# Clinical progress in autism genetics and treatment

Systems biology of autism: from basic science to therapeutic strategies Sept 9-12, 2012

Gholson Lyon, M.D. Ph.D.

# Conflicts of Interest

- I do not receive salary compensation from anyone other than my current employer, CSHL .
- Any revenue that I earn from providing medical care in Utah is donated to UFBR for genetics research.

# Industrialization of Genome Sequencing – Just like what happened in development of MRI

- 09/11/12
  Illumina Announces Expedited Individual Genome Sequencing Service (IGS)

- 09/11/12
  Illumina and Partners HealthCare Announce Alliance to Introduce Next-Generation Sequencing Clinical Interpretation and Reporting Tools

- 09/11/12
  Illumina Launches TruSightTM Targeted Sequencing Content Sets

- Seguin E. 1866, Idiocy and its treatment by the physiological method.
- - “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”.

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."

**Diagnostic Criteria for 299.00 Autistic Disorder**

*Diagnostic and Statistical Manual of Mental Disorders: DSM IV*

(I) A total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)

(A) qualitative impairment in social interaction, as manifested by at least two of the following:

1. marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
2. failure to develop peer relationships appropriate to developmental level
3. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
4. lack of social or emotional reciprocity ( note: in the description, it gives the following as examples: not actively participating in simple social play or games, preferring solitary activities, or involving others in activities only as tools or "mechanical" aids )

(B) qualitative impairments in communication as manifested by at least one of the following:

1. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
2. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
3. stereotyped and repetitive use of language or idiosyncratic language
4. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(C) restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least two of the following:

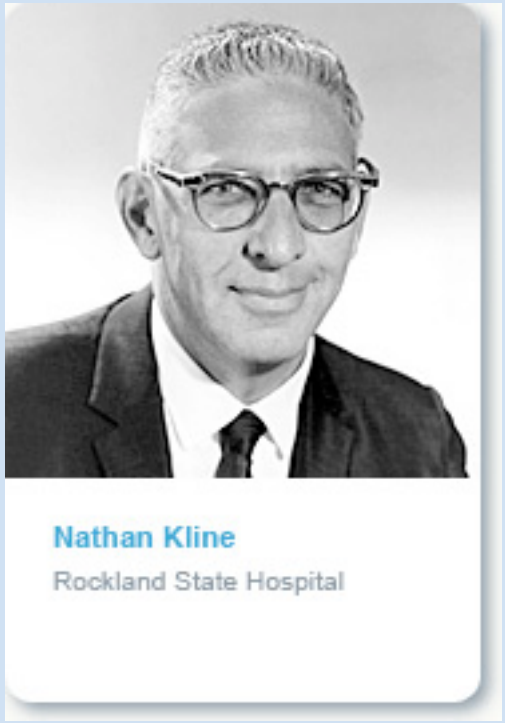
1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2. apparently inflexible adherence to specific, nonfunctional routines or rituals
3. stereotyped and repetitive motor mannerisms (e.g hand or finger flapping or twisting, or complex whole-body movements)
4. persistent preoccupation with parts of objects

(II) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

(A) social interaction
(B) language as used in social communication
(C) symbolic or imaginative play

(III) The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

1957 & 1964
Albert Lasker
Clinical Medical Research Award

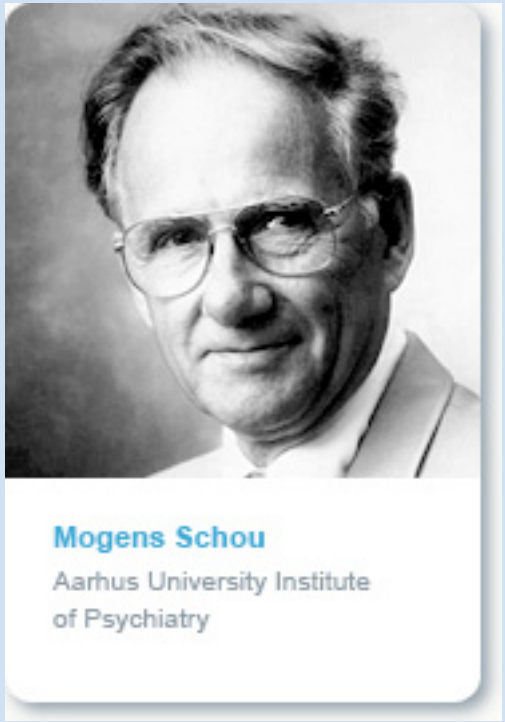



Nathan Kline

1957 - For his demonstrations of the value of Rauwolfia derivatives, especially reserpine, in the treatment of mental and nervous disorders.

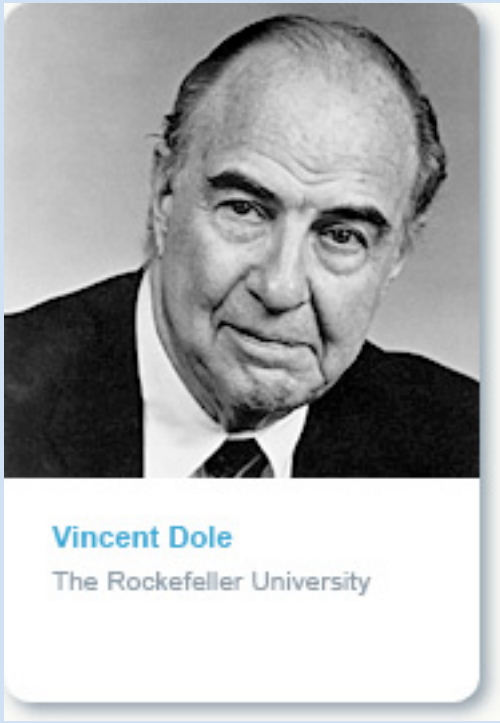
*1964* - For the introduction and use of iproniazid in the treatment of severe depression.

1987 Albert Lasker
Clinical Medical Research Award




Mogens Schou

For his landmark systematic clinical trials of lithium as therapy and prophylaxis for manic depressive illness, which initiated a revolution in the treatment of mental disease.




1988 Albert Lasker
Clinical Medical Research Award

Vincent Dole

For postulating the physiological basis of narcotic addiction and for developing methadone treatment for heroin addiction.

2006 Albert Lasker
Clinical Medical Research Award


Aaron Beck

For the development of cognitive therapy, which has transformed the understanding and treatment of many psychiatric conditions, including depression, suicidal behavior, generalized anxiety, panic attacks, and eating disorders.

# Medications commonly used for autism, mental retardation and/or aggression

- clonidine
- guanfacine
- risperidone
- haloperidol
- quetiapine
- aripiprazole
- lithium
- valproic acid
- methylphenidate
- amphetamines
- fluoxetine

- citalopram
- Trazodone
- benzodiazepines

Infrequently used-

- chlorpromazine
- clozapine
- other SSRIs, SSIs, or TCAs.

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

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

NYU Child Study Center
New York, New York

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

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

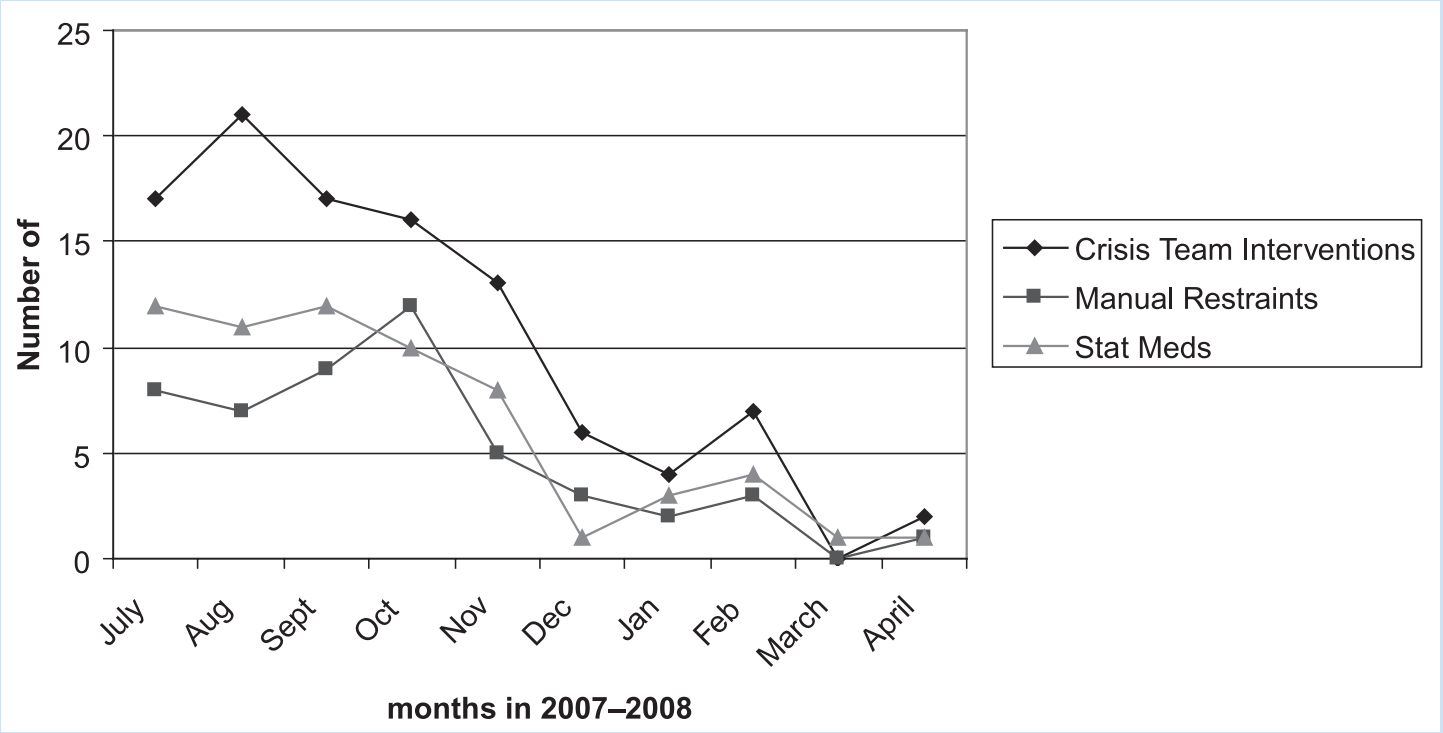



**FIG. 1.** Number of incidents including crisis team interventions (calls overhead for assistance), manual restraints, and urgent medications (by mouth or intramuscular) for each month during the course of this patient's hospitalization.

"We don't have to look for a model organism anymore, because we *are* the model organisms."

– Sydney Brenner, Nobel Laureate, quote in 2008

# 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

# 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% penetrance (or "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

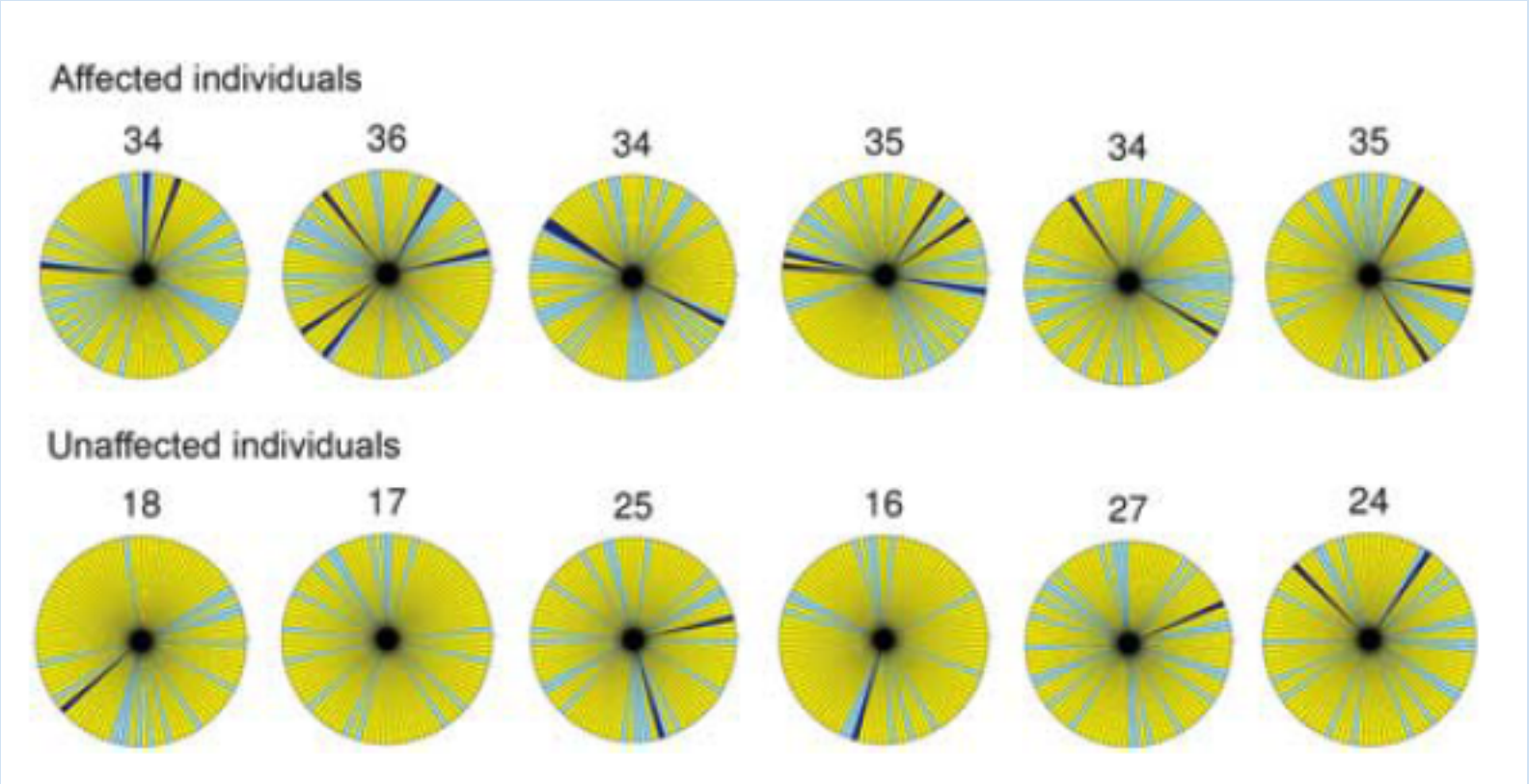
S Hong Lee[1,2], Teresa R DeCandia[3,4], Stephan Ripke[5,6], Jian Yang[2,7], The Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ)[8], The International Schizophrenia Consortium (ISC)[8], The Molecular Genetics of Schizophrenia Collaboration (MGS)[8], Patrick F Sullivan[9], 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

# Penetrance Issues

- We do not really know the penetrance 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.

- There is a **MAJOR** clash of world-views, i.e. do single mutations drive outcome predominately, or are the results modified substantially by genetic background and/or environment? i.e. is there really such a thing as genetic determinism for **MANY** mutations?

# “Biological Indeterminacy”

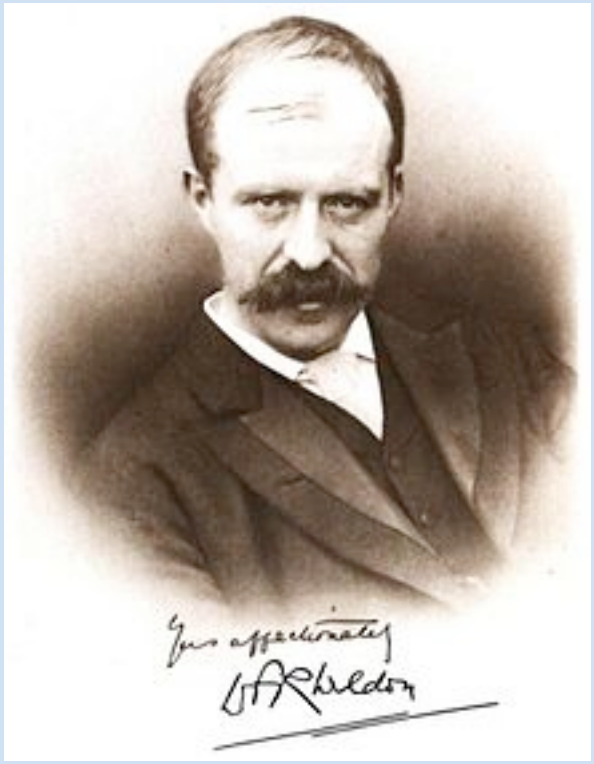
- Bateson became famous as the outspoken Mendelian antagonist of Walter Raphael Weldon, his former teacher, and Karl Pearson who led the biometric school of thinking. This concerned the debate over saltationism versus gradualism (Darwin had been a gradualist, but Bateson was a saltationist). Later, Ronald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

**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



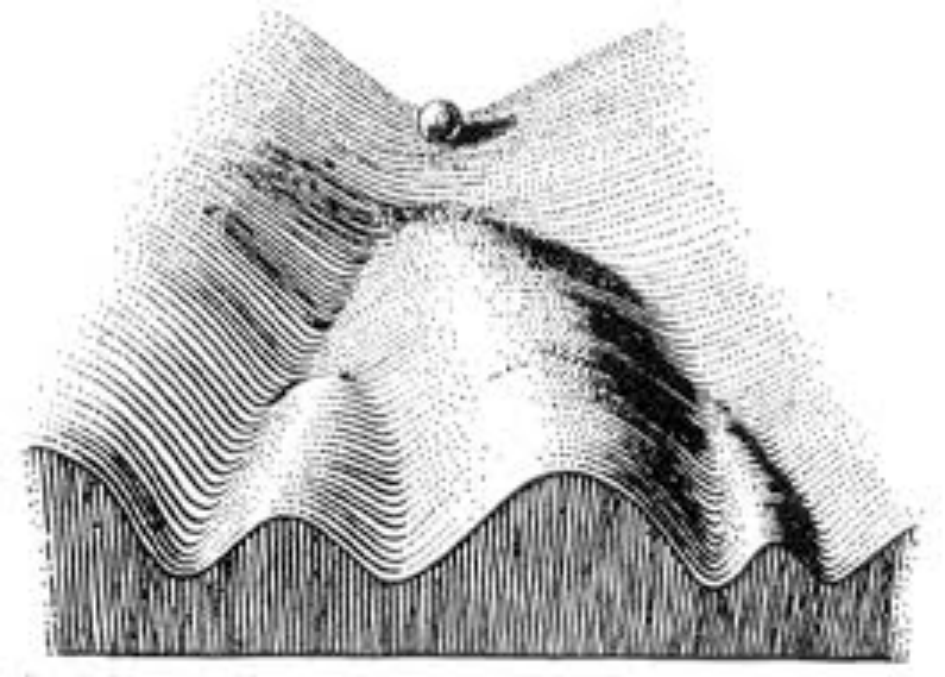
Walter Frank Raphael Weldon

Vs.

William Bateson

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

**Waddington claimed that canals form in the epigenetic landscape during evolution, and that this heuristic is useful for understanding the unique qualities of 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.

# The genetic basis of a new syndrome with severe developmental delay and cardiac abnormalities.

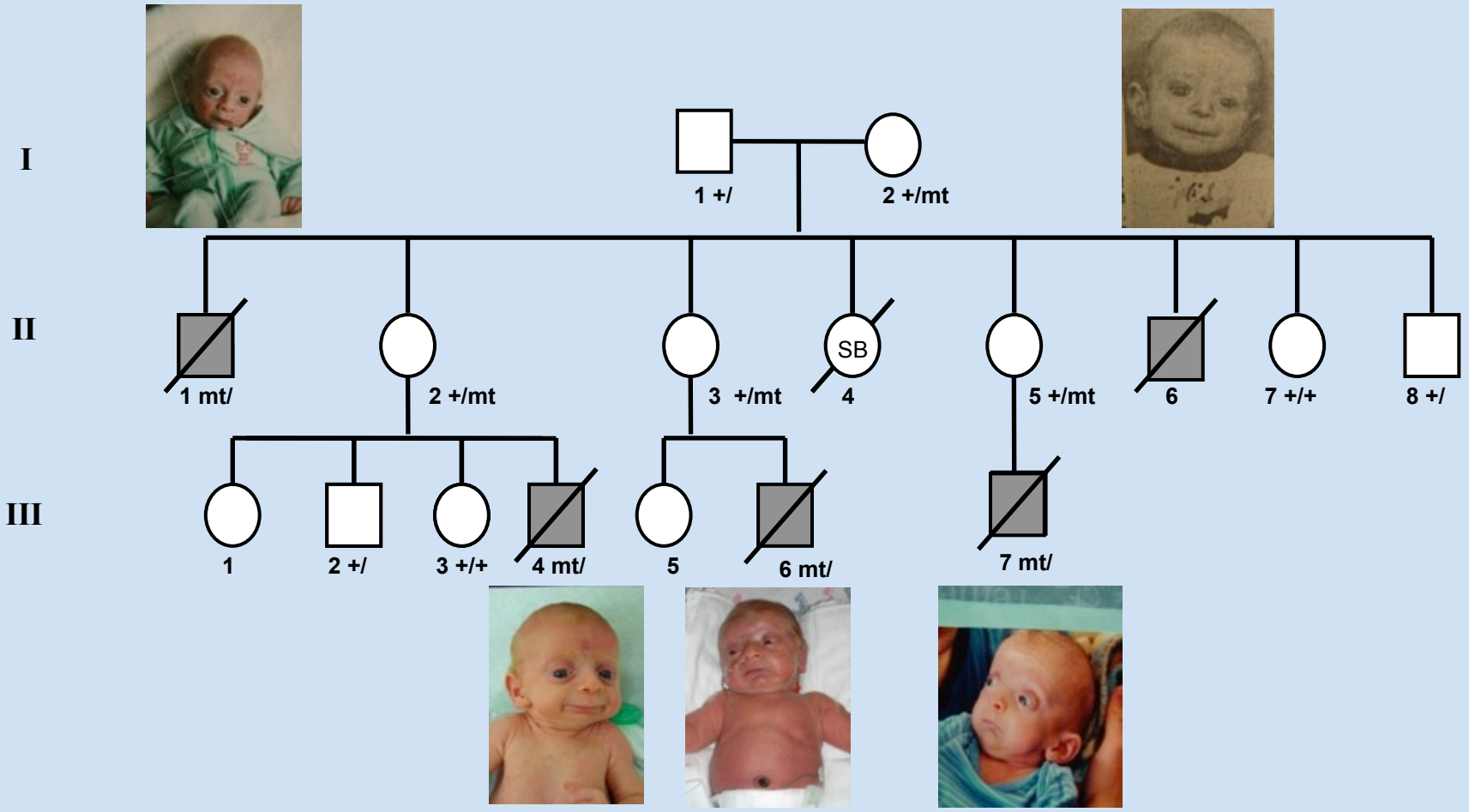
ARTICLE

## 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

# Family now in October 2011, with five mutation-positive boys dying from the disease.



# 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.

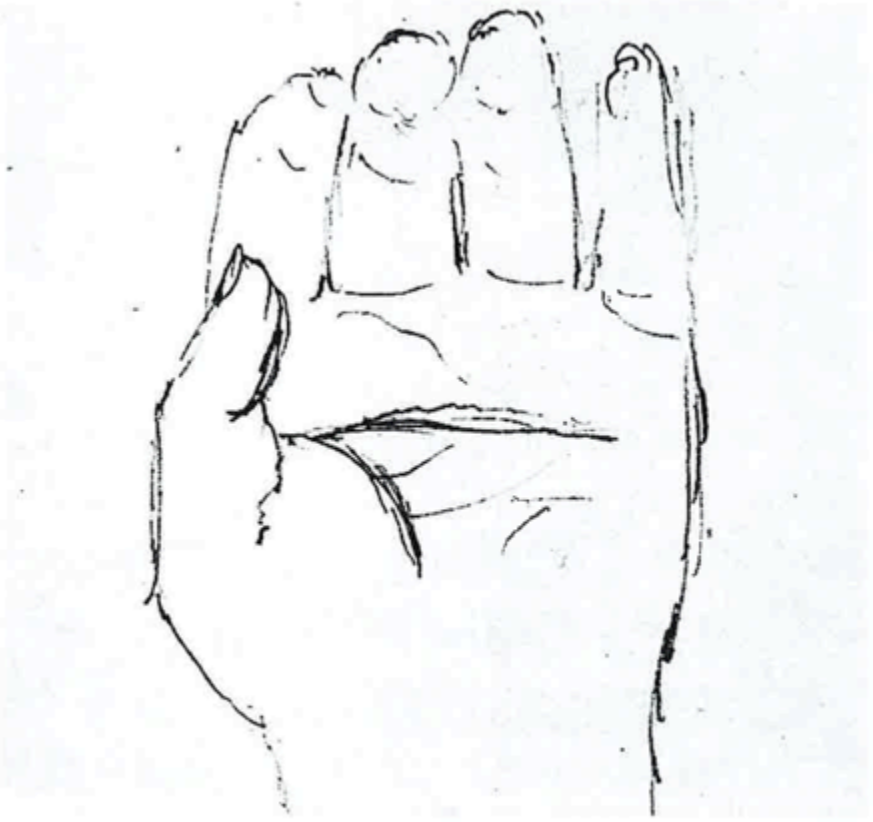

GRUNE & STRATTON

New York

1949

Plate VII—Mongolism in two imbecile brothers aged 10 (Colchester Survey, 1938, Case No. 750) and 5 years, with a normal child aged 2½ 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.

**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? |

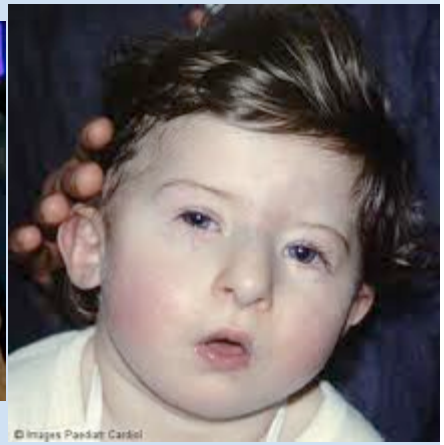
# Down Syndrome

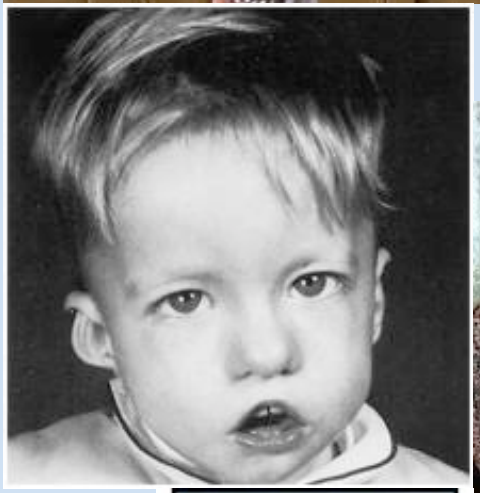
# Down Syndrome

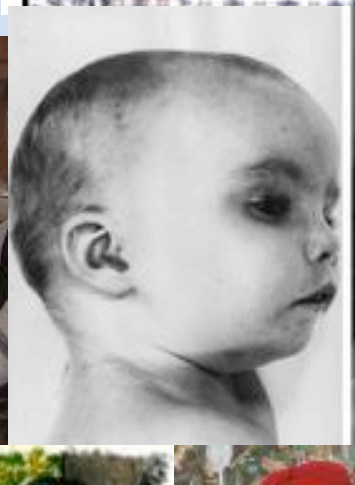
Christopher Joseph "Chris" Burke (born August 26, 1965) is an American actor and folk singer, who lives with Down syndrome, who has become best known for his character Charles "Corky" Thacher on the television series Life Goes On.

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

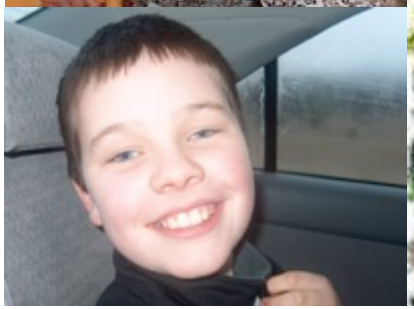
# Velocardiofacial (22q11.2) Syndrome

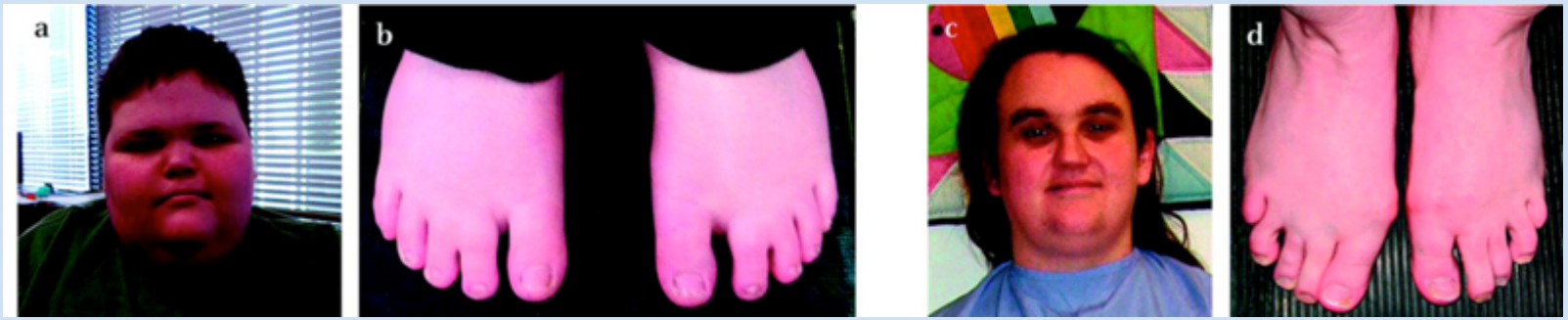









# 16p11.2 deletion




Clinical photographs. (a and b) Proband 2 (de novo deletion 16p11.2). Note long narrow palpebral fissures, short delicate nose, short neck and brachydactyly with 2–3 cutaneous toe syndactyly. (c and d) Mother of proband 3 (both with deletions). Note her large ears, smooth philtrum and short fifth toes.



Fernandez B A et al. J Med Genet 2010;47:195-203

# 16p11.2 duplication


Clinical photographs. (e) Proband 5 who has a maternally inherited duplication. (f) Proband 5 (note smooth philtrum) and her healthy duplication positive sister. (g) Duplication positive mother of proband 5, who also has a smooth philtrum. (h) Proband 6 (inherited duplication and oliogohydramnios sequence). Note her frontal bossing, receding hairline, hypoplastic supraorbital ridges and smooth philtrum. (i) Proband 6's right hand showing fifth finger clinodactyly.



Fernandez B A et al. J Med Genet 2010;47:195-203

JMG

# 16p11.2 deletion, not in mother or father, only in child.

5 years old, but developmental age of 2 year old.
Speaks a few words, almost unintelligible.
Very hyperactive.
Can be withdrawn and has at times been diagnosed with “autism”.

**Current Diagnoses under Evaluation (DSM IV-TR)**

| | | |
|---|---|---|
| **AXIS I** | 299.00 | Autism Disorder |
| | 314.01 | Attention-Deficit-Hyperactivity Disorder, Combined Type |
| **AXIS II** | V71.09 | No Diagnosis |
| **AXIS III** | 16p11.2 | Microdeletion |
| **AXIS IV** | | Psychosocial Stressors: Moderate(Adaptive/Behavioral and Educational/Learning Problems) |
| **AXIS V** | | Current GAF: 60 |

**Assessment Procedures:**

Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
Wide Range Achievement Test 4rd Edition (WRAT-4)
Test of Memory and Learning 2 (TOMAL, 2)
Beery VMI 6th Edition (Beery-Buktenica Developmental Test of Visual-Motor Integration, 6th Edition; Visual Perception, 6th Edition; Motor Coordination, 6th Ed)
Wide Range Assessment of Visual Motor Abilities (WRAVMA)
Conners' Comprehensive Behavior Rating Scales (CBRS) (Parent Report)
The Social Responsiveness Scale
Autism Diagnostic Interview Revised (ADI-R)
Mental Status Examination
Steinmann Neuropsychiatric Developmental Questionnaire
CNS Vital Signs Neuropsychological Screening
Clinical Interview with Patient
Clinical Interview with Parent
Clinical Observations
Review of Medical, Psychiatric, and Scholastic Records

*James Henry Pullen, the* idiot savant *who designed the prize winning exhibit for the Paris exhibition in 1867, dressed in the admiral's uniform which he accepted in return for not pursuing his plan to marry. He also designed a realistic model of the* Great Eastern, *a famous transatlantic vessel built by Brunel.*

Master Craftsman
Most famously designed The Great Eastern, a 10 foot long model ship with incredible detail.

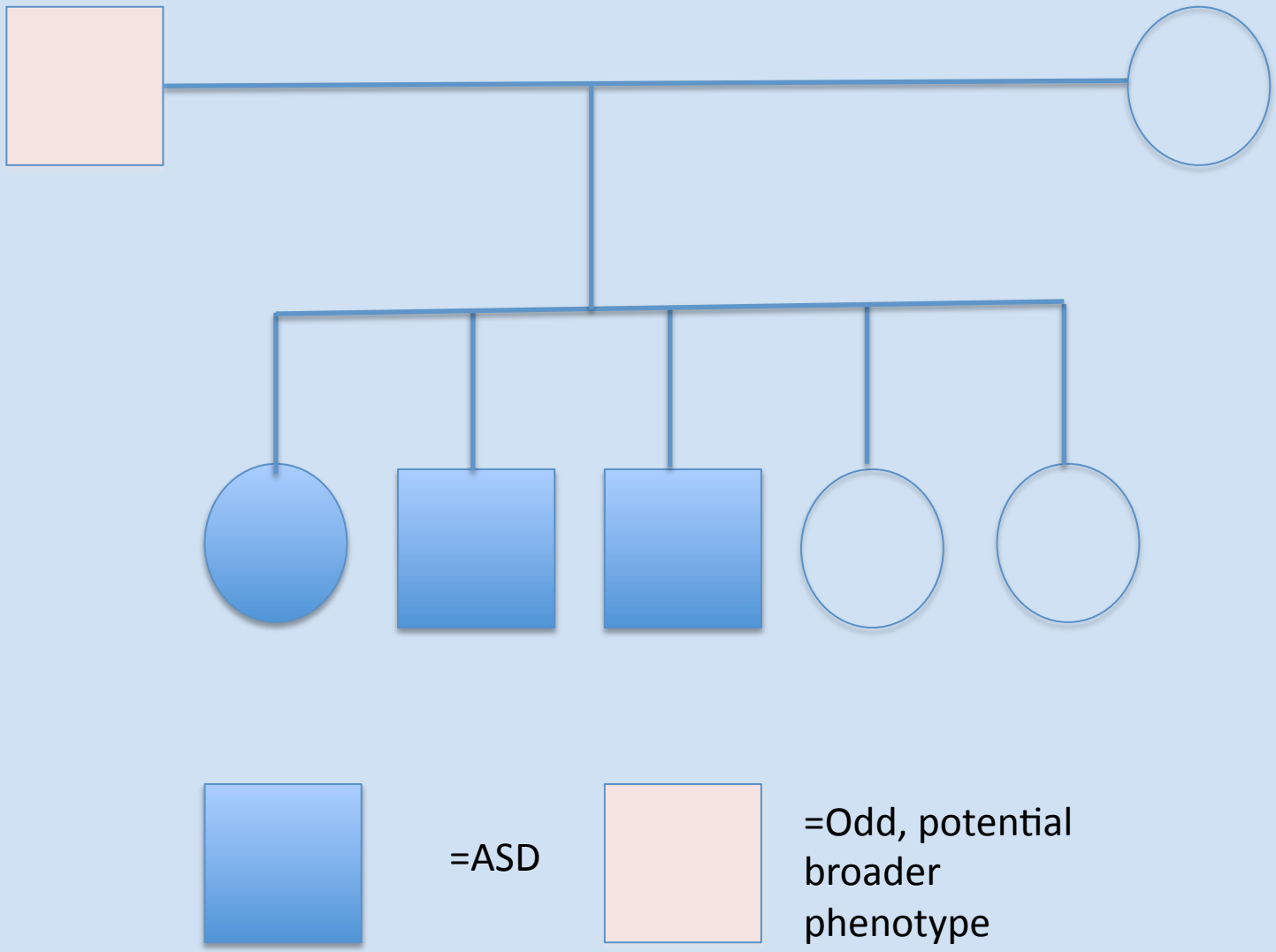
Deaf and nearly mute – Nonverbal,
Obsessed with one topic of building things.
Thought to be mentally retarded.
Usually quiet and reserved, but sometimes was intolerant of advice, suspicious of strangers, and ill-tempered and violent.

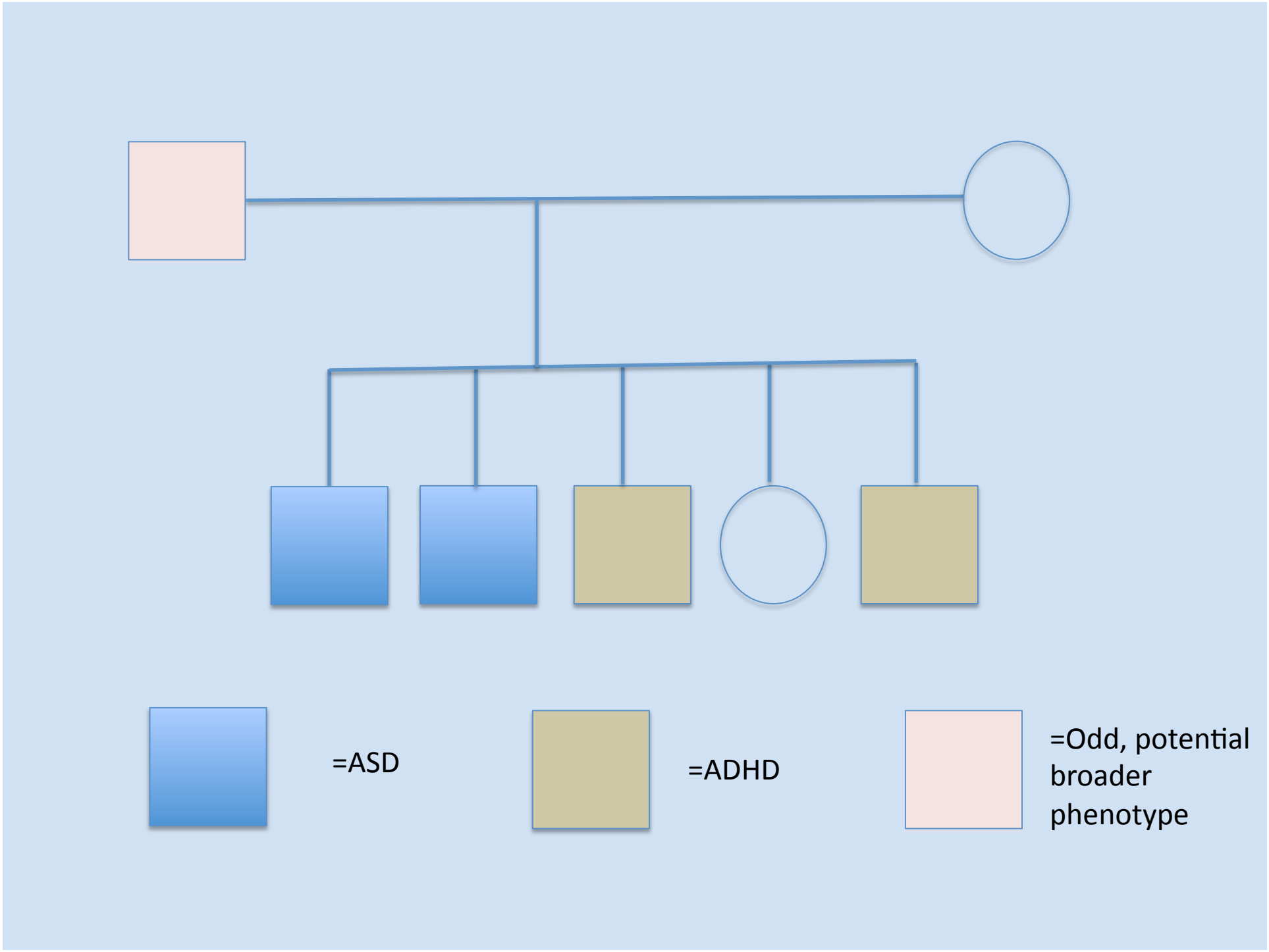
"The clinical and pathological evidence of a pervasive developmental disorder points to a retrospective diagnosis of autism."

*Ir J Psych Med 2005; 22(4): 151-155*

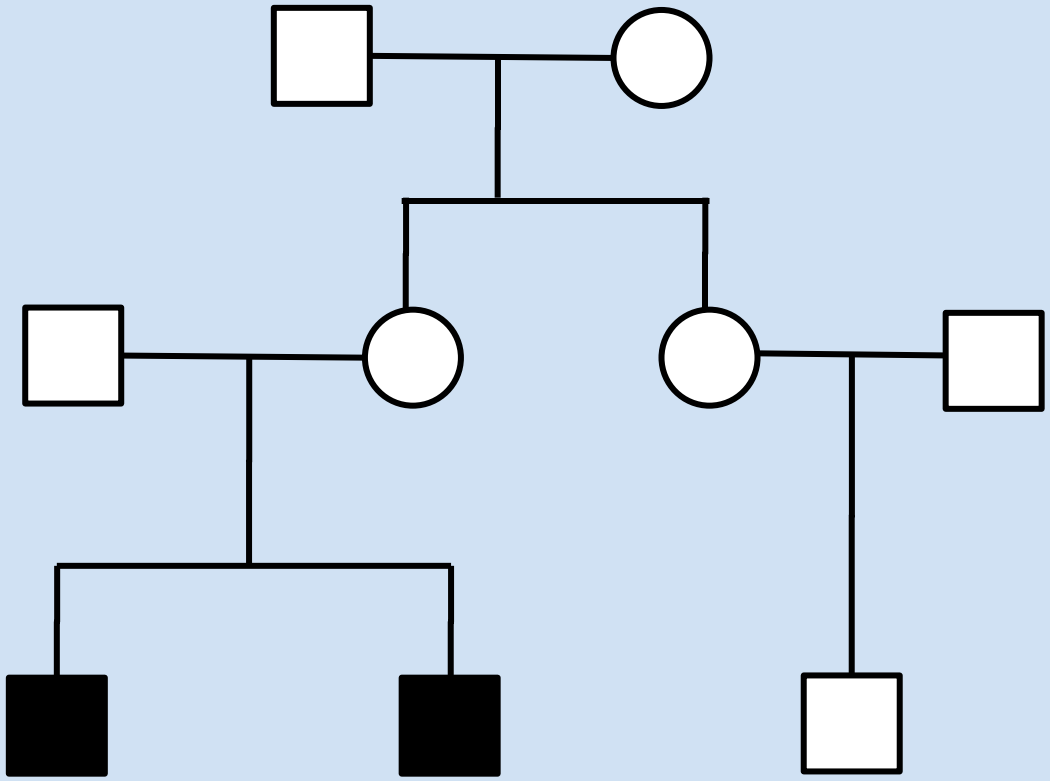
# Sibling Defense Theory

- Defense or modifier Genes? – mutations that somehow protect against or modify the effects of a primary mutation.
- Or, can female gender also somehow be protective with certain mutations?
- Henry Pullen was one of 13 children, but only 3 lived to adult life. His brother, William, was also institutionalized and had exceptional artistic skills. Their parents were first cousins.


=ASD
=Odd, potential broader phenotype


=ASD
=ADHD
=Odd, potential broader phenotype

# 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

Dysmorphic
Mental Retardation
“autism”
“ADHD”
Hearing difficulties

3 years old

5 years old

# Workup Ongoing for past 10 years

- Numerous genetic tests negative, including negative for Fragile X and MANY candidate genes.
- Found one missense mutation in a known mental retardation gene, but the mutation is a very conservative nonsynonymous Asp to Glu. Is it relevant or not? What about the whole rest of the genome?

# 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

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

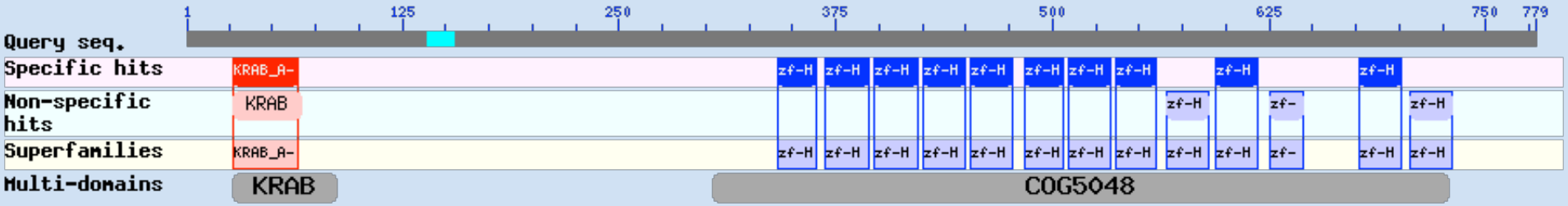
TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa

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

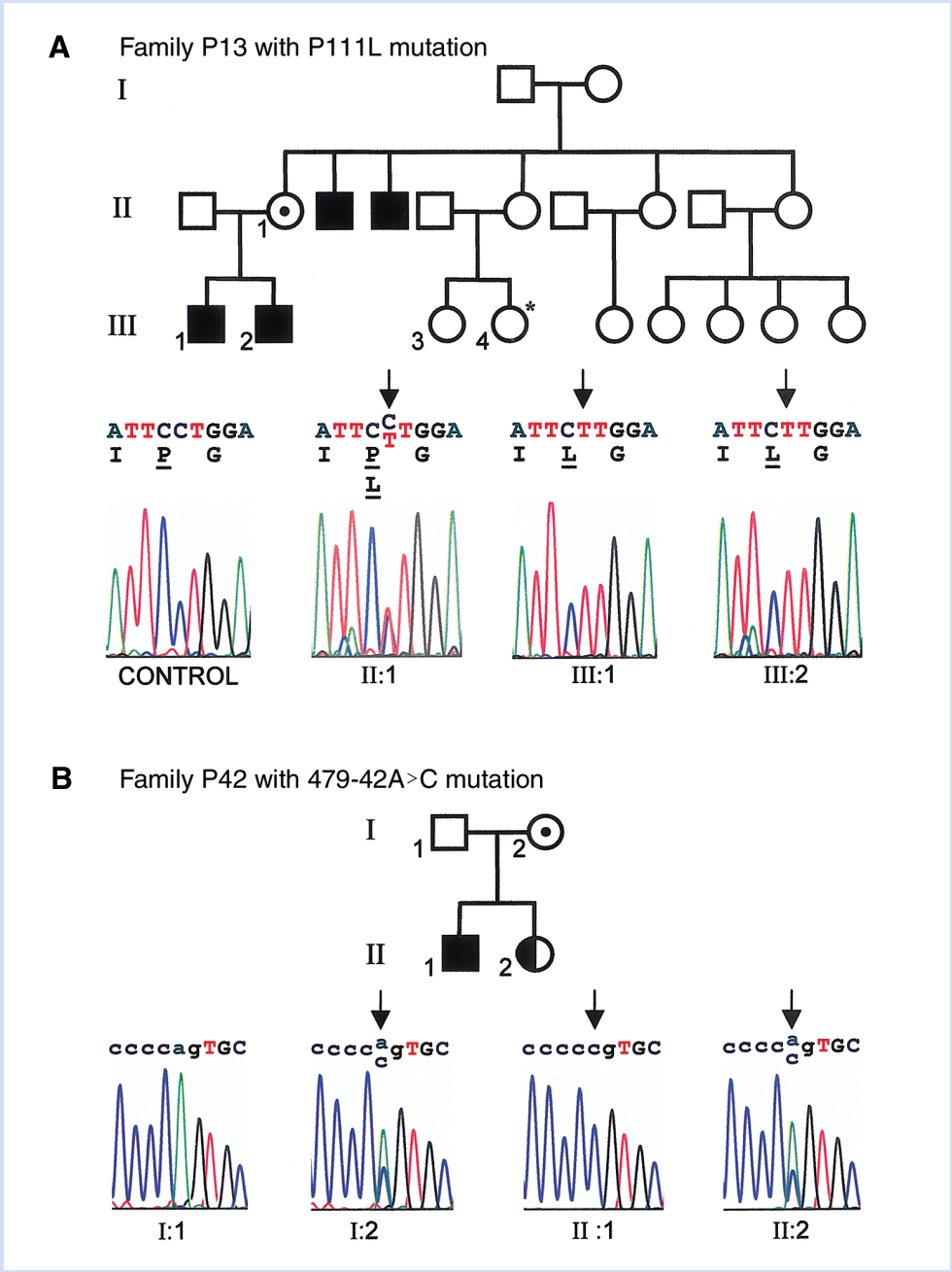
Sarah A. Shoichet,[1] Kirsten Hoffmann,[1] Corinna Menzel,[1] Udo Trautmann,[2] Bettina Moser,[1] Maria Hoeltzenbein,[1] Bernard Echenne,[3] Michael Partington,[4] Hans van Bokhoven,[5] Claude Moraine,[6] Jean-Pierre Fryns,[7] Jamel Chelly,[8] Hans-Dieter Rott,[2] Hans-Hilger Ropers,[1] and Vera M. Kalscheuer[1]

[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

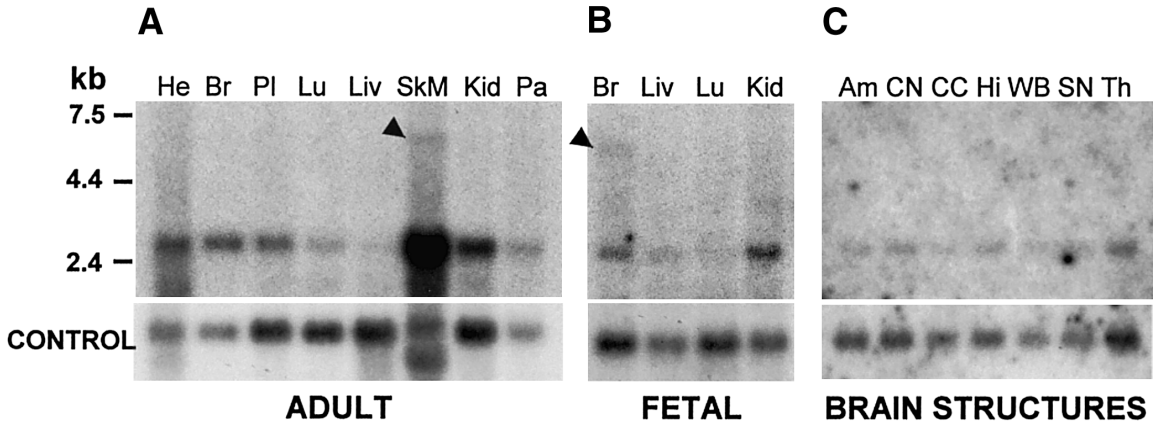



**Figure 6** Northern blot hybridization of *ZNF41*, by use of a probe corresponding to nucleotides 621–1099 of *ZNF41* transcript variant 1. *A*, Adult tissues (left to right): heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas. *B*, Fetal tissues (left to right): brain, lung, 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.

# Genotype First, Phenotype Second AND Longitudinally

*Human Molecular Genetics, 2010, Vol. 19, Review Issue 2* ***R176–R187***
*doi:10.1093/hmg/ddq366*
*Advance Access published on August 31, 2010*

## Phenotypic variability and genetic susceptibility to genomic disorders

**Santhosh Girirajan and Evan E. Eichler***

Department of Genome Sciences, Howard Hughes Medical Institute, University of Washington School of Medicine, PO Box 355065, Foege S413C, 3720 15th Avenue NE, Seattle, WA 98195, USA

## Genome-Wide Association Study of Multiplex Schizophrenia Pedigrees

*Am J Psychiatry Levinson et al.; AiA:1–11*

"Rare CNVs were observed in regions with strong previously documented association with schizophrenia, but with variable patterns of segregation. This should serve as a reminder that we still know relatively little about the distribution of these CNVs in the entire population (e.g., in individuals with no or only mild cognitive problems) or about the reasons for the emergence of schizophrenia in only a minority of carriers, so great caution is required in genetic counseling and prediagnosis."

# 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

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

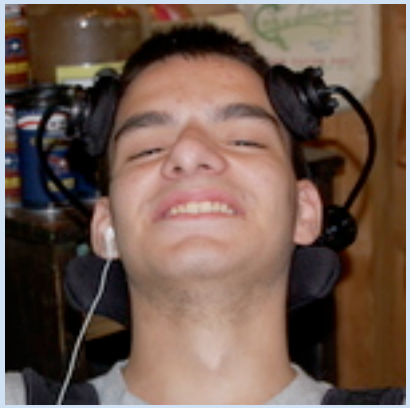
Genome Medicine

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]

# PatientsLikeMe



strapples
Male, 21 years
Chicago, IL

**About strapples**

I am diagnosed with Rett syndrome. It is a true anomaly for a male to be Rett and survive as well as I have. I share more at my website. http://www.alinssite.info

See full biography

**Interests**

Advocacy

ALS Public Registry

Profile Activity **45,870** Views **49** Followers Forum Activity **155** posts **200** helpful marks

**Member since:** Nov 17, 2008 **Last Login** Sep 11, 2012

**Other Conditions**

ASD (Autism Spectrum Disorder) First symptom Aug 1991 Diagnosis Jul 2009

Cerebral Palsy First symptom Aug 1991 Diagnosis Dec 2009

Epilepsy First seizure May 2007 Diagnosis Dec 2009

Kyphoscoliosis First symptom Apr 2005 Diagnosis Sep 2006

**NHS patient records to revolutionise medical research in Britain**

Scientists to hunt for lifesaving information buried in cradle-to-grave data collected by GPs and hospitals

Ian Sample, science correspondent

guardian.co.uk, Tuesday 28 August 2012 14.06 EDT

# For now, more effort should be placed on the following:

- Implementing Standards for a “clinical-grade” exome, and promoting the “networking of science” model.
- Focusing on rare, highly penetrant mutations running in families, with cascade carrier testing of even more relatives as needed.
- The genomic background is much more constant in families.
- The environmental background is sometimes more constant in families.
- This allows one to figure out penetrance of rare variants in these families, along with other issues, such as somatic mosaicism.

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**our study families**

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