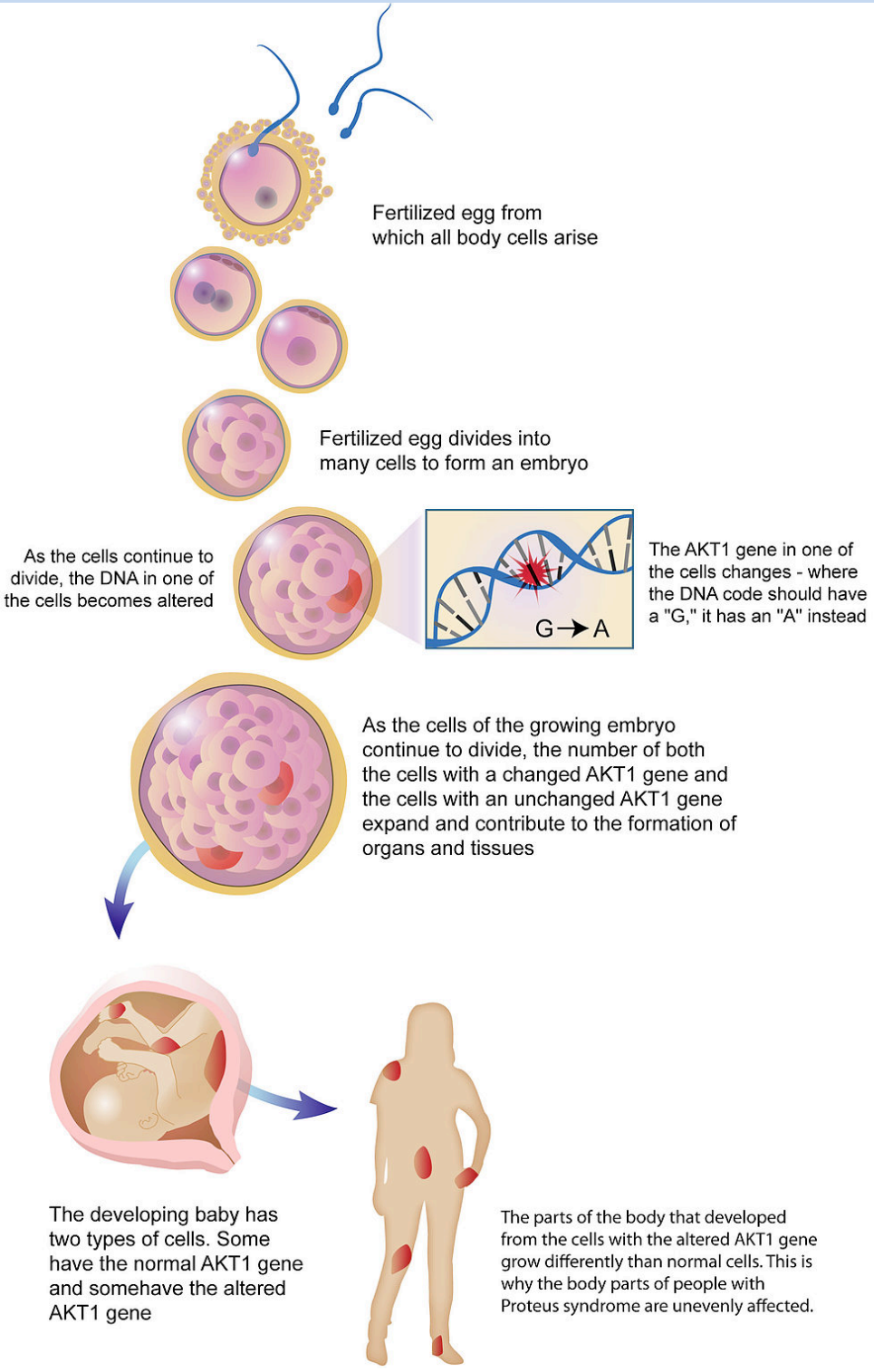
WITH A PREFACE BY

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

GRUNE & STRATTON
New York
1949




Normal cell with 46 chromosomes
missing X chromsome
Cell missing a chromosome
Chromosomal Mosaicism
U.S. National Library of Medicine

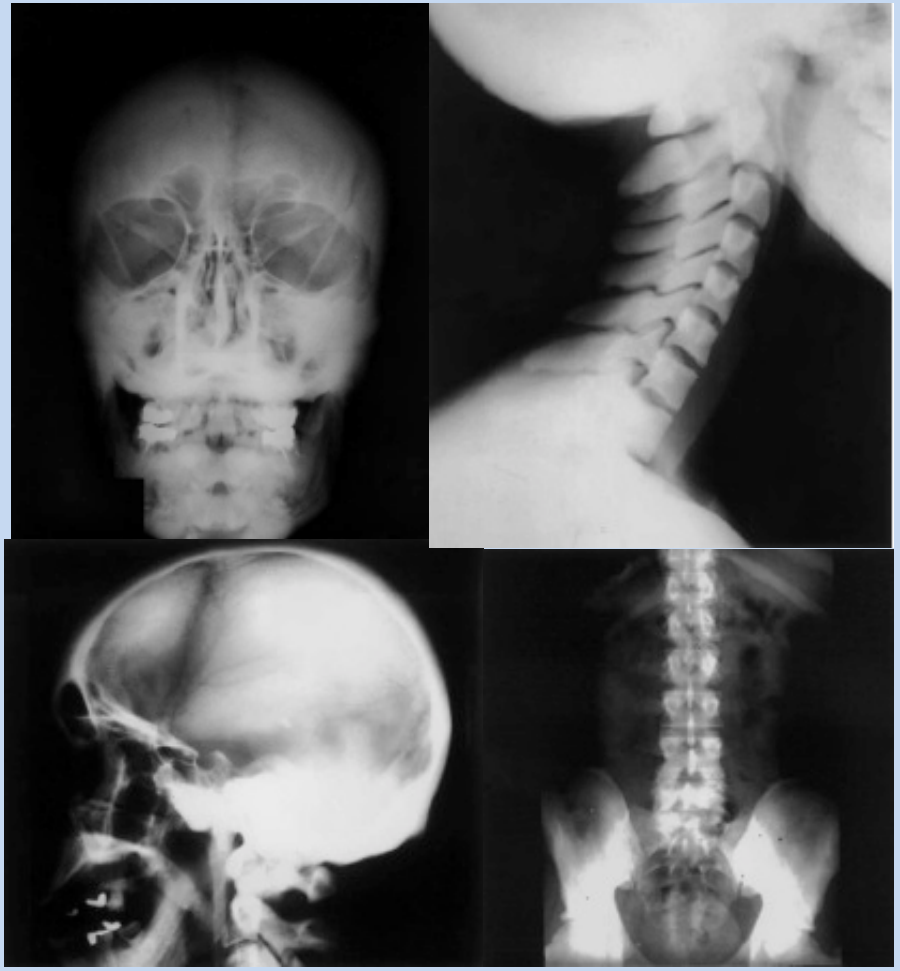

Fertilized egg from which all body cells arise
Fertilized egg divides into many cells to form an embryo
As the cells continue to divide, the DNA in one of the cells becomes altered
G→A
The AKT1 gene in one of the cells changes - where the DNA code should have a "G," it has an "A" instead
As the cells of the growing embryo continue to divide, the number of both the cells with a changed AKT1 gene and the cells with an unchanged AKT1 gene expand and contribute to the formation of organs and tissues
The developing baby has two types of cells. Some have the normal AKT1 gene and somehave the altered AKT1 gene
The parts of the body that developed from the cells with the altered AKT1 gene grow differently than normal cells. This is why the body parts of people with Proteus syndrome are unevenly affected.

General Criteria
Mosaic Distribution Progressive Course Sporadic Occurrence
Specific Criteria
Category A
Cerebriform connective tissue nevus
Category B
Linear epidermal nevus Asymmetric, disproportionate overgrowth of two of: Limbs, skull, external auditory canal, vertebrae, or viscera Specific tumors in the first decade of life: Bilateral ovarian cystadenomas Monomorphic parotid adenomas
Category C
Dysregulated adipose tissue Vascular Malformations Capillary, venous, and/or lymphatic Lung bullae Facial phenotype: Long face, dolichocephaly, down-slanted palpebral fissures, low nasal bridge, wide or anteverted nares, open mouth at rest
The diagnosis of Proteus syndrome requires all three general criteria, plus one criterion from category A, or two criteria from category B, or three criteria from category C. (Adapted from Biesecker, 2006)

Proteus syndrome results from a mutation in the AKT1 gene. This genetic change is not inherited from a parent; it arises randomly in one cell during the early stages of development before birth. As cells continue to grow and divide, some cells will have the mutation and other cells will not. This mixture of cells with and without a genetic mutation is known as mosaicism.

“Superpower” mutations???

Myostatin mutation
Exon 2 allele P198A



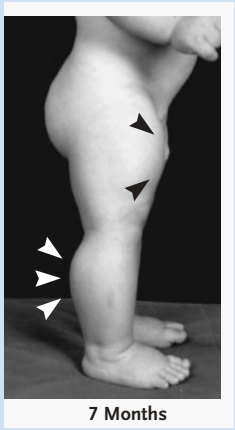
LRP5 mutation
D111Y, G171R, A214T, A214V, A242T, and T253I

**Thanks to George Church for discussions on this.

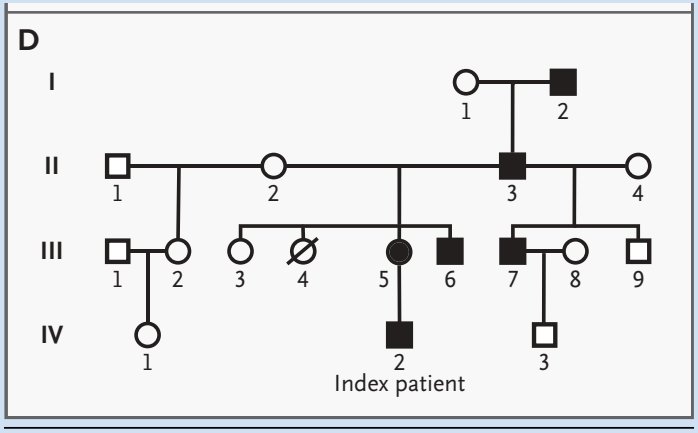
Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child

Markus Schuelke, M.D., Kathryn R. Wagner, M.D., Ph.D., Leslie E. Stolz, Ph.D., Christoph Hübner, M.D., Thomas Riebel, M.D., Wolfgang Kömen, M.D., Thomas Braun, M.D., Ph.D., James F. Tobin, Ph.D., and Se-Jin Lee, M.D., Ph.D.

N ENGL J MED 350;26 WWW.NEJM.ORG JUNE 24, 2004



7 Months



Liam is homozygous for the mutation.

Another example: Liam Hoekstra, known as the world's strongest toddler at age 3, has a condition called myostatin-related muscle hypertrophy which results in increased muscle mass and reduced body fat. Myostatin-related muscle hypertrophy, or muscle enlargement, is an extremely rare genetic condition. – How rare???

http://videos.disabled-world.com/video/159/liam-hoekstra-strongest-boy-in

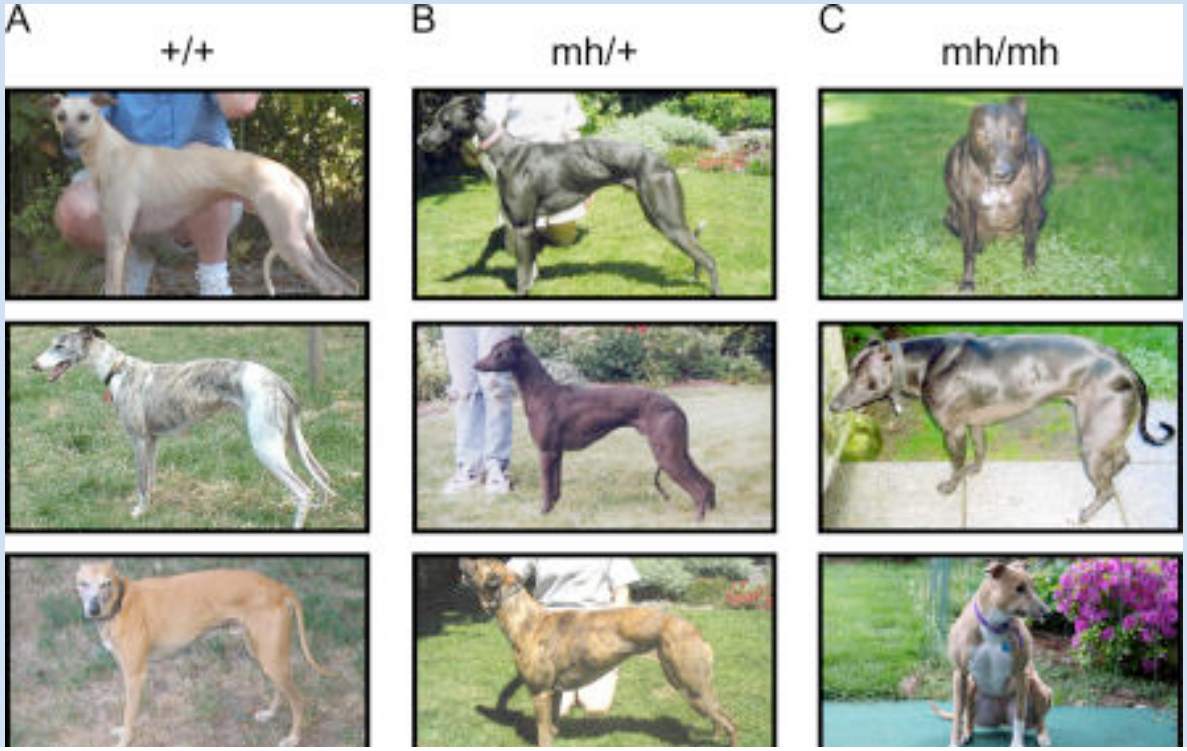
Belgian Blue is a breed of beef cattle from Belgium. The Belgian Blue has a natural mutation in the myostatin gene which codes for the protein, myostatin.

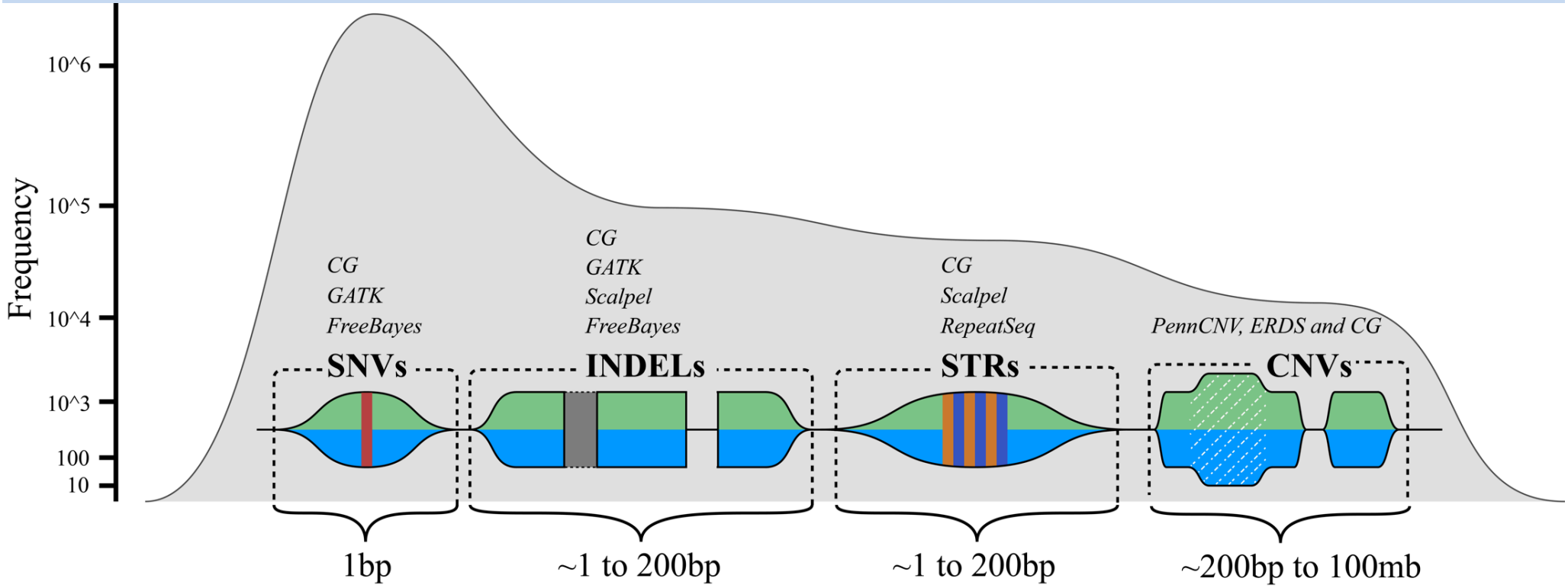
http://en.wikipedia.org/wiki/Belgian_Blue

A Mutation in the Myostatin Gene Increases Muscle Mass and Enhances Racing Performance in Heterozygote Dogs

Dana S. Mosher[1], Pascale Quignon[1], Carlos D. Bustamante[2], Nathan B. Sutter[1], Cathryn S. Mellersh[3], Heidi G. Parker[1], Elaine A. Ostrander[1*]

1 National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States of America, **2** Department of Biological Statistics and Computational Biology, Cornell University, Ithaca, New York, United States of America, **3** Animal Health Trust, Center for Preventive Medicine, Newmarket, United Kingdom




Frequency
10^6
10^5
10^4
10^3
100
10
CG
GATK
FreeBayes
SNVs
CG
GATK
Scalpel
FreeBayes
INDELs
CG
Scalpel
RepeatSeq
STRs
PennCNV, ERDS and CG
CNVs
1bp
~1 to 200bp
~1 to 200bp
~200bp to 100mb

Vignette #1: Discovering a new syndrome and its genetic basis.

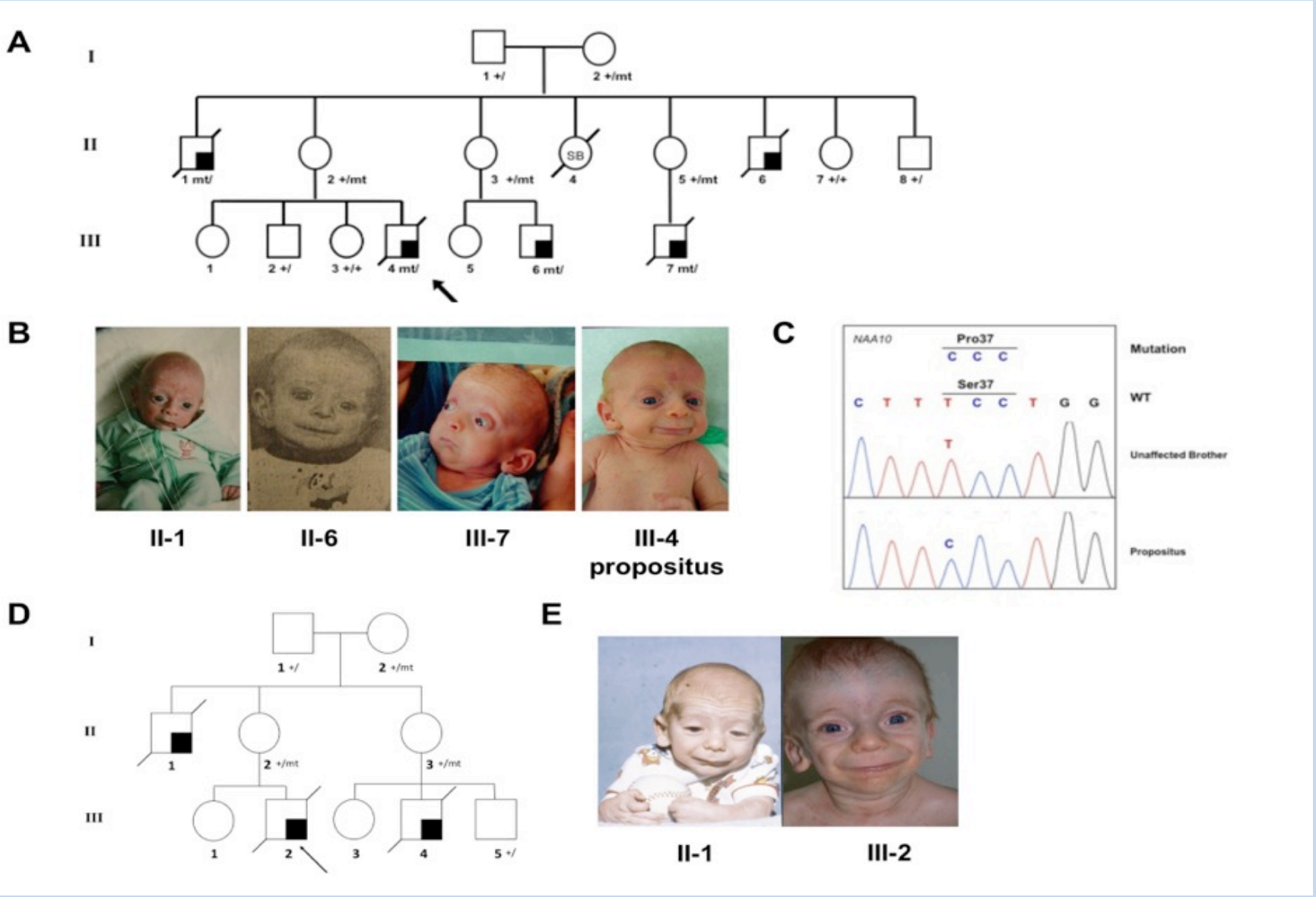
ARTICLE

Using VAAST to Identify an X-Linked Disorder Resulting in Lethality in Male Infants Due to N-Terminal Acetyltransferase Deficiency

Alan F. Rope,[1] Kai Wang,[2,19] Rune Evjenth,[3] Jinchuan Xing,[4] Jennifer J. Johnston,[5] Jeffrey J. Swensen,[6,7] W. Evan Johnson,[8] Barry Moore,[4] Chad D. Huff,[4] Lynne M. Bird,[9] John C. Carey,[1] John M. Opitz,[1,4,6,10,11] Cathy A. Stevens,[12] Tao Jiang,[13,14] Christa Schank,[8] Heidi Deborah Fain,[15] Reid Robison,[15] Brian Dalley,[16] Steven Chin,[6] Sarah T. South,[1,7] Theodore J. Pysher,[6] Lynn B. Jorde,[4] Hakon Hakonarson,[2] Johan R. Lillehaug,[3] Leslie G. Biesecker,[5] Mark Yandell,[4] Thomas Arnesen,[3,17] and Gholson J. Lyon[15,18,20,*]

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

Ogden Syndrome

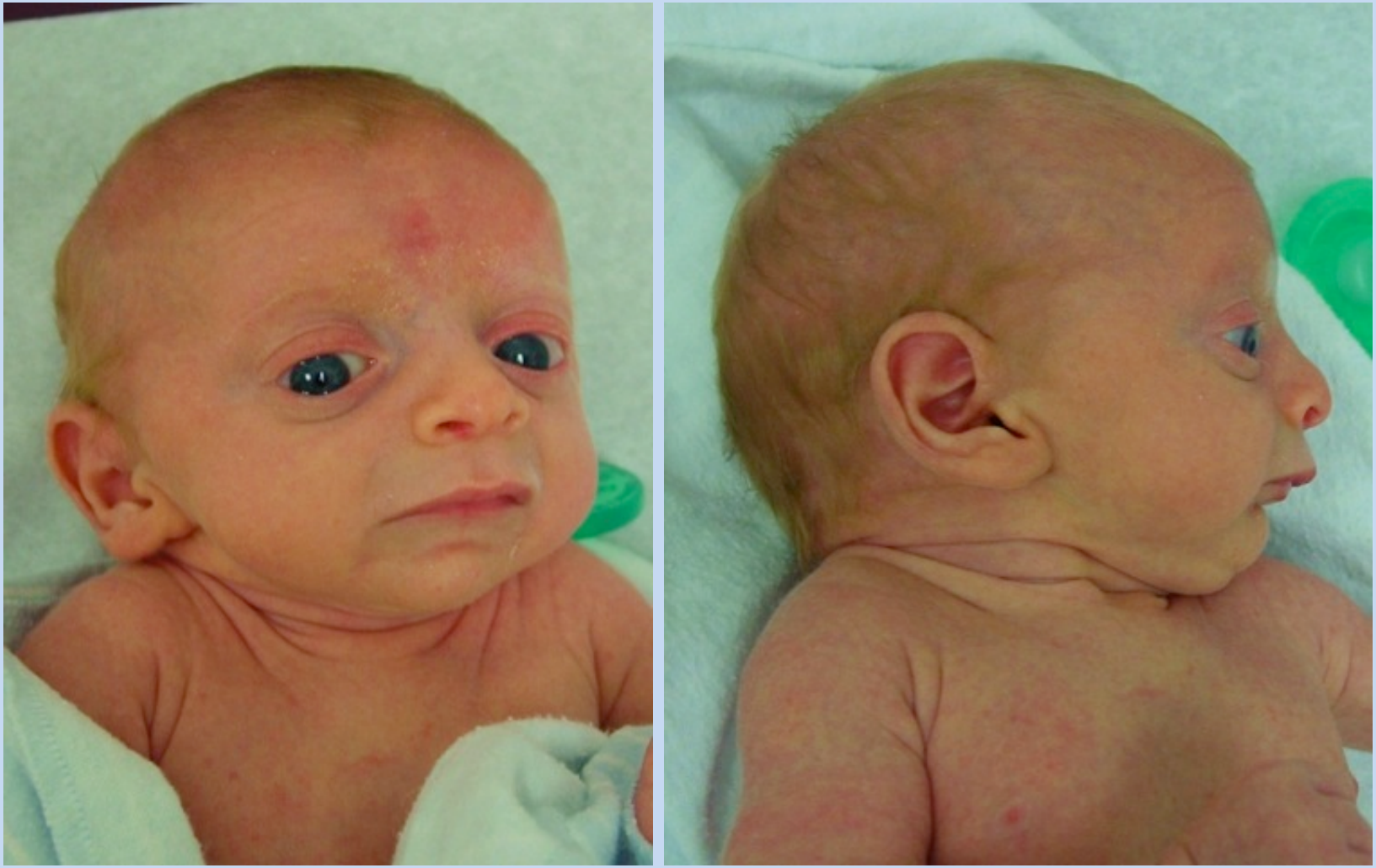


We found the SAME mutation in two unrelated families, with a very similar phenotype in both families, helping prove that this genotype contributes to the phenotype observed.

This is the first boy in the late 1970's.

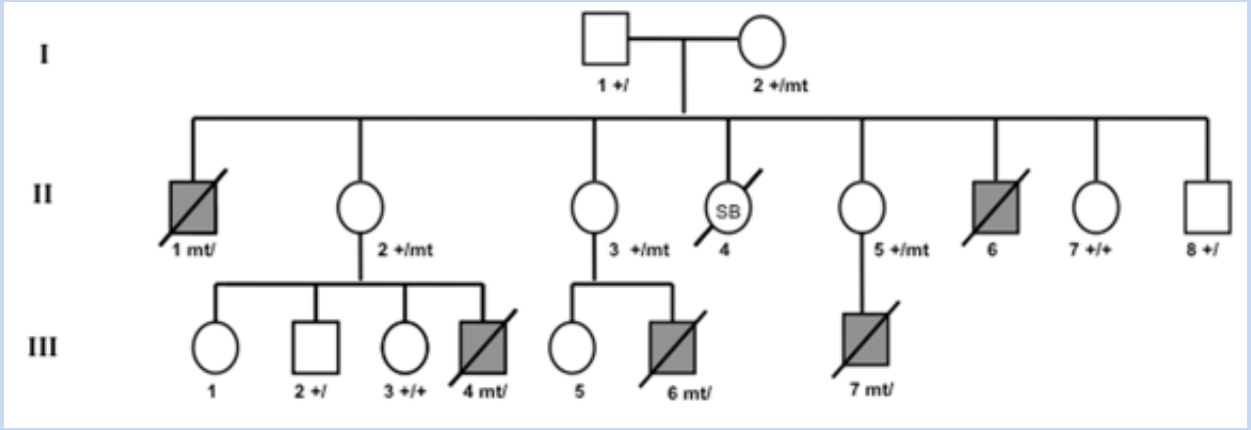
First boy. Called "a little old man" by the family. Died around ~1 year of age, from cardiac arrhythmias.

This is the "Proband" photograph presented at Case Conference.

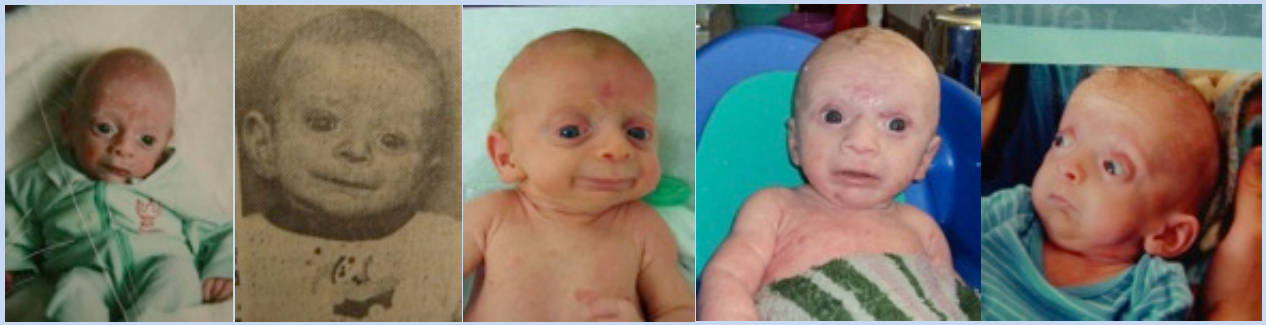


prominence of eyes, down-sloping palpebral fissures, thickened eyelids, large ears, beaking of nose, flared nares, hypoplastic nasal alae, short columella, protruding upper lip, micro-retrognathia

A

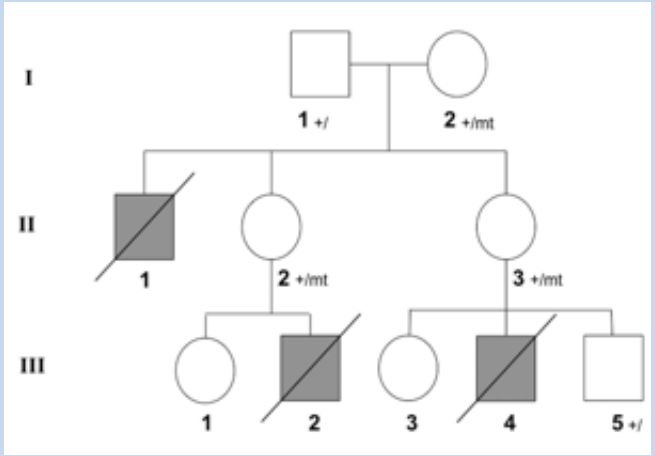


B

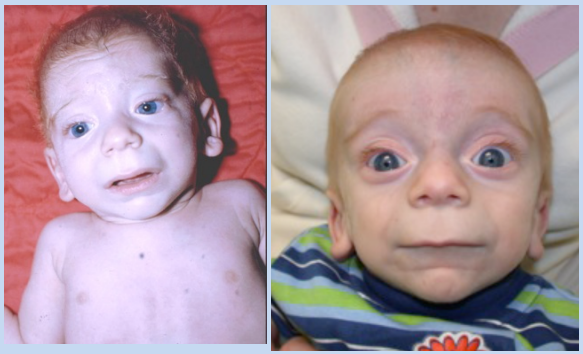


II-1 II-6 III-4 III-6 III-7

C



D

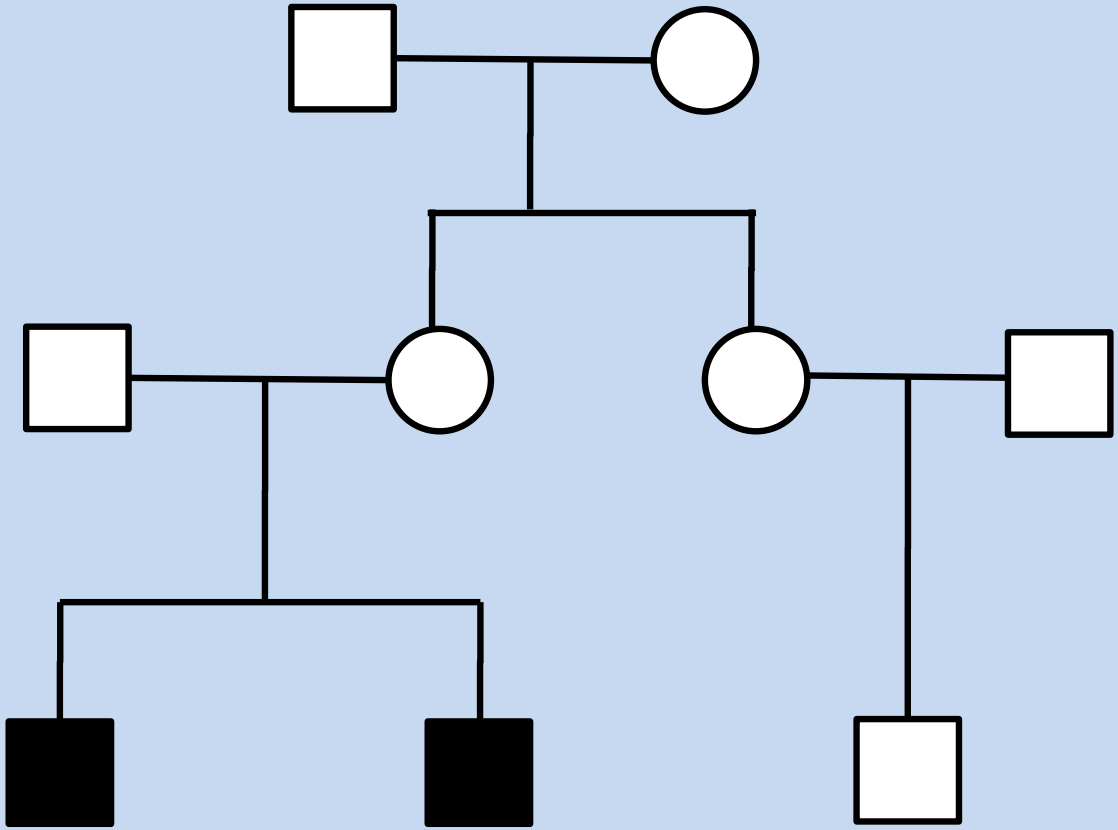


II-1 III-2

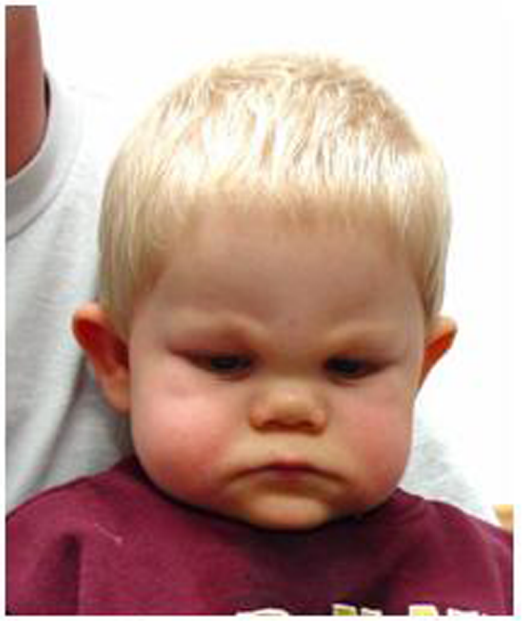
These are the Major Features of the Syndrome.

Table 1. Features of the syndrome	
Growth	post-natal growth failure
Development	global, severe delays
Facial	prominence of eyes, down-sloping palpebral fissures, thickened lids large ears beaking of nose, flared nares, hypoplastic alae, short columella protruding upper lip micro-retrognathia
Skeletal	delayed closure of fontanels broad great toes
Integument	redundancy / laxity of skin minimal subcutaneous fat cutaneous capillary malformations
Cardiac	structural anomalies (ventricular septal defect, atrial level defect, pulmonary artery stenoses) arrhythmias (Torsade de points, PVCs, PACs, SVtach, Vtach) death usually associated with cardiogenic shock preceded by arrythmia.
Genital	inguinal hernia hypo- or cryptorchidism
Neurologic	hypotonia progressing to hypertonia cerebral atrophy neurogenic scoliosis
Shaded regions include features of the syndrome demonstrating variability. Though variable findings of the cardiac, genital and neurologic systems were observed, all affected individuals manifested some pathologic finding of each.	

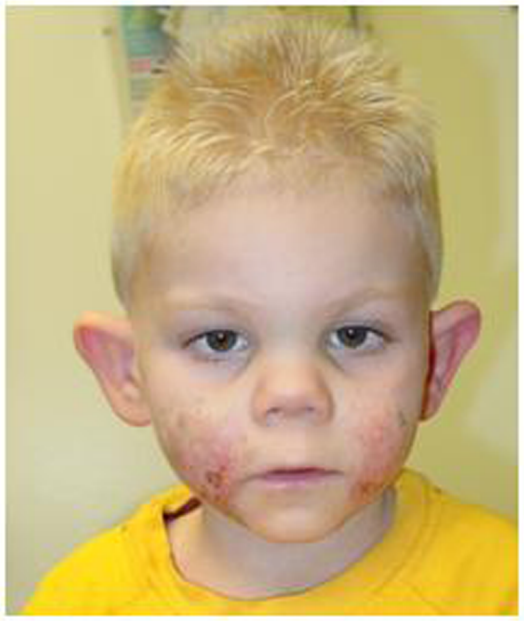
Vignette #2: New Syndrome with Mental Retardation, “Autism”, “ADHD”



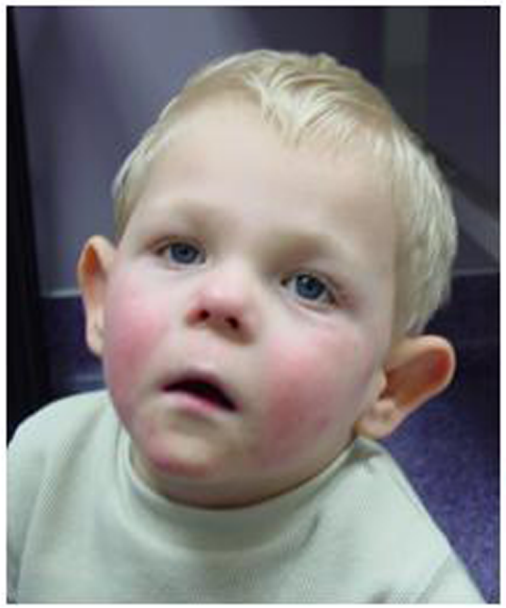
Likely X-linked or Autosomal Recessive, with X-linked being supported by extreme X-skewing in the mother



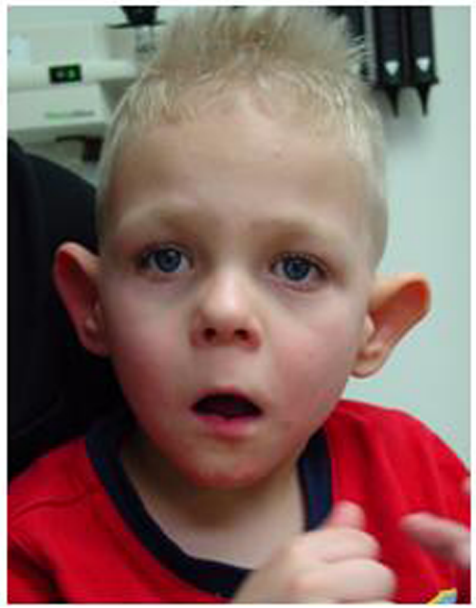
1.5 years old



3.5 years old



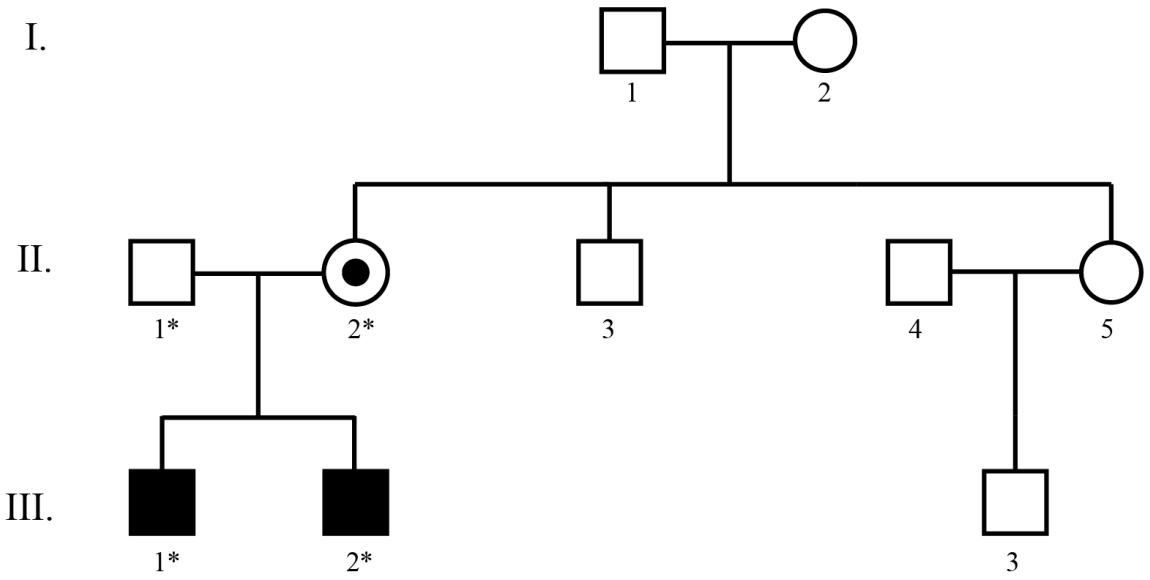
3 years old



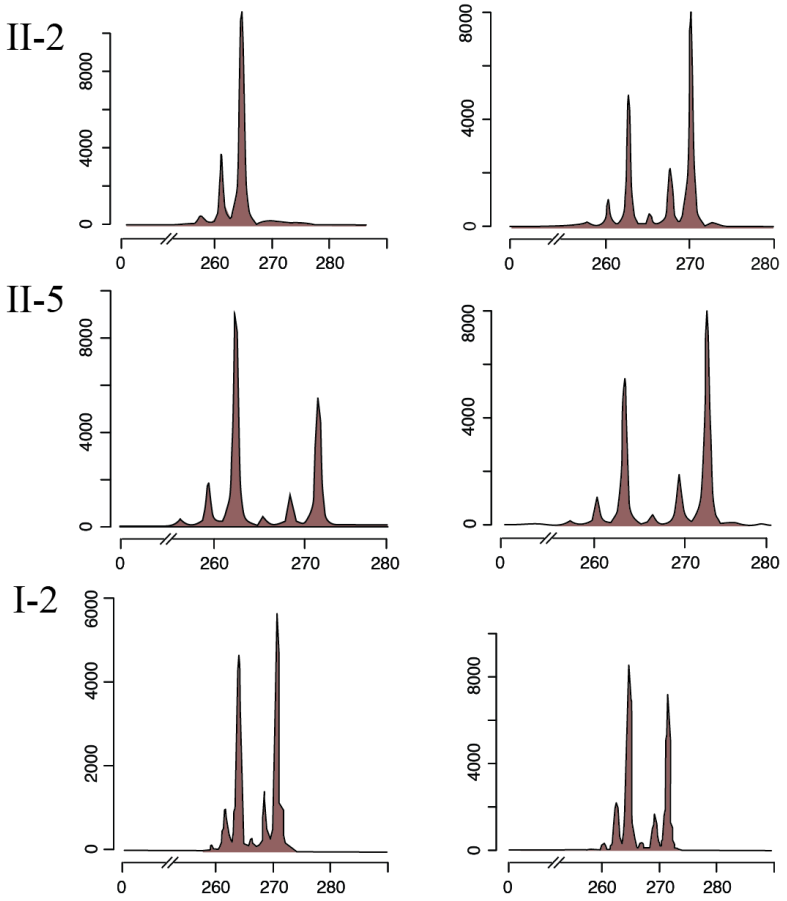
5 years old

Dysmorphic
Mental Retardation
“autism”
“ADHD”
Hearing difficulties

A

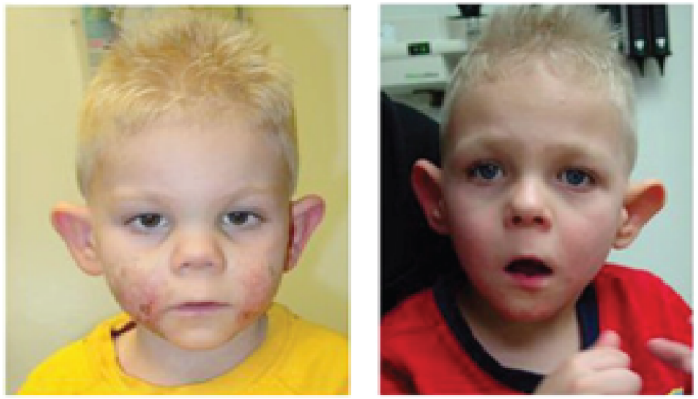


B

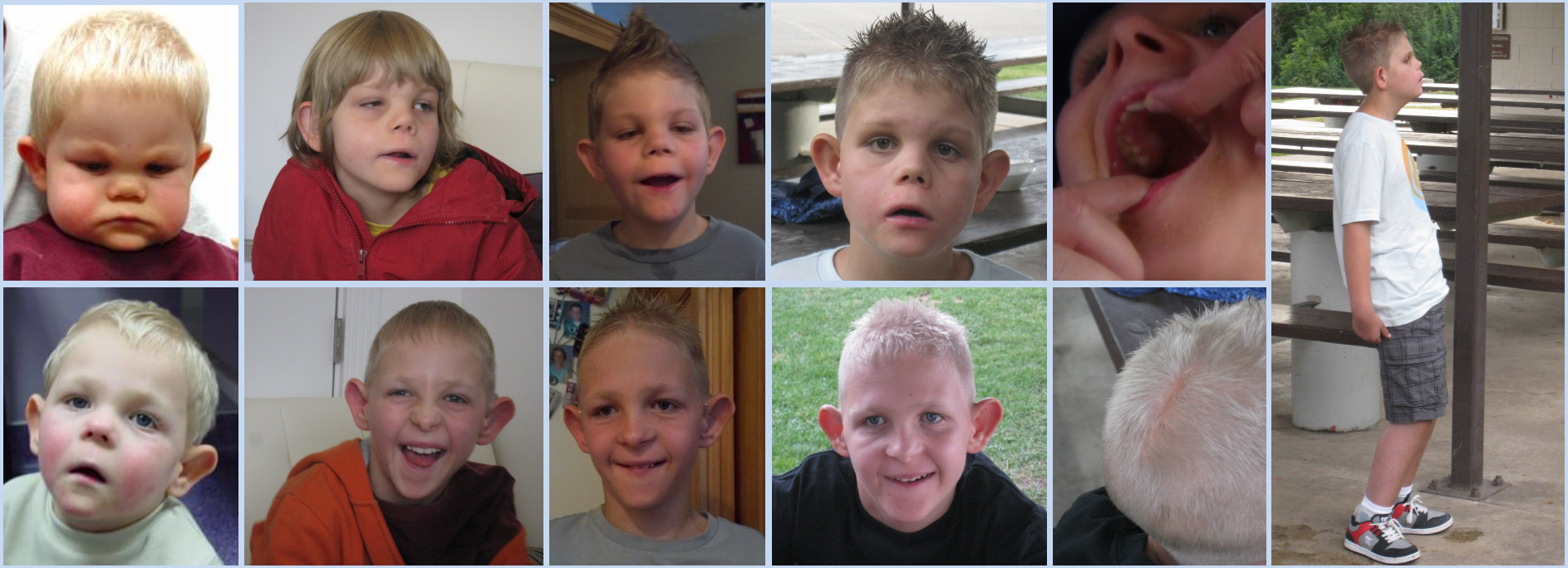


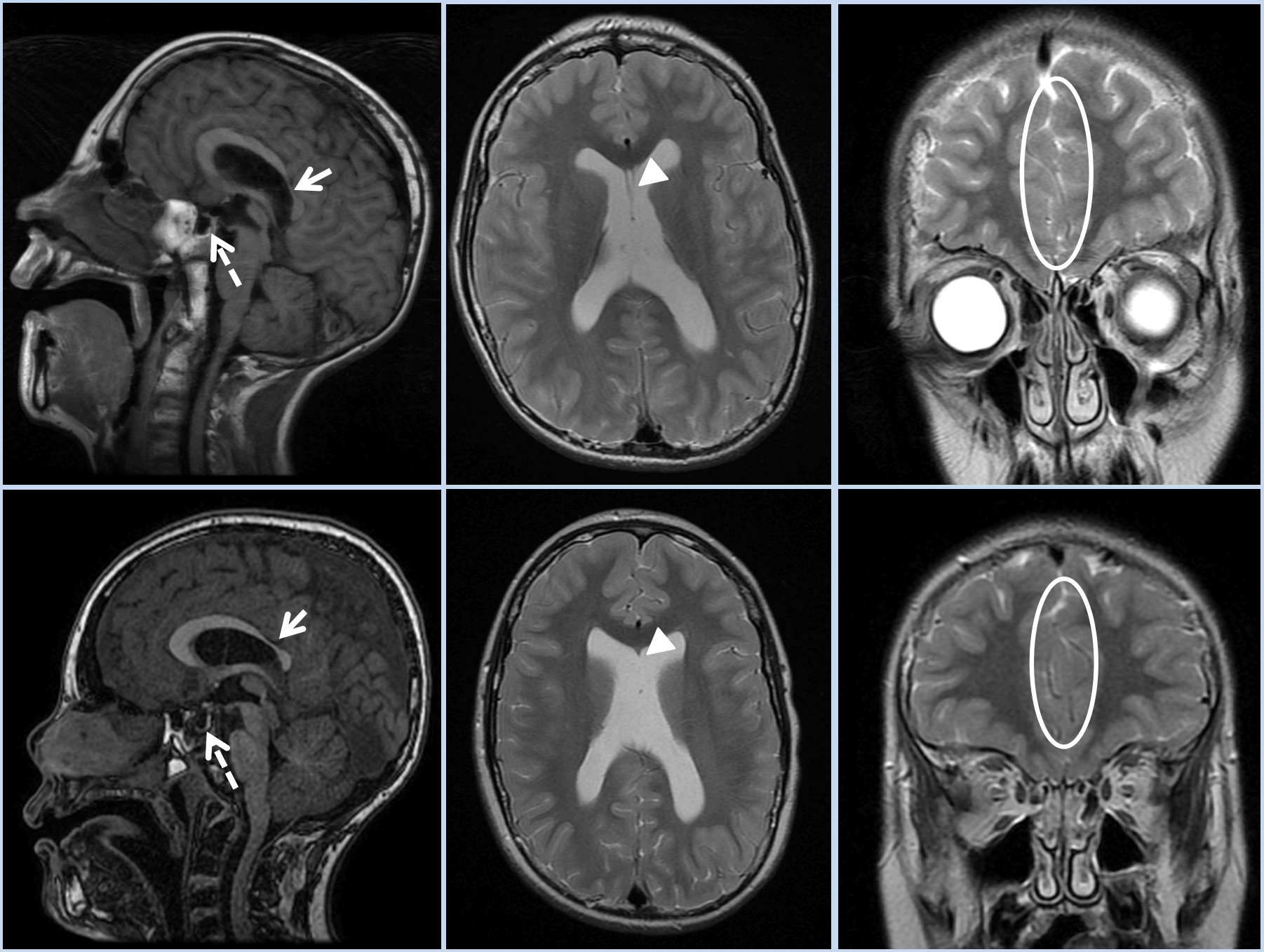
Sample	Allele 1	Allele 2
II-2	0.01	0.99
II-5	0.29	0.71
I-2	0.65	0.35

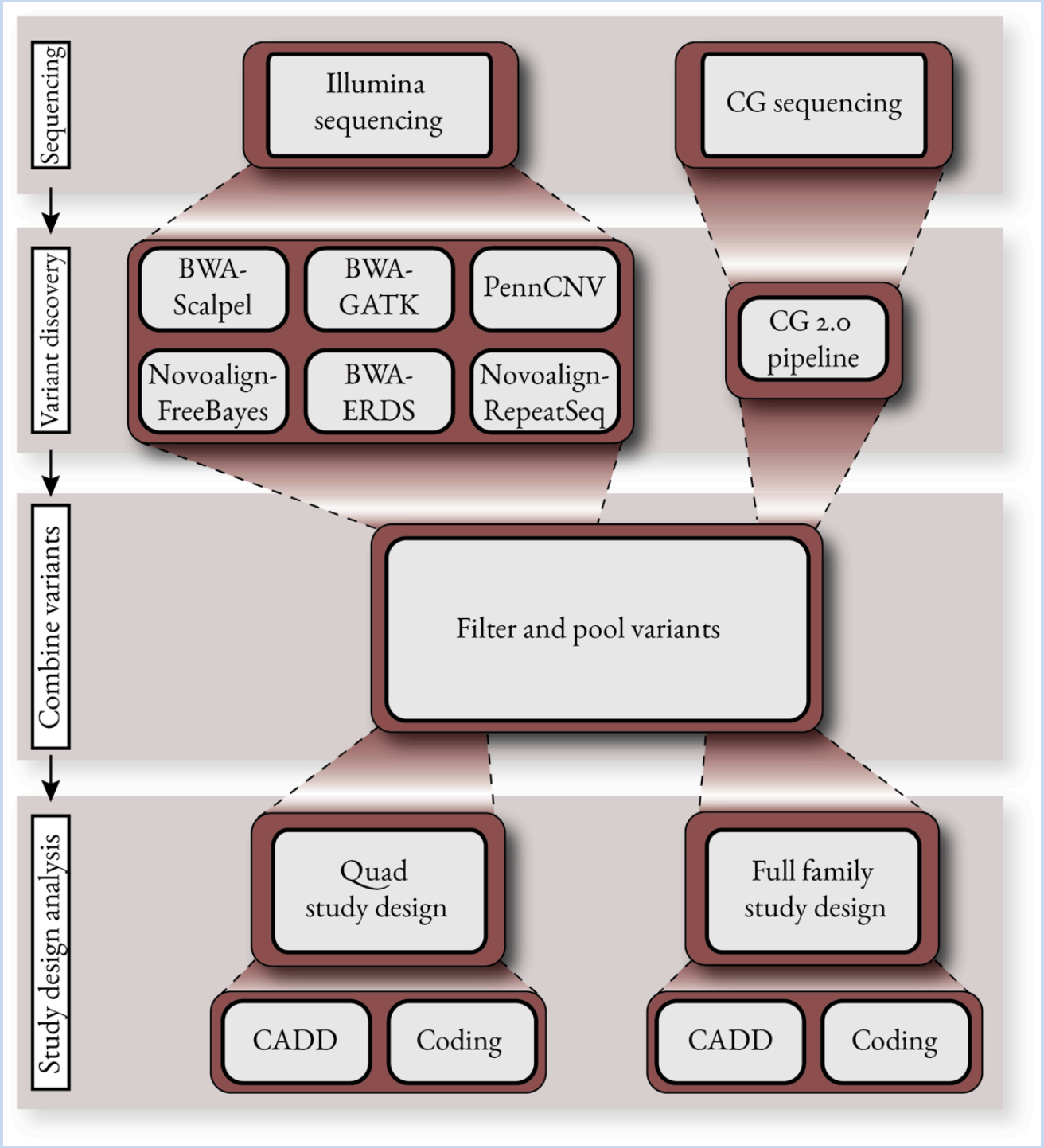
C



III-1. III-2.





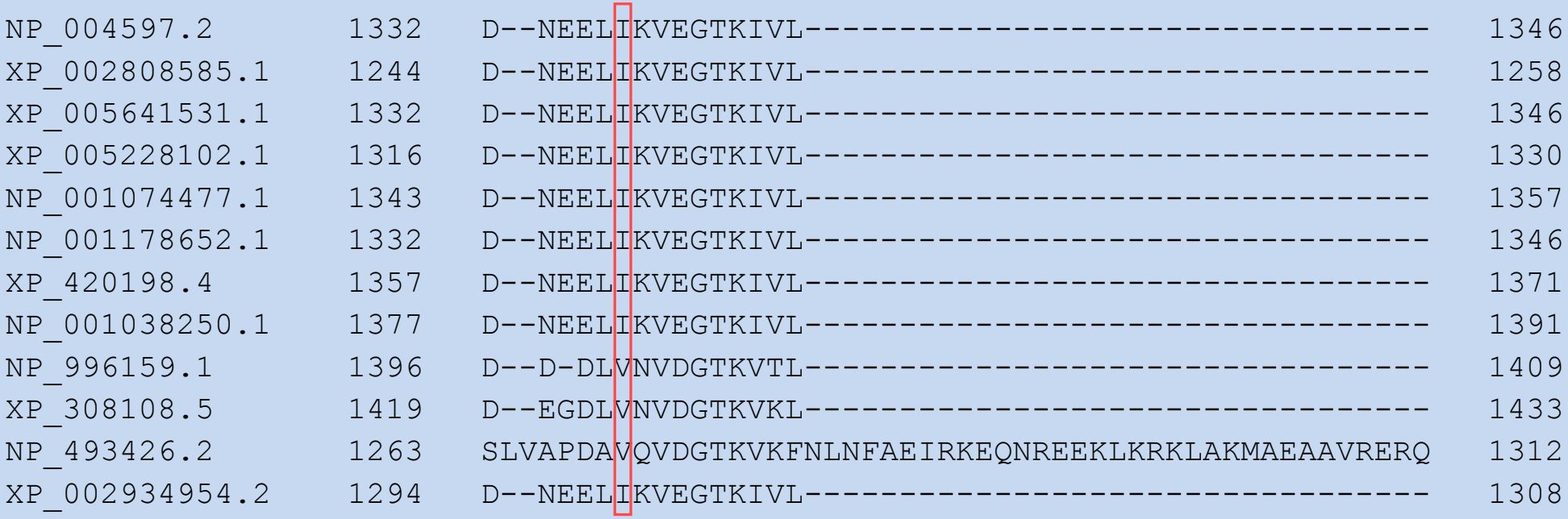

Sequencing
Illumina sequencing
CG sequencing
Variant discovery
BWA-Scalpel
BWA-GATK
PennCNV
Novoalign-FreeBayes
BWA-ERDS
Novoalign-RepeatSeq
CG 2.0 pipeline
Combine variants
Filter and pool variants
Study design analysis
Quad study design
Full family study design
CADD
Coding
CADD
Coding

CADD

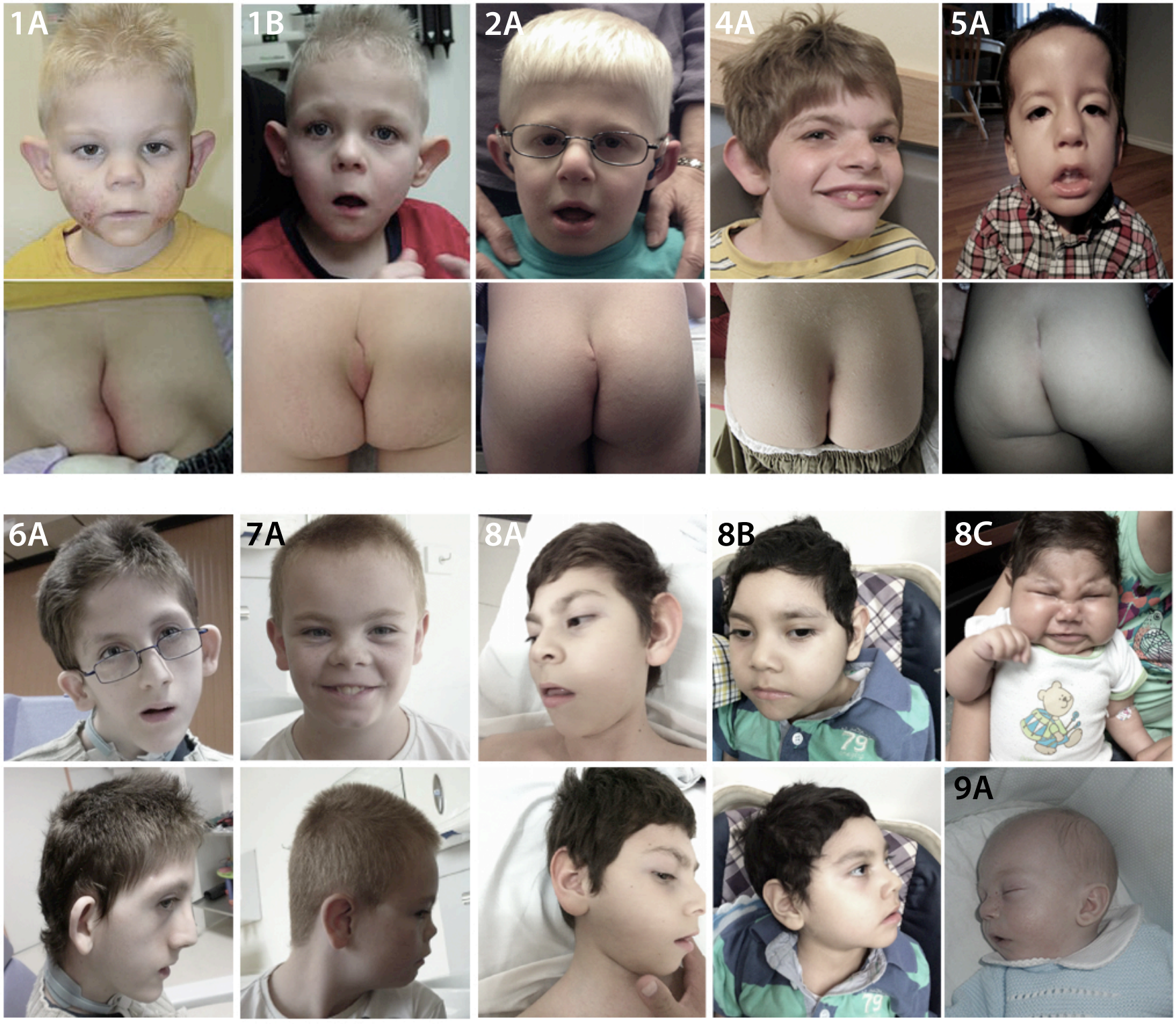
Disease model	Location	Ref	Alt	CADD	Variant Caller	Annotation software	Function
Autosomal recessive	chr1:210851705	TT	T	27.5	CG, GATK, FreeBayes	ANNOVAR, GEMINI, SVS	KCNH1:UTR3
Autosomal recessive	chr1:224772440	AATAATTTG	TA	22.1	CG, GATK, FreeBayes	GEMINI	intergenic
Autosomal recessive	chr2:60537356	TTTTATTT	ATTATTA	22.3	CG, FreeBayes, GATK	GEMINI	intergenic
Autosomal recessive	chr8:109098066	AT	A	24.6	CG, FreeBayes, GATK	GEMINI	intergenic
Autosomal recessive	chr15:66786022	ACAAA	A	23.6	FreeBayes, GATK	GEMINI	SNAPC5:intronic
Autosomal recessive	chr16:49061346	TA	T	25.3	CG, FreeBayes, GATK	ANNOVAR, GEMINI	intergenic
Autosomal recessive	chr16:49612367	GAC	G	20.5	CG, FreeBayes, GATK	GEMINI, SVS	ZNF423:intronic
X-linked	chrX:70621541	T	C	22.9	CG, FreeBayes, GATK	ANNOVAR, GEMINI, SVS	TAF1:NM_004606:I1337T

Coding

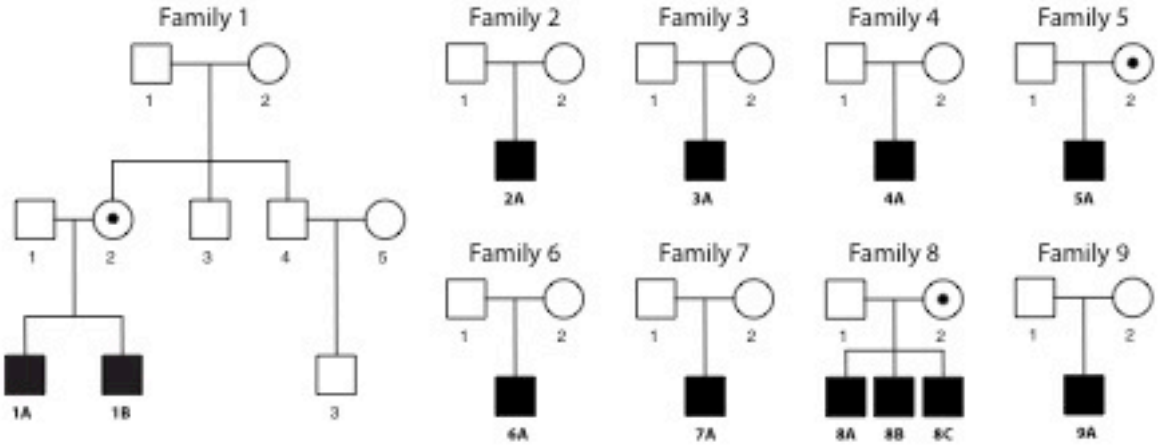
Disease model	Location	Ref	Alt	Gene	Variant Caller	Annotation software	Function
De-novo	chr1:53925373	G	GCCGCCC	DMRTB1	FreeBayes, CG	GEMINI, SVS	nonframeshift
Autosomal recessive	chr10:135438929	T	G	FRG2B	CG, FreeBayes, GATK	ANNOVAR, GEMINI, SVS	NM_001080998:I171L
Autosomal recessive	chr10:135438951	GGCCC	AGCCT	FRG2B	FreeBayes	GEMINI, SVS	nonframeshift
Autosomal recessive	chr10:135438967	C	T	FRG2B	GATK, FreeBayes	GEMINI, SVS	NM_001080998:R158Q
Autosomal recessive	chr15:85438314	C	CTTG	SLC28A1	CG, FreeBayes, GATK	GEMINI	nonframeshift
X-linked	chrX:34961492	T	C	FAM47B	CG, FreeBayes, GATK	GEMINI	NM_152631:Y182H
X-linked	chrX:70621541	T	C	TAF1	CG, FreeBayes, GATK	ANNOVAR, GEMINI, SVS	NM_004606:I1337T



H.sapiens, *M.mulatta*, *C.lupus*, *B.taurus*, *M.musculus*, *R.norvegicus*, *G.gallus*, *X.tropicalis*, *D.rerio*, *D.melanogaster*, *A.gambiae*, and *C.elegans*, listed from top to bottom.


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

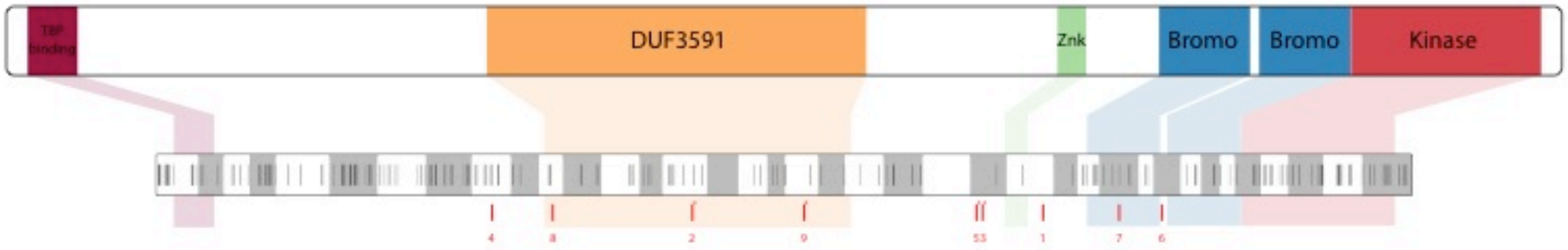
A

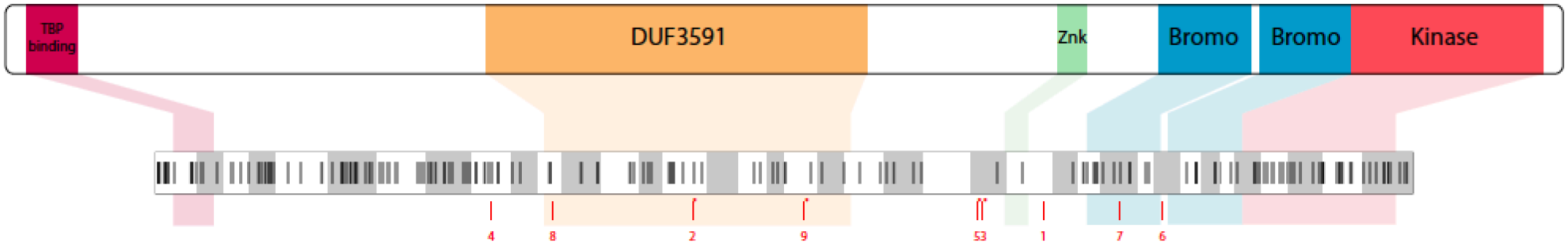


B

Variant	Family	CADD	SIFT	GERP++	phyloP
c.4010T>C	1	27	0.003	5.6	7.695
c.2419T>C	2	23.7	0.004	4.7	7.691
c.3736C>T	3	35	0.000	5.54	2.216
c.1514T>A	4	29.9	0.000	5.51	7.655
c.3708A>G	5	6.17	1.000	-0.087	1.681
c.4549A>C	6	20.8	0.000	4.65	8.910
c.4355G>A	7	29.9	0.001	4.17	9.259
c.1786C>T	8	29.3	0.008	5.97	7.408
c.2926G>C	9	30	0.000	4.81	9.412

C





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

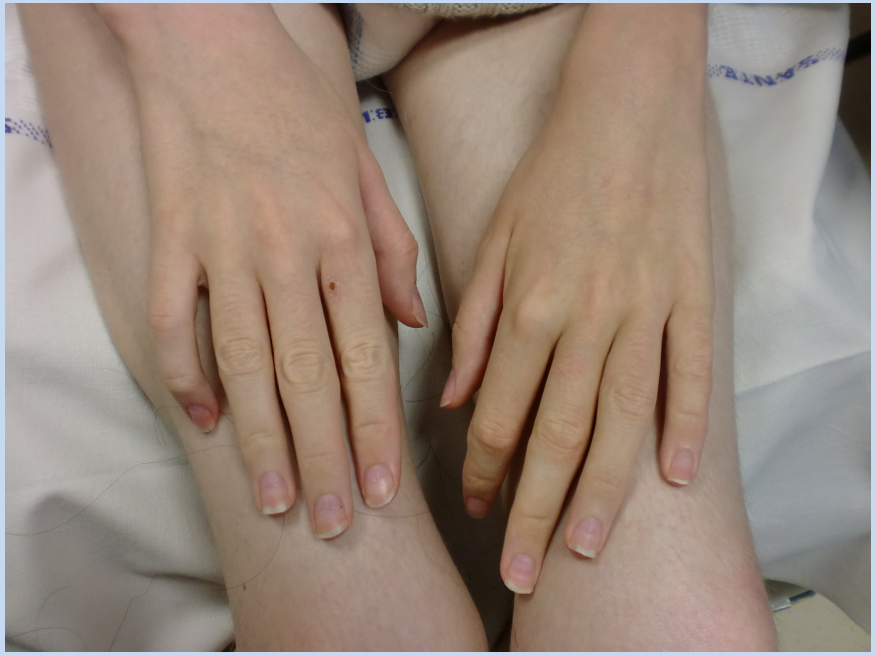
Table 1. Summary of the Clinical Features of *TAF1* ID Syndrome

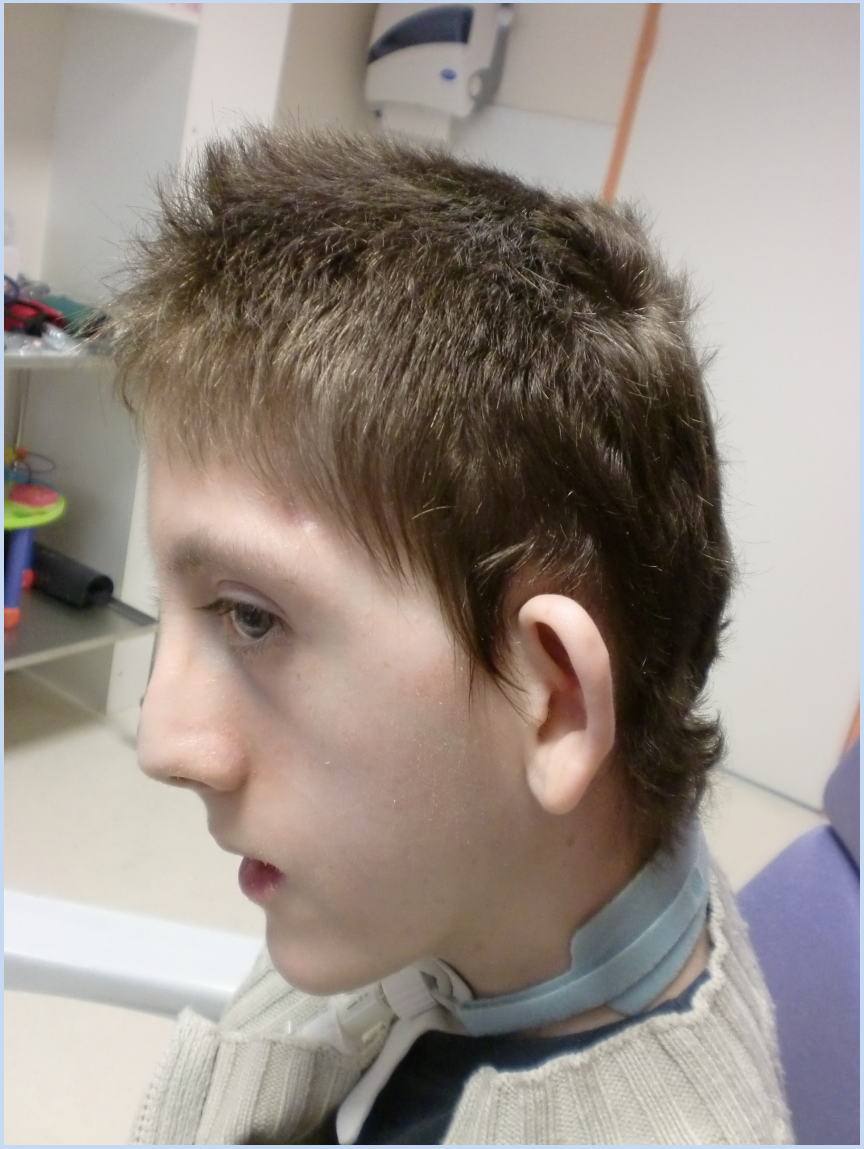
Features (Human Phenotype Ontology Nos.)	Proband													
	1A	1B	2A	3A	4A	5A	6A	7A	8A	8B	8C	9A	10A[a]	11A[a]
Sex	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Age (years)	15	13	5	6	9	3	22	11	9	4	1	3	16	8
Postnatal growth retardation (HP: 0008897)	+	+	+	+	+	+	−	−	+	+	+	+	UK	+
Delayed gross motor development (HP: 0002194)	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Delayed speech and language development (HP: 0000750)	+	+	+	+	+	+	+	+	+	+	+	UK	+	+
Oral-pharyngeal dysphagia (HP: 0200136)	+	+	+	+	UK	+	UK	−	+	+	+	UK	+	UK
Prominent supraorbital ridges (HP: 0000336)	+	+	−	+	UK	−	+	−	+	+	+	+	+	+
Downslanted palpebral fissures (HP: 0000494)	+	+	+	−	+	+	+	−	+	+	+	−	+	UK
Sagging cheeks	+	+	−	−	−	+	−	−	+	+	+	+	+	+
Long philtrum (HP: 0000343)	+	+	+	+	+	+	−	+	+	+	+	+	−	−
Low-set ears (HP: 0000369)	+	+	+	+	+	+	+	−	+	+	+	+	−	+
Protruding ears (HP: 0000411)	+	+	+	+	+	+	+	−	+	+	+	−	−	+
Long face (HP: 0000276)	+	+	−	−	UK	+	+	−	+	+	+	+	+	+
High palate (HP: 0000218)	UK	UK	+	+	−	+	+	−	+	+	+	+	+	+
Pointed chin (HP: 0000307)	+	+	−	−	+	+	+	−	+	+	+	−	+	+
Anteverted nares (HP: 0000463)	−	−	+	+	+	+	−	+	+	+	+	+	−	+
Hearing impairment (HP: 0000365)	+	+	+	+	UK	+	−	−	+	+	+	−	UK	−
Chromic otitis media (HP: 0000389)	+	+	+	−	+	+	−	+	+	+	+	−	UK	−
Strabismus (HP: 0000486)	+	+	+	+	UK	+	+	−	+	−	−	+	+	−
Microcephaly (HP: 0000252)	+	+	+	+	+	−	−	+	+	+	+	+	−	−
Hypoplasia of the corpus callosum (HP: 0002079)	+	+	+	UK	+	+	+	UK	+	+	+	+	UK	−
Generalized hypotonia (HP: 0001290)	+	+	+	+	+	+	+	−	+	+	+	+	−	+
Unusual gluteal crease with sacral caudal remnant and sacral dimple (abnormal sacral segmentation [HP: 0008468] and prominent protruding coccyx [HP: 0008472])	+	+	+	+	+	+	+	+	+	+	+	+	UK	−
Joint hypermobility (HP: 0001382)	+	+	−	+	UK	+	−	−	+	+	+	+	−	UK
Autistic behaviors (HP: 0000729)	+	+	+	−	UK	UK	+	+	+	+	+	−	+	+
Intellectual disability (HP: 0001249)	+	+	+	+	+	UK	+	+	+	+	+	+	+	+

This table demonstrates clinical features shared by eight or more probands across all affected individuals in the families. See Table S5 for a more comprehensive phenotypic table that includes phenotypic and clinical idiosyncrasies. Abbreviations are as follows: M, male; and UK, unknown.
[a]Probands containing duplications; they are generally less similar to the probands containing SNVs and share fewer common clinical features.

Table 2. Summary of *TAF1* Variants across All Affected Individuals in This Study

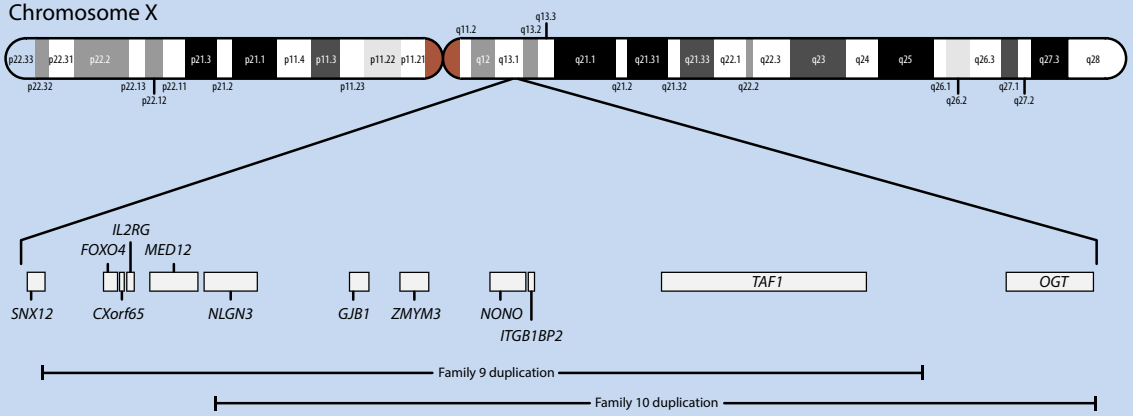
Proband	Inheritance	Genetic Background	*TAF1* Mutation (hg19)
1A	maternal	European decent	chrX: g.70621541T>C (c.4010T>C; p.Ile1337Thr)
1B	maternal	European decent	chrX: g.70621541T>C (c.4010T>C; p.Ile1337Thr)
2A	de novo	European decent	chrX: g.70607243T>C (c.2419T>C; p.Cys807Arg)
3A	de novo	European decent	chrX: g.70618477C>T (c.3736C>T; p.Arg1246Trp)
4A	de novo	European decent	chrX: g.70601686T>A (c.1514T>A; p.Ile505Asn)
5A	maternal	Ecuadorian	chrX: g.70618449A>G (c.3708A>G; r.[3708a>g; 3681_3708del28]; p.Arg1228Ilefs*16)
6A	de novo	European decent	chrX: g.70643003A>C (c.4549A>C; p.Asn1517His)
7A	de novo	British	chrX: g.70627912G>A (c.4355G>A; p.Arg1431His)
8A	maternal	Colombian	chrX: g.70602671C>T (c.1786C>T; p.Pro596Ser)
8B	maternal	Colombian	chrX: g.70602671C>T (c.1786C>T; p.Pro596Ser)
8C	maternal	Colombian	chrX: g.70602671C>T (c.1786C>T; p.Pro596Ser)
9A	de novo	Spanish	chrX: g.70612503G>C (c.2926G>C; p.Asp976His)
10A	maternal	Albanian	0.423 Mb duplication including *TAF1* and other genes at Xq13.1(70,370,794–70,794,385); deletion containing *KANSL1* and other genes at 17q21.31 (0.63 Mb)
11A	de novo	Greek	0.42 Mb duplication including *TAF1* and other genes: arr Xq13.1(70,287,519–70,711,110)×2

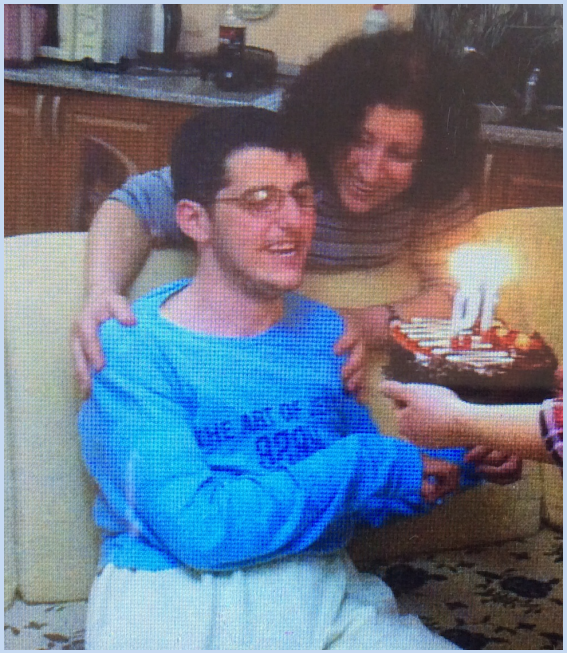


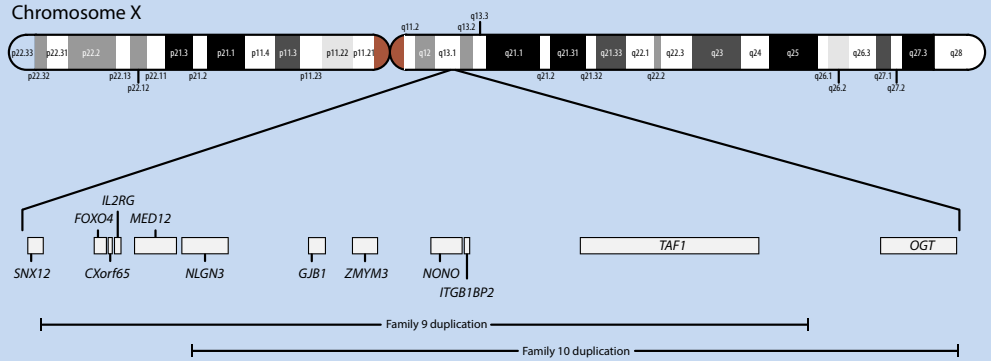


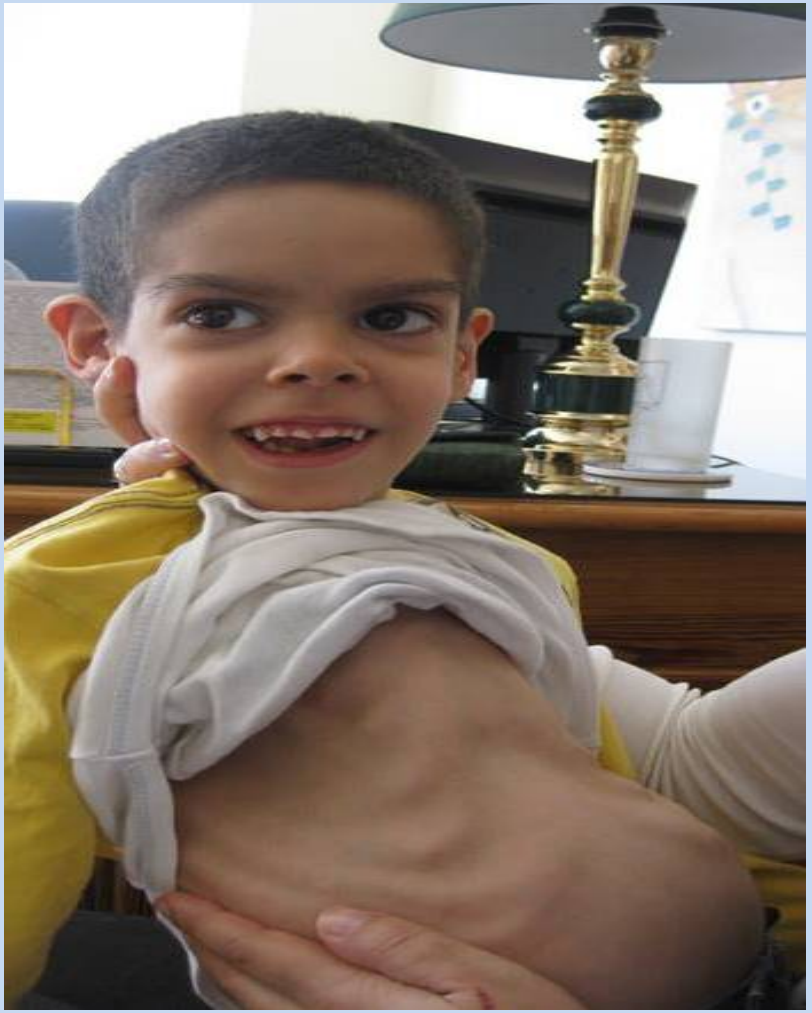
A

B

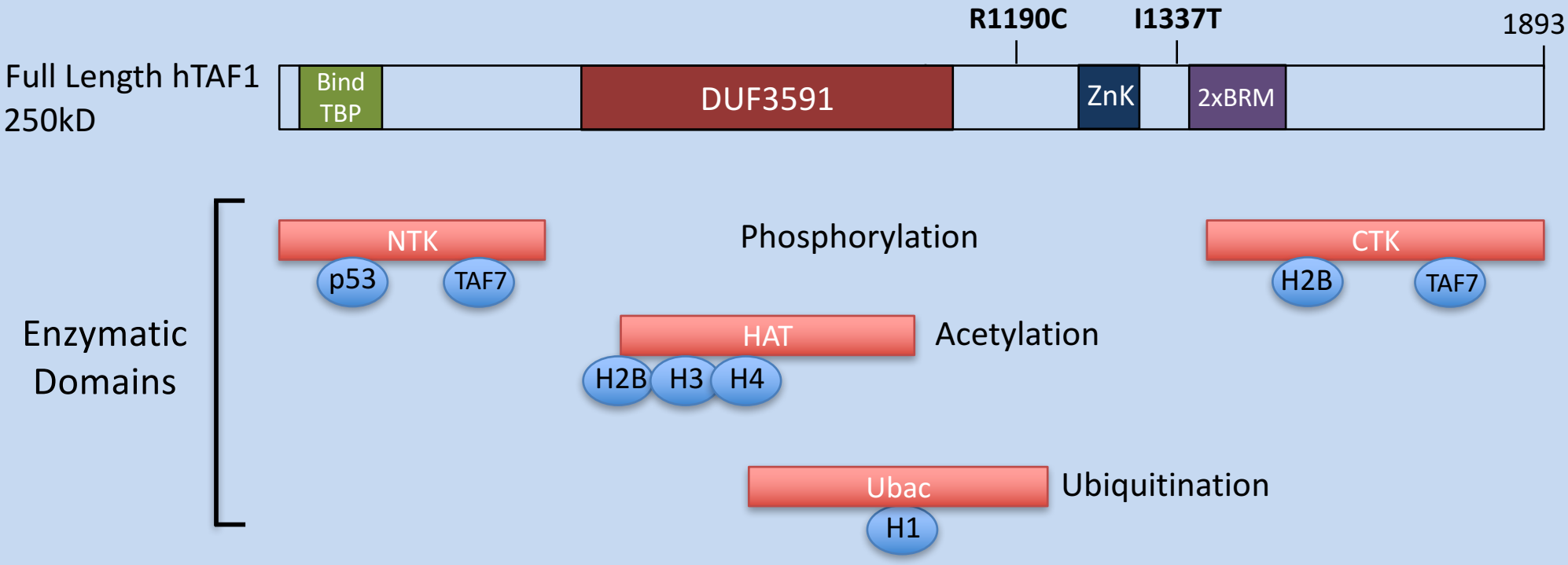

Chromosome X
p22.33
p22.32
p22.31
p22.2
p22.13
p22.12
p22.11
p21.3
p21.2
p21.1
p11.4
p11.3
p11.23
p11.22
p11.21
q11.2
q12
q13.1
q13.2
q13.3
q21.1
q21.2
q21.31
q21.32
q21.33
q22.1
q22.2
q22.3
q23
q24
q25
q26.1
q26.2
q26.3
q27.1
q27.2
q27.3
q28
IL2RG
FOXO4
MED12
SNX12
CXorf65
NLGN3
GJB1
ZMYM3
NONO
ITGB1BP2
TAF1
OGT
Family 9 duplication
Family 10 duplication



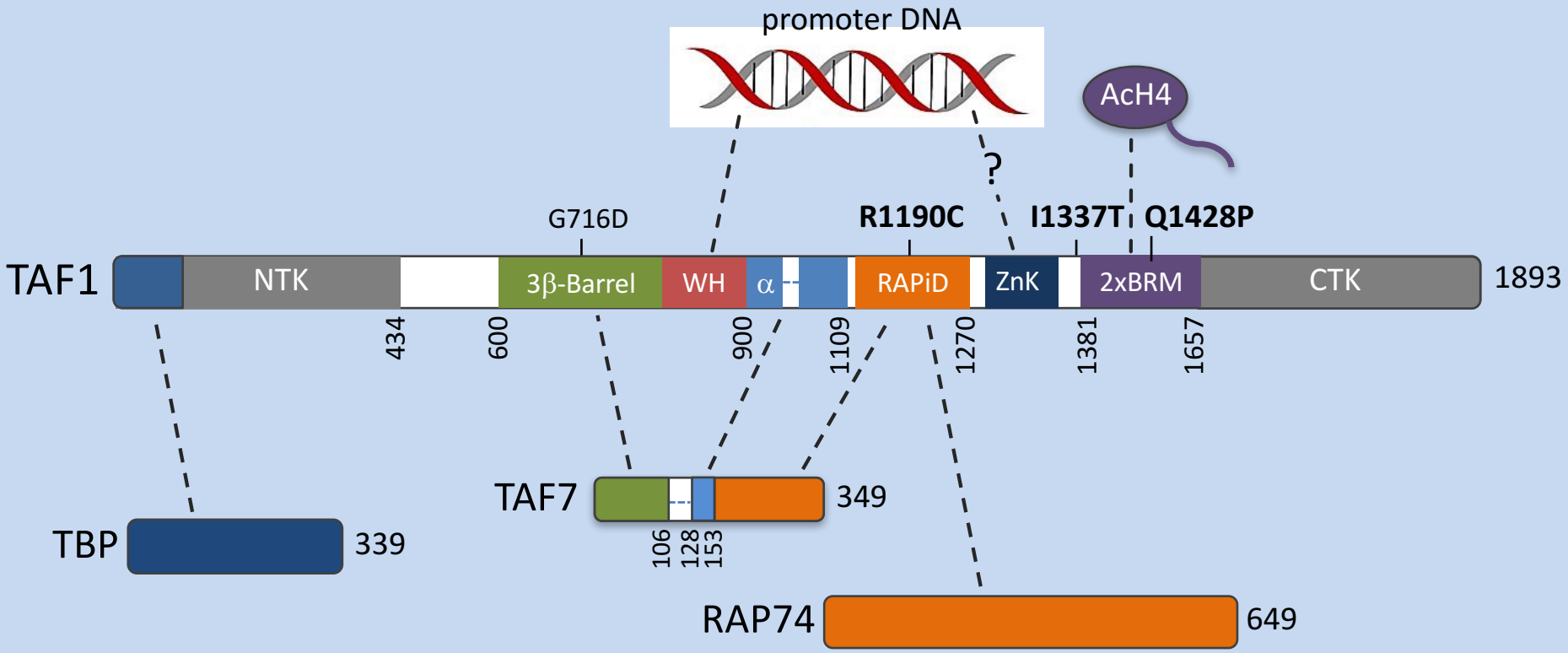

Chromosome X
IL2RG
FOXO4
MED12
SNX12
CXorf65
NLGN3
GJB1
ZMYM3
NONO
ITGB1BP2
TAF1
OGT
Family 9 duplication
Family 10 duplication



Functional Map of Human TAF1

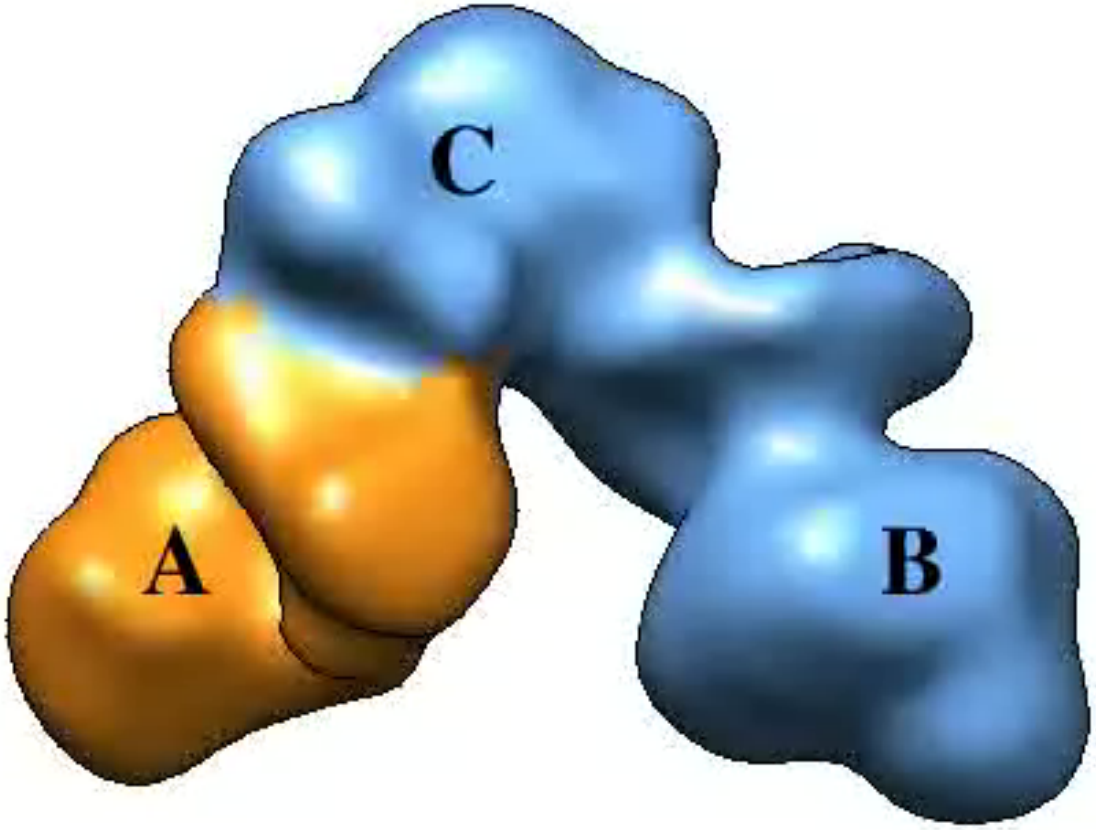


N-terminal Kinase (NTK): 1-437
Acetyltransferase (HAT) : 517-976
C-terminal Kinase (CTK): 1425-1893



TBP binding: 1-77
N-terminal Kinase (NTK): 1-437
RAP74 Interaction Domain (RAPiD): 1120-1270
Zinc Knuckle (Zn): 1282- 1317
Double Bromodomain (2xBRM): 1381-1657
C-terminal Kinase (CTK): 1425-1893

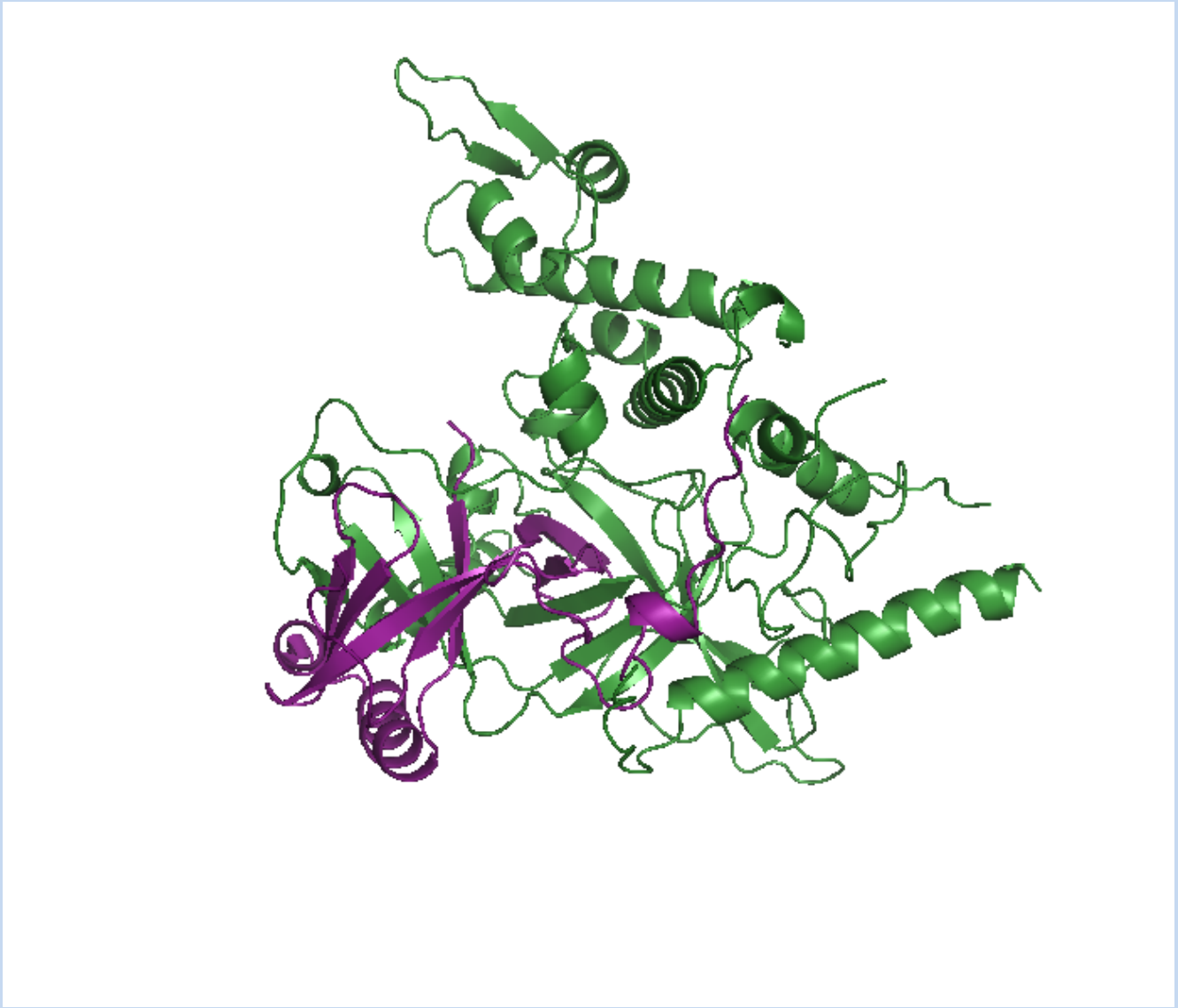
TFIID - Canonical state



Lobe A: orange

BC core: blue

Human TAF1-TAF7 structure



Rare Variants – CNVs, SNVs, indels, etc… in Rare AND Common diseases

High Frequencies of De Novo CNVs in Bipolar Disorder and Schizophrenia

Dheeraj Malhotra,[1,2,22] Shane McCarthy,[22] Jacob J. Michaelson,[1,2] Vladimir Vacic,[15,22] Katherine E. Burdick,[23] Seungtai Yoon,[5,22] Sven Cichon,[10,11,12] Aiden Corvin,[17] Sydney Gary,[22] Elliot S. Gershon,[21] Michael Gill,[17] Maria Karayiorgou,[18] John R. Kelsoe,[2,4,20] Olga Krastoshevsky,[19] Verena Krause,[19] Ellen Leibenluft,[7] Deborah L. Levy,[19] Vladimir Makarov,[5,22] Abhishek Bhandari,[1,2,22] Anil K. Malhotra,[6] Francis J. McMahon,[14] Markus M. Nöthen,[10,11,16] James B. Potash,[8] Marcella Rietschel,[13] Thomas G. Schulze,[9] and Jonathan Sebat[1,2,3,4,22,*]

Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease

Manuel A Rivas[1–3], Mélissa Beaudoin[4,23], Agnes Gardet[5,23], Christine Stevens[2,23], Yashoda Sharma[6], Clarence K Zhang[6], Gabrielle Boucher[4], Stephan Ripke[1,2], David Ellinghaus[7], Noel Burtt[2], Tim Fennell[2], Andrew Kirby[1,2], Anna Latiano[8], Philippe Goyette[4], Todd Green[2], Jonas Halfvarson[9], Talin Haritunians[10], Joshua M Korn[2], Finny Kuruvilla[2,11], Caroline Lagacé[4], Benjamin Neale[1,2], Ken Sin Lo[4], Phil Schumm[12], Leif Törkvist[13], National Institute of Diabetes and Digestive Kidney Diseases Inflammatory Bowel Disease Genetics Consortium (NIDDK IBDGC)[14], United Kingdom Inflammatory Bowel Disease Genetics Consortium[14], International Inflammatory Bowel Disease Genetics Consortium[14], Marla C Dubinsky[15], Steven R Brant[16,17], Mark S Silverberg[18], Richard H Duerr[19,20], David Altshuler[1,2], Stacey Gabriel[2], Guillaume Lettre[4], Andre Franke[7], Mauro D'Amato[21], Dermot P B McGovern[10,22], Judy H Cho[6], John D Rioux[4], Ramnik J Xavier[1,2,5] & Mark J Daly[1,2]

Evolution and Functional Impact of Rare Coding Variation from Deep Sequencing of Human Exomes

Jacob A. Tennessen,[1]* Abigail W. Bigham,[2]*† Timothy D. O'Connor,[1]* Wenqing Fu,[1] Eimear E. Kenny,[3] Simon Gravel,[3] Sean McGee,[1] Ron Do,[4,5] Xiaoming Liu,[6] Goo Jun,[7] Hyun Min Kang,[7] Daniel Jordan,[8] Suzanne M. Leal,[9] Stacey Gabriel,[4] Mark J. Rieder,[1] Goncalo Abecasis,[7] David Altshuler,[4] Deborah A. Nickerson,[1] Eric Boerwinkle,[6,10] Shamil Sunyaev,[4,8] Carlos D. Bustamante,[3] Michael J. Bamshad,[1,2]‡ Joshua M. Akey,[1]‡ Broad GO, Seattle GO, on behalf of the NHLBI Exome Sequencing Project

Lyon and Wang *Genome Medicine* 2012, 4:58
http://genomemedicine.com/content/4/7/58

REVIEW

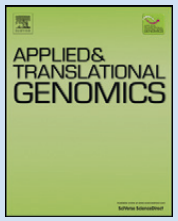
Identifying disease mutations in genomic medicine settings: current challenges and how to accelerate progress

Gholson J Lyon[*1,2] and Kai Wang[*2,3]

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,**]

[a] *Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, NY, United States*
[b] *Utah Foundation for Biomedical Research, Salt Lake City, UT, United States*
[c] *New York Genome Center, New York City, NY, United States*

13

HUMAN GENETICS AND CLINICAL ASPECTS OF NEURODEVELOPMENTAL DISORDERS

GHOLSON J. LYON[1,2,3] AND JASON O'RAWE[1,4]

[1]*Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 11724 USA*

[2]*Institute for Genomic Medicine, Utah Foundation for Biomedical Research, E 3300 S, Salt Lake City, UT, 84106 USA*

[3]*Department of Psychiatry, Stony Brook University, 100 Nicolls Road, Stony Brook, NY, 11794 USA*

[4]*Graduate Program in Genetics, Stony Brook University, Stony Brook, NY, 11794 USA*

- Seguin E. 1866, - “our incomplete studies do not permit actual classification; but it is better to leave things by themselves rather than to force them into classes which have their foundation only on paper”- from Idiocy and its treatment by the physiological method.

- Walter Frank Raphael Weldon 1902 – “the accumulation of records, in which results are massed together in ill-defined categories of variable and uncertain extent, can only result in harm”.

OBSERVATIONS ON AN ETHNIC CLASSIFICATION OF IDIOTS *

J. LANGDON H. DOWN M.D., *London*

London Hospital Clinical Lecture Report. 3, 259-262, 1866.

"Those who have given any attention to congenital mental lesions, must have been frequently puzzled how to arrange, in any satisfactory way, the different classes of this defect which may have come under their observation. Nor will the difficulty be lessened by an appeal to what has been written on the subject. The systems of classification are generally so vague and artificial, that, not only do they assist but feebly, in any mental arrangement of the phenomena represented, but they completely fail in exerting any practical influence on the subject."

A Genotype-First Approach to Defining the Subtypes of a Complex Disease

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http://dx.doi.org/10.1016/j.cell.2014.02.002

Medical genetics typically entails the detailed characterization of a patient's phenotypes followed by genotyping to discover the responsible gene or mutation. Here, we propose that the systematic discovery of genetic variants associated with complex diseases such as autism are progressing to a point where a reverse strategy may be fruitful in assigning the pathogenic effects of many different genes and in determining whether particular genotypes manifest as clinically recognizable phenotypes. This "genotype-first" approach for complex disease necessitates the development of large, highly integrated networks of researchers, clinicians, and patient families, with the promise of improved therapies for subsets of patients.

Prioritization of neurodevelopmental disease genes by discovery of new mutations

Alexander Hoischen[1], Niklas Krumm[2] & Evan E Eichler[2,3]

Advances in genome sequencing technologies have begun to revolutionize neurogenetics, allowing the full spectrum of genetic variation to be better understood in relation to disease. Exome sequencing of hundreds to thousands of samples from patients with autism spectrum disorder, intellectual disability, epilepsy and schizophrenia provides strong evidence of the importance of *de novo* and gene-disruptive events. There are now several hundred new candidate genes and targeted resequencing technologies that allow screening of dozens of genes in tens of thousands of individuals with high specificity and sensitivity. The decision of which genes to pursue depends on many factors, including recurrence, previous evidence of overlap with pathogenic copy number variants, the position of the mutation in the protein, the mutational burden among healthy individuals and membership of the candidate gene in disease-implicated protein networks. We discuss these emerging criteria for gene prioritization and the potential impact on the field of neuroscience.

Table 4 Recurrent identical *de novo* mutations in 6 genes identified in 11 exome studies with different neurodevelopmental phenotypes

Gene	Coding effect	Mutation (genomic DNA level)	Mutation (cDNA level)	Mutation (protein level)	Study	Disorder
ALG13	Missense	ChrX(GRCh37):g.110928268A>G	NM_001099922.2:c.320A>G	p.Asn107Ser	de Ligt *et al.*[1]	ID
ALG13	Missense	ChrX(GRCh37):g.110928268A>G	NM_001099922.2:c.320A>G	p.Asn107Ser	Allen *et al.*[11]	EE
ALG13	Missense	ChrX(GRCh37):g.110928268A>G	NM_001099922.2:c.320A>G	p.Asn107Ser	Allen *et al.*[11]	EE
KCNQ3	Missense	Chr8(GRCh37):g.133192493G>A	NM_001204824.1:c.328C>T	p.Arg110Cys	Rauch *et al.*[2]	ID
KCNQ3	Missense	Chr8(GRCh37):g.133192493G>A	NM_001204824.1:c.328C>T	p.Arg110Cys	Allen *et al.*[11]	EE
SCN1A	Splice donor	LRG_8:g.24003G>A	NM_006920.4:c.602+1G>A	p.?	Allen *et al.*[11]	EE
SCN1A	Splice donor	LRG_8:g.24003G>A	NM_006920.4:c.602+1G>A	p.?	Allen *et al.*[11]	EE
CUX2	Missense	Chr12(GRCh37):g.111748354G>A	NM_015267.3:c.1768G>A	p.Glu590Lys	Rauch *et al.*[2]	ID
CUX2	Missense	Chr12(GRCh37):g.111748354G>A	NM_015267.3:c.1768G>A	p.Glu590Lys	Allen *et al.*[11]	EE
SCN2A	Missense	Chr2(GRCh37):g.166198975G>A	NM_021007.2:c.2558G>A	p.Arg853Gln	Allen *et al.*[11]	EE
SCN2A	Missense	Chr2(GRCh37):g.166198975G>A	NM_021007.2:c.2558G>A	p.Arg853Gln	Allen *et al.*[11]	EE
DUSP15	Missense	Chr20(GRCh37):g.30450489G>A	NM_080611.2:c.320C>T	p.Thr107Met	Neale *et al.*[7]	ASD
DUSP15	Missense	Chr20(GRCh37):g.30450489G>A	NM_080611.2:c.320C>T	p.Thr107Met	Fromer *et al.*[10]	SCZ

EE, epileptic encephalopathies; ASD, autism spectrum disorder; ID, intellectual disability; SCZ, schizophrenia.

Mutations as “Difference Makers”

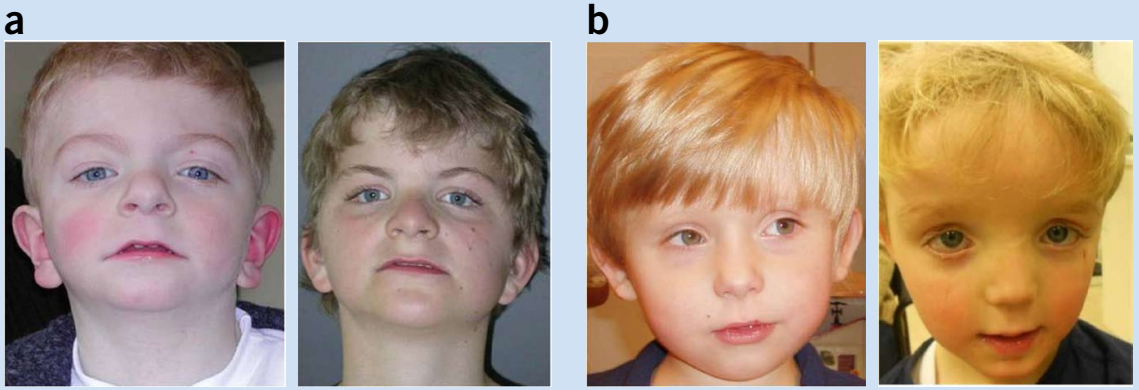


Figure 3 Phenotypic similarity of two patients with identical *PACS1 de novo* mutations and two patients with similar *ADNP* mutations. (**a**) These two unrelated patients show identical *de novo* point mutations (c.607C>T; p.Arg203Trp) in *PACS1* (RefSeq NM_018026.3)[53]. The striking similarity in phenotype includes low anterior hairline, highly arched eyebrows, synophrys, hypertelorism with downslanted palpebral fissures, long eyelashes, a bulbous nasal tip, a flat philtrum with a thin upper lip, downturned corners of the mouth and low-set ears. Reprinted from ref. 53, Copyright (2012), with permission from The American Society of Human Genetics. (**b**) These two unrelated patients both show LoF mutations in *ADNP* (c.2496_2499delTAAA; p.Asp832Lysfs*80 and c.2157C>G; p.Tyr719*)[44] resulting in a new SWI-SNF–related autism syndrome. Patients present with clinical similarities, including a prominent forehead, a thin upper lip and a broad nasal bridge. Reprinted from ref. 44.

Refining analyses of copy number variation identifies specific genes associated with developmental delay

Bradley P Coe[1], Kali Witherspoon[1], Jill A Rosenfeld[2], Bregje W M van Bon[3,4], Anneke T Vulto-van Silfhout[3], Paolo Bosco[5], Kathryn L Friend[4], Carl Baker[1], Serafino Buono[5], Lisenka E L M Vissers[3], Janneke H Schuurs-Hoeijmakers[3], Alex Hoischen[3], Rolph Pfundt[3], Nik Krumm[1], Gemma L Carvill[6], Deana Li[7], David Amaral[7], Natasha Brown[8,9], Paul J Lockhart[8,10], Ingrid E Scheffer[11], Antonino Alberti[5], Marie Shaw[4], Rosa Pettinato[5], Raymond Tervo[12], Nicole de Leeuw[3], Margot R F Reijnders[3], Beth S Torchia[2], Hilde Peeters[13,14], Elizabeth Thompson[4,15], Brian J O'Roak[1,18], Marco Fichera[5,18], Jayne Y Hehir-Kwa[3], Jay Shendure[1], Heather C Mefford[6], Eric Haan[4,15], Jozef Gécz[4,16], Bert B A de Vries[3], Corrado Romano[5] & Evan E Eichler[1,17]

Copy number variants (CNVs) are associated with many neurocognitive disorders; however, these events are typically large, and the underlying causative genes are unclear. We created an expanded CNV morbidity map from 29,085 children with developmental delay in comparison to 19,584 healthy controls, identifying 70 significant CNVs. We resequenced 26 candidate genes in 4,716 additional cases with developmental delay or autism and 2,193 controls. An integrated analysis of CNV and single-nucleotide variant (SNV) data pinpointed 10 genes enriched for putative loss of function. Follow-up of a subset of affected individuals identified new clinical subtypes of pediatric disease and the genes responsible for disease-associated CNVs. These genetic changes include haploinsufficiency of *SETBP1* associated with intellectual disability and loss of expressive language and truncations of *ZMYND11* in individuals with autism, aggression and complex neuropsychiatric features. This combined CNV and SNV approach facilitates the rapid discovery of new syndromes and genes involved in neuropsychiatric disease despite extensive genetic heterogeneity.

Table 2 Intersection of CNV and exome data

		Exome data			Array CGH			
Gene	Isoform	1,879 published cases LoF	1,879 published cases *de novo* LoF (ESP average read depth >20, Dustmasked)	6,500 ESP LoF (ESP average read depth >20, Dustmasked)	Signature deletions (n = 29,085)	Control deletions (n = 19,584)	Combined LoF P value	Combined LoF q value[e]
ANK2[a]	NM_020977.3[b]	1	1	0	5	0	0.0171	0.169
ARHGAP5	NM_001030055.1	1	1	0	7	0	0.0061	0.0833
BCL11A	NM_022893.3	1	0	0	4	0	0.0286	0.244
CAPRIN1	NM_005898.4	1	1	0	4	0	0.0286	0.244
CARKD	NM_001242881.1[c]	1	1	0	12	4	0.0363	0.28
CHD2[a]	NM_001271.3	3	3	0	0	0	0.0113	0.127
CHD8[a]	NM_001170629.1	3	3	0	2	0	0.00402	0.0703
CSDE1	NM_001130523.2	1	1	0	3	0	0.0479	0.311
CUL3[a]	NM_003590.4	2	2	0	5	0	0.00383	0.0703
DLL1	NM_005618.3	1	0	0	32	1	2.17×10^{-7}	2.68×10^{-5}
DYRK1A[a]	NM_001396.3	2	2	0	11	0	1.74×10^{-4}	8.60×10^{-3}
FAM8A1	NM_016255.2	1	1	0	5	0	0.0171	0.169
FOXP1[a]	NM_001244810.1	1	1	0	4	0	0.0286	0.244
GRIN2B[a]	NM_000834.3	3	3	0	2	0	0.00402	0.0703
GTPBP4	NM_012341.2	1	1	0	3	0	0.0479	0.311
LTN1	NM_015565.2	1	1	0	6	0	0.0102	0.12
MBD5[a]	NM_018328.4	1	1	0	16	6	0.0343	0.273
MYT1L	NM_015025.2	1	1	0	8	0	0.00365	0.0703
NAA15	NM_057175.3	2	2	0	5	3	0.0296	0.244
NCKAP1	NM_205842.1	2	2	0	7	0	0.00137	0.0564
NFIA	NM_001134673.3	1	1	0	3	0	0.0479	0.311
NRXN1[a]	NM_001135659.1	1	1	0	30	9	0.00427	0.0703
NTM	NM_001144058.1	1	1	0	40	0	2.53×10^{-10}	6.25×10^{-8}
PCOLCE	NM_002593.3	1	1	0	7	0	0.0061	0.0833
PHF2	NM_005392.3	1	1	0	4	0	0.0286	0.244
RAB2A	NM_002865.2	1	1	0	3	0	0.0479	0.311
SCN1A[a]	NM_001165963.1	4	4	0	10	1	7.36×10^{-5}	4.55×10^{-3}
SCN2A[a]	NM_021007.2	6	5	0	10	0	7.34×10^{-7}	6.04×10^{-5}
SLC6A1	NM_003042.3	1	1	0	6	0	0.0102	0.12
SRM	NM_003132.2	1	1	0	9	0	0.00218	0.0703
STXBP1[a]	NM_003165.3	2	2	0	4	0	0.00641	0.0833
SUV420H1	NM_016028.4[d]	1	1	0	3	0	0.0479	0.31135
SYNGAP1[a]	NM_006772.2	4	4	0	0	1	0.00252	0.0703
TBR1	NM_006593.2	2	2	0	7	1	0.00522	0.0806
UBN2	NM_173569.3	1	1	0	5	0	0.0171	0.169
WAC	NM_016628.4	1	1	0	3	0	0.0479	0.31135
WDFY3	NM_014991.4	1	1	0	8	0	0.00365	0.0703
ZMYND11	NM_006624.5	1	1	0	8	0	0.00365	0.0703

LOF, loss of function.
[a]Disease gene in OMIM. [b]Variant 2; this is the major form of ankyrin in the adult brain. [c]Variant 2; this isoform and variants 3 and 4 are shorter than variant 1. [d]Variant 2; this isoform is shorter and has a distinct C terminus in comparison to isoform 1. [e]Please see the **Supplementary Note** for discussion of the q values shown.

Table 4 Brief phenotypic description of cases with *SETBP1* loss-of-function variants

Case	Age at examination	Sex	Alteration	Inheritance	Cognitive	Hyperactive or ADHD	Social difficulties	Other behavioral difficulties	Speech delay	Motor delay	Facial dysmorphism	Seizures or EEG abnormalities
DNA03-00335	14 years	M	p.Ile822Tyrfs*13	*De novo*	Normal IQ			+	+	+	+	
DNA-008897	73 years	M	p.Leu411Glyfs*6		Profound ID		+	+	+	+	+	
Troina 1274	19 years	M	p.Trp532*	*De novo*	Severe ID			+	+	+	+	–
Troina 1512	17 years	M	p.Ser1011*	*De novo*	Mild ID	+ (3y 8m)	+		+	+	+	–
Troina 3097	34 years	F	p.Arg143Valfs*64		Severe ID				+	+	+	+
DNA11-21308Z	36 years	F	p.Arg625*		Mild to moderate ID	+	+	+	+	+	+	
DNA11-19324Z	9 years	F	p.Arg626*		2- to 2.5-year delay at 9 years old				+	–	+	–
DNA08-08272	9 years	M	p.Gly15Argfs*47		Mild ID	+		+	+	+	+	+
Rauch *et al.*	13 years	F	p.Lys592*		Mild ID	+	+		+	–	+	
9886269	5 years	M	Deletion	*De novo*	Global delay	+			+	+	+	+
Marseglia *et al.*	15 years	M	Deletion	*De novo*	Mild ID	+	+	+	+	+	+	+
Filges *et al.* pt. 1	7 years	M	Deletion	*De novo*	Moderate ID				+	+	+	+
Filges *et al.* pt. 2	4 years	M	Deletion	*De novo*					+	+	+	

ID, intellectual disability; EEG, electroencephalogram; M, male; F, female.

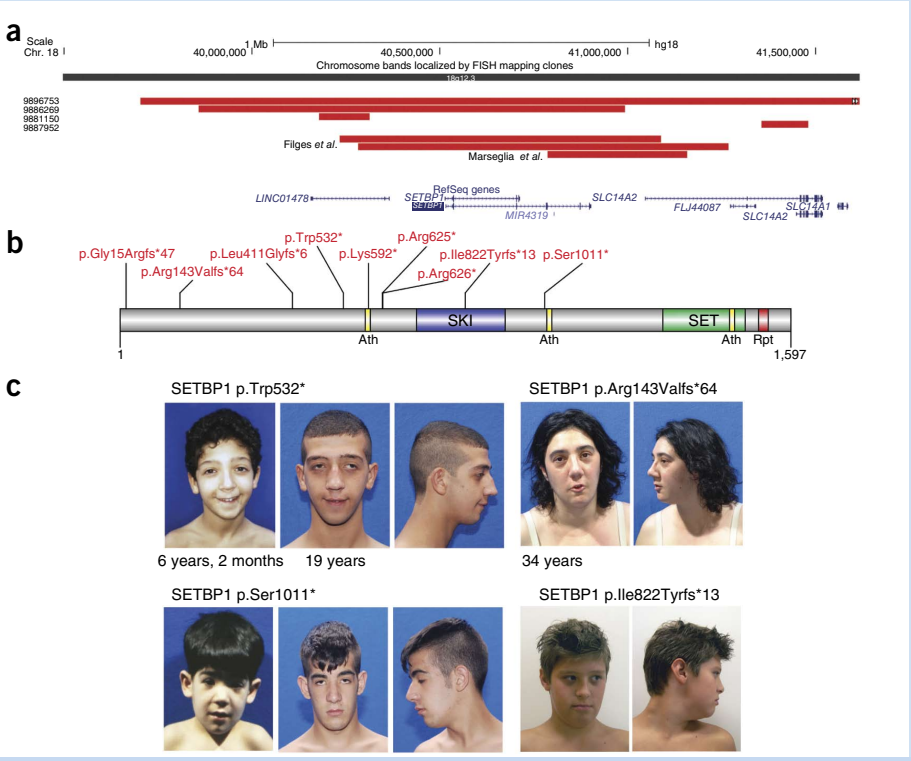


Figure 1 Truncating *SETBP1* mutations and associated phenotypes. (**a**) CNV data define a focal CNV region around *SETBP1*. Combining a focal *de novo* deletion observed in our study (9886269) with CNVs from Filges *et al.*[41] and Marseglia *et al.*[42] (red bars) highlights minimal common regions, including *SETBP1* and *LINC01478*. (**b**) Targeted resequencing identified eight truncating variants in SETBP1 and none in controls. Integration of published exome data identified one additional case and no truncating events in controls. Ath, AT hook; SKI, SKI-homologous region; SET, SET-binding domain; Rpt, repeat. (**c**) Phenotypic assessment (summarized in **Table 4**) identified a recognizable phenotype, including IQ deficits ranging from mild to severe, impaired speech and distinctive facial features. See the **Supplementary Note** for additional photographs of affected individuals and clinical descriptions. We obtained informed consent to publish the photographs.

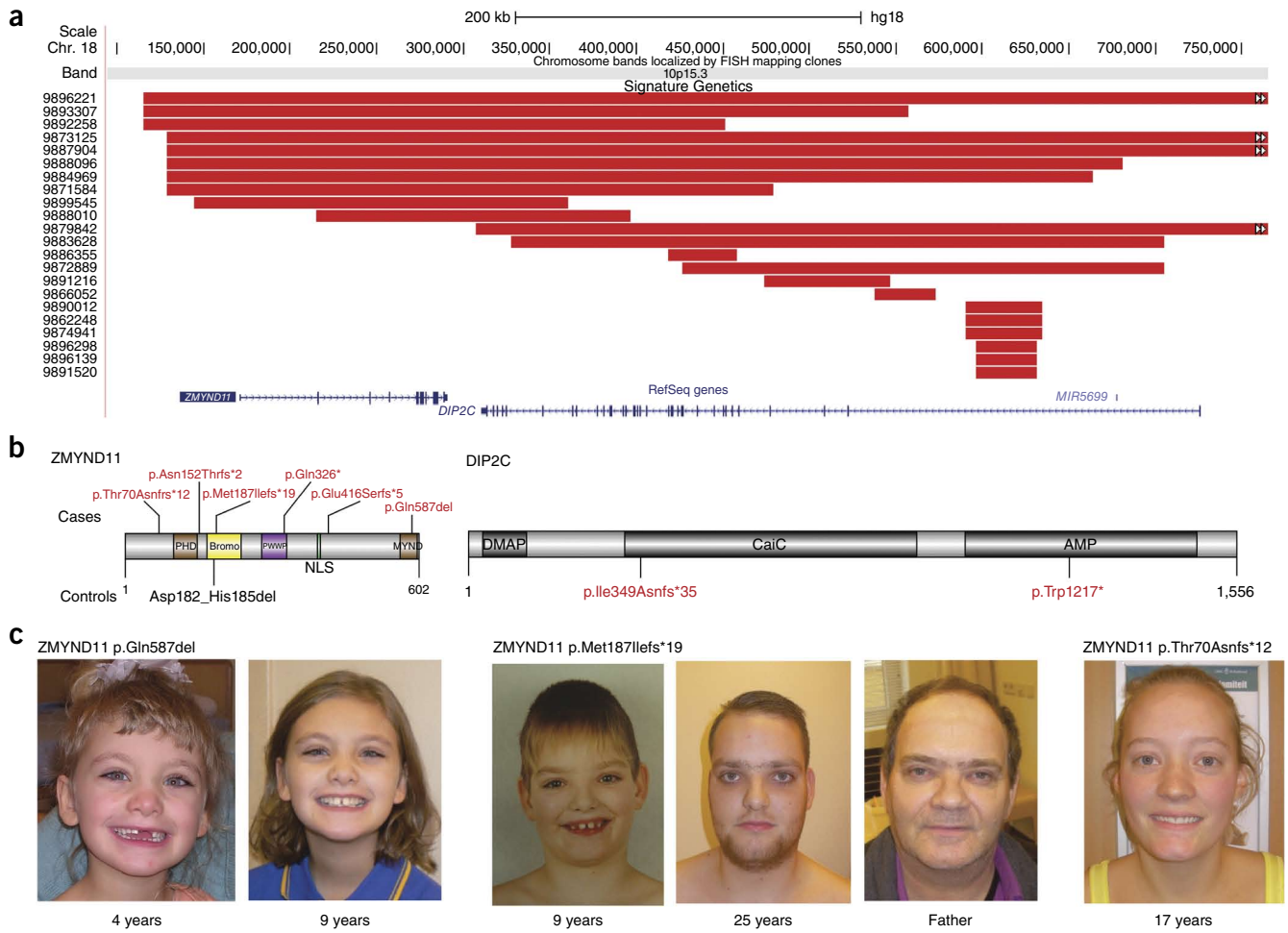


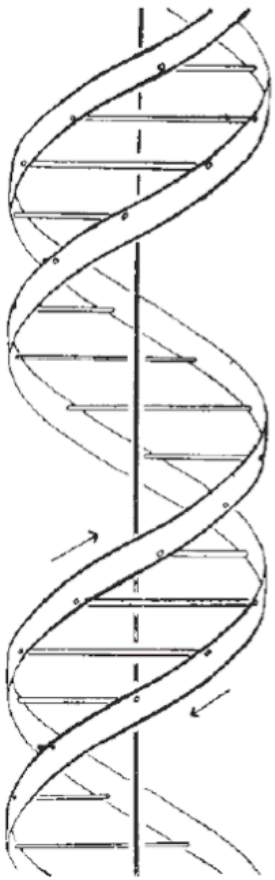
Figure 2 Truncating *ZMYND11* mutations and associated phenotypes. (**a**) CNV data refine a focal CNV deletion region (red bars) containing two genes (*ZMYND11* and *DIP2C*). (**b**) Targeted resequencing identified five truncating variants and one single-amino-acid deletion predicted to behave as loss-of-function variants by removing a critical binding residue in the MYND domain (Gln587). Analysis of control resequencing and exome data identified no additional truncating events in *ZMYND11* but highlighted two truncating mutations in *DIP2C*. PHD, plant homeodomain; Bromo, bromodomain; PWWP, conserved ProTrpTrpPro motif; NLS, nuclear localization sequence; MYND, zinc finger MYND type (myeloid, Nervy and DEAF-1); DMAP, DNA methyltransferase–associated protein; CaiC, crotonobetaine/carnitine-CoA ligase; AMP, AMP-dependent synthetase/ligase. (**c**) Phenotypic assessment (summarized in **Table 5**) showed a consistent phenotype characterized by mild intellectual disability accompanied by speech and motor delays, as well as complex neuropsychiatric behavioral and characteristic facial features. See the **Supplementary Note** for additional photographs of the affected individuals and clinical descriptions. We obtained informed consent to publish the photographs.

Researchers develop genetic profile of the Netherlands

- “The Genome of the Netherlands can greatly accelerate research into genes that play a key role in the development of chronic and age-related diseases. We can now focus specifically on the disease-causing genes”.
- “A noticeable result is that every participant in this research on average turned out to have twenty mutations that were thought to cause rare diseases, although the participants were perfectly healthy”.

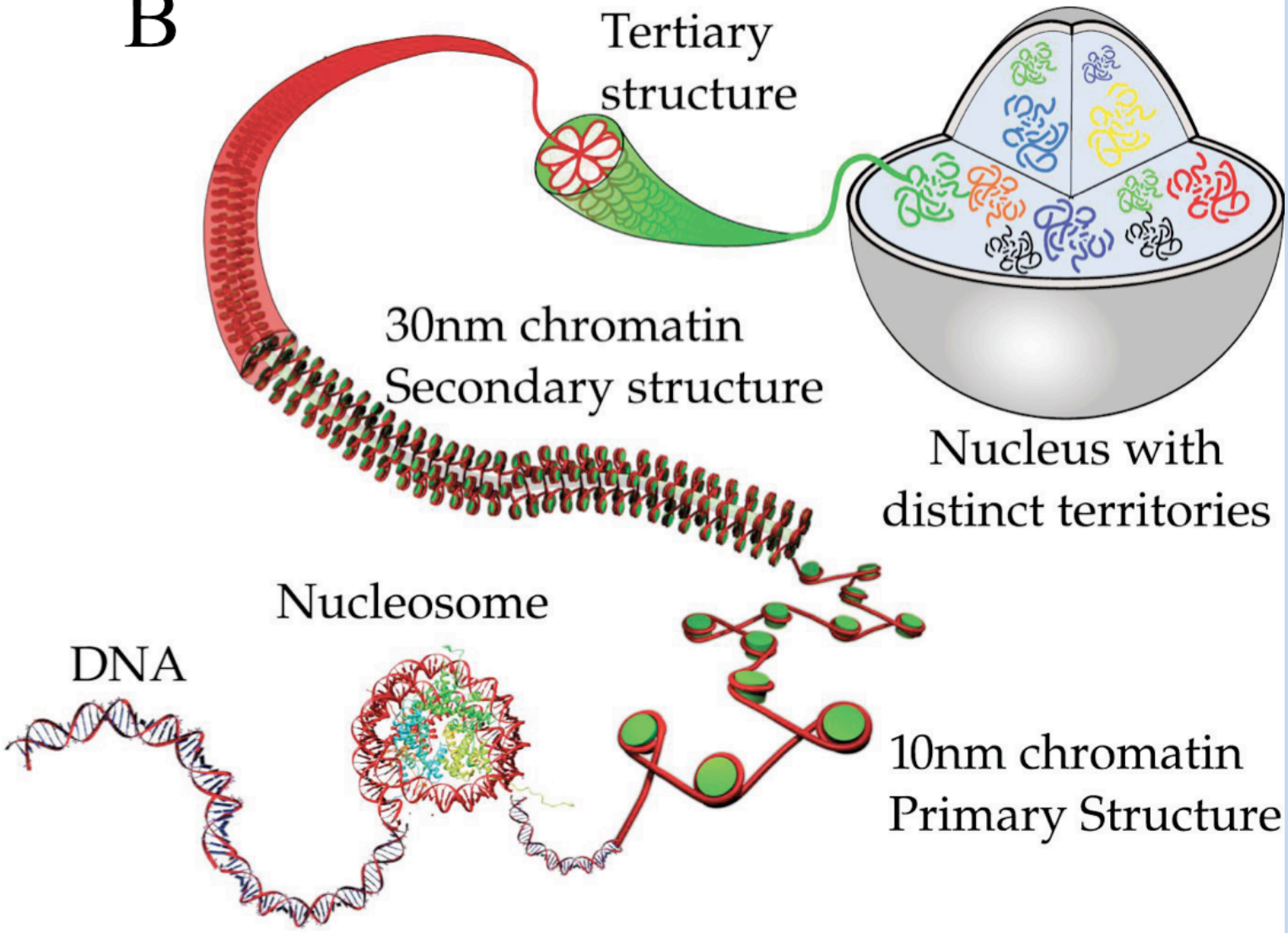
http://medicalxpress.com/news/2014-06-genetic-profile-netherlands.html

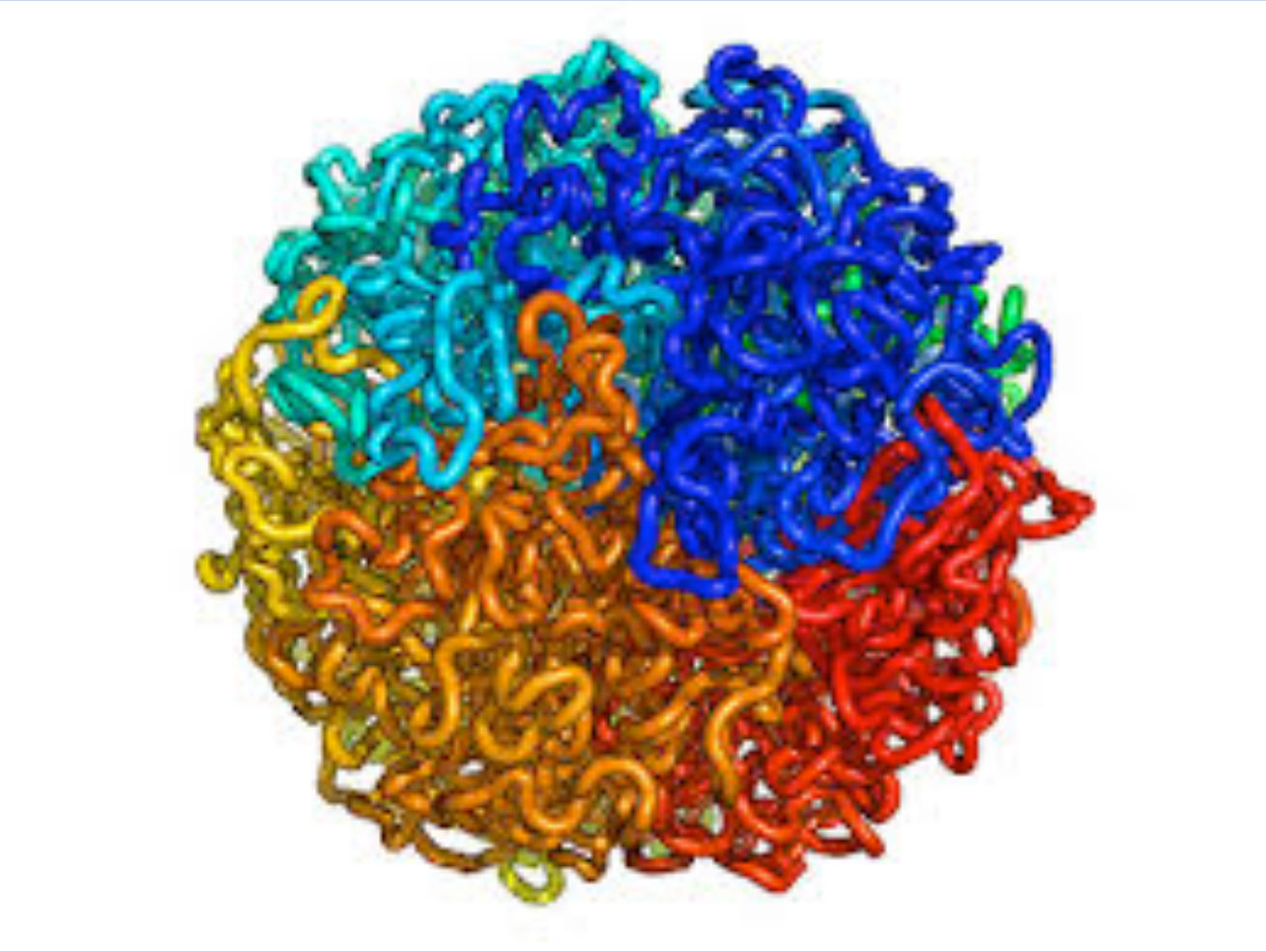
A



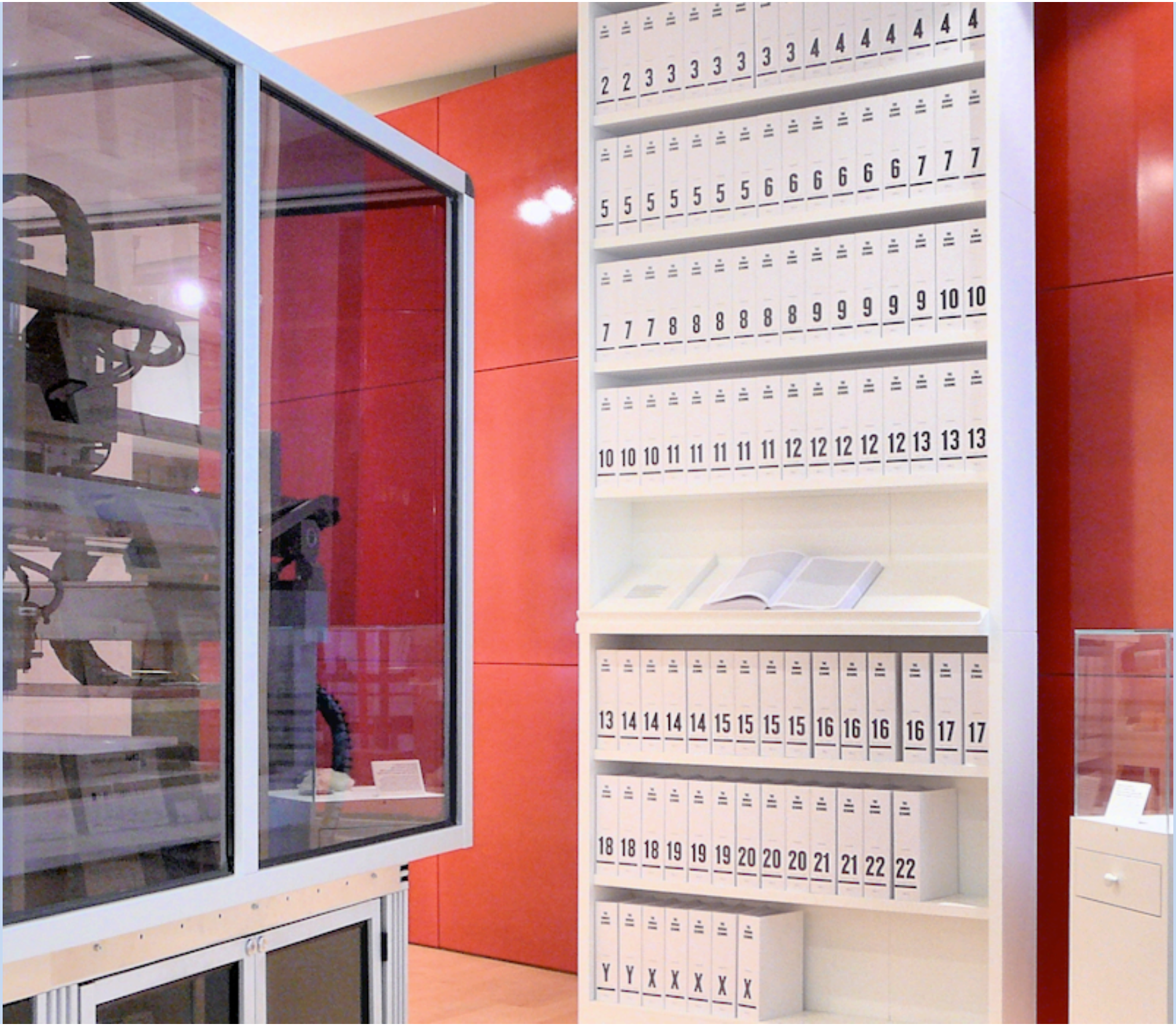
This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

B





“There are ~12 billion nucleotides in every cell of the human body, and there are ~25-100 trillion cells in each human body. Given somatic mosaicism, epigenetic changes and environmental differences, no two human beings are the same, particularly as there are only ~7 billion people on the planet”.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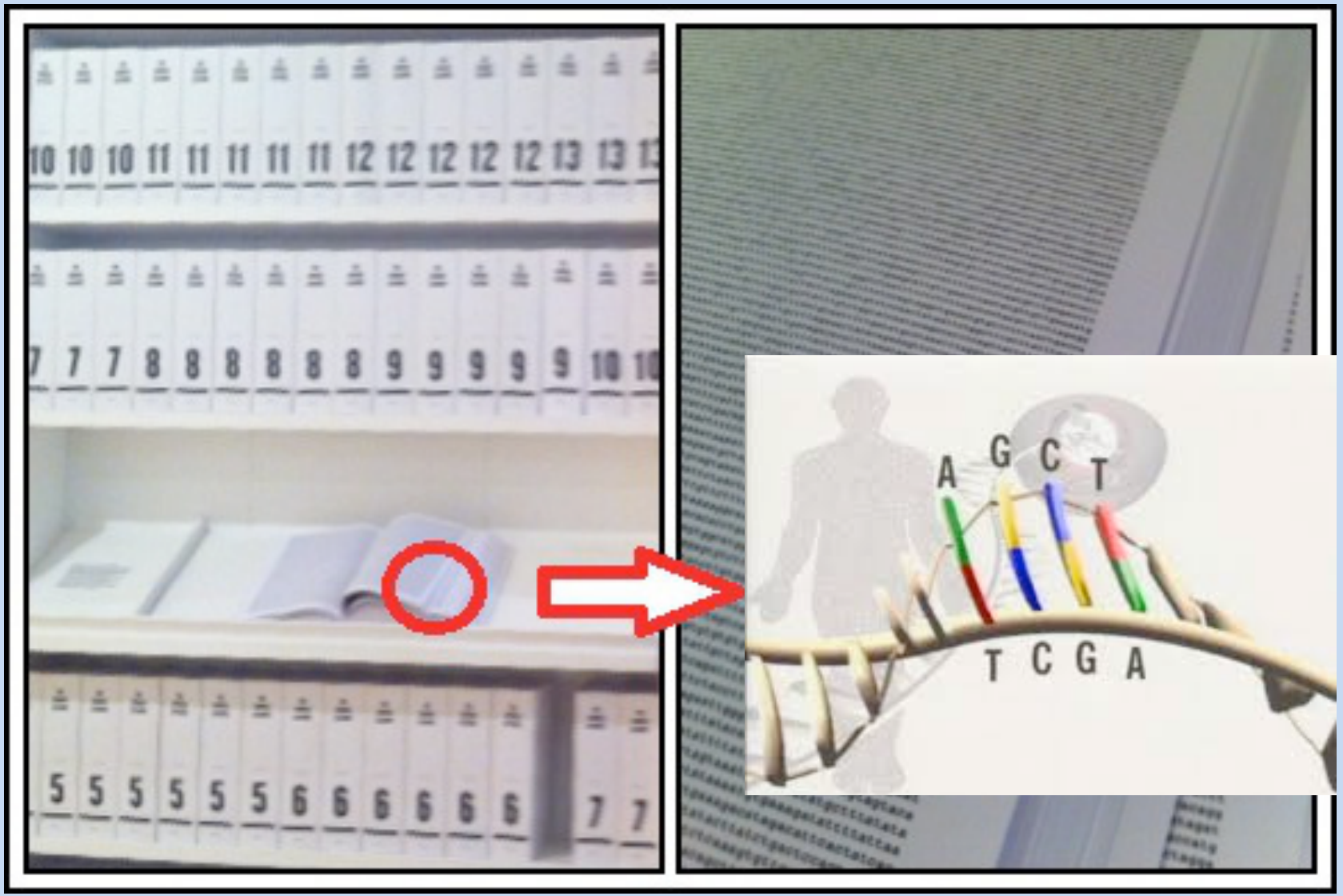
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In the year 2014....
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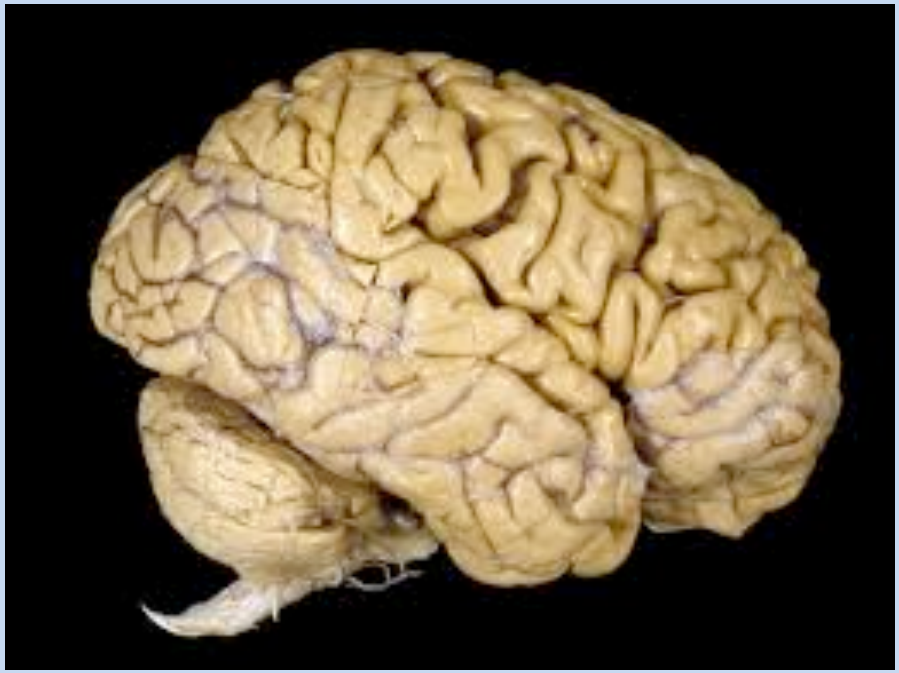
Is orders of magnitudes easier than this:



Clinical Validity with Worldwide Human Genetic Variation "database"?

ancestry.com

PatientsLikeMe

Google

23andMe

Million Veteran Program:
A Partnership with Veterans

100,000 British Genomes

Clinical Validity?

This is SO complex that the only solid way forward is with a “networking of science” model, i.e. online database with genotype and phenotype longitudinally tracked for thousands of volunteer families.

PatientsLikeMe

Lost in Translation

- We need to focus on the extremes, i.e. severe illness, not just the “average” person, i.e. a new focus on rare variant diseases uncovers fundamentally important biological processes.
- Many exciting genetic discoveries are being made and published.
- There is much fanfare and media coverage.
- But, then the genetic researchers move on to the next disease, expecting someone else will engage with the families and perform counseling, education and carrier screening.
- This does not happen mostly (certainly not always).
- Only 0.5% of the 38 MILLION published papers are cited more than 200 times, and HALF are never cited (from Topol, Creative Destruction of Medicine, 2012).

Systemic Barriers

- Sometimes just simple lack of communication between researchers and the physicians and genetic counselors.
- We only have 1500 medical geneticists and 2000 certified genetic counselors for 310 million people in America!
- Insurance will often deny coverage of genetic testing, particularly for novel mutations, so genetic testing is much under-utilized relative to procedure-based medicine.

Systemic Barriers cont….

- Physicians and health care system woefully uneducated regarding genetics.
- Current sequencing (exomes and whole genomes) being sequenced in random laboratories with no clinical standards in place (although people trying to change this).

Cystic Fibrosis

- Gene cloned in 1989
- Finally, drugs screened in human cells, restoring CFTR function, in particular mutated version, G551D.
- Trials for one mutated version G551D, present in 4% of CF patients. The drug worked.
- FDA approval in record time.
- Cost of Drug? $294,000 per year, to be taken for a lifetime. For 60 years, that is ~$18 million per person.
- 4% of 30,000 people with CF in US = 1200.
- So, $21.6 billion to treat 1200 people for 60 years (assuming lower than average lifespan).

A case for cystic fibrosis carrier testing in the general population

Belinda J McClaren, Sylvia A Metcalfe, David J Amor, MaryAnne Aitken and John Massie

MJA • Volume 194 Number 4 • 21 February 2011

- From 2000-2004, 82 children born with CF in Victoria, Australia.
- 5 of these (6%) were from families with known history of CF.
- Even when a family history is known, most relatives do not undertake carrier testing. In an audit of cascade carrier testing after a diagnosis of CF through newborn screening, only 11.8% of eligible (non-parent) (82/716) relatives were tested.
- The other 94% could have been prevented with carrier screening too.

ARTICLE

Uptake of carrier testing in families after cystic fibrosis diagnosis through newborn screening

Belinda J McClaren[1,2,3], Sylvia A Metcalfe*[,1,2], MaryAnne Aitken[2,4], R John Massie[2,5,6], Obioha C Ukoumunne[2,7] and David J Amor[2,3,8]

Clan Genomics and the Complex Architecture of Human Disease

James R. Lupski,[1,2,3,*] John W. Belmont,[1,2] Eric Boerwinkle,[4,5] and Richard A. Gibbs[1,5,*]