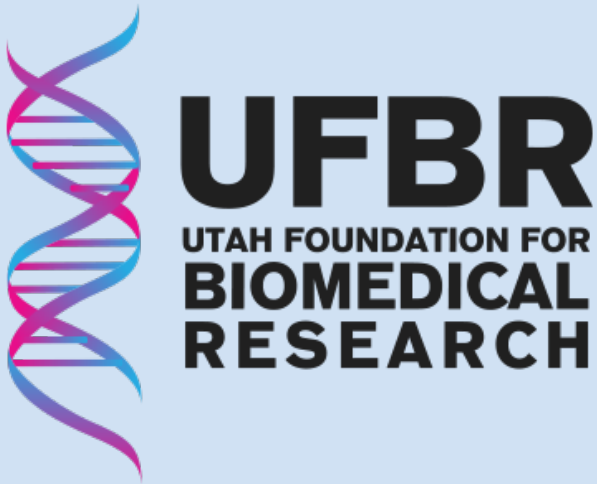
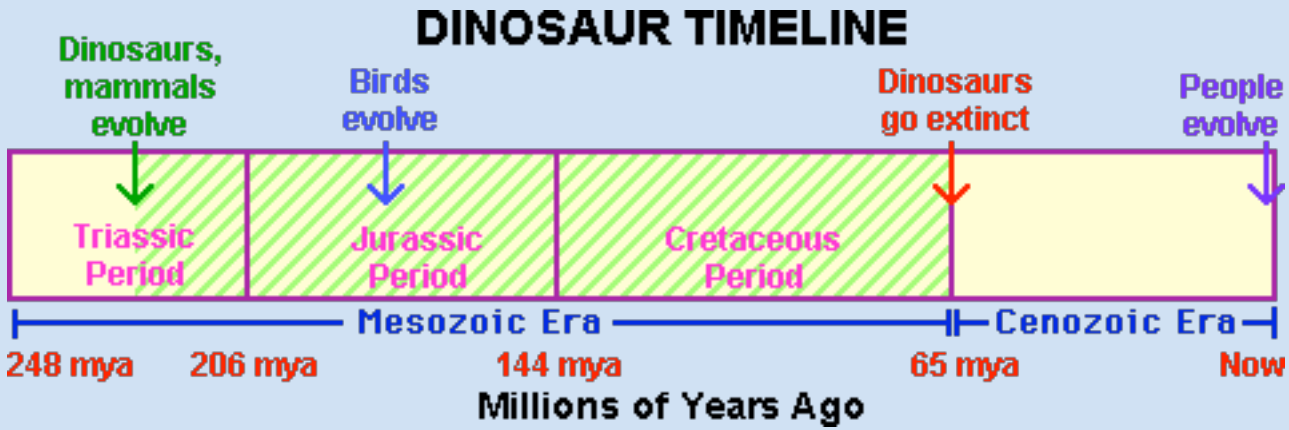
Human Genetic Variation and the Genotype-Phenotype Problem

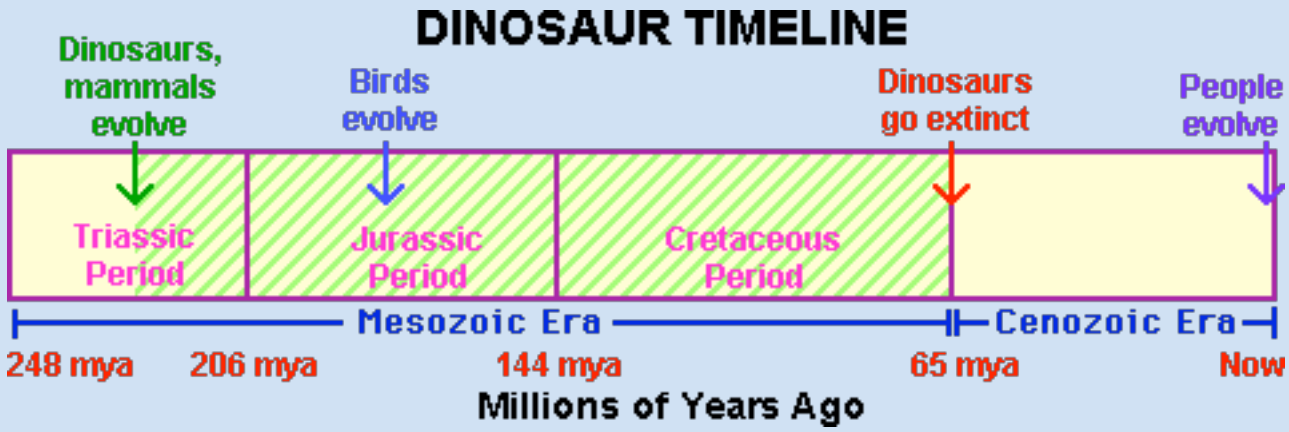
Gholson Lyon, M.D. Ph.D.




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


The Earth
is 4.5 Billion
Years Old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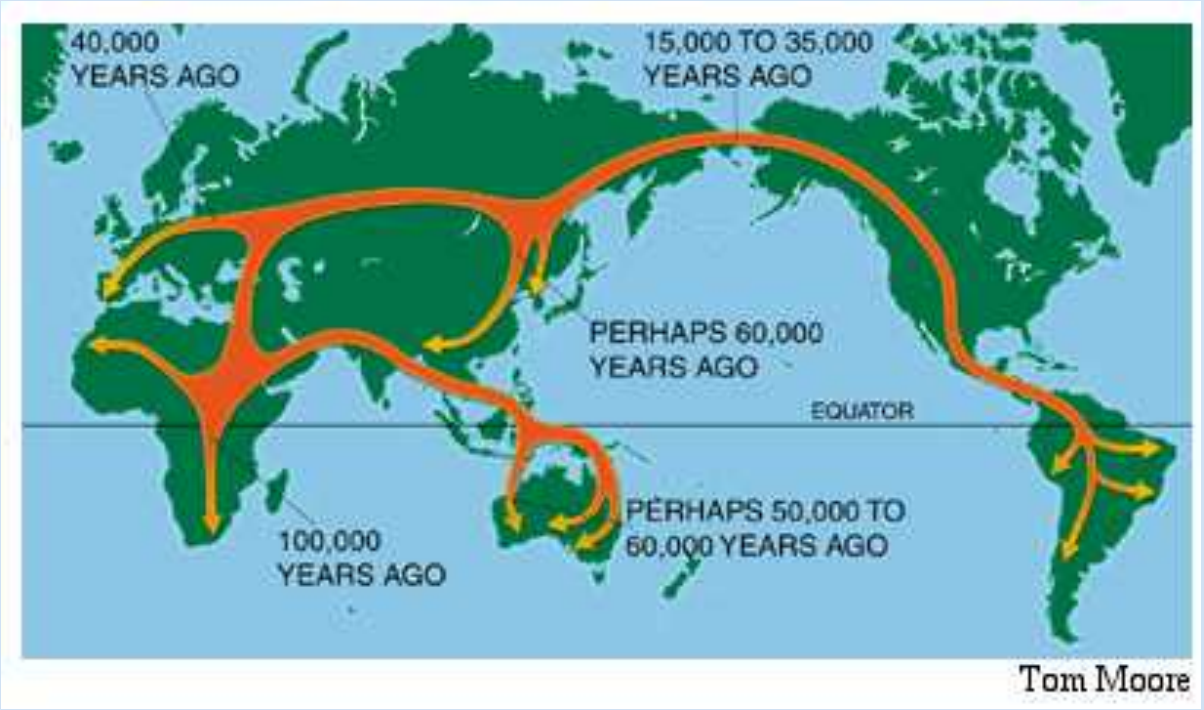
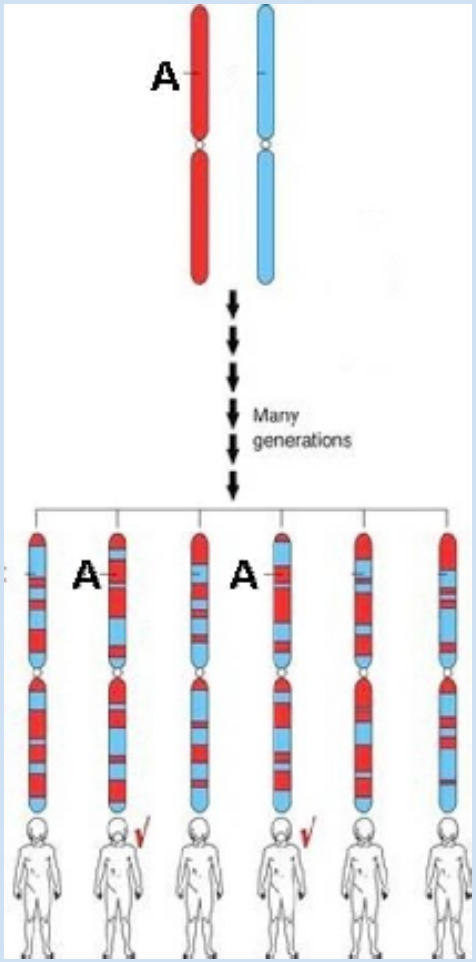
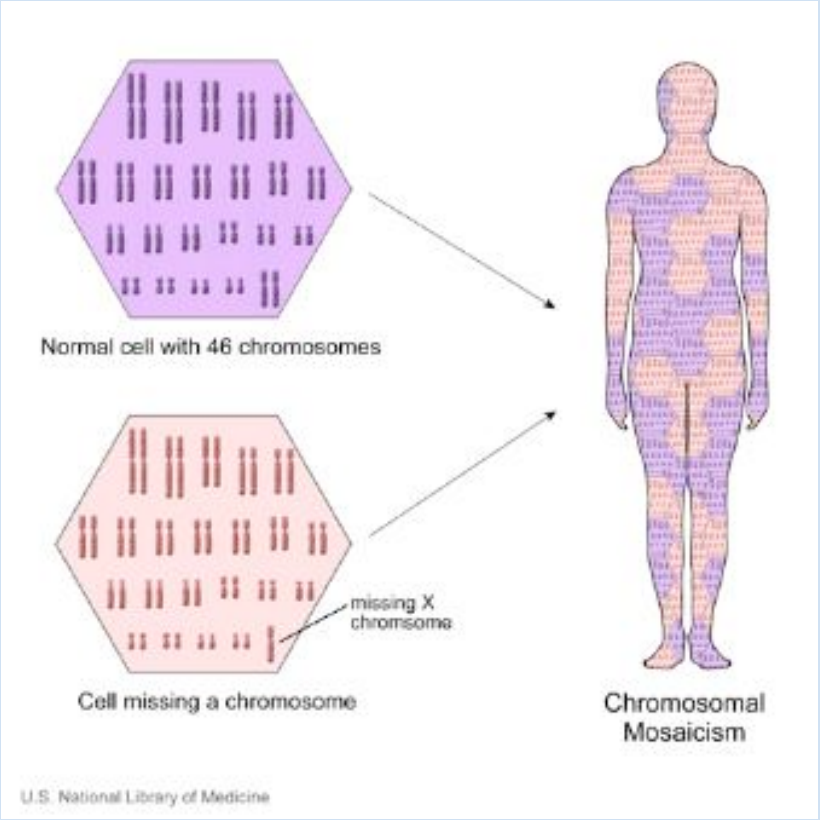
206 mya
144 mya
65 mya
Now
Millions of Years Ago

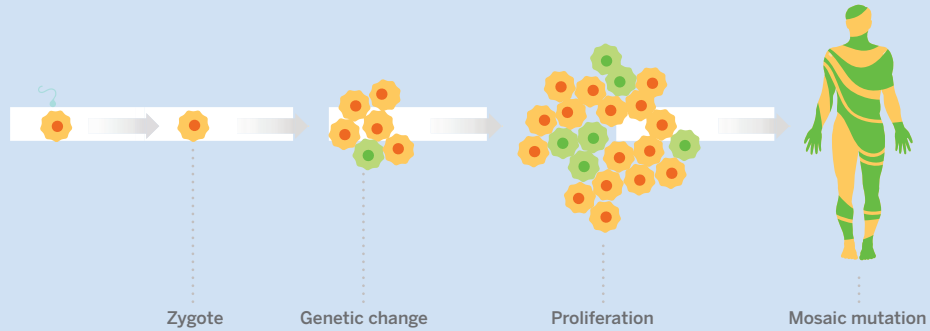

Gulf of Mexico
Campeche Escarpment
Outer rim of buried impact crater
Yucatán Peninsula





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

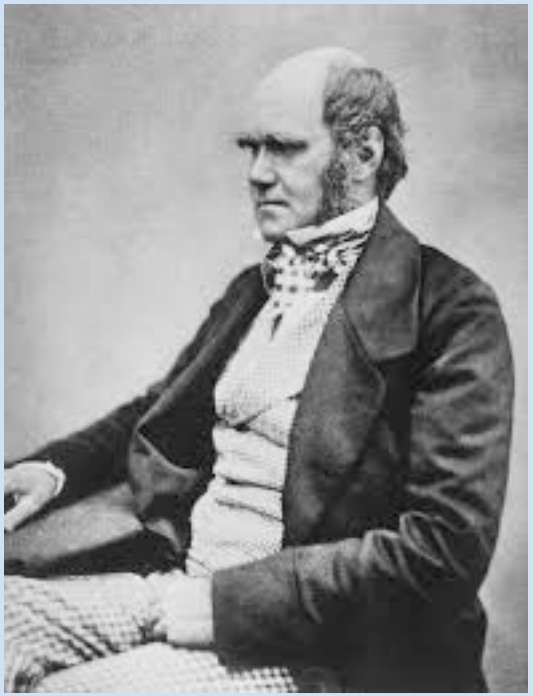




CLINICAL TESTING

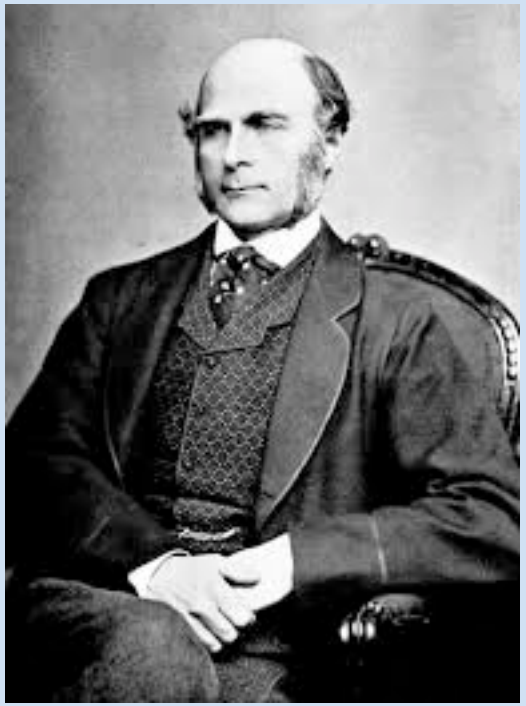
Harmful mutations can fly under the radar

With more sensitive genetic tests, researchers are hunting the roots of disease in the human “mosaic”

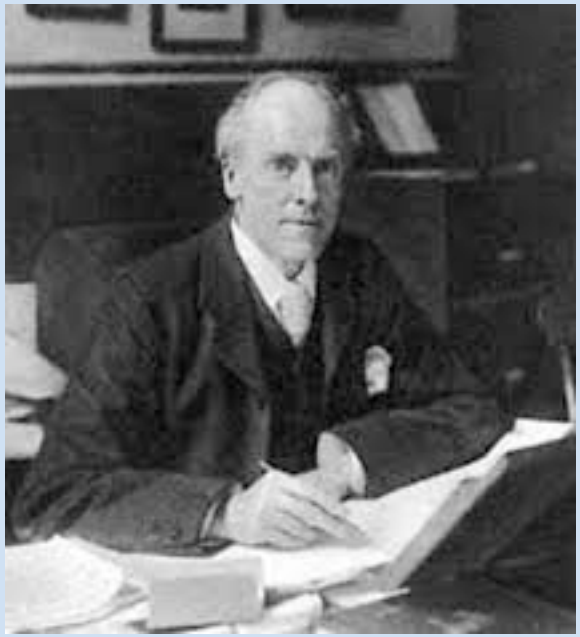


Charles Darwin
1809-1882

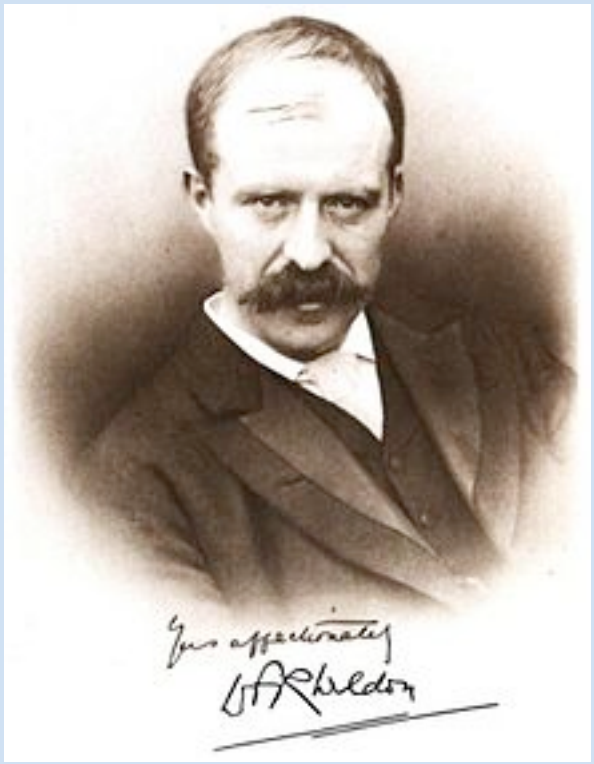
Gregor Mendel
1822-1884



Frances Galton
1822-1911

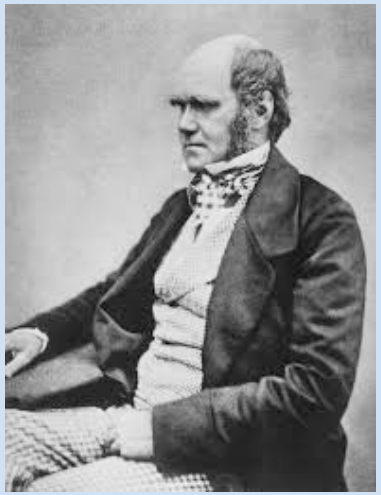


Karl Pearson
1857-1936



Walter Frank Raphael Weldon
1860-1906

William Bateson
1861-1926



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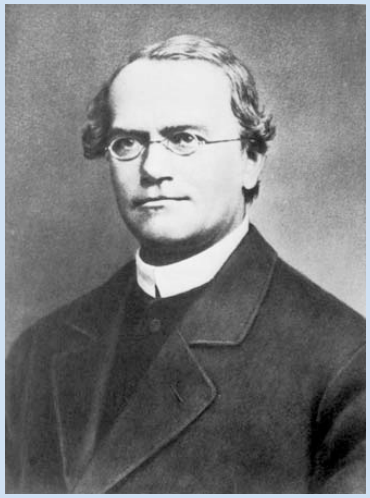

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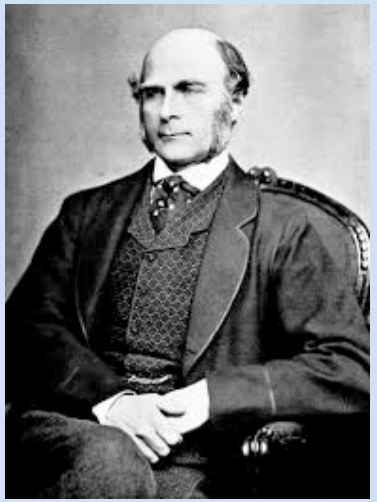

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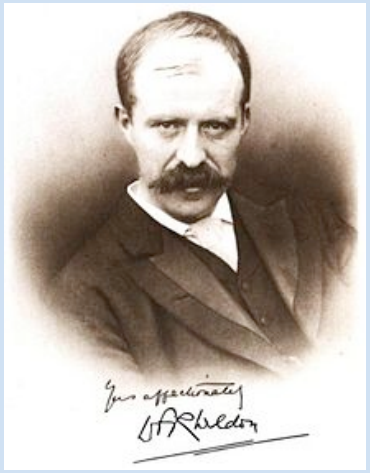


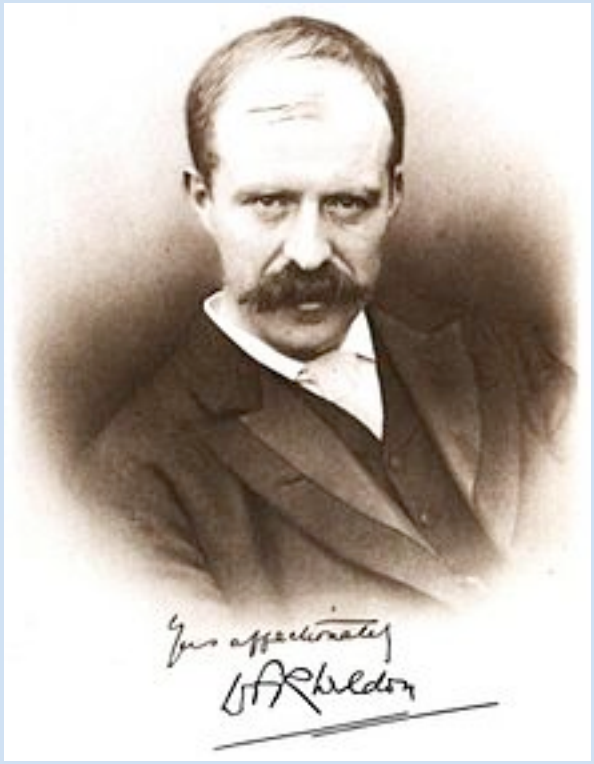
Walter Frank Raphael
Weldon
1860-1906

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.

Weldon, W. F. R. 1902. Mendel's laws of alternative inheritance in peas. *Biometrika*, 1:228-254.

- *“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).*

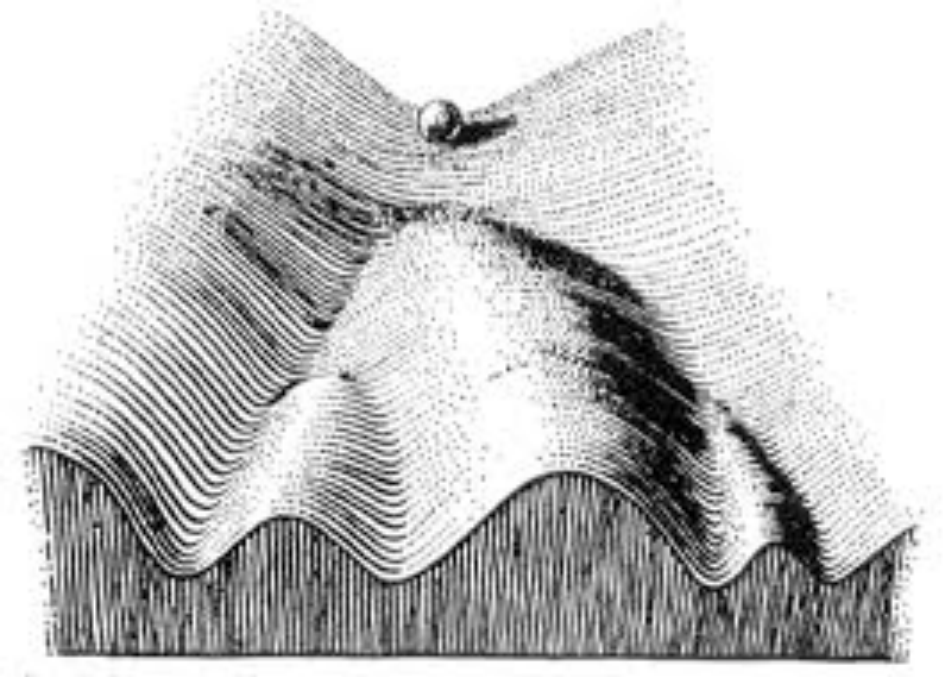

Walter Frank Raphael Weldon 1860–1906
A Memoir
Karl Pearson

“Biological Indeterminacy”

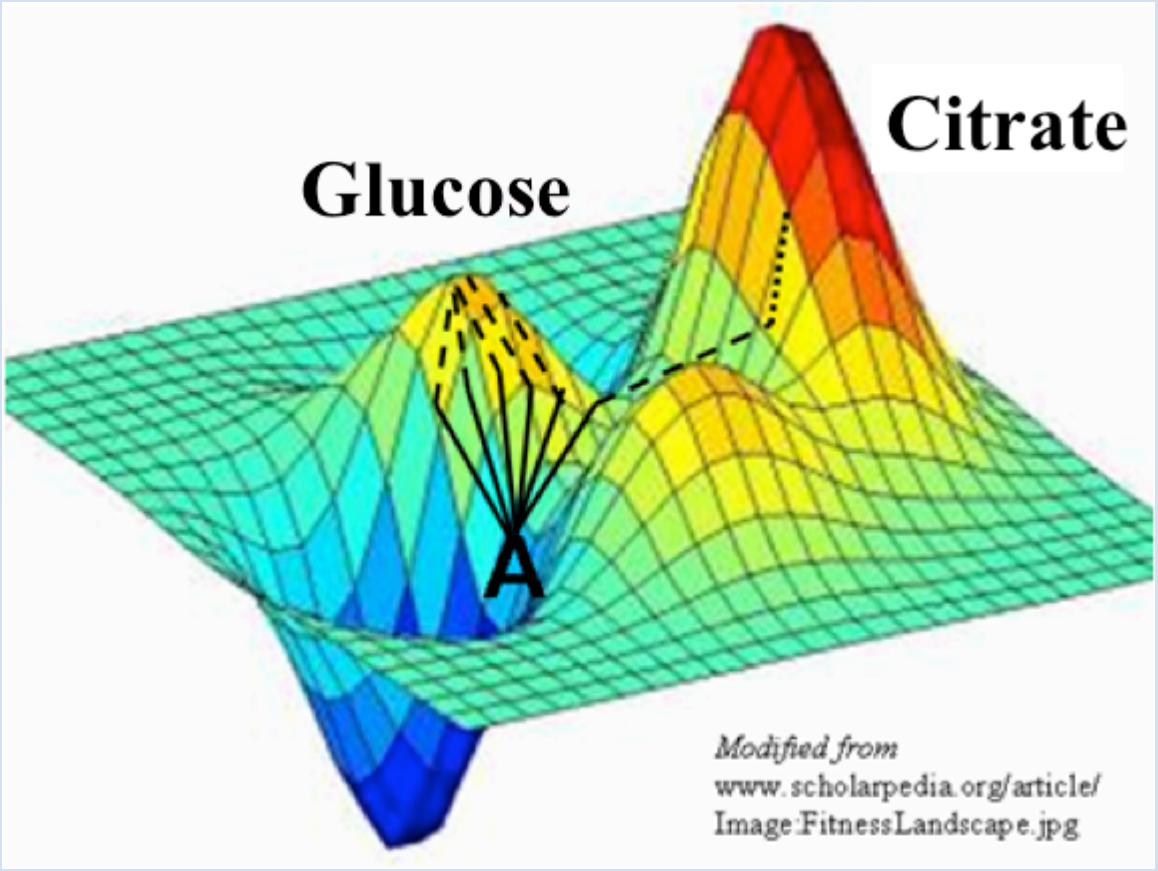
- Bateson became famous as the outspoken Mendelian antagonist of Walter Raphael Weldon, his former teacher, and Karl Pearson who led the biometric school of thinking. This concerned the debate over saltationism versus gradualism (Darwin had been a gradualist, but Bateson was a saltationist). Later, Ronald 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

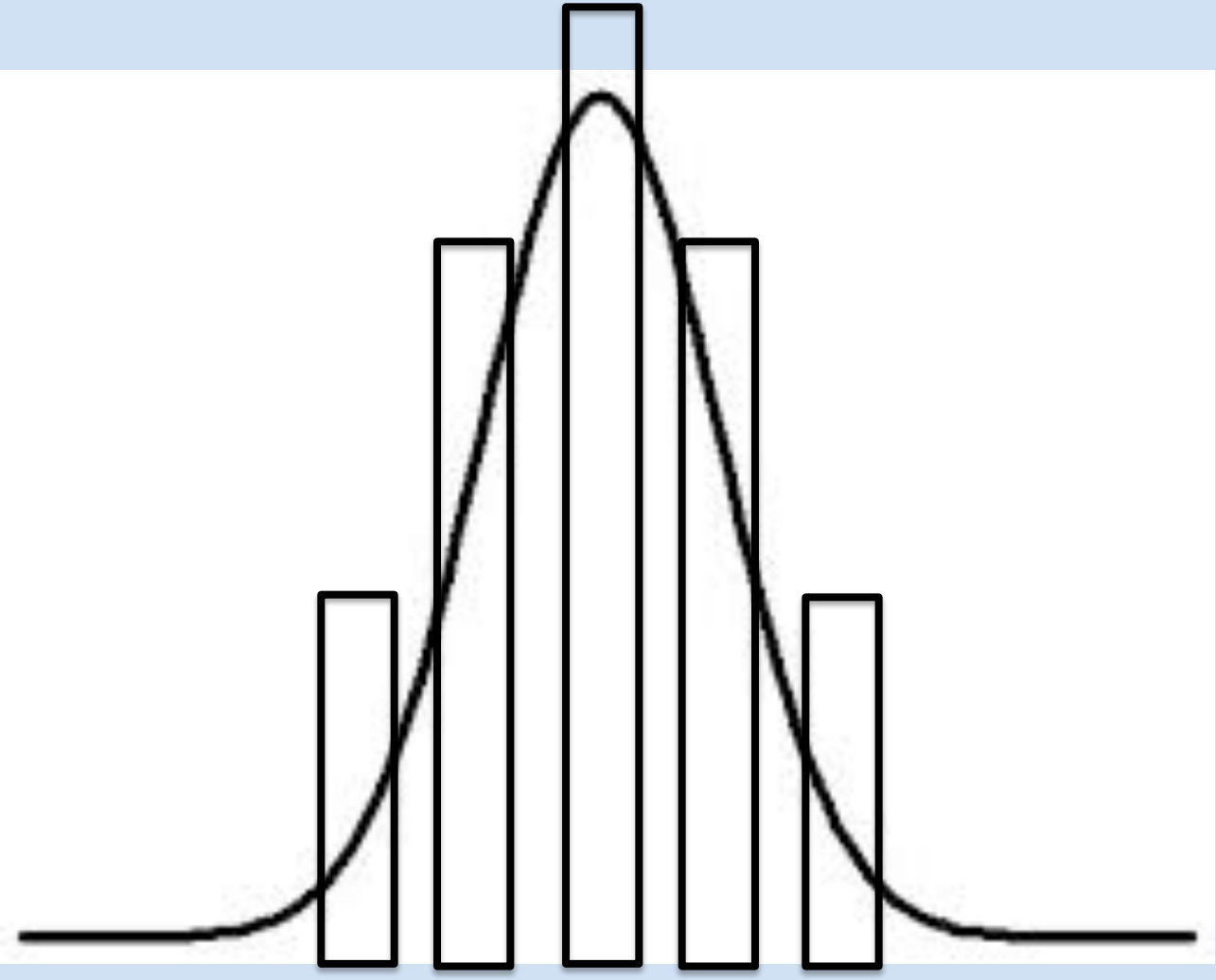
Environment matters!

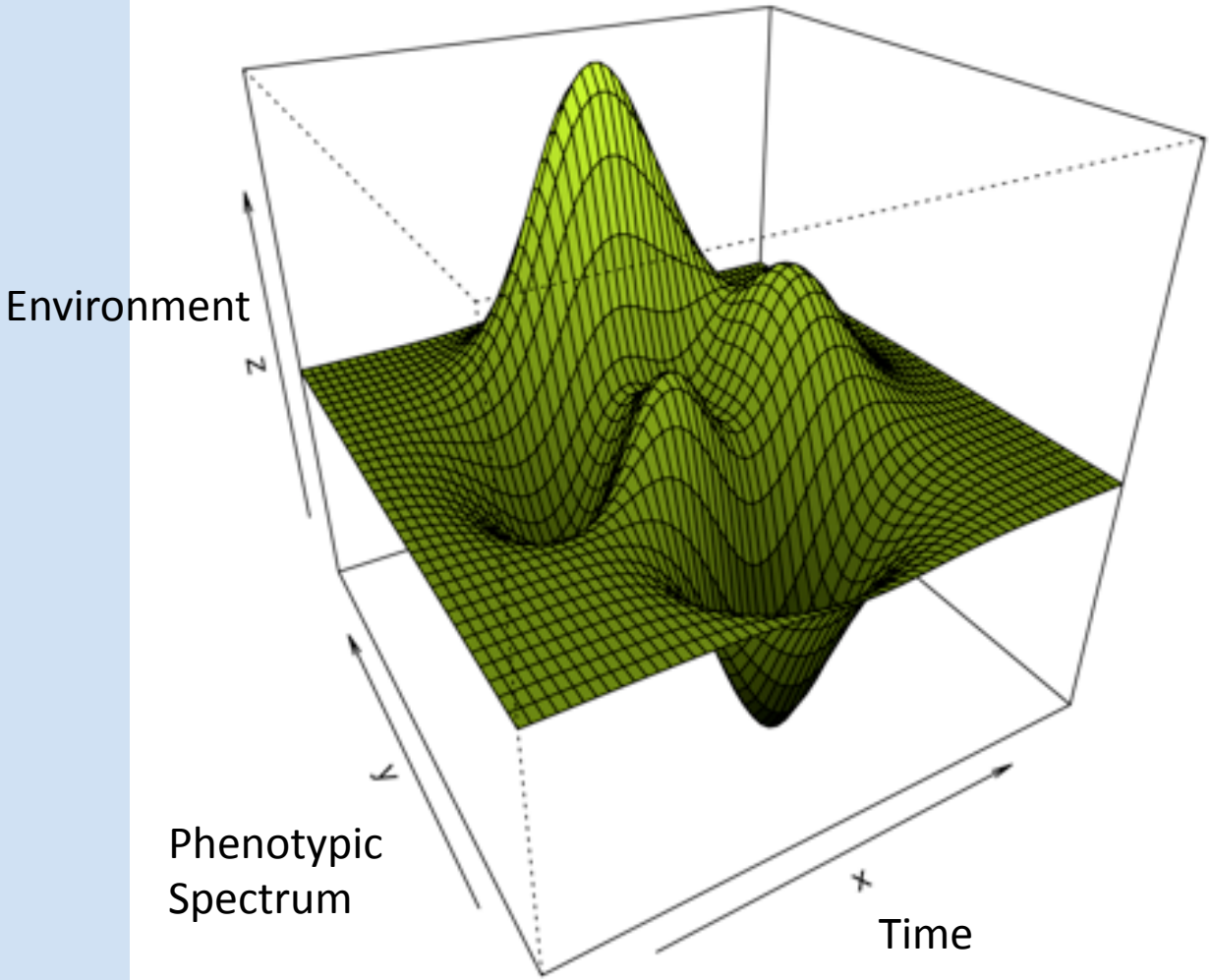
Ancestry matters!

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.

Some Definitions …

- The words “penetrance” and “expressivity”, defined classically as:
- Penetrance: whether someone has ANY symptoms of a disease, i.e. all or none, 0% or 100%. **Nothing in between.**
- Expressivity: how much disease (or how many symptoms) someone with 100% penetrance has.
- This has led to endless confusion!
- Some just use the word “penetrance” to mean the expressivity of disease, i.e. incomplete penetrance, and maybe we should combine the two terms into ONE word with the full expression from 0-100% of phenotypic spectrum.

Definitions. It is unknown what portion of autism will be oligogenic vs. polygenic

- **Oligogenic** – multiple mutations together contributing to aggregate disease, BUT with only 1 mutation of ~ >10% "effect size in EACH person.
- **Polygenic** – Dozens to hundreds of mutations in different genes in the SAME person, together contributing to the disease in the SAME person, hence **additive** and/or **epistatic** contribution with ~0.01-1% penetrance for each mutation.

Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs

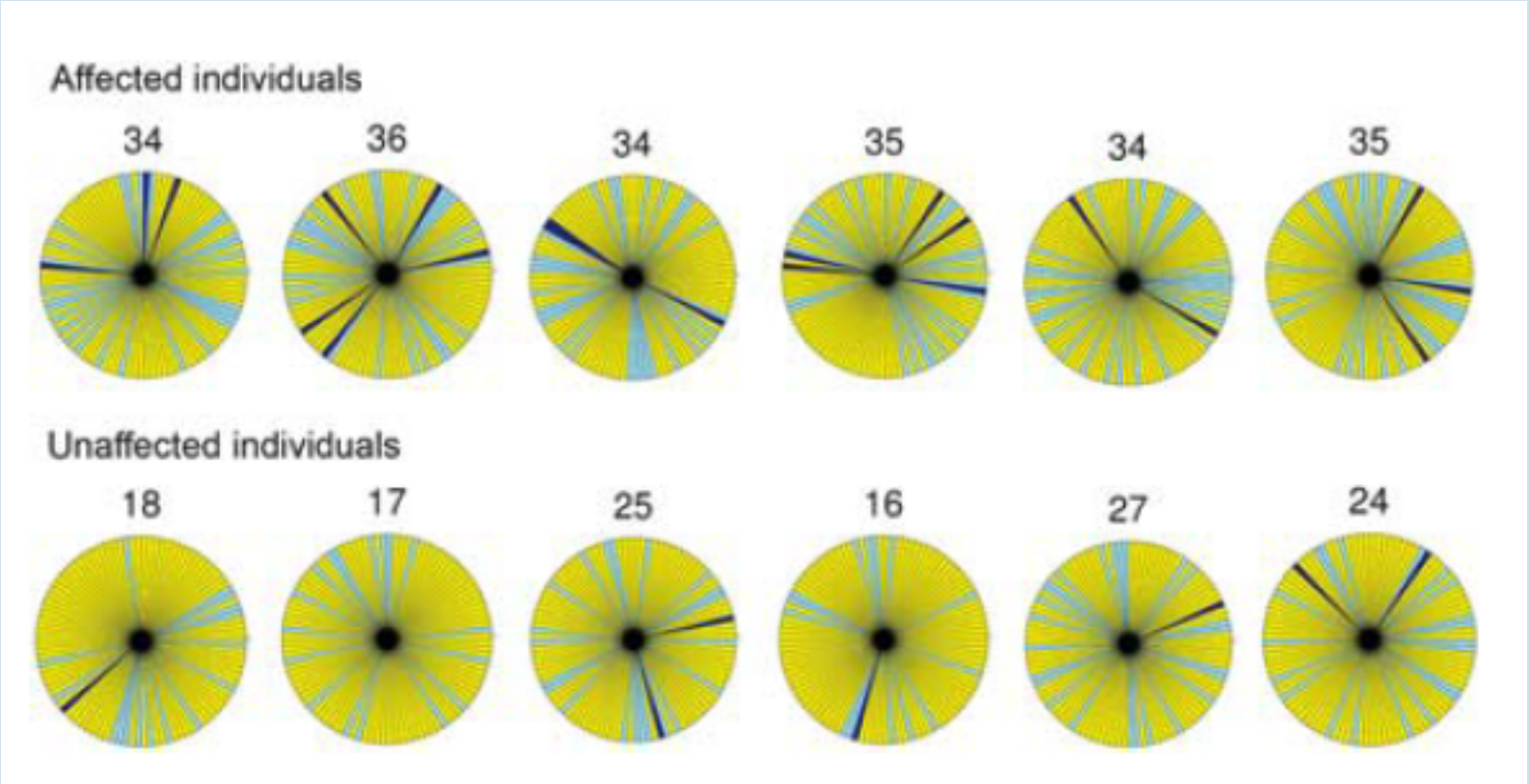
S Hong Lee[1,2], Teresa R DeCandia[3,4], Stephan Ripke[5,6], Jian Yang[2,7], The Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ)[8], The International Schizophrenia Consortium (ISC)[8], The Molecular Genetics of Schizophrenia Collaboration (MGS)[8], Patrick F Sullivan[9], Michael E Goddard[10,11], Matthew C Keller[3,4,12], Peter M Visscher[1,2,7,12] & Naomi R Wray[1,2,12]

NATURE GENETICS ADVANCE ONLINE PUBLICATION

Received 16 August 2011; accepted 17 January 2012; published online 19 February 2012; doi:10.1038/ng.1108

"Of complex genetic diseases, schizophrenia has perhaps been the subject of the most speculation and debate relating to its genetic architecture[4,5], and the relative importance of common causal variants remains controversial[6,7]."

Example of Polygenic Model



Visscher et al. 2011

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.
- Complexity, or “The False Negative Problem”

Archibald Garrod

Garrod, Archibald E. 1902. The Incidence of Alkaptonuria: A Study in Chemical Individuality. *Lancet*, vol. ii, pp. 1616–1620.

THE INCIDENCE OF ALKAPTONURIA: A STUDY IN CHEMICAL INDIVIDUALITY

ARCHIBALD E. GARROD

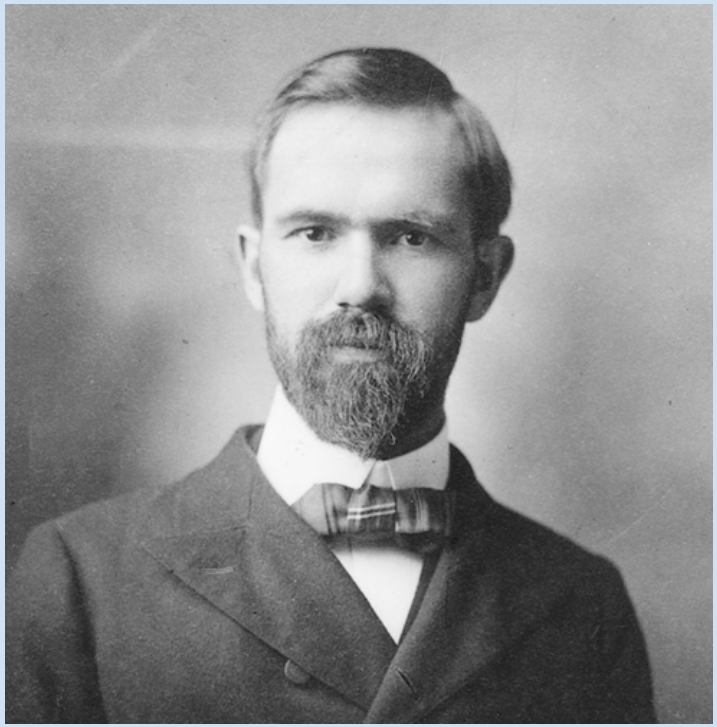
Physician to the Hospital for Sick Children, Great Ormondstreet, Demonstrator of Chemical Pathology at St. Bartholemew's Hospital

ALL THE MORE RECENT WORK on alkaptonuria has tended to show

1857-1936

Observed and deduced genetic pattern for 4 human diseases: alkaptonuria, cystinuria, pentosuria, and albinism.

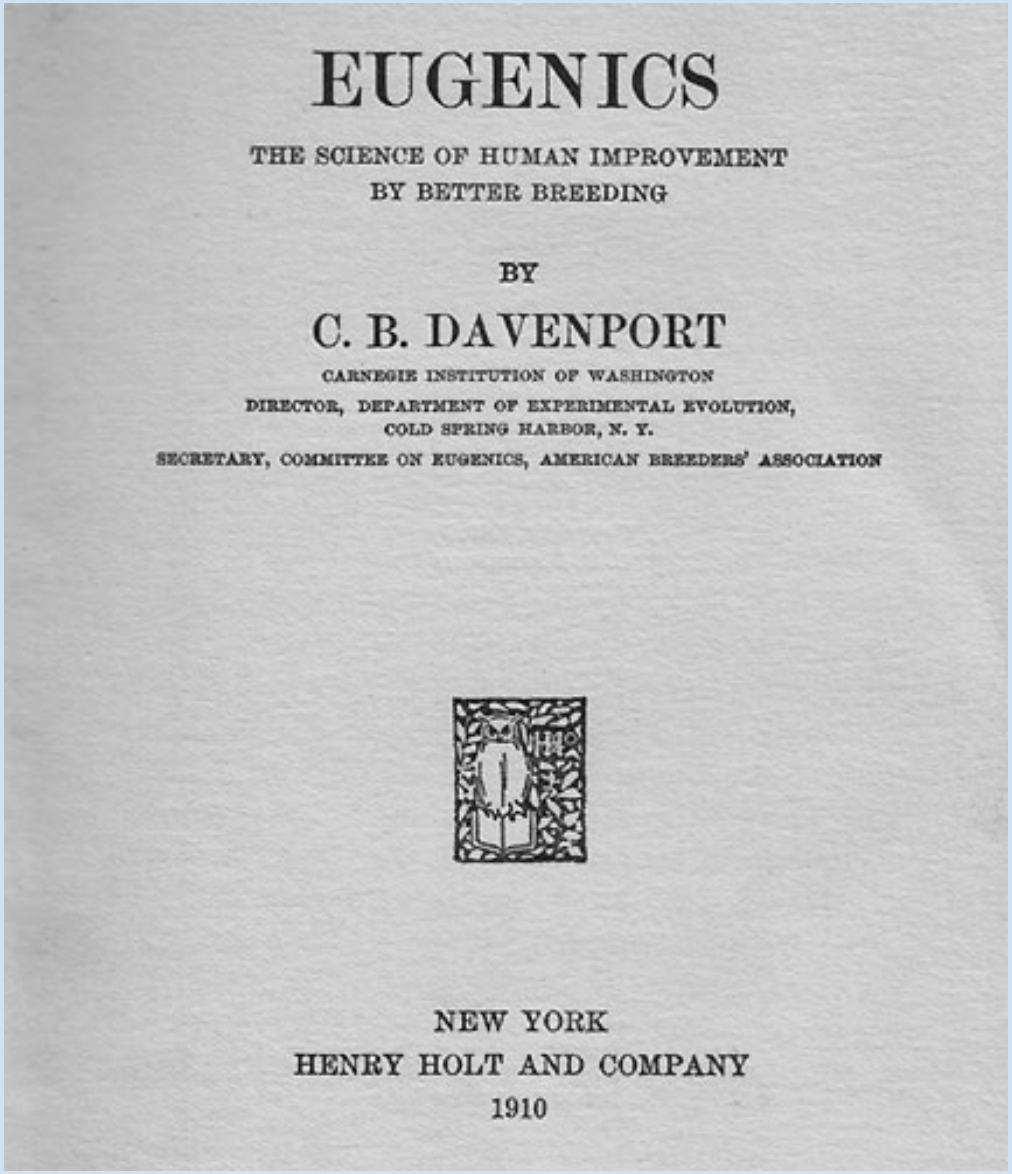
Definitive Biography: Archibald Garrod & the Individuality of Man, by Alexander Bearn.



Director, 1866-1944
Charles Davenport

Station for Experimental Evolution – 1904
(Carnegie Institution of Washington)

Davenport on Applying Human Genetics



EUGENICS

THE SCIENCE OF HUMAN IMPROVEMENT
BY BETTER BREEDING

BY

C. B. DAVENPORT

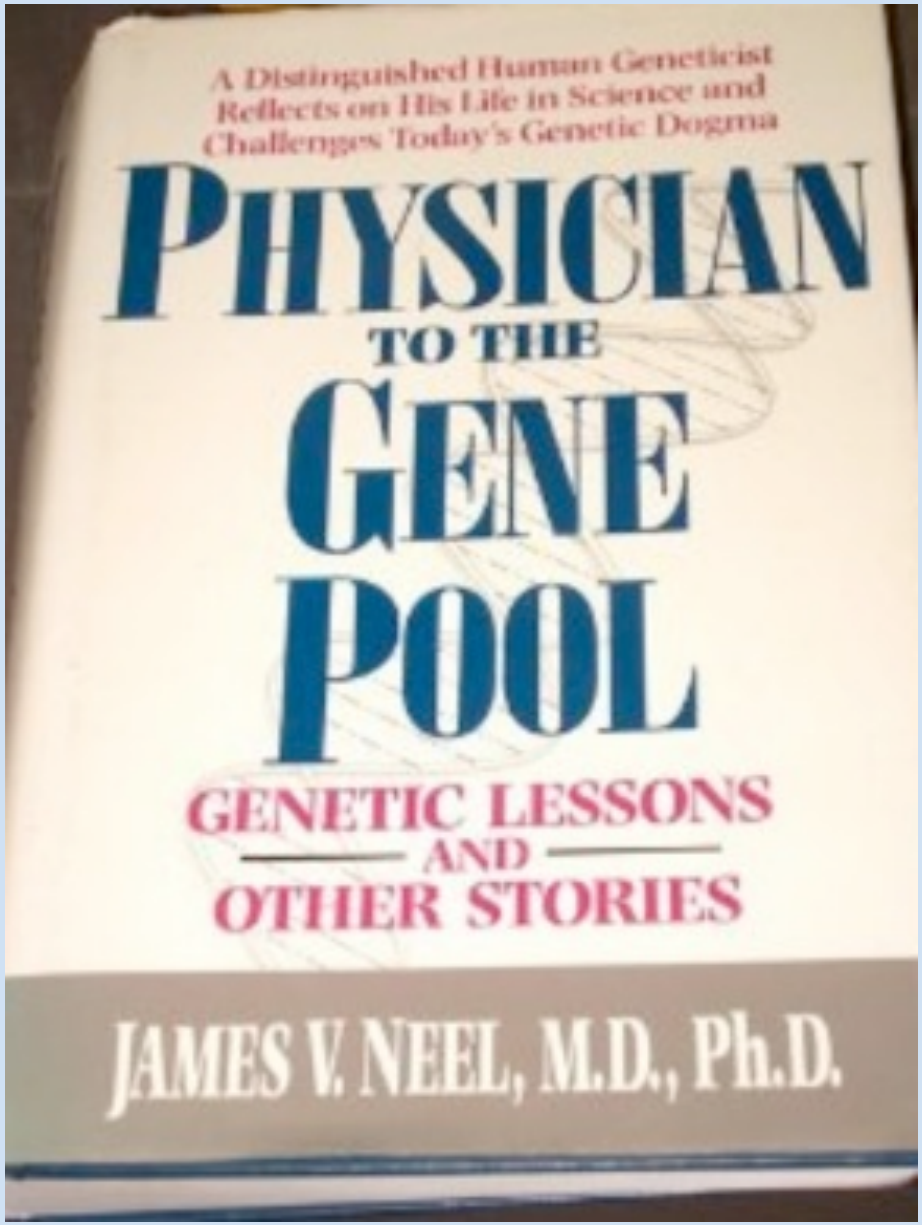
CARNEGIE INSTITUTION OF WASHINGTON
DIRECTOR, DEPARTMENT OF EXPERIMENTAL EVOLUTION,
COLD SPRING HARBOR, N. Y.
SECRETARY, COMMITTEE ON EUGENICS, AMERICAN BREEDERS' ASSOCIATION

NEW YORK
HENRY HOLT AND COMPANY
1910

Shall we not…take the steps that scientific study dictates as necessary, to dry up the springs that feed the torrent of defective and degenerate protoplasm?

Critique of Davenport

- “Most studies were performed by volunteers of class I social standing, who were given a summer’s training, then turned loose.” James Neel’s book, p. 15.
- From Heron (quoted from Neel): “the material has been collected in an unsatisfactory manner, the data have been tabled in a most slipshod fashion, and the Mendelian conclusions drawn have no justification whatever”.


A Distinguished Human Geneticist
Reflects on His Life in Science and
Challenges Today's Genetic Dogma
PHYSICIAN
TO THE
GENE
POOL
GENETIC LESSONS
AND
OTHER STORIES
JAMES V. NEEL, M.D., Ph.D.

Geneticists Begin to Criticize the Eugenicists

A mingled mess of ill-grounded and uncritical sociology, economics, anthropology and politics, full of emotional appeals to class and race prejudices, solemnly put forward as *science,* and unfortunately accepted as such by the general public.

R. Pearl, *The Present State of Eugenics,* 1928

Geneticists Begin to Criticize the Eugenicists

Social reforms might, perhaps, more quickly and efficiently get at the root of a part of the trouble, and until we know how much the environment is responsible for, I am inclined to think that the student of human heredity will do well to recommend more enlightenment on the social causes of deficiencies rather than more elimination in the present deplorable state of our ignorance as to the causes of mental differences.

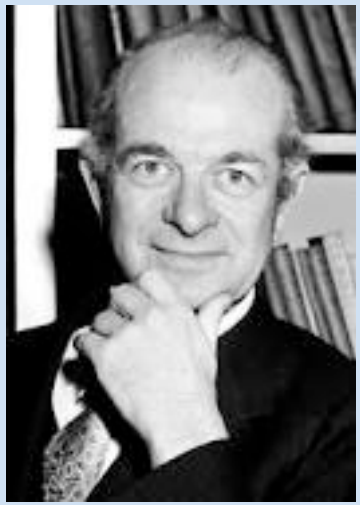
T. H. Morgan, *Evolution & Genetics,* 1925

November 25, 1949, Vol. 110 SCIENCE 543

Sickle Cell Anemia, a Molecular Disease[1]

Linus Pauling, Harvey A. Itano,[2] S. J. Singer,[2] and Ibert C. Wells[3]

Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California[4]



1901-1994

The results indicate that a significant difference exists between the electrophoretic mobilities of hemoglobin derived from erythrocytes of normal individuals and from those of sickle cell anemic individuals. The two types of hemoglobin are particularly easily distinguished as the carbonmonoxy compounds at pH 6.9 in phosphate buffer of 0.1 ionic strength. In this buffer the sickle cell anemia carbonmonoxyhemoglobin moves as a positive ion, while the normal compound moves as a negative ion, and there is no detectable amount of one type present in the other.[4] The hemoglobin derived from erythrocytes of individuals with sicklemia, however, appears to be a mixture of the normal hemoglobin and sickle cell anemia hemoglobin in roughly equal proportions. Up to the present time the hemoglobins of 15 persons with sickle cell anemia, 8 persons with sicklemia, and 7 normal adults have been examined. The hemoglobins of normal adult white and negro individuals were found to be indistinguishable.

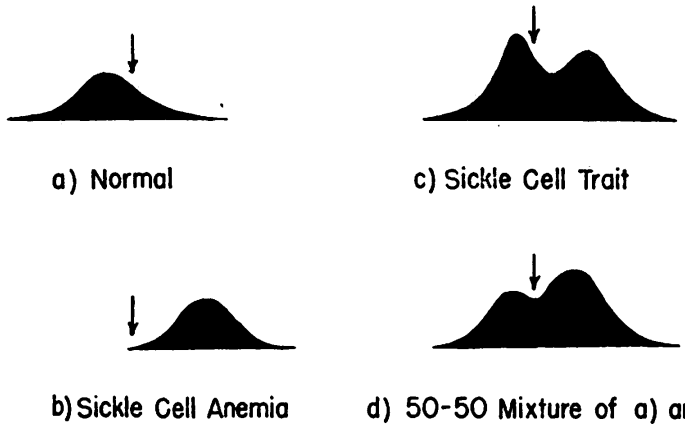


FIG. 3. Longsworth scanning diagrams of carbonmonoxyhemoglobins in phosphate buffer of 0.1 ionic strength and pH 6.90 taken after 20 hours' electrophoresis at a potential gradient of 4.73 volts/cm.

The first time a genetic disease was linked to a mutation of a specific protein.

The Inheritance of Sickle Cell Anemia[1]

James V. Neel

Heredity Clinic, Laboratory of Vertebrate Biology, University of Michigan, Ann Arbor

1915-2000

was recognized as a clinical entity (*5*). On the basis of a study of one large family, Taliaferro and Huck (*15*) postulated that the ability to sickle was due to a single dominant gene. At that time the clinical distinction between sicklemia and sickle cell anemia had not been clearly drawn, and the inference was that this gene was more strongly expressed in some individuals (sickle cell anemia) than in others (sicklemia). This has remained the accepted hypothesis up to the present time. Several years ago the author, in a review on the clinical detection of the genetic carriers of inherited disease (*9*), was led to suggest an alternative hypothesis—namely, that there existed in Negro populations a gene which in heterozygous condition results in sicklemia, and in homozygous condition in sickle cell anemia. This hypothesis has a counterpart in the relationship which has been demonstrated to exist between thalassemia major and minor (*10, 16*).

Thus far we have tested 42 parents of 29 patients with sickle cell anemia for the occurrence of sickling. In 13 instances both parents were studied and in 16, only one. Tests have been conducted in a variety of ways; especial reliance has been placed on a combination of the techniques described by Scriver and Waugh (*11*) and Hansen-Pruss (*7*), whereby a tourniquet is applied to a finger for 3–5 minutes, and then a drop of static blood from the finger is placed on a slide to which a small amount of Janus green or methylene blue has been added, and it is quickly covered with a cover slip which is sealed with vaseline. Observations are made at intervals up to 72 hours. Five preparations have been made for each individual. Every parent tested to date has sickled. This is the result expected from the homozygous-heterozygous hypothesis outlined above. On the other hand, the probability of the occurrence of such a number of positive parents under the variable dominant hypothesis is $(0.765)^{42}$, or 0.000013.

Biochimica et Biophysica Acta

Volume 36, Issue 2, December 1959, Pages 402–411

Abnormal human haemoglobins. III the chemical difference between normal and sickle cell haemoglobins

V.M. Ingram*

Molecular Biology Unit of the Medical Research Council, Cavendish Laboratory, University of Cambridge England

Received 20 September 1958, Revised 13 July 1959, Available online 17 December 2002

Cloning the gene for an inherited human disorder—chronic granulomatous disease—on the basis of its chromosomal location

Brigitte Royer-Pokora[*], Louis M. Kunkel[†], Anthony P. Monaco[†], Sabra C. Goff[*], Peter E. Newburger[‡], Robert L. Baehner[*], F. Sessions Cole[§], John T. Curnutte[‖] & Stuart H. Orkin[*¶≠]

[*] Division of Hematology-Oncology, The Children's Hospital, Dana-Farber Cancer Institute, Department of Pediatrics, [†] Division of Genetics, The Children's Hospital, Department of Pediatrics and the Program in Neuroscience, [§] Division of Cell Biology, The Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115, USA
[‡] Division of Pediatric Hematology, Department of Pediatrics, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA
[‖] Division of Pediatric Hematology, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA
[¶] Howard Hughes Medical Institute, Children's Hospital, Boston, Massachusetts 02115, USA

The gene that is abnormal in the X-linked form of the phagocytic disorder chronic granulomatous disease has been cloned without reference to a specific protein by relying on its chromosomal map position. The transcript of the gene is expressed in the phagocytic lineage of haematopoietic cells and is absent or structurally abnormal in four patients with the disorder. The nucleotide sequence of complementary DNA clones predicts a polypeptide of at least 468 amino acids with no homology to proteins described previously.

NATURE VOL. 322 3 JULY 1986

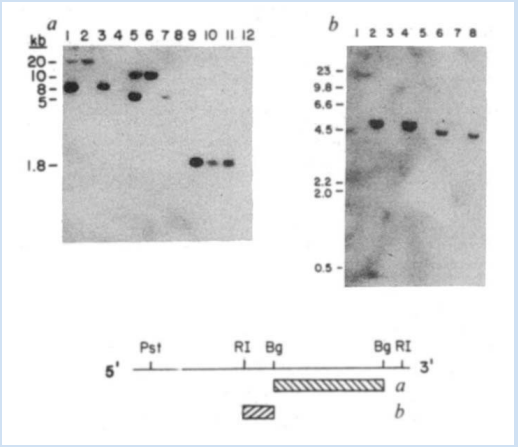


Fig. 5 Partial gene deletion in an X-CGD patient. Total cellular DNAs (5 μg per lane) were digested with *Bam*HI (*a*, lanes 1–4), *Hin*dIII (*a*, 5–8; *b*, 1–4) or *Bgl*II (*a*, 9–12; *b*, 5–8), electrophoresed, and hybridized with the regions of the 379 cDNA indicated at the bottom of the figure. *a*, DNAs from mother of patient J.W. (lanes 1, 5, 9), X-CGD patient J.W. (lanes 2, 6, 10) and Xp21 deletion patient N.F.[13] affected with CGD and DMD (lanes 4, 8, 12). Lanes 3, 7, 11, normal DNA. *b*, DNAs from patient J.W. (lanes 1, 5), mother of J.W. (lanes 2, 6) and patient N.F. (lanes 3, 7). Lanes 4, 8, normal DNA.

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

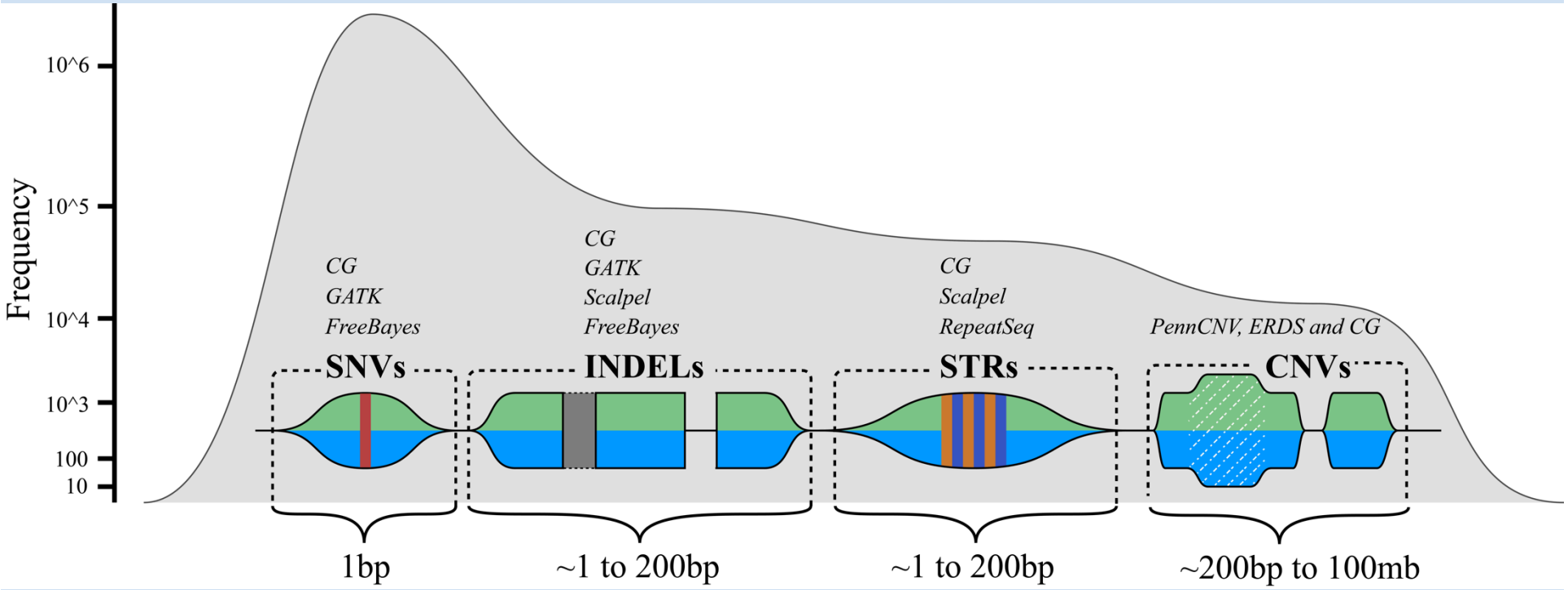
MJA • Volume 194 Number 4 • 21 February 2011

- 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]

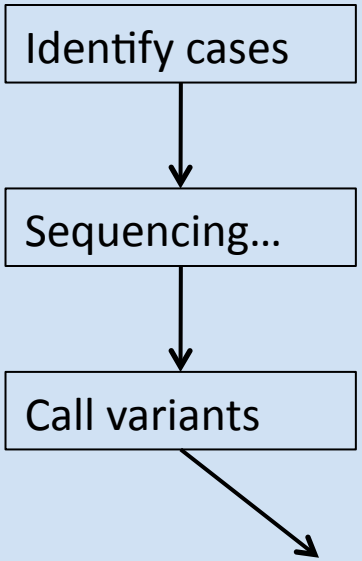

Frequency
10^6
10^5
10^4
10^3
100
10
CG
GATK
FreeBayes
SNVs
CG
GATK
Scalpel
FreeBayes
INDELs
CG
Scalpel
RepeatSeq
STRs
PennCNV, ERDS and CG
CNVs
1bp
~1 to 200bp
~1 to 200bp
~200bp to 100mb

The Genomic Data Deluge

- Pre-sequencing era: not so much data
  - 1. High-quality data
  - 2. Well designed software tools

- Sequencing era: too much data
  - 1. Noisy data
  - 2. Massive quantity to handle

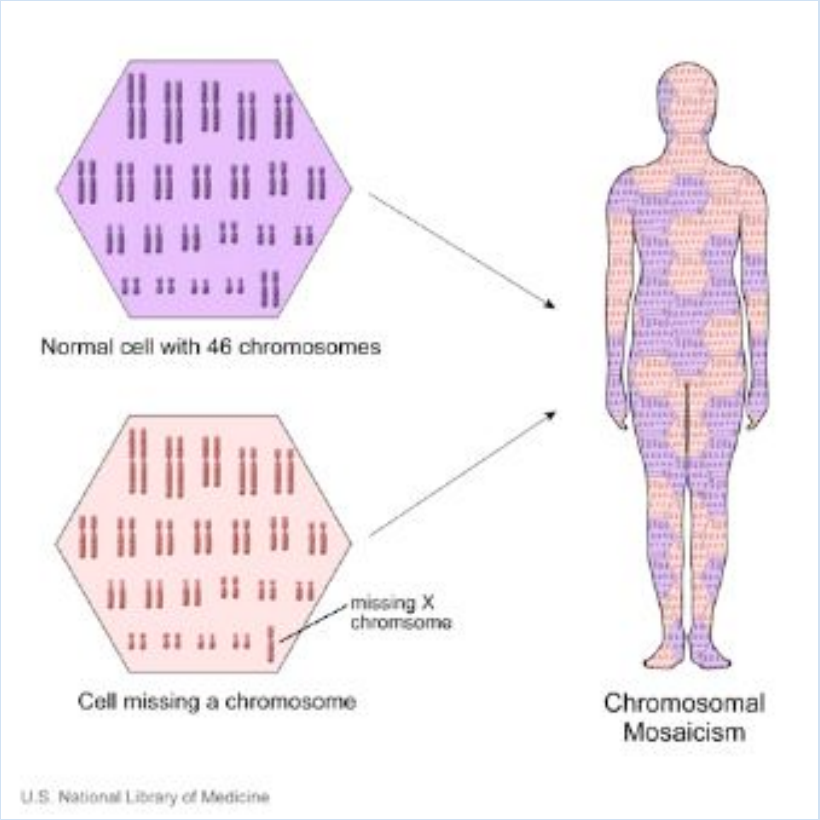
A typical exome sequencing study

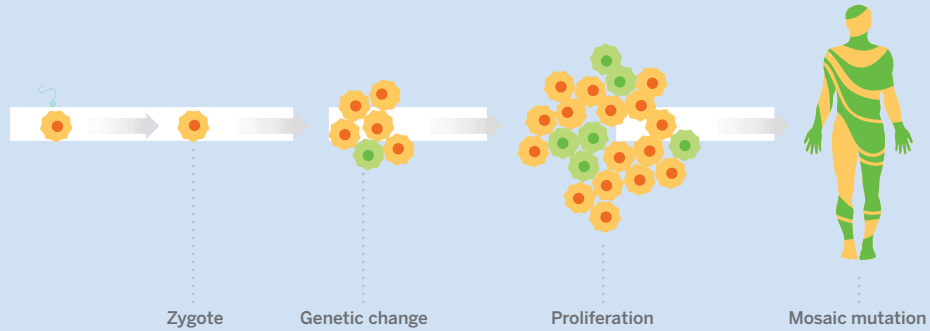


We need functional interpretation of personal genomes!

What to do next?

3 million SNPs
0.5 million indels
1 thousand structural variants
Which one causes the disease?
Which ones confer susceptibility?

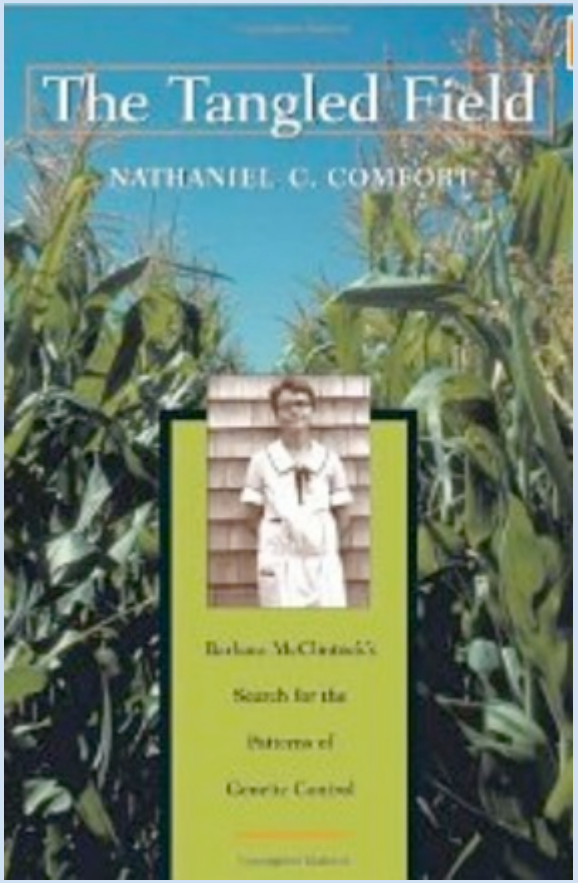




CLINICAL TESTING

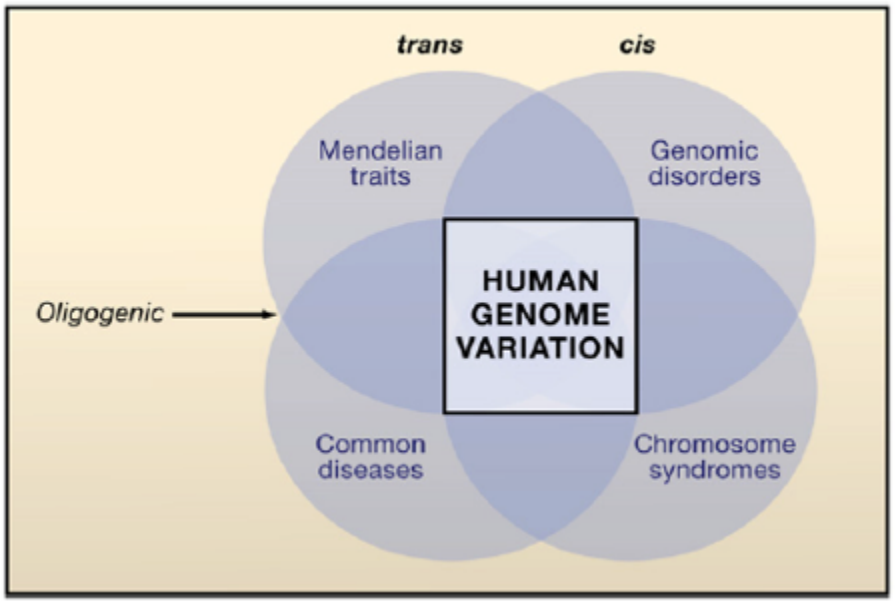
Harmful mutations can fly under the radar

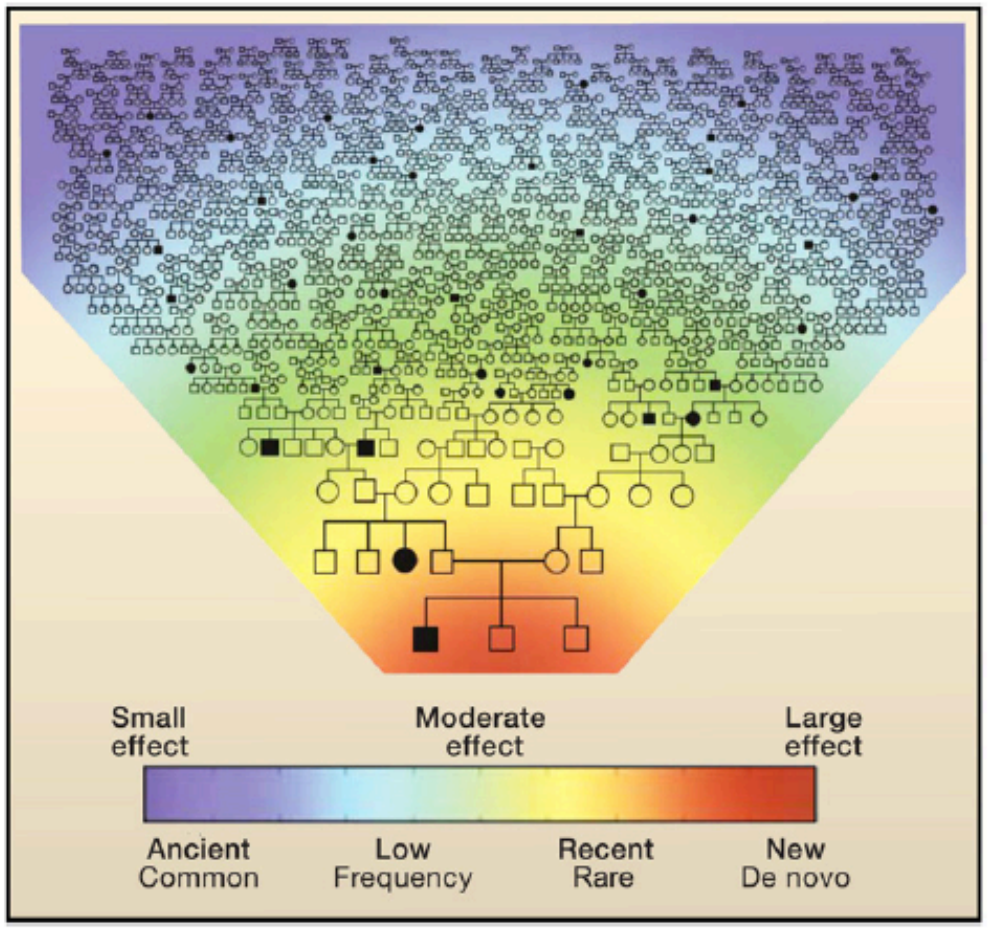
With more sensitive genetic tests, researchers are hunting the roots of disease in the human “mosaic”


The Tangled Field
NATHANIEL C. COMFORT

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,*]





The Biology of MENTAL DEFECT

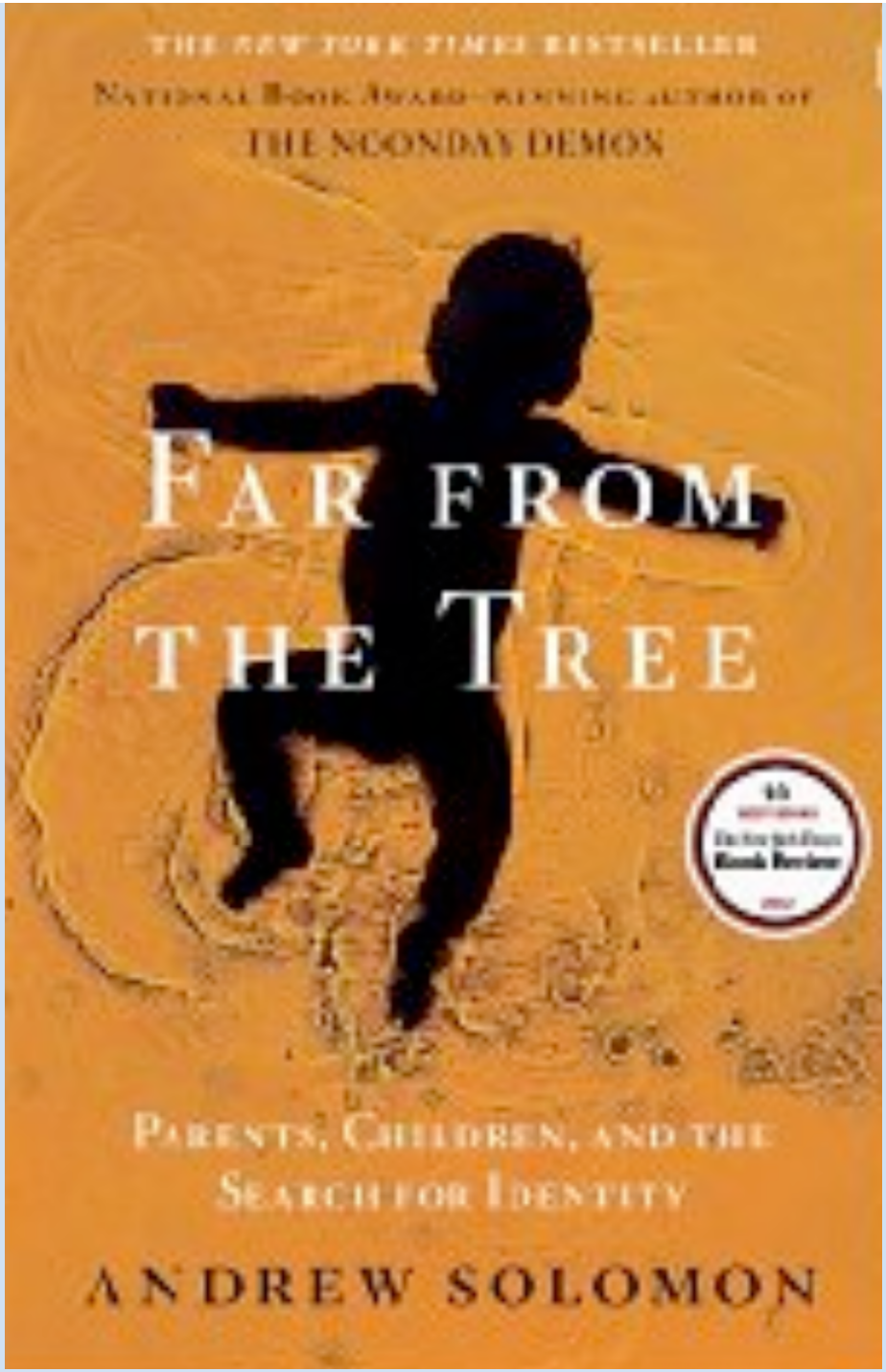
BY

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

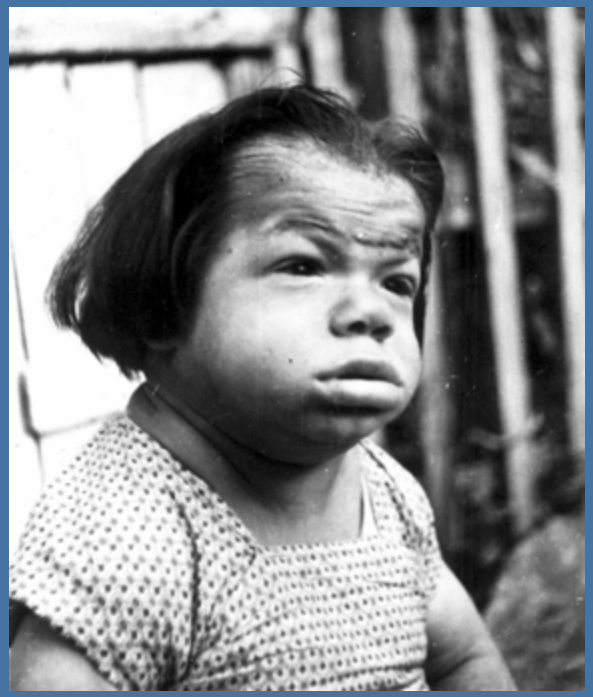
WITH A PREFACE BY

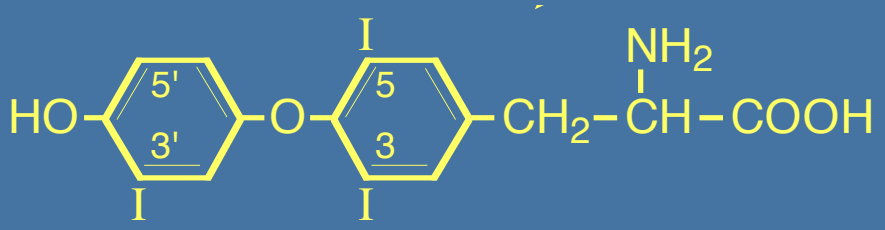
PROFESSOR J. B. S. HALDANE, F.R.S.

GRUNE & STRATTON
New York
1949



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





Thyroid Hormone

- 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."

The Biology of MENTAL DEFECT

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

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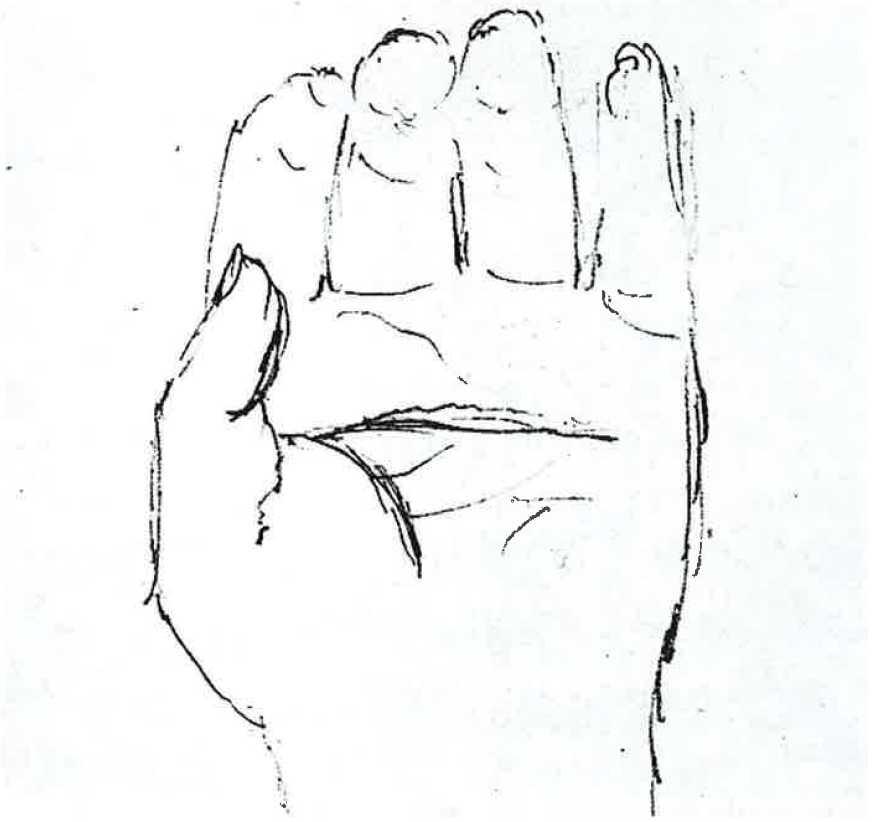
New York

1949

Plate VII—Mongolism in two imbecile brothers aged 10 (Colchester Survey, 1938, Case No. 750) and 5 years, with a normal child aged $2\frac{1}{2}$ years.

As compared with the normal child, the younger mongoloid is seen to have a small head, decreased stature and dysplastic features. The characteristic fold of skin covering the inner canthus of each eye (epicanthic fold) was clearly marked in this case.



Reginald Langdon Down was the first to describe the pattern of creases in the palm in Down's syndrome patients. He drew this sketch in 1908.

Published in "Biology of Mental Defect", by Lionel Penrose, 1949
And "John Langdon Down: A Caring Pioneer", by O Conor Ward, 1998.

Mary A, the first Down's syndrome patient admitted to Normansfield, photographed when she was 19 and again when she was 55. She lived to the age of 58.

Florence T, a Down's syndrome patient at Normansfield. Photographed in 1886 when she was seven and again in 1899 aged 20.

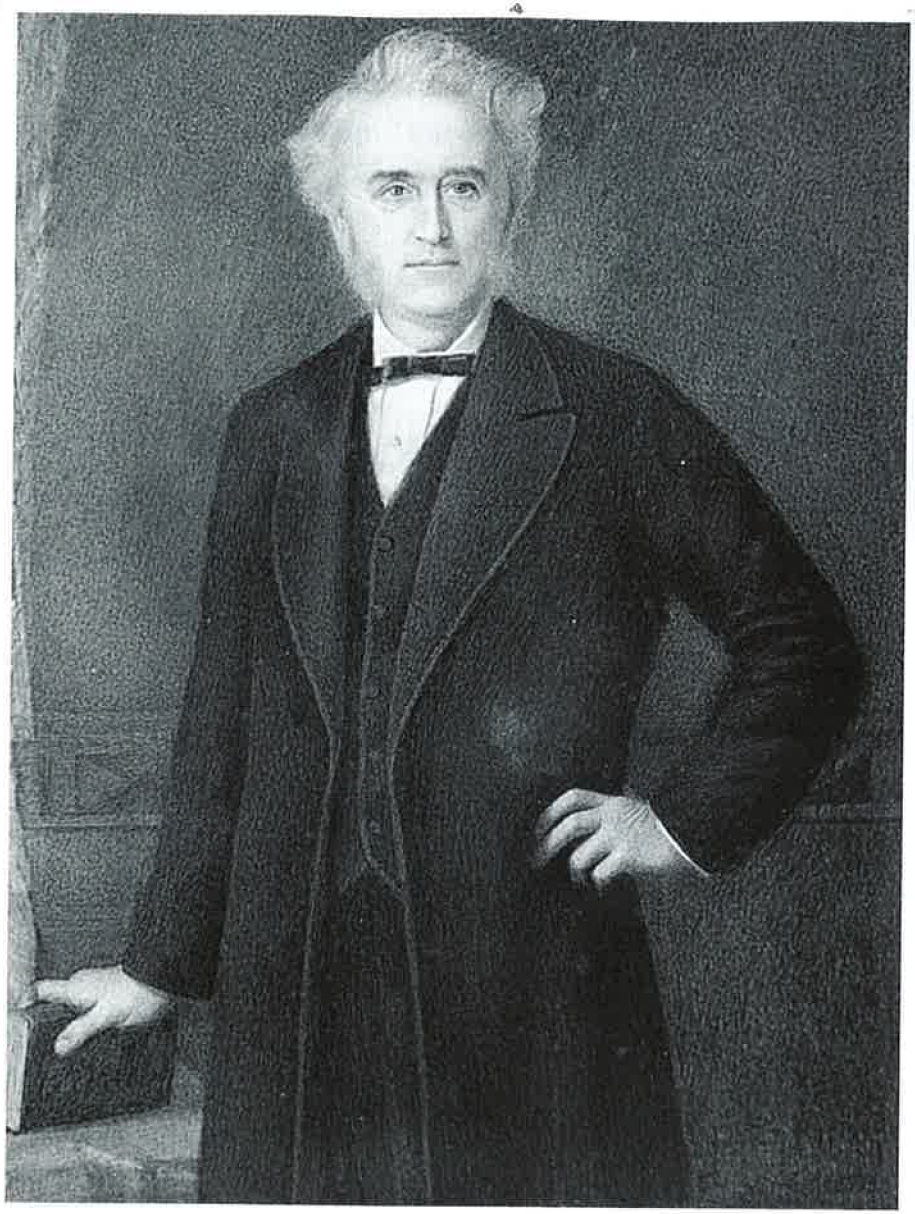
Published in “John Langdon Down: A Caring Pioneer”, by O Conor Ward, 1998.

Langdon Down began to take clinical photographs in 1862. His first photograph of an Earlswood resident with Down's syndrome was this unnamed girl in the 1865 series. She was probably the first ever Down's syndrome patient to be photographed.

Published in "John Langdon Down: A Caring Pioneer", by O Conor Ward, 1998.

Four Down's syndrome patients. Part of the Earlswood series, photographed in 1865.

Langdon Down in court dress, 1887, when he gave the welcome address to the Prince and Princess of Wales at the opening of the London Hospital Nursing School.



Portrait of Langdon Down, painted by Sydney Hodges in 1883.

Dr Reginald Langdon Down with his daughters Stella and Elspie. Stella married Russell Brain and became Lady Brain. Elspie was an artist. The only son was John, who had Down's syndrome.

Dr Percival Langdon Down with his wife and children. His son Norman, was to be the last Langdon Down superintendent of Normansfield, ending a family connection that had lasted for 102 years. The elder daughter, Molly, was also a doctor and worked in Normansfield.

Langdon Down's personal patients with his syndrome[2]

Name	Age Admitted	Date Admitted	Outcome	Comment
Mary A	19	12.5.68	Died 1907, age 58	Cardiac failure, Alzheimer's
Cecelia GA	10	7.6.68	Died 31.1.70, age 12	Fatal scarlet fever
Herbert H	8	15.7.68	Discharged 10.10.68	Improved
Edward GP	11	1.5.69	Died 1908, age 50	
Laura M	7	5.4.69	Died 5.4.77, age 15	Tuberculosis: Query
Walter AP	4	4.11.75	Discharged 27.1.77	Masturbation cured
Margaret DE	11	14.4.74	Died 15.5.74, age 11	Fatal scarlet fever
Norah MT	12	23.4.74	Died 26.6.74, age 12	Acute Bronchitis
James DKW	5	10.1.77	Died 30.12.77, age 12	Bronchitis and Pneumonia
Norman MB	10	14.2.77	Died 12.1.12, age 45	Alzheimer's?
Thomas N	6	13.11.77	Died 1896, age 25	Cardiac failure
Margaret AW	4	11.3.80	Died 1885, age 9	Sudden death on holiday
George HW	6	27.3.80	Died 27.11.80, age 7	Laryngo bronchitis, croup
Cathy MS	9	28.3.82	Died 20.8.82, age 9	Bronchitis and pneumonia
Lucy EN	11	22.8.82	Died 3.11.85, age 14	Broncho-pneumonia, cardiac failure
Ada FH	15	2.12.82	Alive 1895	
Elizabeth G	5	27.10.83	Discharged 16.2.87	Improved
Florence ET	7	8.3.86	Alive 1895	
David AH	6	5.4.72	Died 1915. age 49	Late onset of blindness and deafness
Constance AW	13	31.7.86	Discharged 12.5.88	Improved
Ann MR	17	18.11.86	Discharged 26.5.91	Improved
John GT	15	6.7.74	Died 4.6.18, age 59	Alzheimer's?

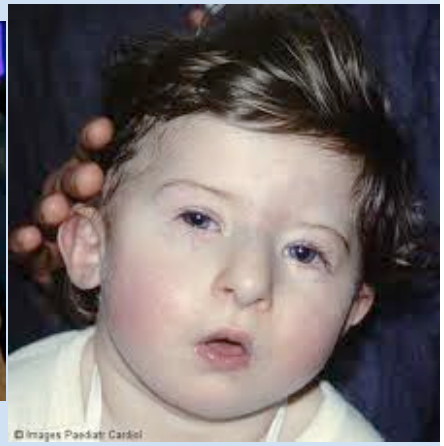
Down Syndrome

Down Syndrome

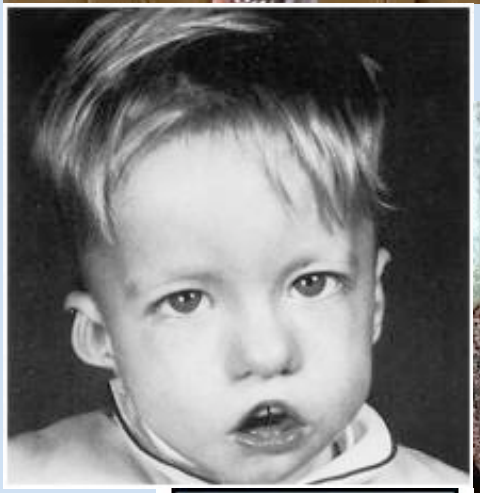
Christopher Joseph "Chris" Burke (born August 26, 1965) is an American actor and folk singer, who lives with Down syndrome, who has become best known for his character Charles "Corky" Thacher on the television series Life Goes On.

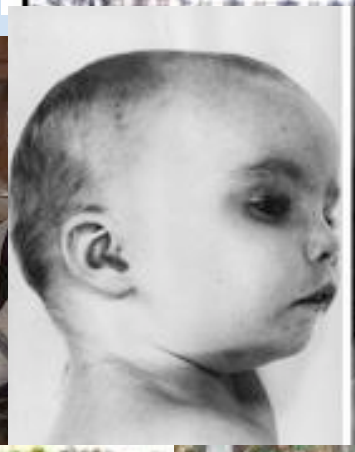
And there are people with Mosaic Down Syndrome, who are much less affected.

Velocardiofacial (22q11.2) Syndrome

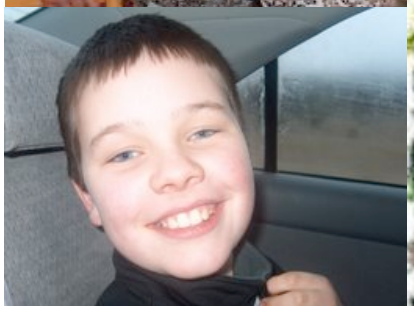













Rare Variants – CNVs, SNVs, indels, etc… in Rare AND Common diseases

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

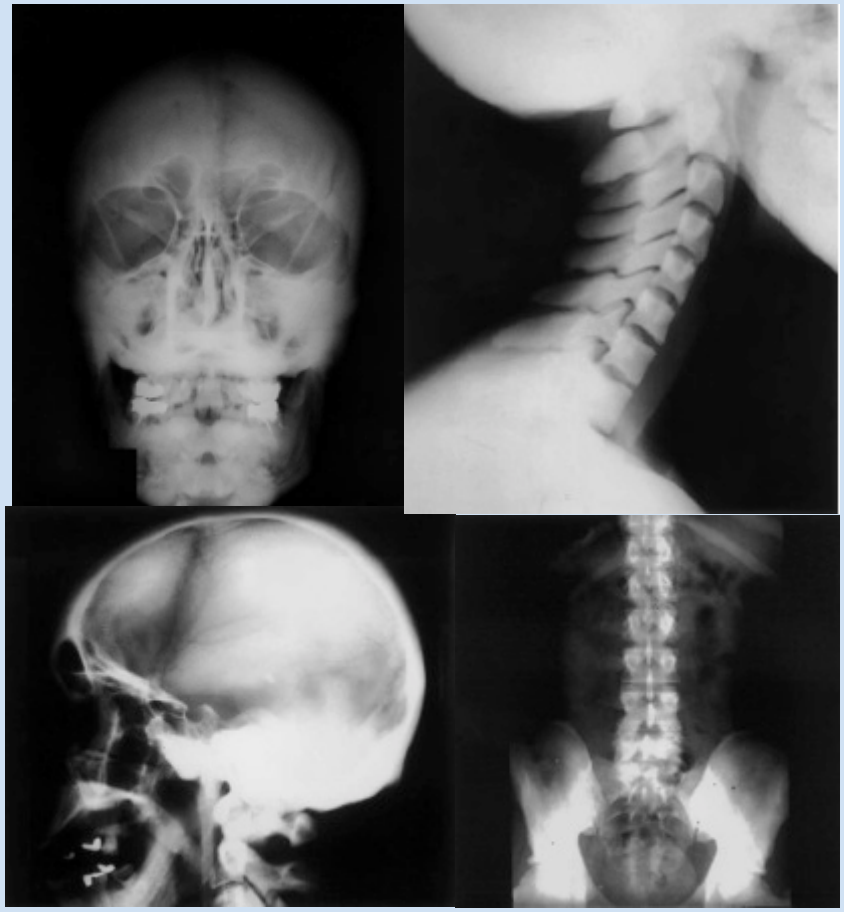
Manuel A Rivas[1–3], Mélissa Beaudoin[4,23], Agnes Gardet[5,23], Christine Stevens[2,23], Yashoda Sharma[6], Clarence K Zhang[6], Gabrielle Boucher[4], Stephan Ripke[1,2], David Ellinghaus[7], Noel Burtt[2], Tim Fennell[2], Andrew Kirby[1,2], Anna Latiano[8], Philippe Goyette[4], Todd Green[2], Jonas 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

“Superpower” mutations???

Myostatin mutation
Exon 2 allele P198A



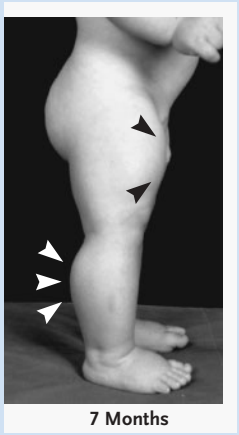
LRP5 mutation
D111Y, G171R, A214T, A214V, A242T, and T253I

**Thanks to George Church for discussions on this.

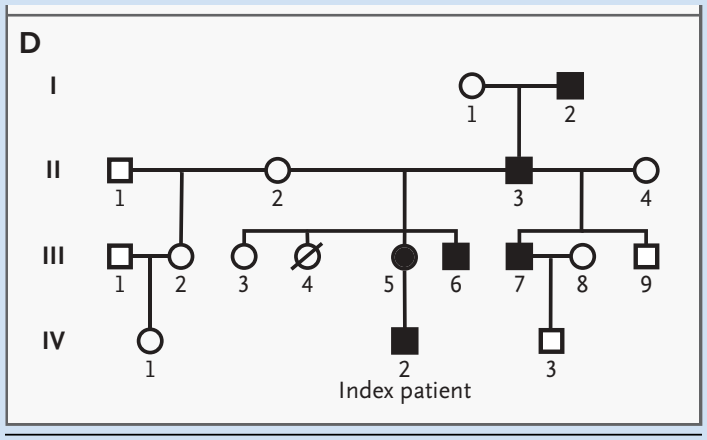
Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child

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.

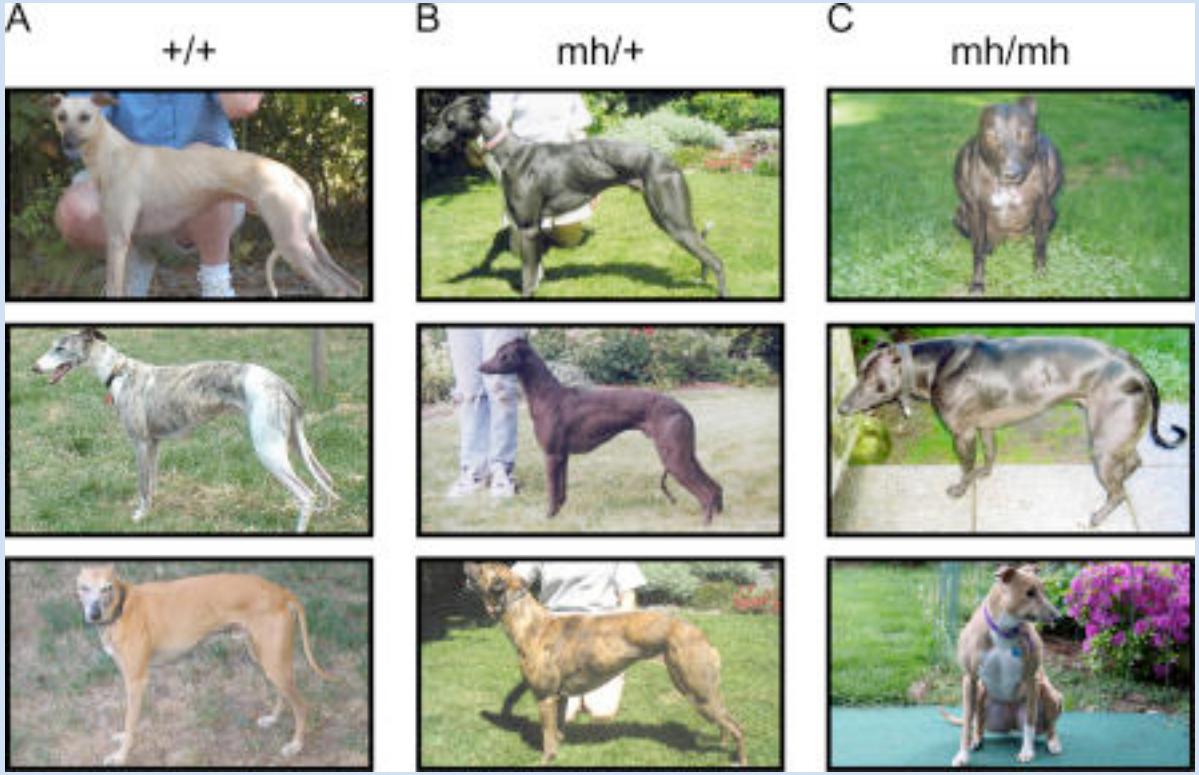
http://en.wikipedia.org/wiki/Belgian_Blue

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

PLoS Genetics | www.plosgenetics.org May 2007 | Volume 3 | Issue 5 | e79



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*

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Clinical genetics of neurodevelopmental disorders

Gholson J Lyon, Jason O'Rawe

bioRxiv doi: 10.1101/000687

New Results

> ...as described at http://creativecommons.org/licenses/by/3.0/ Clinical genetics of neurodevelopmental disorders **Gholson** J Lyon 1 3 glyon@cshl.edu , http://lyonlab.cshl.edu/ Jason O'Rawe 2 jazon33y@gmail.com * Corresponding author...

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

Holly A. Stessman,[1] Raphael Bernier,[2] and Evan E. Eichler[1,3,*]
[1]Department of Genome Sciences, University of Washington, Seattle, WA 98195, USA
[2]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195, USA
[3]Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195, USA
*Correspondence: eee@gs.washington.edu
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”

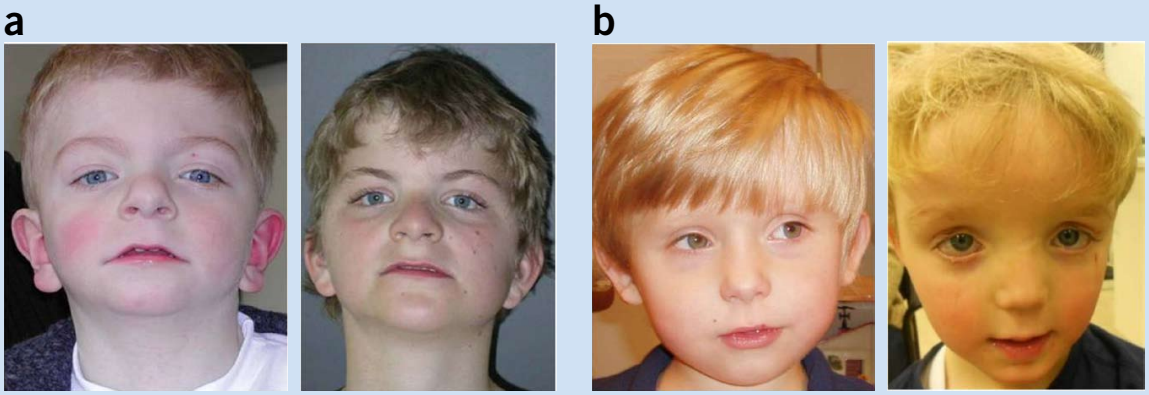

Figure 3 Phenotypic similarity of two patients with identical *PACS1 de novo* mutations and two patients with similar *ADNP* mutations. (**a**) These two unrelated patients show identical *de novo* point mutations (c.607C>T; p.Arg203Trp) in *PACS1* (RefSeq NM_018026.3)[53]. The striking similarity in 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.

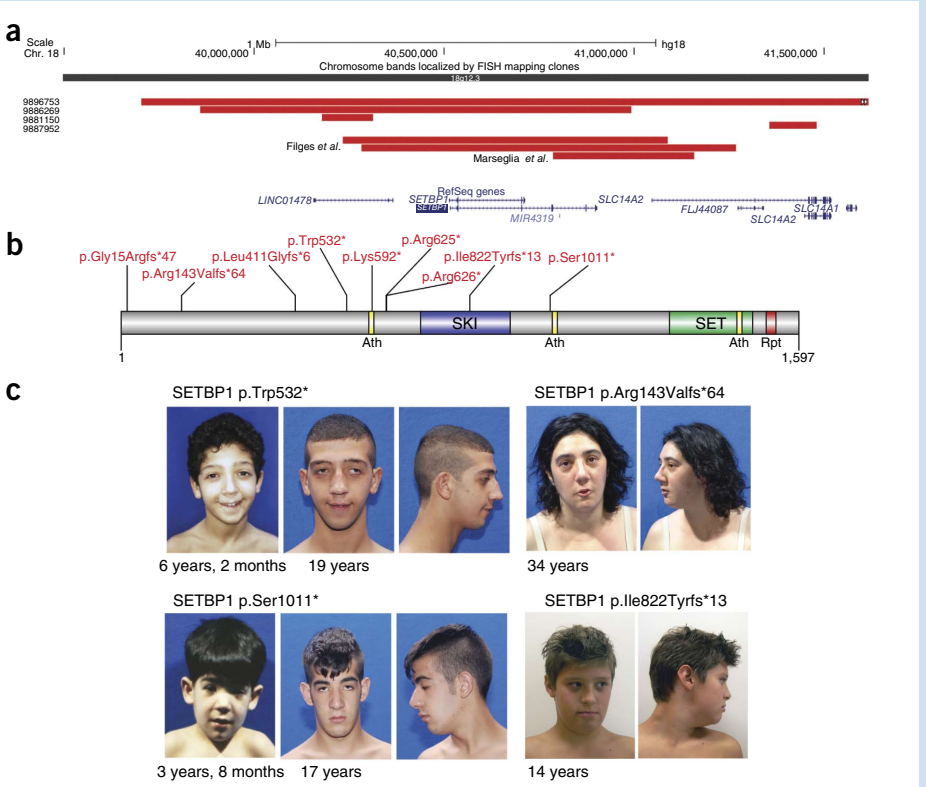

Figure 1 Truncating *SETBP1* mutations and associated phenotypes. (**a**) CNV data define a focal CNV region around *SETBP1*. Combining a focal *de novo* deletion observed in our study (9886269) with CNVs from Filges *et al.*[41] and Marseglia *et al.*[42] (red bars) highlights minimal common regions, 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.

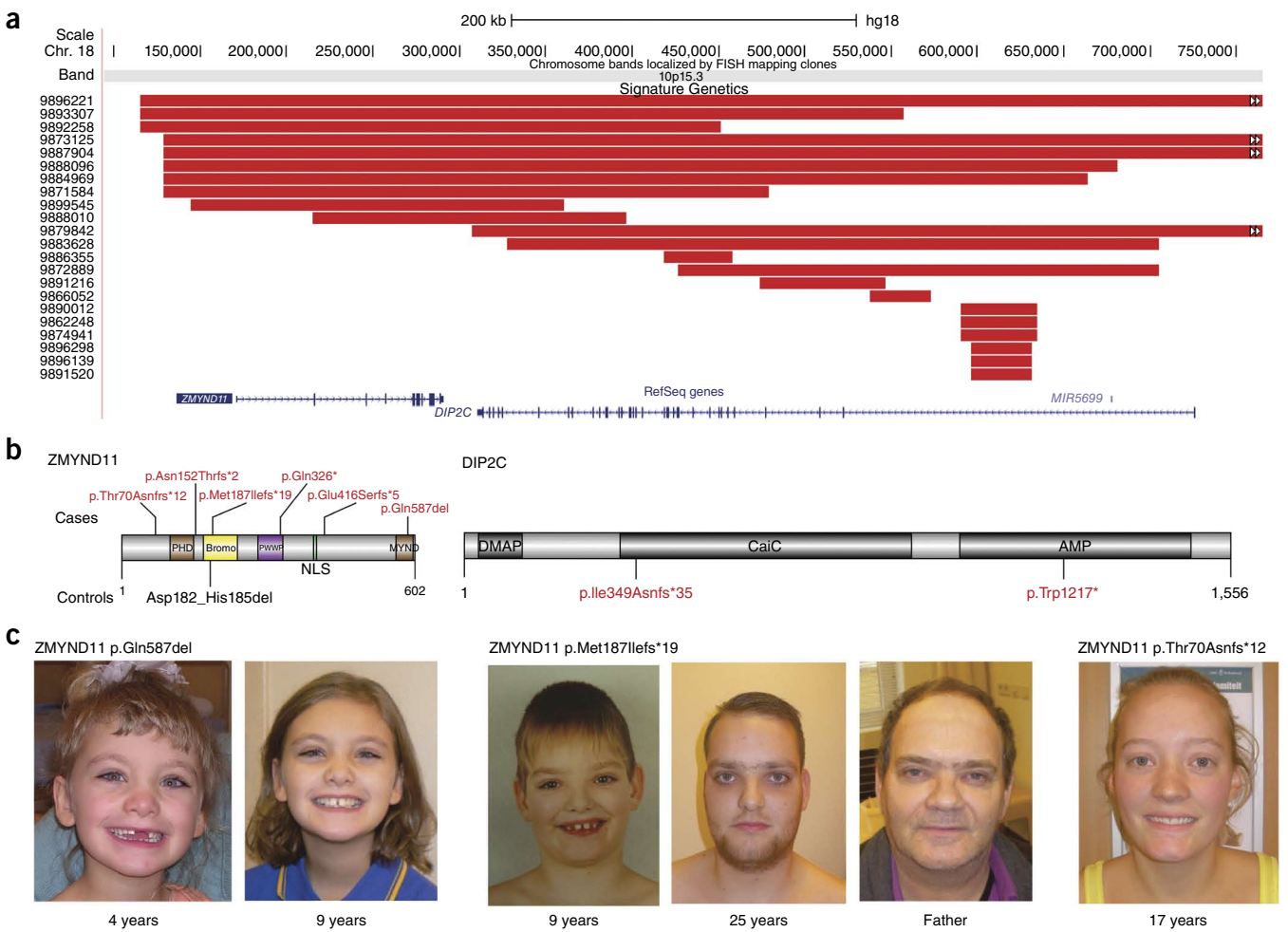

Figure 2 Truncating *ZMYND11* mutations and associated phenotypes. (**a**) CNV data refine a focal CNV deletion region (red bars) containing two genes (*ZMYND11* and *DIP2C*). (**b**) Targeted resequencing identified five truncating variants and one single-amino-acid deletion predicted to behave as loss-of-function 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.

Table 5 Brief phenotypic description of cases with *ZMYND11* loss-of-function variants

Case	Age at examination	Sex	Alteration	Inheritance	Cognitive	Speech delay	Social difficulties	Behavioral problems	Facial dysmorphism
Adelaide20124	4 and 9 years	F	p.Gln587del	*De novo*	Global DD	+	+		+
Adelaide3553	22 years	M	p.Asn152Thrfs*26		Global DD	+		+	
DNA-017151	17 years	F	p.Thr70Asnfs*12	*De novo*	Normal IQ	+	+	+	+
DNA04-02424	41 years	M	p.Gln326*		Mild ID	+	+	+	+
DNA05-04370		M	p.Glu416Serfs*5		Severe ID	+	+		+
DNA-013587	25 years	M	p.Met187Ilefs*19	Inherited	Global DD	+	+	+	+
Father of DNA-013587		M	p.Met187Ilefs*19	Carrier	DD			+	

DD, developmental delay; ID, intellectual disability; M, male; F, female.

Molecular Genetics & Genomic Medicine

Open Access

ORIGINAL ARTICLE

Disease variants in genomes of 44 centenarians

Yun Freudenberg-Hua[1,2], Jan Freudenberg[3], Vladimir Vacic[4], Avinash Abhyankar[4], Anne-Katrin Emde[4], Danny Ben-Avraham[5], Nir Barzilai[5], Dayna Oschwald[4], Erika Christen[1], Jeremy Koppel[1,2], Blaine Greenwald[2], Robert B. Darnell[4,6], Soren Germer[4], Gil Atzmon[5] & Peter Davies[1]

[1]The Litwin-Zucker Research Center for the Study of Alzheimer's Disease and Memory Disorders, The Feinstein Institute for Medical Research, North Shore-LIJ, Manhasset, New York 11030

[2]Division of Geriatric Psychiatry, Zucker Hillside Hospital, North Shore-LIJ, Glen Oaks, New York 11040

[3]Robert S. Boas Center for Genomics and Human Genetics, The Feinstein Institute for Medical Research, North Shore-LIJ, Manhasset, New York 11030

[4]New York Genome Center, 101 Avenue of the Americas, New York, New York 10013

[5]Institute for Aging Research Departments of Medicine and Genetics, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461

[6]Department of Molecular Neuro-Oncology, Howard Hughes Medical Institute, The Rockefeller University, 1230 York Avenue, New York, New York 10065

“Number of genes causing autism”

- Exome sequencing on 3000 quad families, i.e. mother, father, two children.
- Looking for newly arising mutation in child with autism, not found in parents or unaffected sibling.
- Estimating ~500 “genes” involved.

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

MICROBIAL EVOLUTION

Global epistasis makes adaptation predictable despite sequence-level stochasticity

Sergey Kryazhimskiy,[1,3]*† Daniel P. Rice,[1,3]* Elizabeth R. Jerison,[2,3] Michael M. Desai[1,2,3]†

Epistatic interactions between mutations can make evolutionary trajectories contingent on the chance occurrence of initial mutations. We used experimental evolution in *Saccharomyces cerevisiae* to quantify this contingency, finding differences in adaptability among 64 closely related genotypes. Despite these differences, sequencing of 104 evolved clones showed that initial genotype did not constrain future mutational trajectories. Instead, reconstructed combinations of mutations revealed a pattern of diminishing-returns epistasis: Beneficial mutations have consistently smaller effects in fitter backgrounds. Taken together, these results show that beneficial mutations affecting a variety of biological processes are globally coupled; they interact strongly, but only through their combined effect on fitness. As a consequence, fitness evolution follows a predictable trajectory even though sequence-level adaptation is stochastic.

SCIENCE sciencemag.org

27 JUNE 2014 • VOL 344 ISSUE 6191

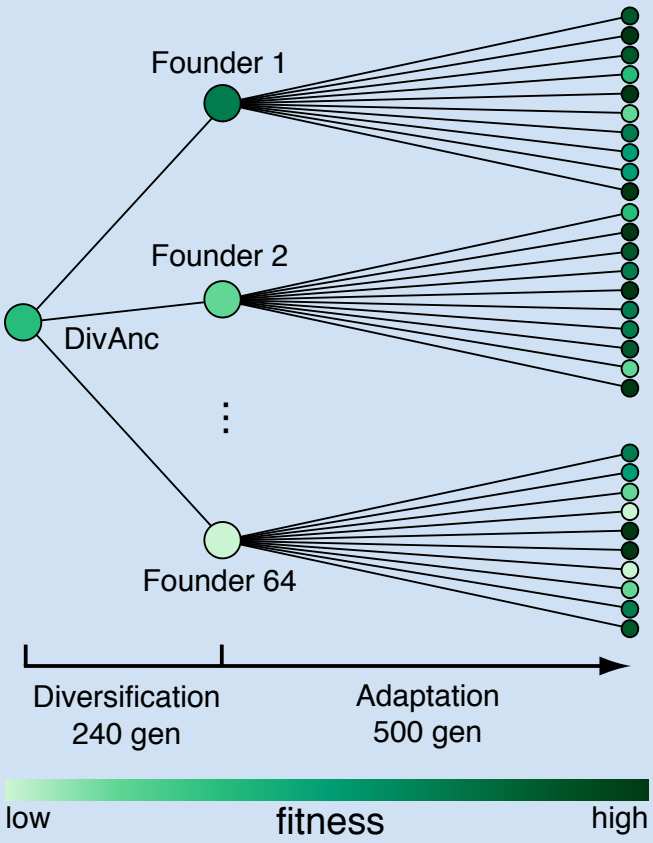

Figure S1. Experimental design. We created many independent lines from a single clone (DivAnc) which came from a previous evolution experiment in the same environment (15) and evolved each of them for 240 generations (Diversification). We then selected a single "Founder" clone from 64 of these lines (chosen to span a range of fitness) and evolved 10 independent replicate populations descended from each Founder for 500 generations (Adaptation).

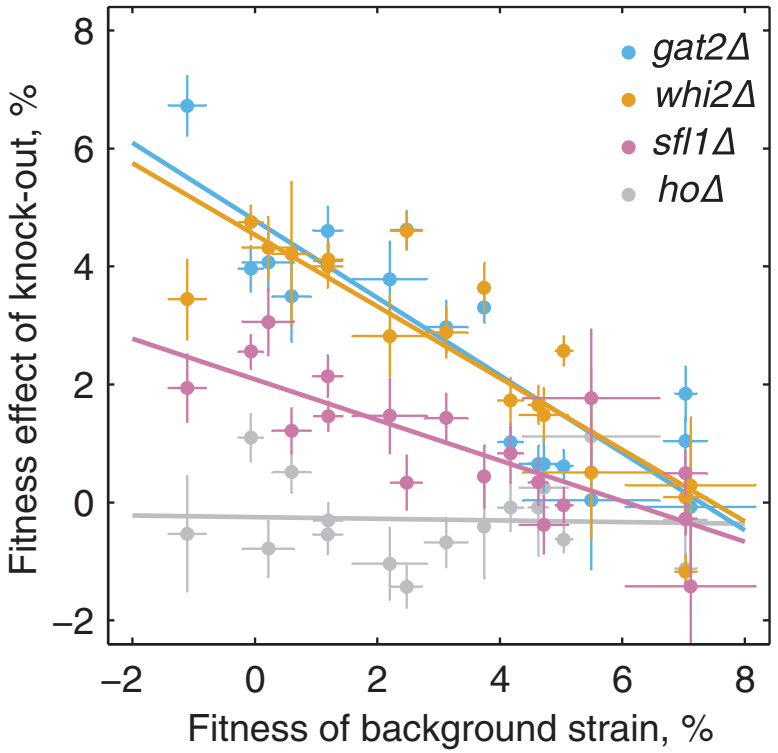

Fig. 3. Diminishing-returns epistasis among specific mutations. The fitness effect of knocking out genes *gat2*, *whi2*, and *sfl1* declines with the fitness of the background strain. The *ho* knockout is a negative control. Error bars are SEM over biological replicates.

- “Yet despite their lack of apparent functional relationship, these mutations are globally coupled by diminishing-returns epistasis; their effects are strongly mediated by background fitness but are otherwise essentially independent of the specific identity of mutations present in the background. The biological basis of this global coupling remains unknown”.

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.53.6607

JOURNAL OF CLINICAL ONCOLOGY

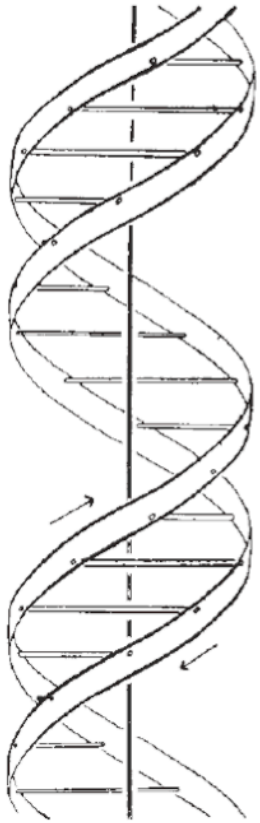
ORIGINAL REPORT

Clinical Evaluation of a Multiple-Gene Sequencing Panel for Hereditary Cancer Risk Assessment

Allison W. Kurian, Emily E. Hare, Meredith A. Mills, Kerry E. Kingham, Lisa McPherson, Alice S. Whittemore, Valerie McGuire, Uri Ladabaum, Yuya Kobayashi, Stephen E. Lincoln, Michele Cargill, and James M. Ford

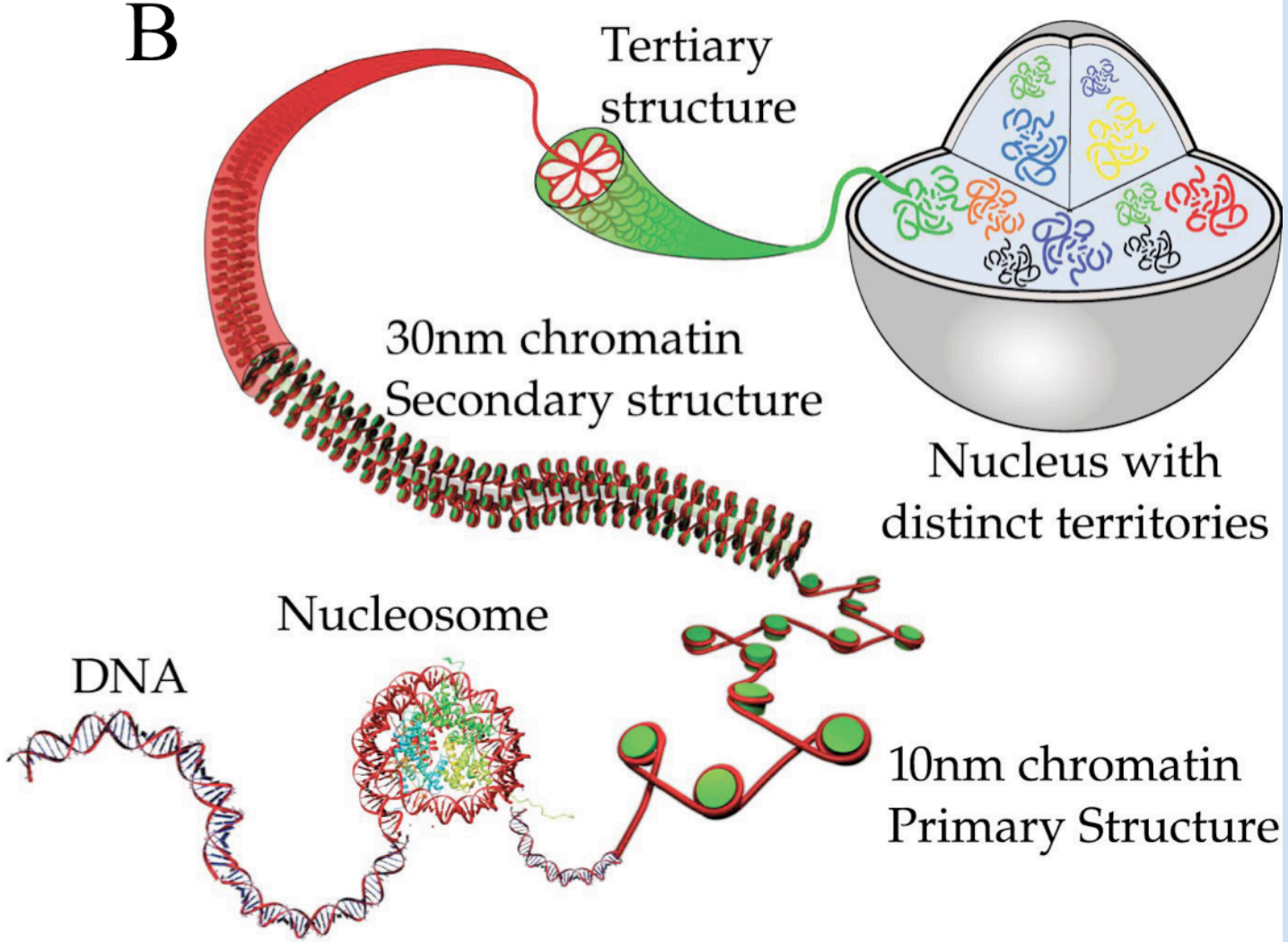
Processed as a Rapid Communication manuscript

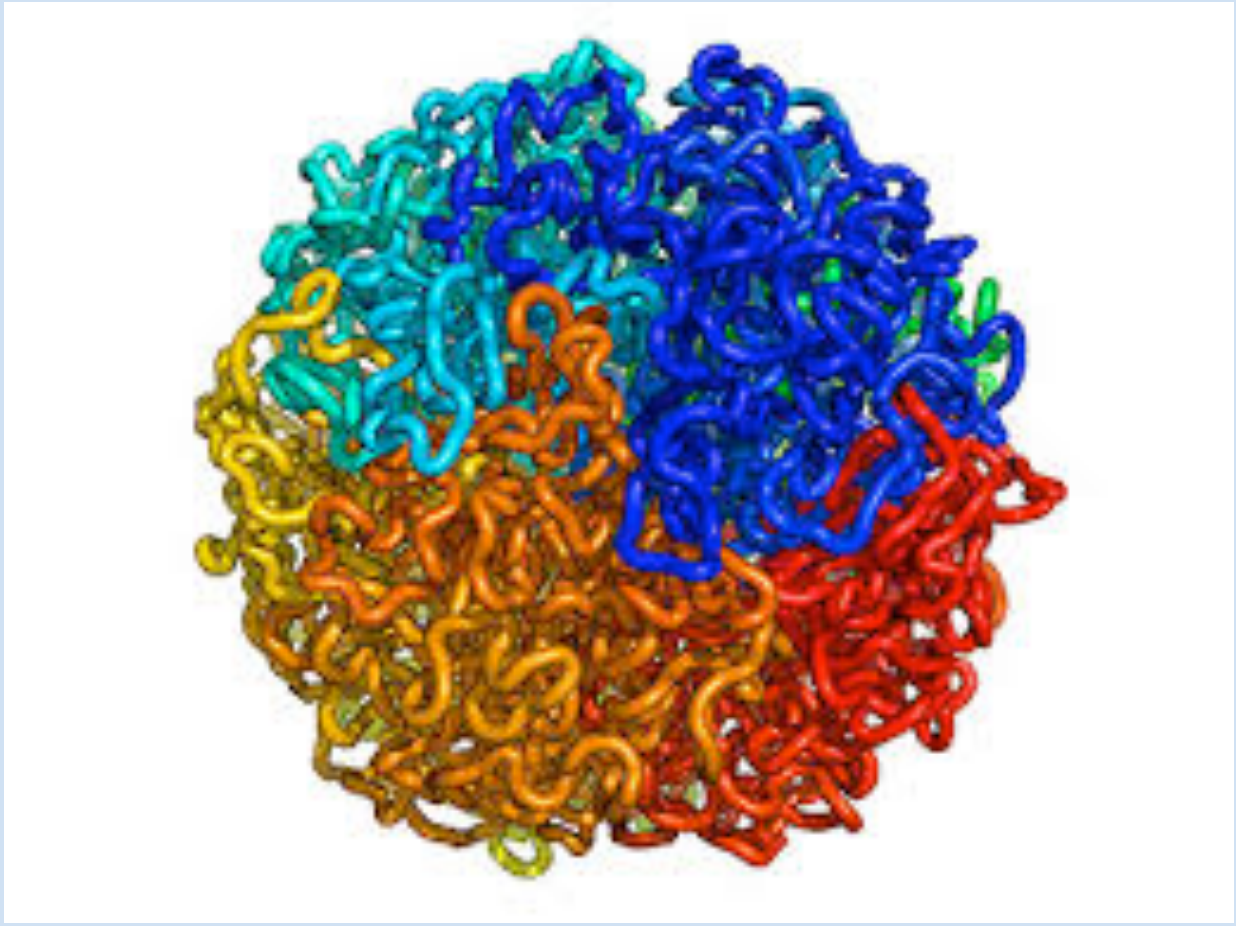
A



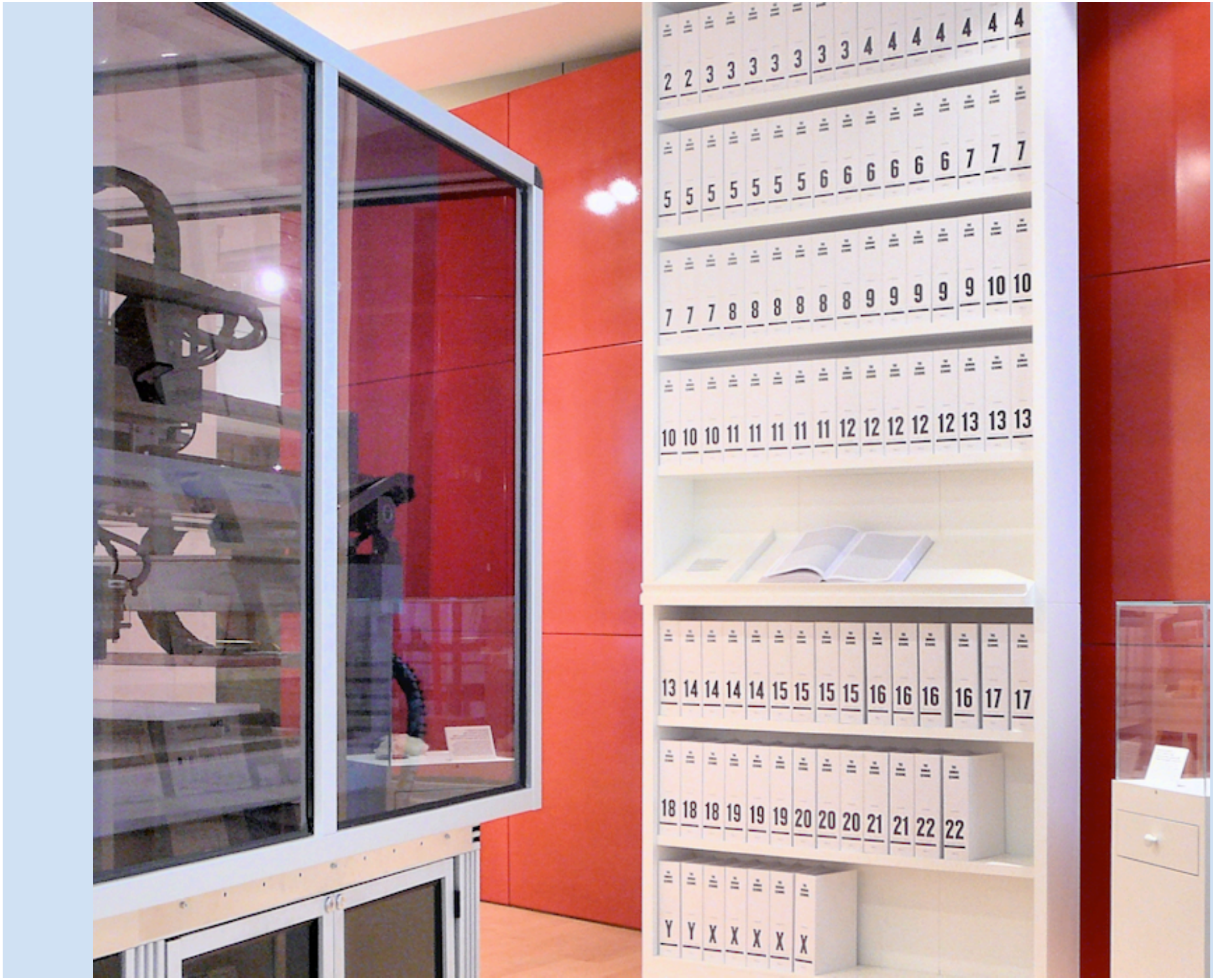
This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

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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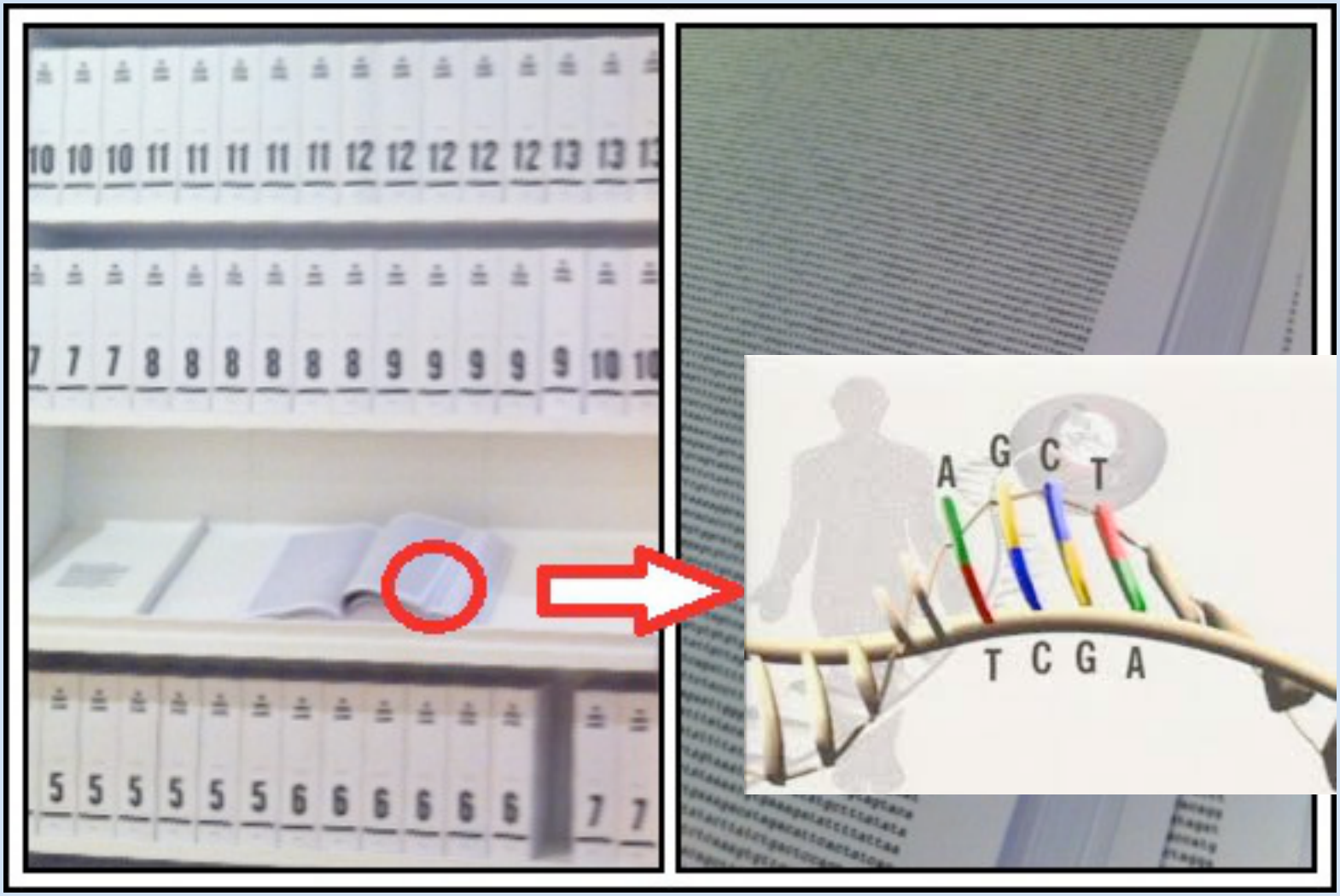
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In the year 2014….
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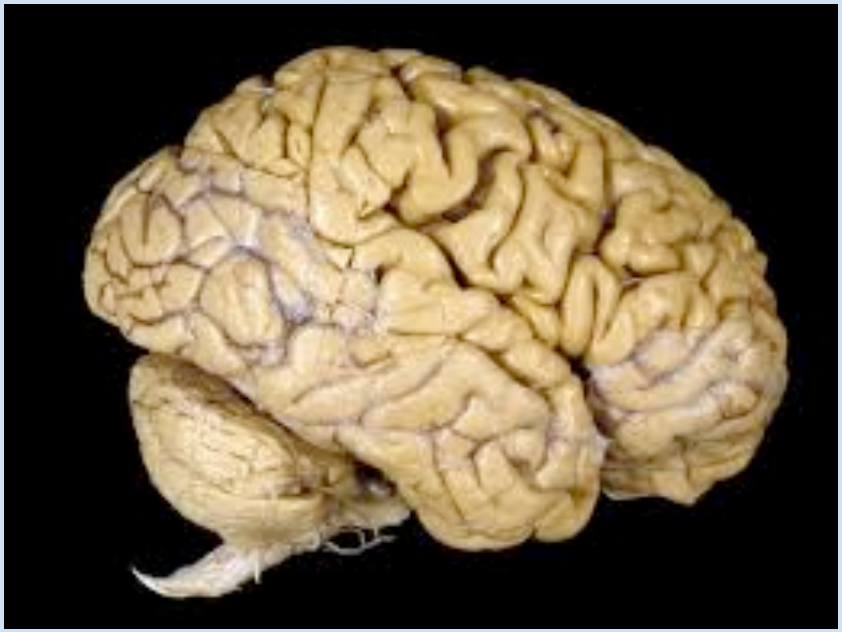
Is orders of magnitudes easier than this:



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).

The End of Main Talk:
Vignettes to follow, if time allows.

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

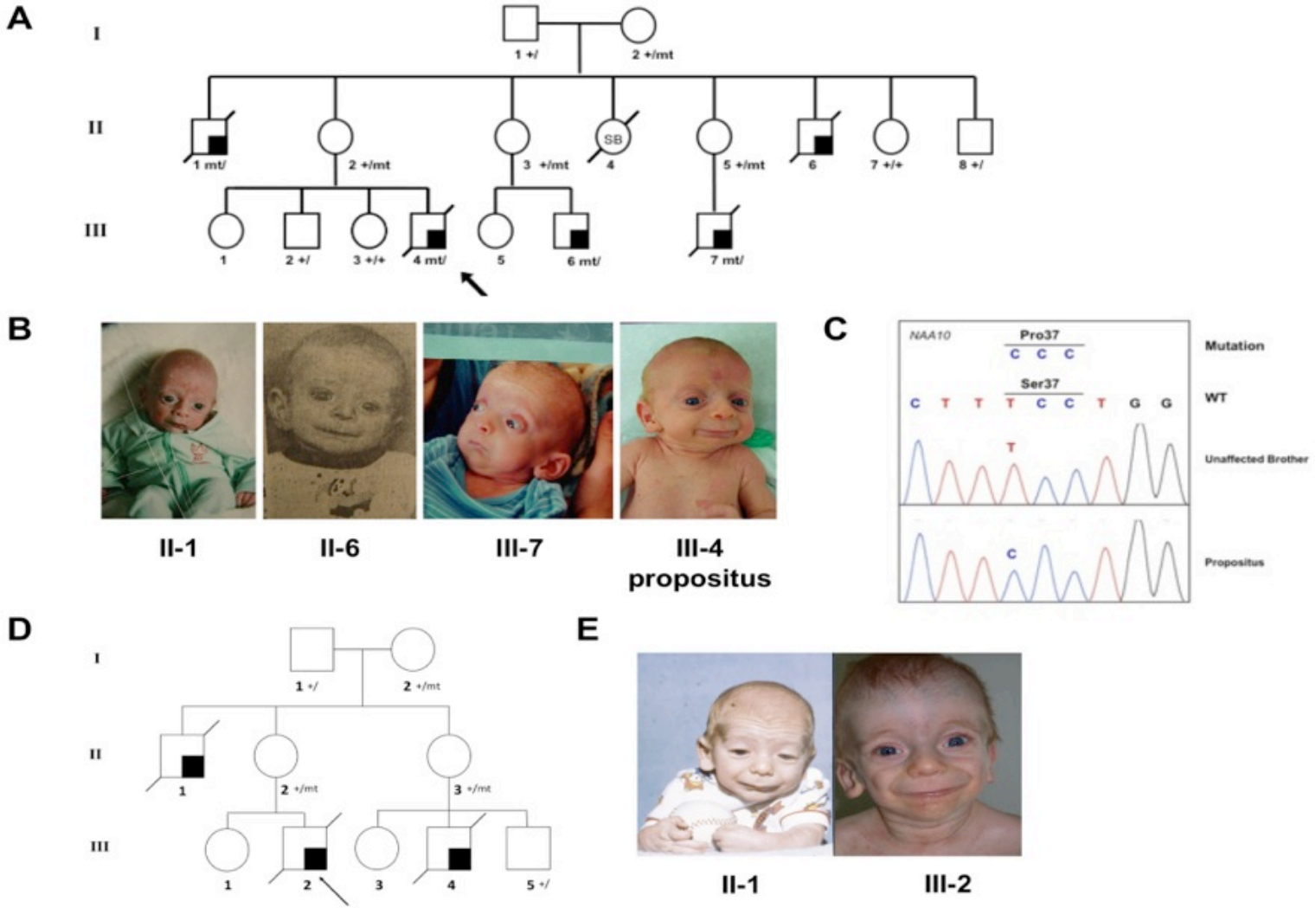
ARTICLE

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

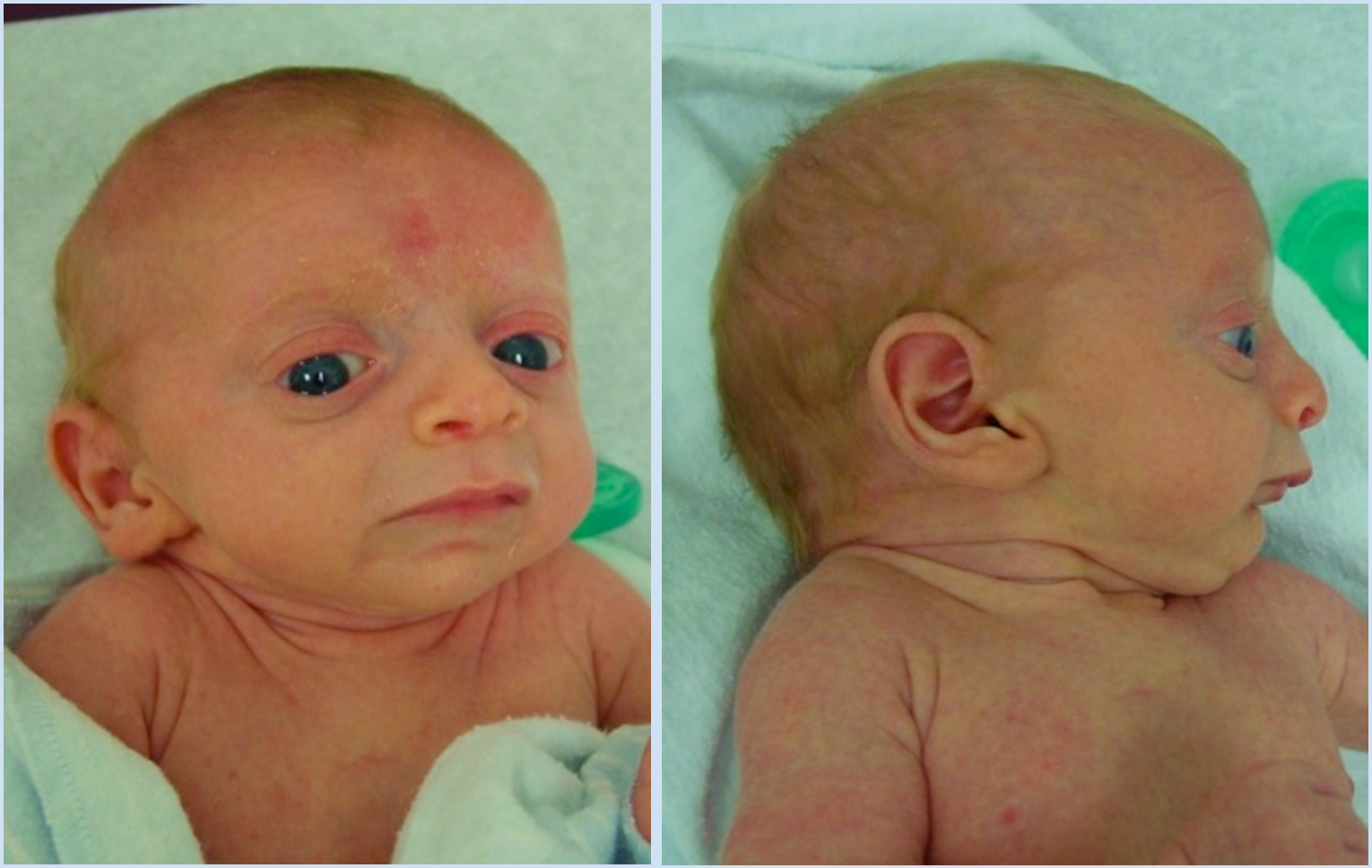


We found the SAME mutation in two unrelated families, with a very similar phenotype in both families, helping prove that this genotype contributes to the phenotype observed.

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

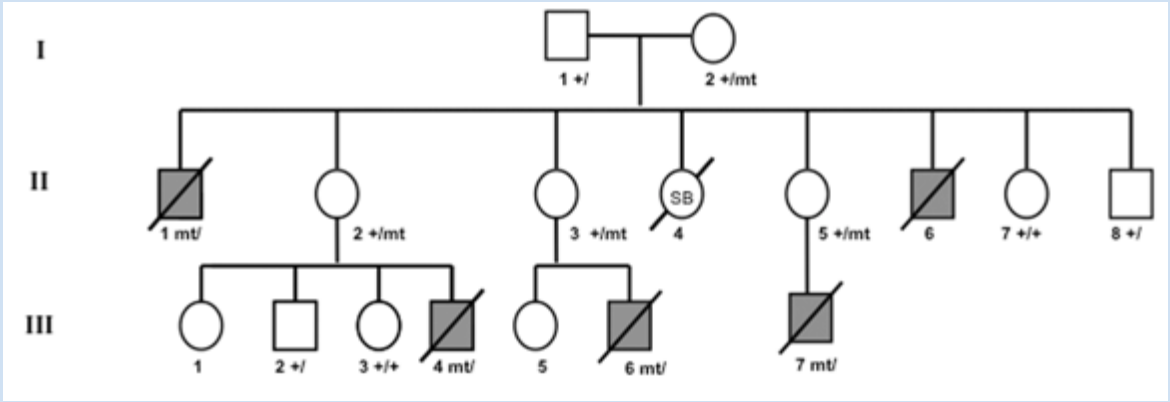
First boy. Called "a little old man" by the family. Died around ~1 year of age, from cardiac arrhythmias.

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

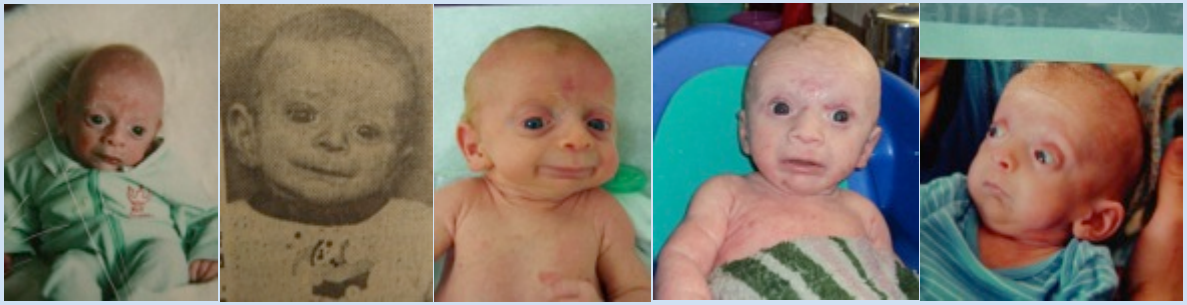


prominence of eyes, down-sloping palpebral fissures, thickened eyelids, large ears, beaking of nose, flared nares, hypoplastic nasal alae, short columella, protruding upper lip, micro-retrognathia

A

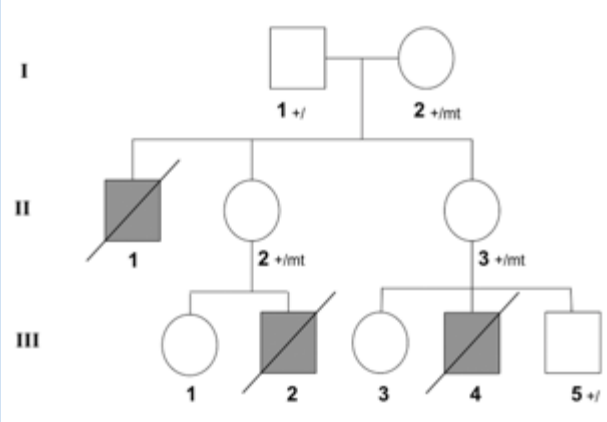


B

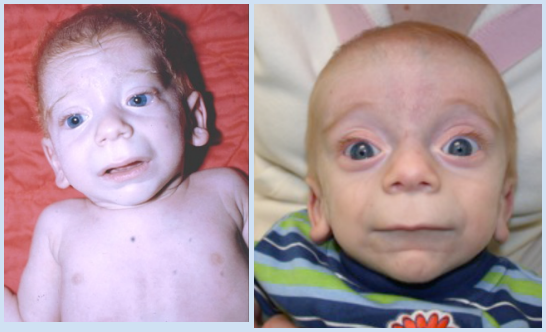


II-1 II-6 III-4 III-6 III-7

C



D

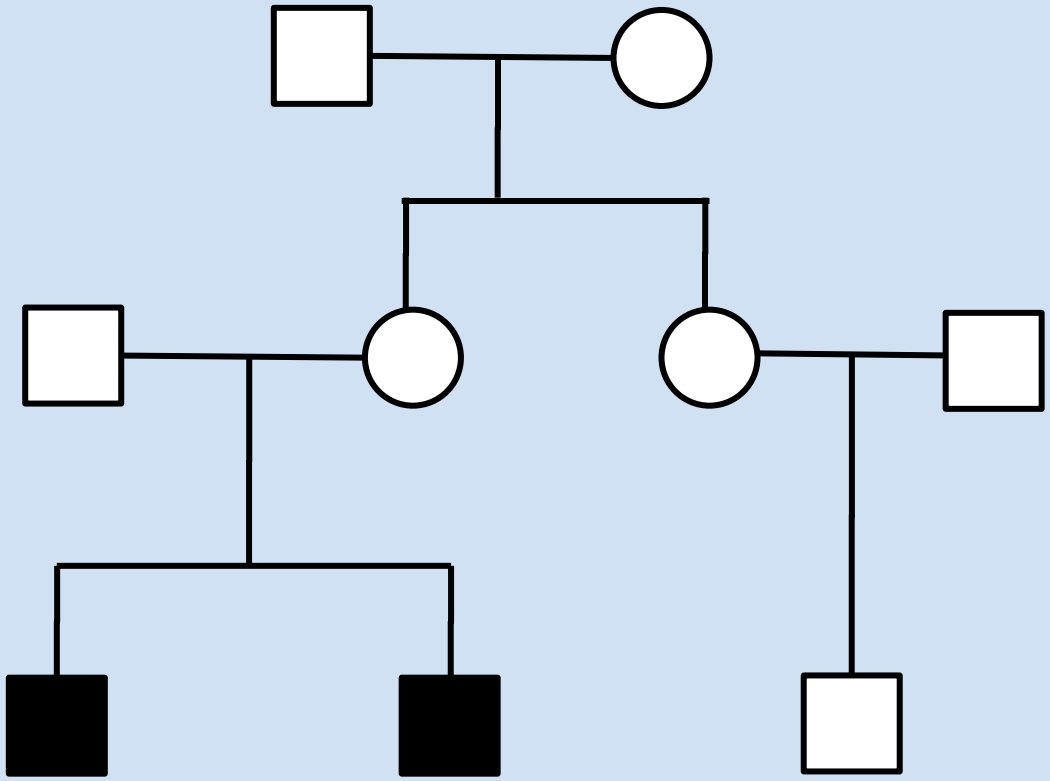


II-1 III-2

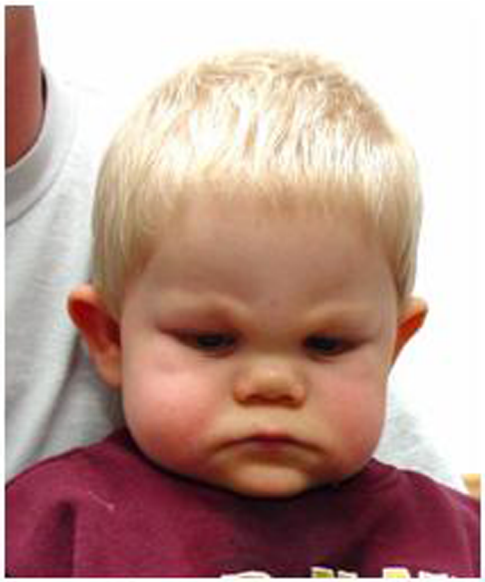
These are the Major Features of the Syndrome.

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.	

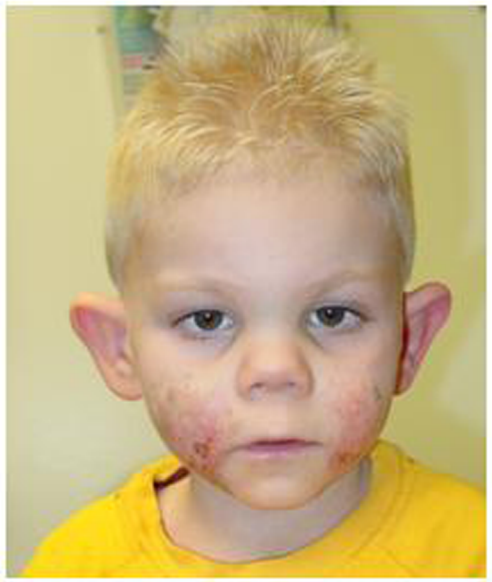
Vignette #2: New Syndrome with Mental Retardation, “Autism”, “ADHD”



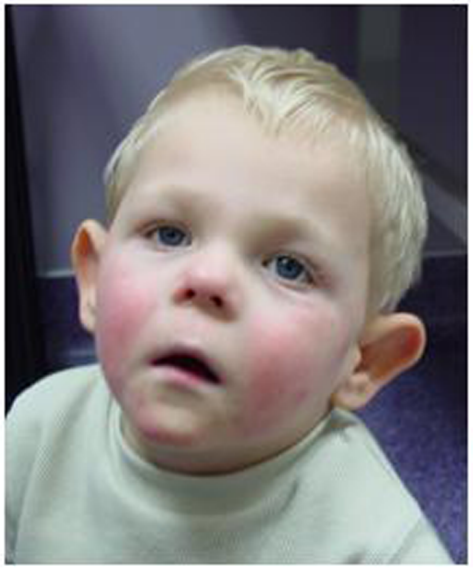
Likely X-linked or Autosomal Recessive, with X-linked being supported by extreme X-skewing in the mother



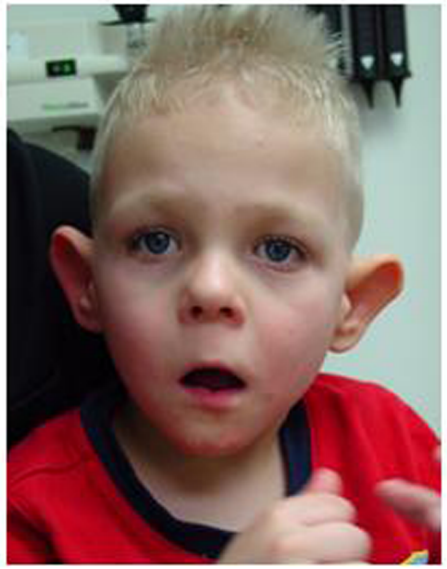
1.5 years old



3.5 years old



3 years old

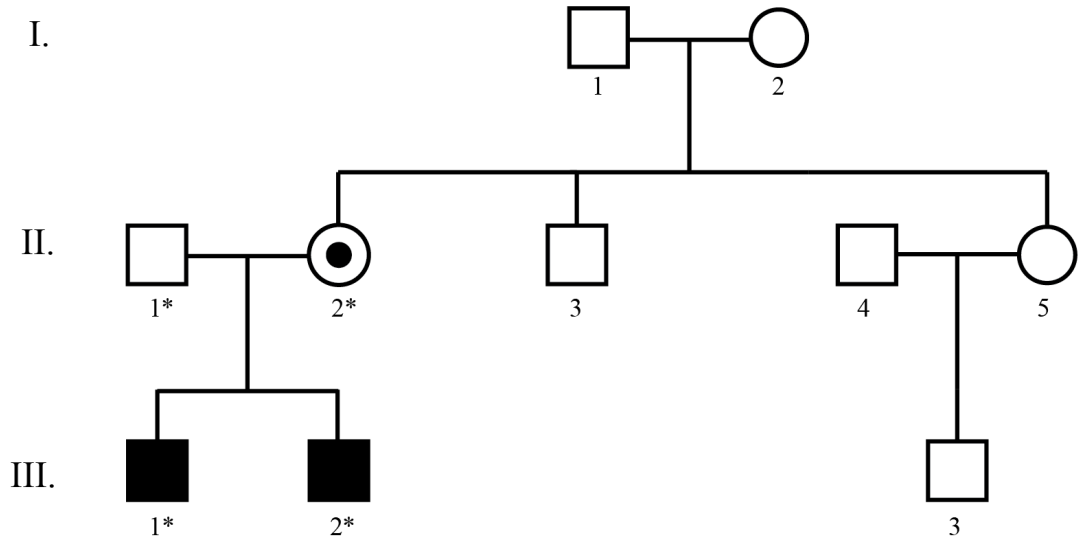


5 years old

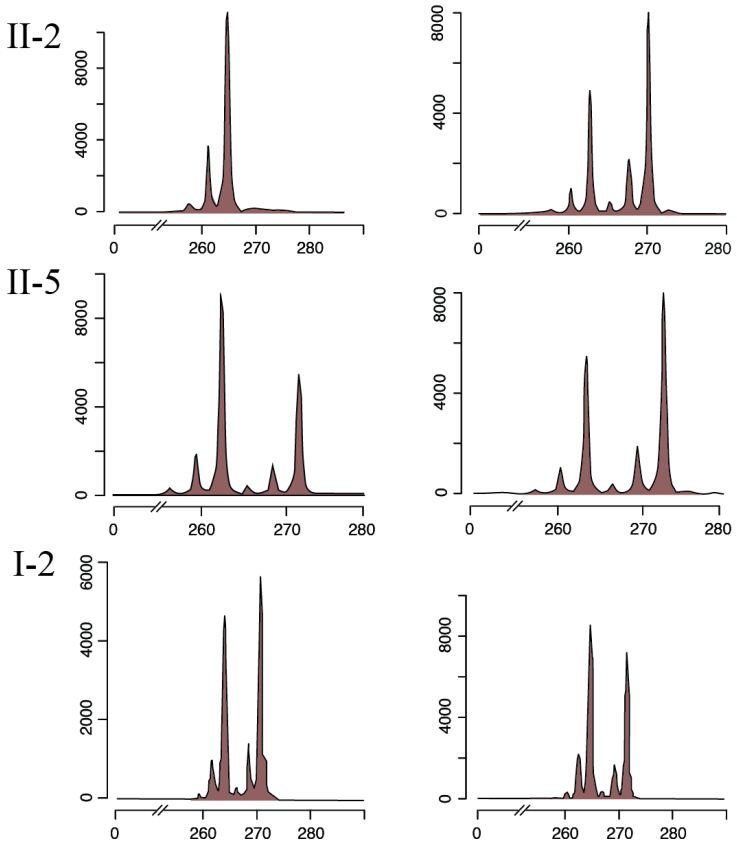
Dysmorphic
Mental Retardation
“autism”
“ADHD”
Hearing difficulties

UFBR Family 3

A

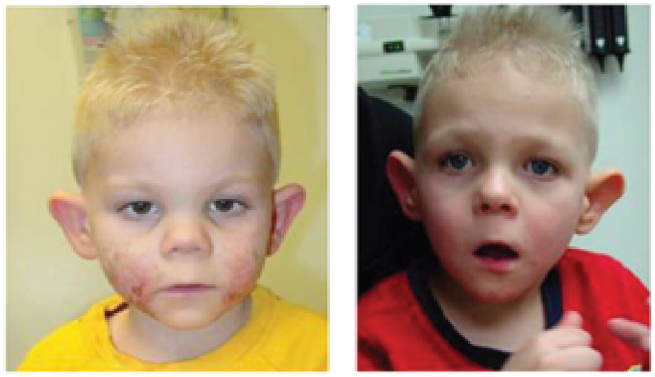


B



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

C



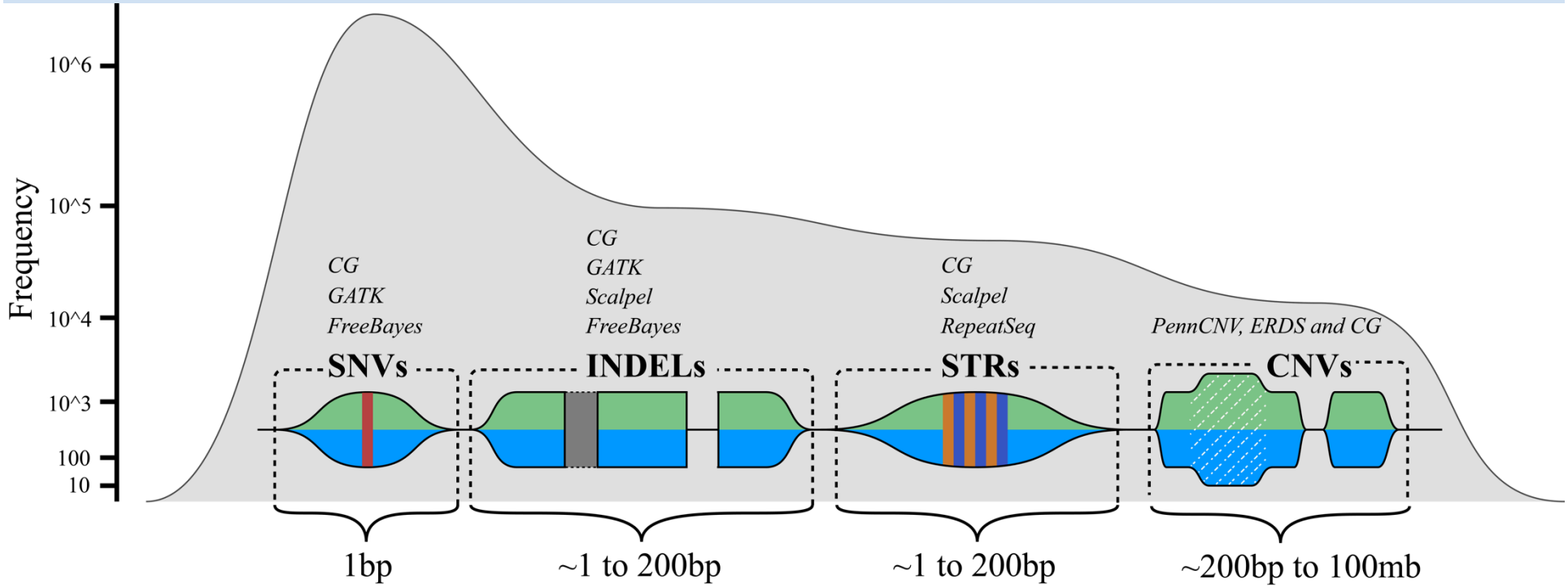
III-1. III-2.

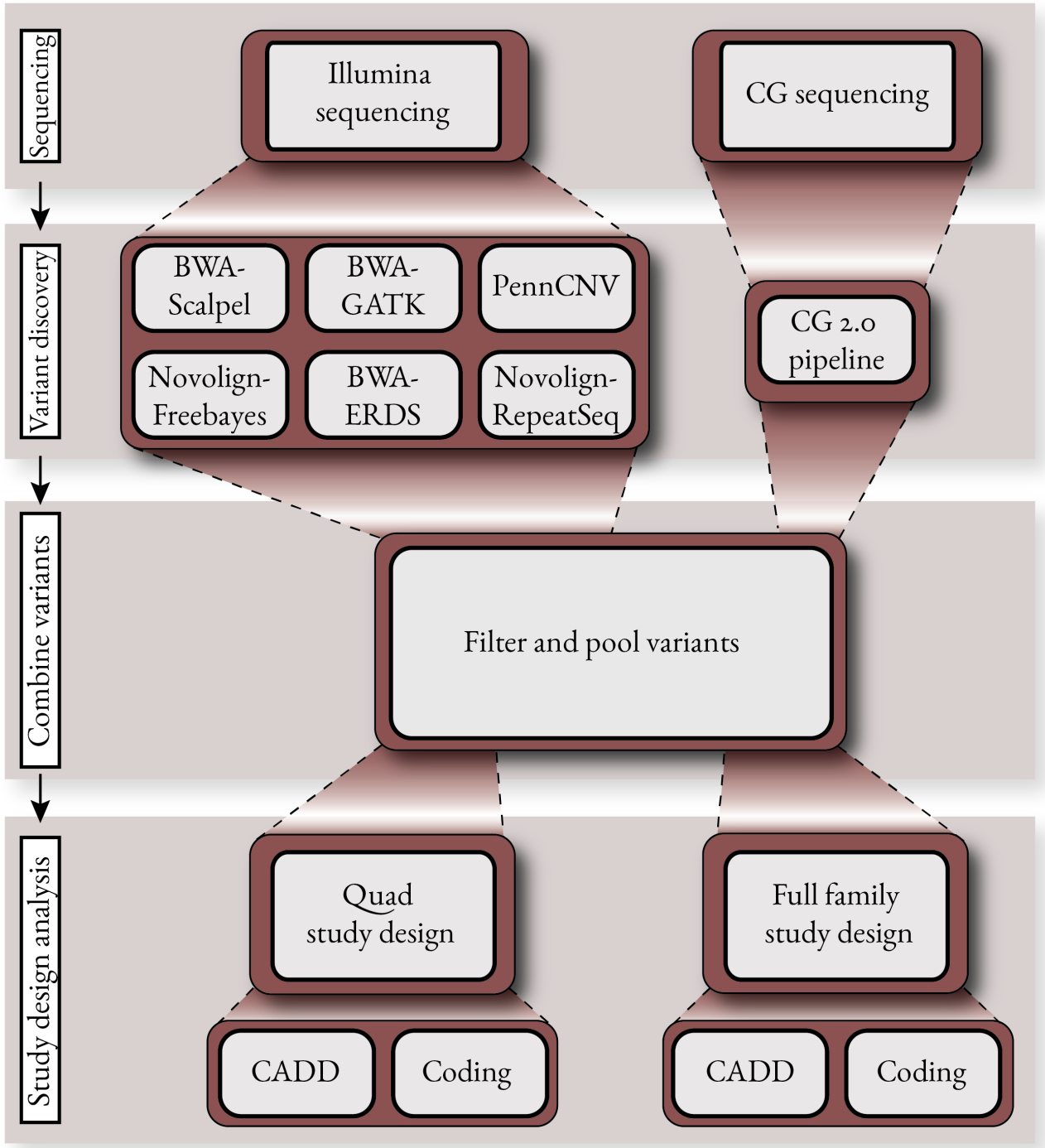
Workup Ongoing for past 10 years

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

Sequenced whole genomes of Mother, Father and Two Boys, using Complete Genomics

- Sequenced “whole” genomes to obtain noncoding and other non-exonic regions.
- No obvious pathogenic CNVs – microarrays normal.
- ~6 million variants total in the 4 people different from Hg19 reference genome.
- No homozygous autosomal recessive mutations found.
- No Nonsense/Frameshift mutations in both boys.
- 2 mutations present in mother and two boys, on X-chromosome, not in father, not in dbSNP135, not in 1000Genomes April 2012 release, and not in NHLBI 6500 Exomes


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


Sequencing
Illumina sequencing
CG sequencing
Variant discovery
BWA-Scalpel
BWA-GATK
PennCNV
Novolign-Freebayes
BWA-ERDS
Novolign-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 full

Disease model	Location	Reference allele	Alternative allele	CADD score	Annotation software	Function
Autosomal recessive	chr1:210851705	TT	T	27.5	ANNOVAR, GEMINI, SVS	UTR3
Autosomal recessive	chr1:224772440	AATAATTTG	TA	22.1	GEMINI	intergenic
Autosomal recessive	chr2:60537356	TTTTATTT	ATTATTA	22.3	GEMINI	intergenic
Autosomal recessive	chr8:109098066	AT	A	24.6	GEMINI	intergenic
Autosomal recessive	chr15:66786022	ACAAA	A	23.6	GEMINI	intronic:SNAPC5
Autosomal recessive	chr16:49061346	TA	T	25.3	ANNOVAR, GEMINI	intergenic
Autosomal recessive	chr16:49612367	GAC	G	20.5	GEMINI, SVS	intronic:ZNF423
X-linked	chrX:70621541	T	C	22.9	ANNOVAR, GEMINI, SVS	TAF1:NM_138923:I1316T

Coding full

Disease model	Location	Reference allele	Alternative allele	Gene name	Annotation software	Function
De-novo	chr1:53925373	G	GCCGCCC	DMRTB1	GEMINI, SVS	nonframeshift
Autosomal recessive	chr10:135438929	T	G	FRG2B	ANNOVAR, GEMINI, SVS	NM_001080998:I171L
Autosomal recessive	chr10:135438951	GGCCC	AGCCT	FRG2B	GEMINI, SVS	nonframeshift
Autosomal recessive	chr10:135438967	C	T	FRG2B	GEMINI, SVS	NM_001080998:R158Q
Autosomal recessive	chr15:85438314	C	CTTG	SLC28A1	GEMINI	nonframeshift
X-linked	chrX:34961492	T	C	FAM47B	GEMINI	NM_152631:Y182H
X-linked	chrX:70621541	T	C	TAF1	ANNOVAR, GEMINI, SVS	NM_138923:I1316T

X:70621541-SNV Nonsyn SNV TAF1 c.4010T>C **p.Ile1337Thr**

2 mutations present in mother and two boys, on X-chromosome, not in father, not in dbSNP135, not in 1000Genomes April 2012 release, and not in NHLBI 6500 Exomes

- Nonsyn SNV ZNF41 c.1191C>A p.Asp397Glu
- Nonsyn SNV TAF1 c.4010T>C p.Ile1337Thr

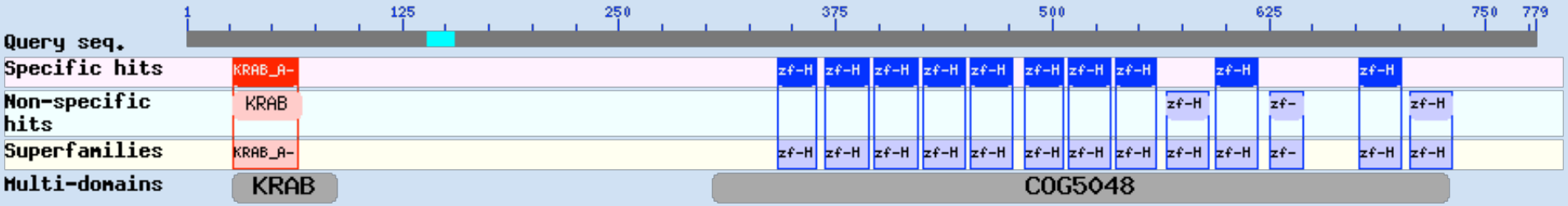
TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa

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

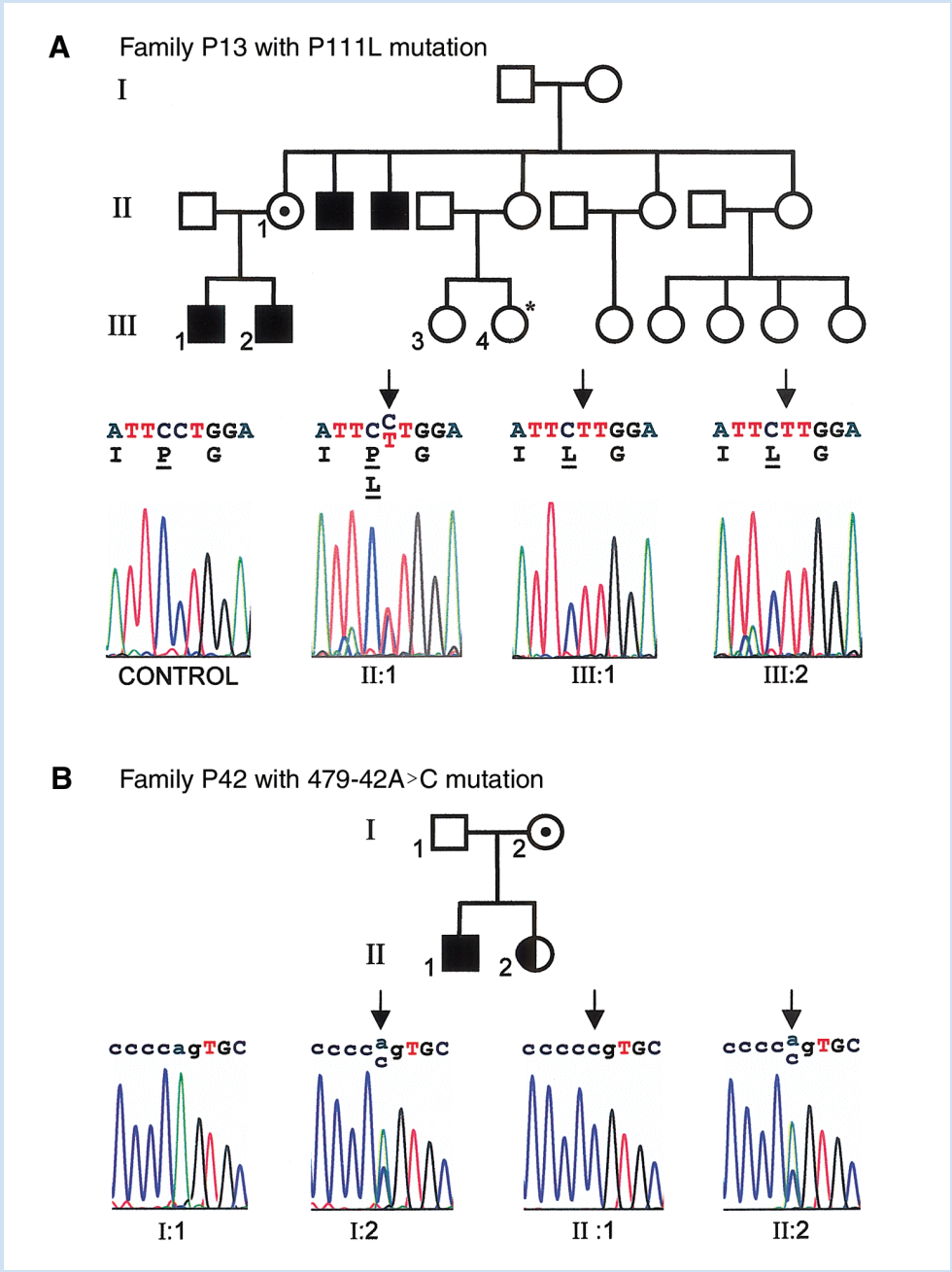
Sarah A. Shoichet,[1] Kirsten Hoffmann,[1] Corinna Menzel,[1] Udo Trautmann,[2] Bettina Moser,[1] Maria Hoeltzenbein,[1] Bernard Echenne,[3] Michael Partington,[4] Hans van Bokhoven,[5] Claude Moraine,[6] Jean-Pierre Fryns,[7] Jamel Chelly,[8] Hans-Dieter Rott,[2] Hans-Hilger Ropers,[1] and Vera M. Kalscheuer[1]

[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



- KRAB (Kruppel-associated box) domain -A box.
- The KRAB domain is a transcription repression module, found in a subgroup of the zinc finger proteins (ZFPs) of the C2H2 family, KRAB-ZFPs. KRAB-ZFPs comprise the largest group of transcriptional regulators in mammals, and are only found in tetrapods.
- The KRAB domain is a protein-protein interaction module which represses transcription through recruiting corepressors. The KAP1/ KRAB-AFP complex in turn recruits the heterochromatin protein 1 (HP1) family, and other chromatin modulating proteins, leading to transcriptional repression through heterochromatin formation.


A
Family P13 with P111L mutation
I
II
III
1
2
3
4
*
ATTCCTGGA
I P G
ATTCCTTGGA
I P L G
ATTCTTGGA
I L G
ATTCTTGGA
I L G
CONTROL
II:1
III:1
III:2
B
Family P42 with 479-42A>C mutation
I
II
1
2
1
2
ccccagTGC
ccccagTGC
ccccgTGC
ccccagTGC
I:1
I:2
II :1
II:2

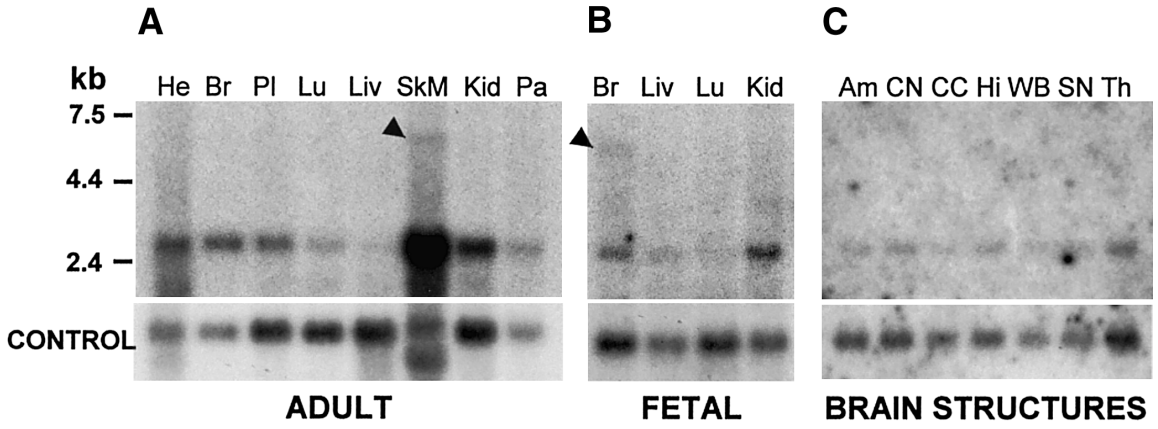


Figure 6 Northern blot hybridization of *ZNF41*, by use of a probe corresponding to nucleotides 621–1099 of *ZNF41* transcript variant 1. *A*, Adult tissues (left to right): heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas. *B*, Fetal tissues (left to right): brain, lung, liver, and kidney. *C*, Adult brain structures (left to right): amygdala, caudate nucleus, corpus callosum, hippocampus, whole brain, substantia nigra, and thalamus. Black arrowheads highlight the presence of a novel 6-kb transcript. *Actin* (*A* and *C*) or *GAPDH* (*B*) served as controls for RNA loading.

Proving Causality

- Will need to find a second, unrelated family with same exact mutation and similar phenotype.
- Can also perform in vitro/in vivo studies and structural modeling, and make knock-in mice and/or test in zebrafish, etc… for biological function.

Contents lists available at ScienceDirect

Pediatric Neurology

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

Original Article

Microcephaly Thin Corpus Callosum Intellectual Disability Syndrome Caused by Mutated *TAF2*

Shlomit Hellman-Aharony MSc [a], Pola Smirin-Yosef MSc [a], Ayelet Halevy MD [b], Metsada Pasmanik-Chor PhD [c], Adva Yeheskel MSc [c], Adi Har-Zahav MSc [a], Idit Maya MD [d], Rachel Straussberg MD [a,b], Dvir Dahary MSc [f], Ami Haviv PhD [f], Mordechai Shohat MD [a,d,e], Lina Basel-Vanagaite MD, PhD [a,d,e,*]

[a] *Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel*
[b] *Department of Pediatric Neurology and Child Development, Schneider Children's Medical Center of Israel, Petah Tikva, Israel*
[c] *Bioinformatics Unit, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel*
[d] *Raphael Recanati Genetic Institute, Rabin Medical Center, Beilinson Campus and Schneider Children's Medical Center of Israel, Petah Tikva, Israel*
[e] *Felsenstein Medical Research Center, Rabin Medical Center, Beilinson Campus, Sackler Faculty of Medicine, Tel Aviv University, Israel*
[f] *Toldot Genetics Ltd., Hod Hasharon, Israel*

Structural and functional insight into TAF1–TAF7, a subcomplex of transcription factor II D

Suparna Bhattacharya[a], Xiaohua Lou[a,b], Peter Hwang[c], Kanagalaghatta R. Rajashankar[d], Xiaoping Wang[e], Jan-Åke Gustafsson[b], Robert J. Fletterick[c], Raymond H. Jacobson[e], and Paul Webb[a,1]

[a]Genomic Medicine Program, Houston Methodist Research Institute, Houston, TX 77030; [b]Center for Nuclear Receptors and Cell Signaling, University of Houston, Houston, TX 77204; [c]University of California Medical Center, San Francisco, CA 94158; [d]The Northeastern Collaborative Access Team and Department of Chemistry and Chemical Biology, Cornell University, Argonne National Laboratory, Argonne, IL 60439; and [e]Department of Molecular Biology and Biochemistry, MD Anderson Cancer Center, Houston, TX 77030

Contributed by Jan-Åke Gustafsson, May 13, 2014 (sent for review April 17, 2014; reviewed by Fraydoon Rastinejad and Stephen K. Burley)

The End of Lecture

Extra Slides to Follow

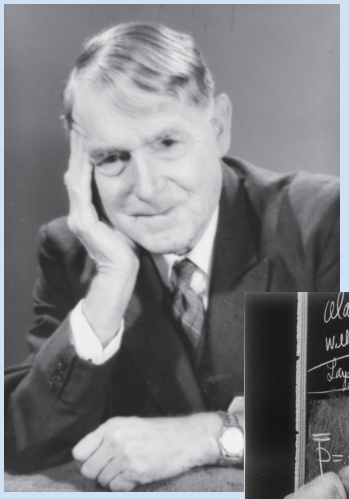
Scientific Basis for the Support of Biomedical Science

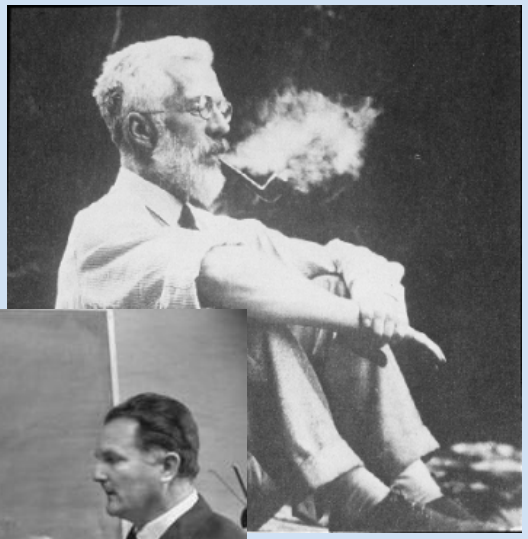
Julius H. Comroe, Jr., and Robert D. Dripps

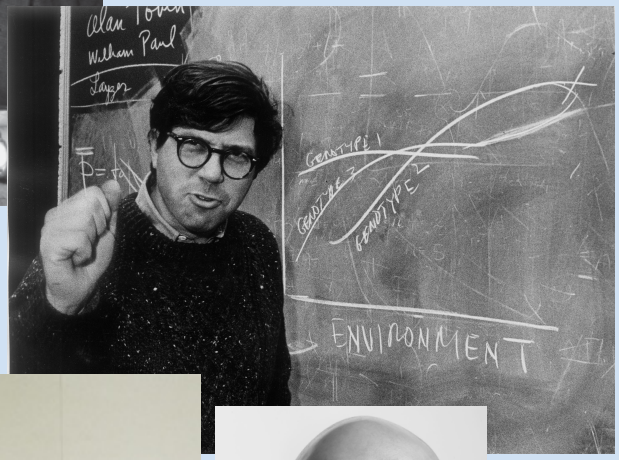
Science. 1976 Apr 9;192(4235):105-11.

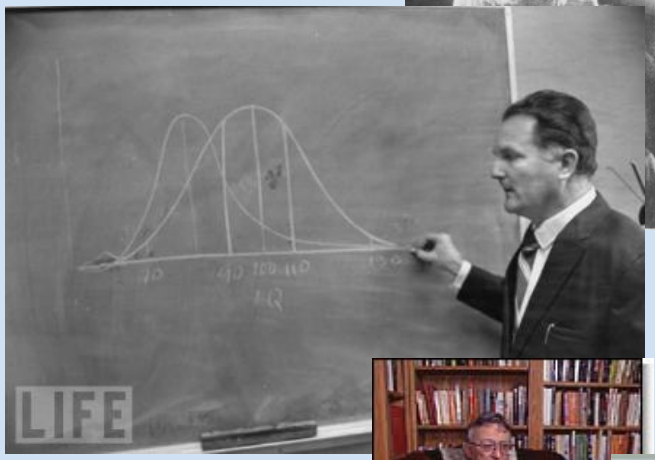
"scientific advance requires far more work than that reported by the discoverer or by those who wrote key articles essential for his discovery…. scientists earlier and later than the discoverer have always been essential to each discovery and its full development."

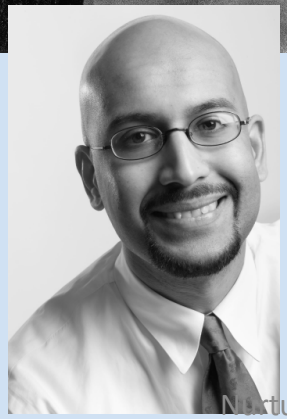
The Explanatory Divide

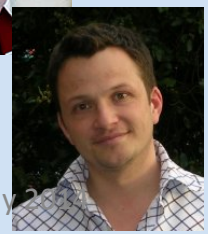




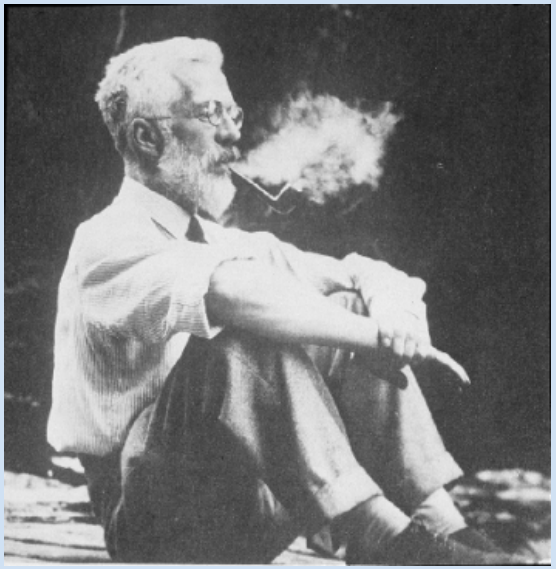




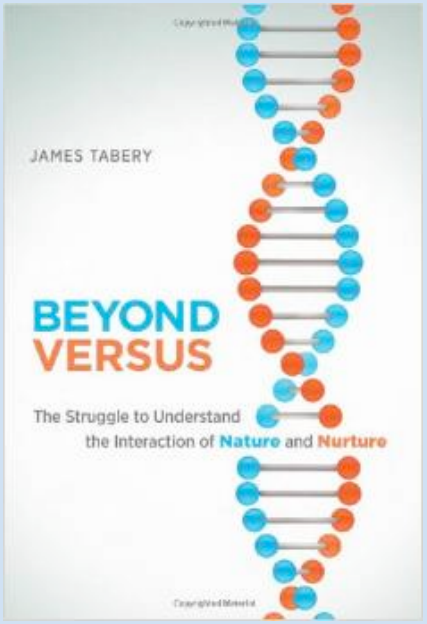




Lancelot Hogben
1895-1972



Ronald Fisher
1890-1962

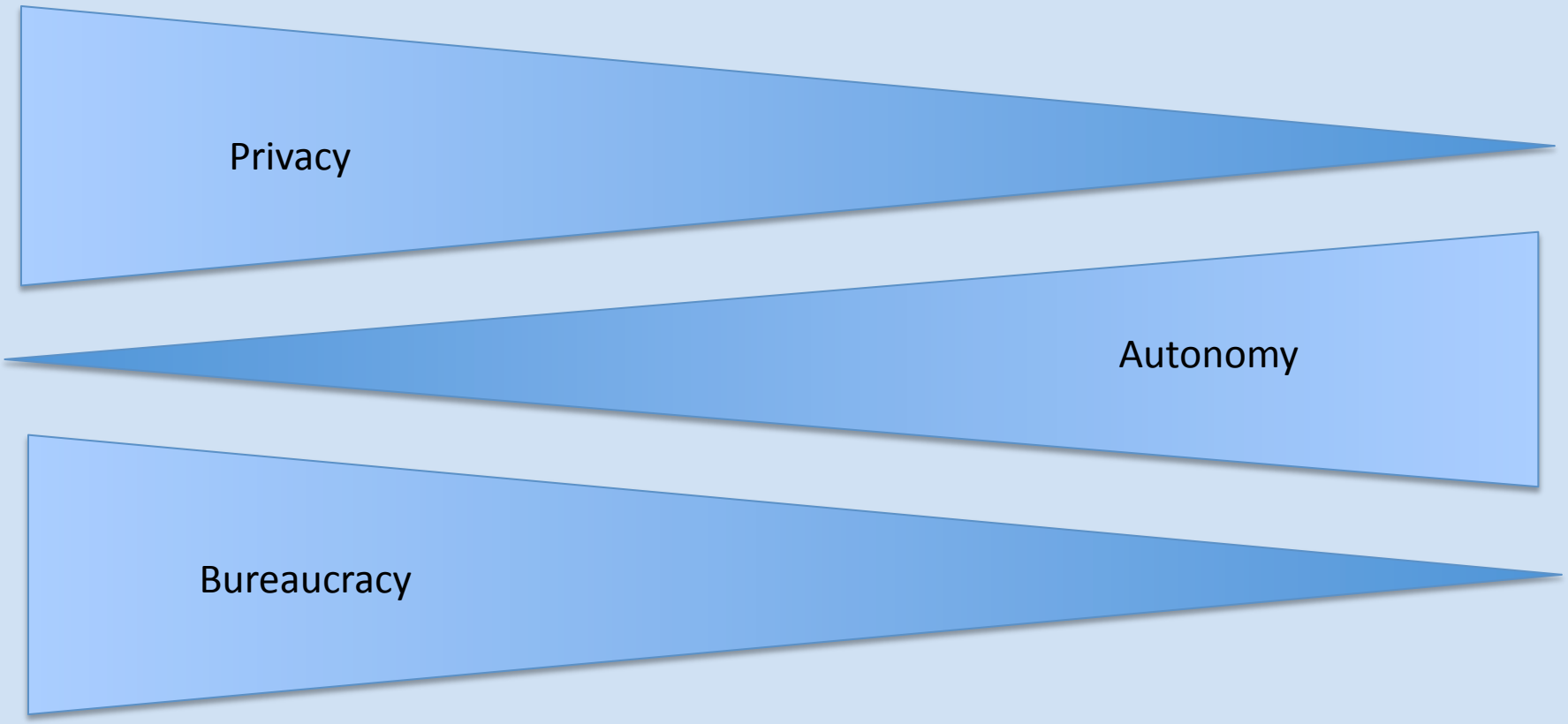


Quote from Leroy Hood, 2012

- "I argue that the data for every patient should belong to society and not the individual," Hood says. "It's society that has created the tools to enable the data to help with the individual's health and, even more important, it's critical that that data be available after anonymization for people to analyze and mine for the predictive medicine of the future. This is what's going to revolutionize medicine for your children and your grandchildren."

- Yes, BUT it should not skip the step of the actual individual! Generate the data for the individual and obtain consent to anonymize and use that data for the future.
- So many papers describe mutations that are found, but very little discussion, if any, on whether these results were given back to the families.

Autonomy vs. Privacy vs. Bureaucracy



PRIVACY and PROGRESS in Whole Genome Sequencing

Presidential Commission
for the Study of Bioethical Issues

October 2012

Published online 4 October 2011 | *Nature* **478**, 17 (2011) |
doi:10.1038/478017a

News

Secrets of the human genome disclosed

Meeting debates ethics of revealing genetic findings.

Erika Check Hayden

NEW YORK

Should people be told about any nasty surprises that scientists discover in their DNA during research projects?

The question is becoming increasingly pertinent, as thousands of people sign up for studies in which their genomes will be sequenced. But, at present, federal laws in the United States prohibit researchers from telling patients about mutations that might affect them or their families unless a certified clinical lab has confirmed the results — something that is not done in most research projects. This means that patients often do not learn about their mutations until the studies are finally published, a restriction that is meant to ensure they are not misinformed by incomplete research.

> **"These disclosures have societal implications that need to be considered."**

The ethical dilemmas became all too real last year for geneticist Gholson Lyon, a geneticist at the Utah Foundation for Biomedical Research in Salt Lake City. He was studying an extended family in which some of the boys had been born with a constellation of symptoms, including thick, wrinkly skin, and who ultimately died of cardiac disease before their first birthdays. By November 2010, Lyon had convincing evidence that a genetic mutation was causing the disease. That's when he learned that one of the women in the family was four months pregnant with a boy.

Policy and Governance

"If you sequence people's exomes you're going to find stuff," said Gholson Lyon, a physician and researcher previously at the University of Utah, now at Cold Spring Harbor Laboratory.

As part of his research, Dr. Lyon worked with a family in Ogden, Utah. Over two generations, four boys had died from an unknown disease with a distinct combination of symptoms—an aged appearance, facial abnormalities, and developmental delay. Dr. Lyon sought to identify the genetic cause of this disease, and collected blood samples from 12 family members who had signed consent forms. The family members understood these forms to mean that they would have access to their results.

Dr. Lyon has become an outspoken advocate for conducting whole genome sequencing in laboratories that satisfy the federal standards so that researchers can return results to participants, if appropriate. Dr. Lyon wants clear guidance for laboratories conducting genetic research and clear language in consent forms that clarifies the results that participants should expect to have returned from the researchers.

Recommendation 4.1

Funders of whole genome sequencing research, relevant clinical entities, and the commercial sector should facilitate explicit exchange of information between genomic researchers and clinicians, while maintaining robust data protection safeguards, so that whole genome sequence and health data can be shared to advance genomic medicine.

Performing all whole genome sequencing in CLIA-approved laboratories would remove one of the barriers to data sharing. It would help ensure that whole genome sequencing generates high-quality data that clinicians and researchers can use to draw clinically relevant conclusions. It would also ensure that individuals who obtain their whole genome sequence data could share them more confidently in patient-driven research initiatives, producing more meaningful data. That said, current sequencing technologies and those in development are diverse and evolving, and standardization is a substantial challenge. Ongoing efforts, such as those by the Standardization of Clinical Testing working group are critical to achieving standards for ensuring the reliability of whole genome sequencing results, and facilitating the exchange and use of these data.[216]

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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

Table 1
Processes involved in a CLIA-certified genetic test.

Preanalytic system
1) Test request and specimen collection criteria
2) Specimen submission, handling and referral procedures
3) Preanalytic systems assessment
Analytic system
1) A detailed step-by-step procedure manual
2) Test systems, equipment, instruments, reagents, materials and supplies
3) Establishment and verification of performance specifications
4) Maintenance and function checks
5) Calibration and calibration verification procedures
6) Control procedures, test records, and corrective actions
7) Analytic systems assessment
Post-analytic system
1) Test report, including (among other things):
a) interpretation
b) reference ranges and normal values
2) Post-analytic systems assessment

1. Sample Collection and handling

2. Sequencing/Analytics

3. Interpretation

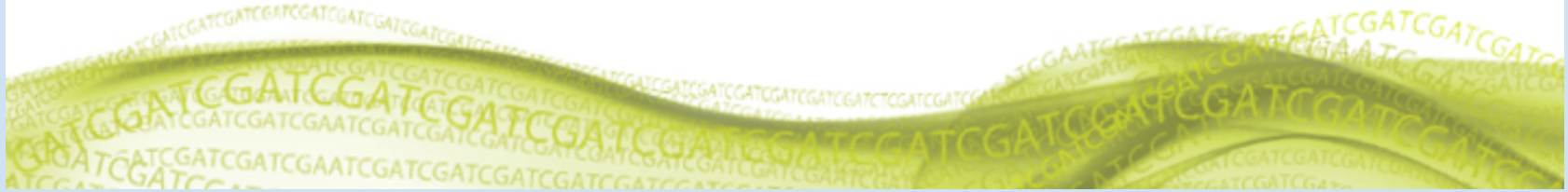
Individual Genome Sequencing Service

Available from Illumina's CLIA-certified laboratory.

"This laboratory test was developed, and its performance characteristics were determined by the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited). Consistent with laboratory-developed tests, it has not been cleared or approved by the U.S. Food and Drug Administration. If you have any questions or concerns about what you might learn through your genome sequence information, you should contact your doctor or a genetic counselor. Please note that Illumina does not accept orders for Individual Genome Sequencing services from Florida and New York."

Understand Your Genome Symposium

During this two-day educational event, industry experts will discuss the clinical implementation of whole-genome next-generation sequencing (NGS) technology.



illumina®

Ordering Physician:
Gholson Lyon, MD
Steinmann Institute
10 West Broadway, Suite #820
Salt Lake City, UT 84101

Individual Genome Sequence Results

Clinical Report

www.everygenome.com
CLIA#: 05D1092911

Hum Genet (2009) 126:317–324
DOI 10.1007/s00439-009-0690-1

HISTORICAL AND PERSONAL PERSPECTIVES

Fiftieth anniversary of trisomy 21: returning to a discovery

Marthe Gautier · Peter S. Harper

Published online: 30 June 2009

"In reality, discoveries are due to people at the edge of the formalised groups of researchers"

Pierre Laszlo

Fifty years ago, I was the co-author[1] of the first paper that showed the presence of an additional chromosome (Lejeune et al. 1959) in the syndrome identified by Langdon Down in 1866 and commonly known as "mongolism" in France at the time. This, the first autosomal chromosome aberration recognised in the cells of the human species, was named trisomy 21. I thought it would be of historical interest to bring my own personal testimony as an actor in that discovery.

HISTORY OF SCIENCE

After More Than 50 Years, a Dispute Over Down Syndrome Discovery

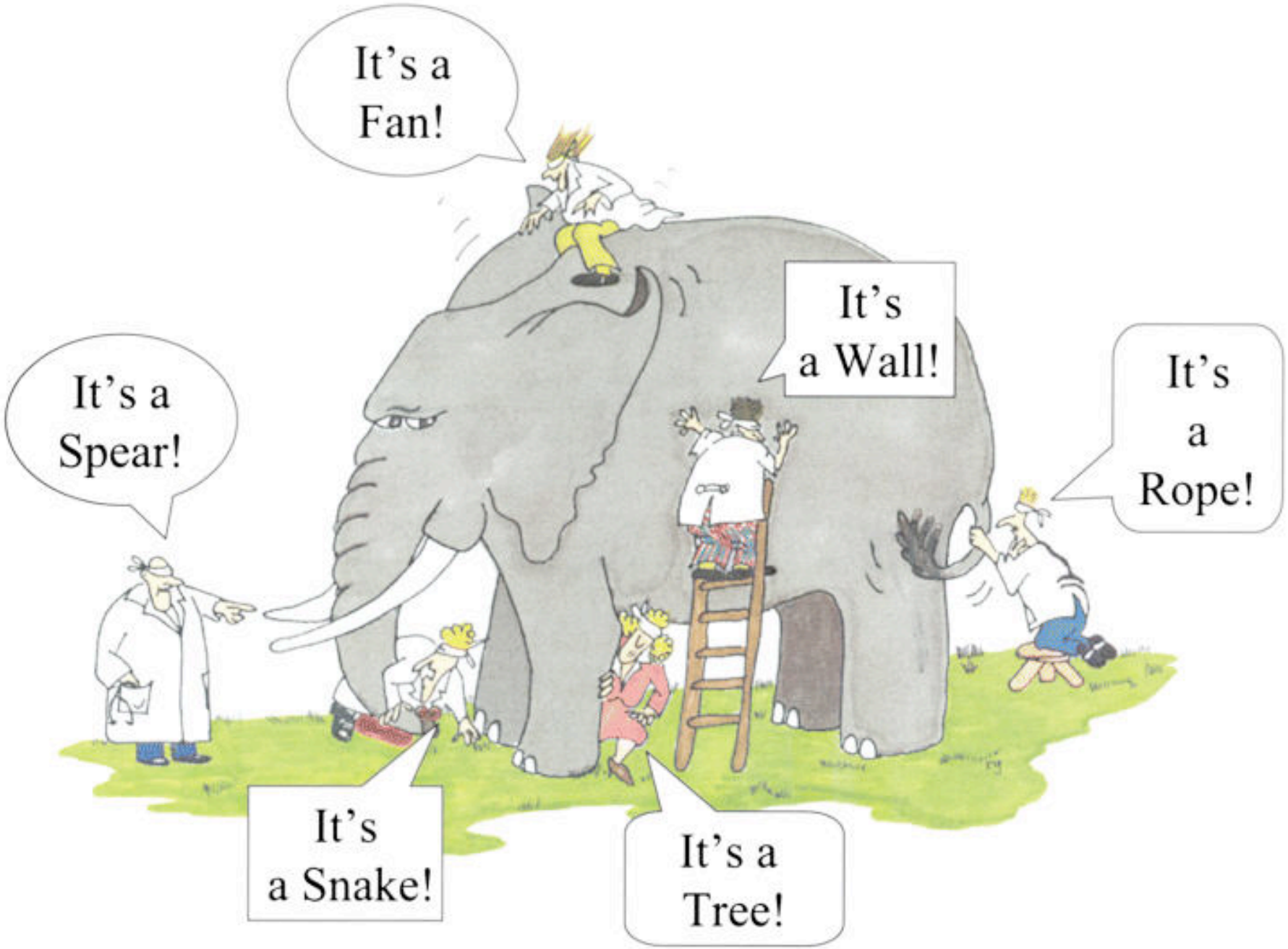
BRAIN 2025

A SCIENTIFIC VISION

Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Working Group Report to the Advisory Committee to the Director, NIH

June 5, 2014

National Institutes of Health
Turning Discovery into Health


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