Clinical Genomics of Neuropsychiatric Illnesses

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Acknowledgments

Omicia

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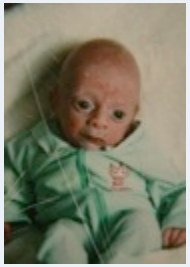
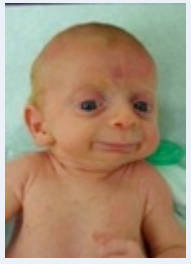
our study families

Ogden Syndrome

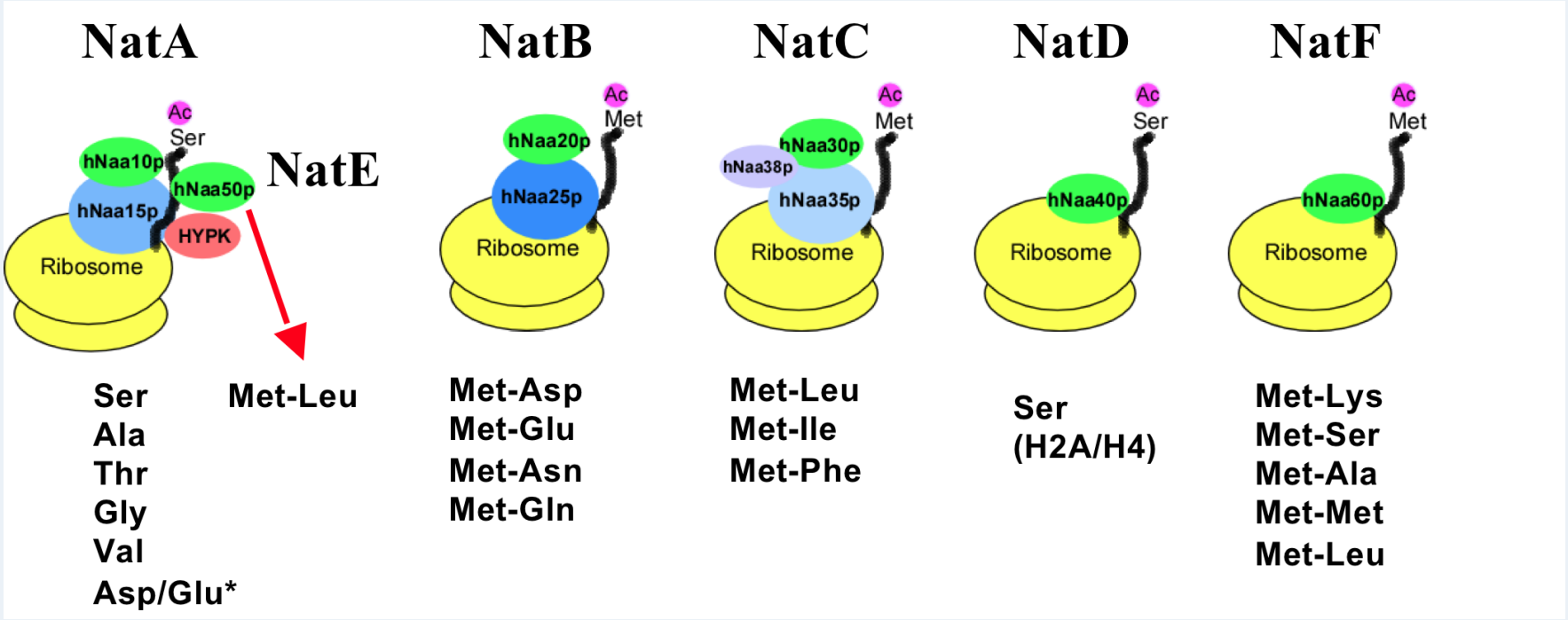




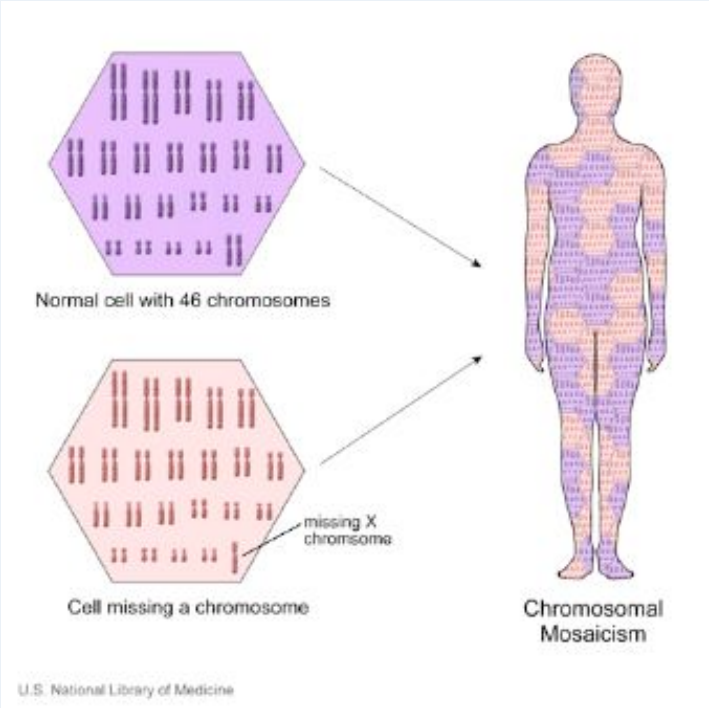
These are the Major Features of the Syndrome.

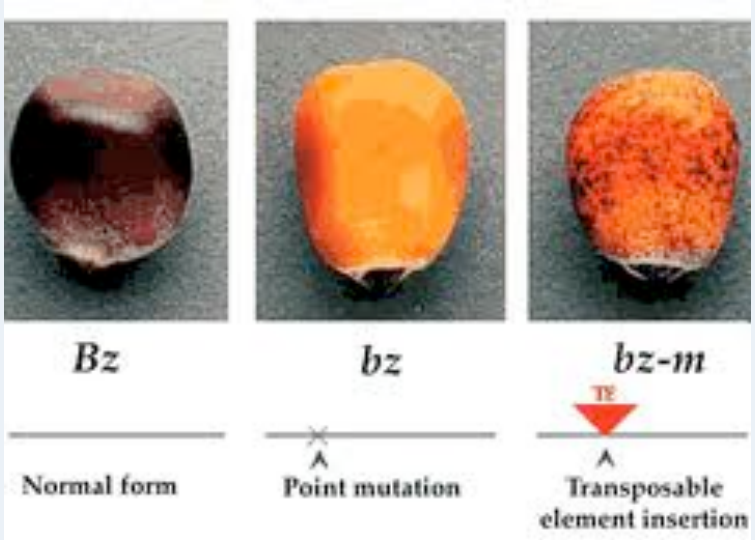
Table 1. Features of the syndrome	
Growth	post-natal growth failure
Development	global, severe delays
Facial	prominence of eyes, down-sloping palpebral fissures, thickened lids large ears beaking of nose, flared nares, hypoplastic alae, short columella protruding upper lip micro-retrognathia
Skeletal	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.	

The mutation disrupts the N-terminal acetylation machinery (NatA) in human cells.



Slide courtesy of Thomas Arnesen





Source: http://www.thenakedscientists.com/HTML/features/article/jamilcolumn1.htm/

Take Home Message

Genotype ≠ Phenotype

Environment matters!
Ancestry matters!
Genomic background matters!
Longitudinal course matters!

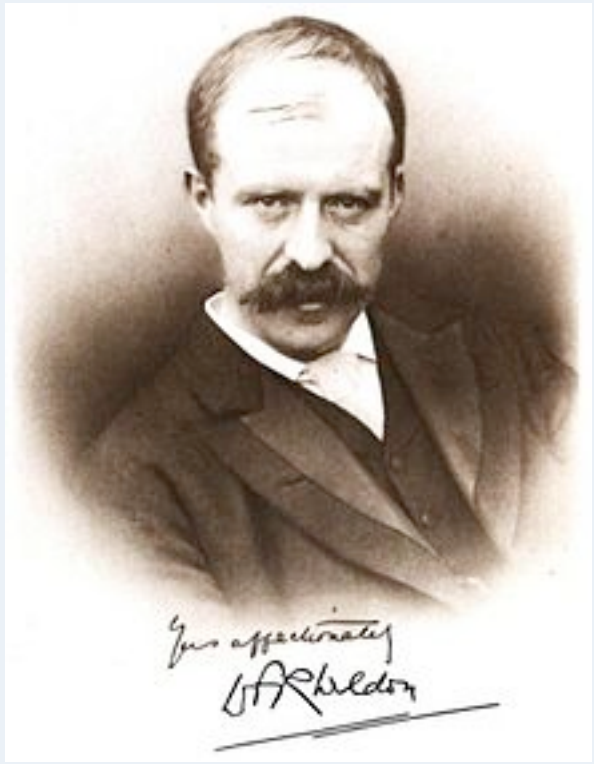
We can only begin to really understand this if we utilize the power of intense networking via internet-enabled archiving and distribution of data.

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

- There are ~25-100 TRILLION cells in each human body, with ~6 billion nucleotides per cell.
- There is extensive modification of DNA, RNA and proteins both spatially and temporally.
- There are higher level mechanisms of somatic mosaicism, heterosis, and likely ancestral inheritance.



Vs.

Walter Frank Raphael Weldon

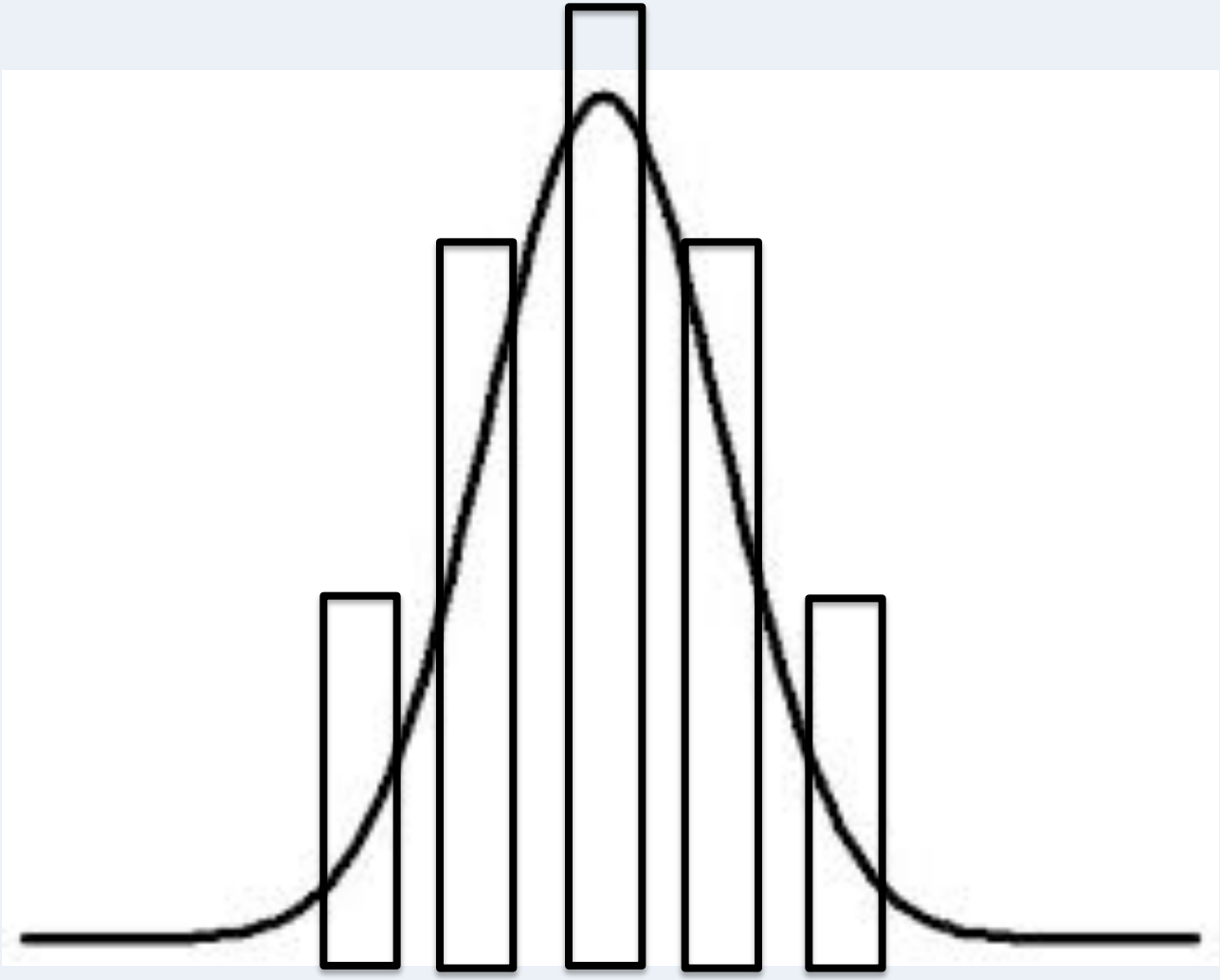
William Bateson

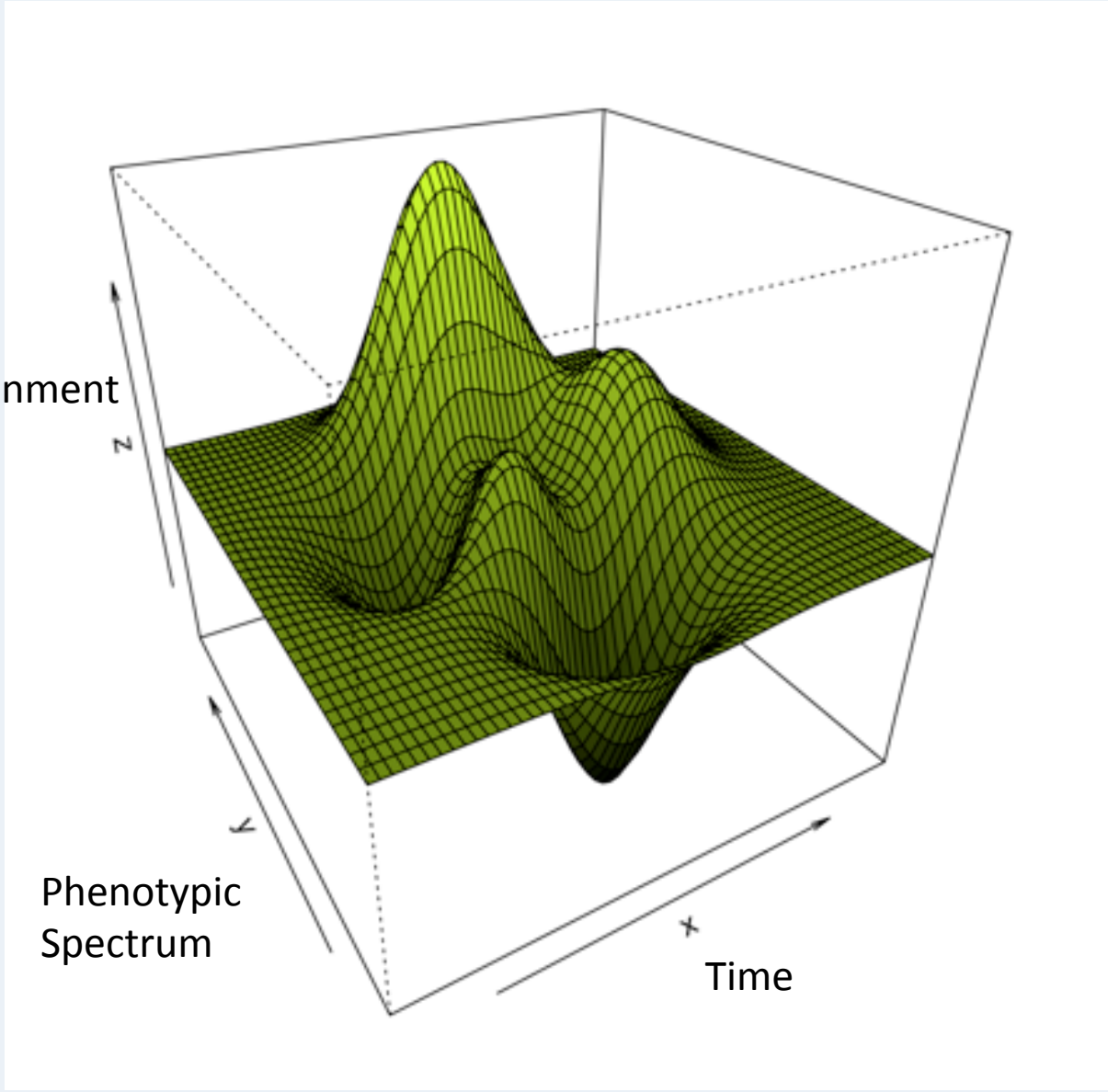
Forthcoming by Greg Radick. Scholarly edition of W. F. R. Weldon's Theory of Inheritance (1904-1905), coedited with Annie Jamieson.

Plate I.

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

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.

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Clinical genetics of neurodevelopmental disorders

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bioRxiv posted online November 18, 2013
Access the most recent version at doi:10.1101/000687

Schizophrenia Studies Find Genetic Risk Spread Across Shared Pathways
January 22, 2014
http://www.genomeweb.com/schizophrenia-studies-find-genetic-risk-spread-across-shared-pathways

> A co-author on both of the papers, called the findings "sobering but also revealing."
> "[I]t suggests that many genes underlie risk for schizophrenia and so any two patients are unlikely to share the same profile of risk genes," he said.

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

Special Report Series, No. 229

Privy Council

MEDICAL RESEARCH COUNCIL

A CLINICAL AND GENETIC STUDY OF 1280 CASES OF MENTAL DEFECT

by

L. S. PENROSE

LONDON

HIS MAJESTY'S STATIONERY OFFICE

1938

Universal Decimal Classification

616.89 : 575.1

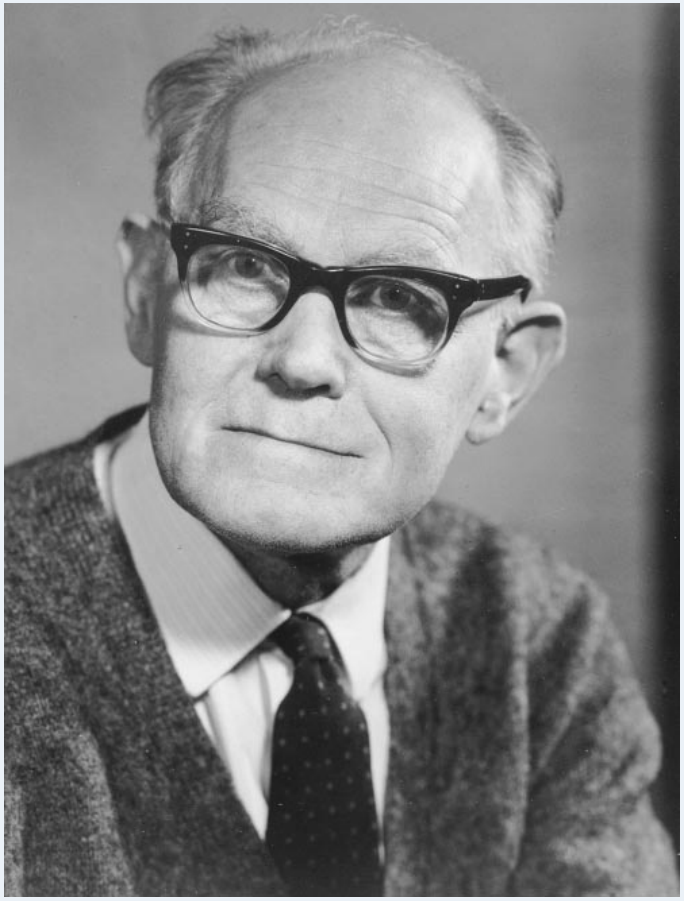
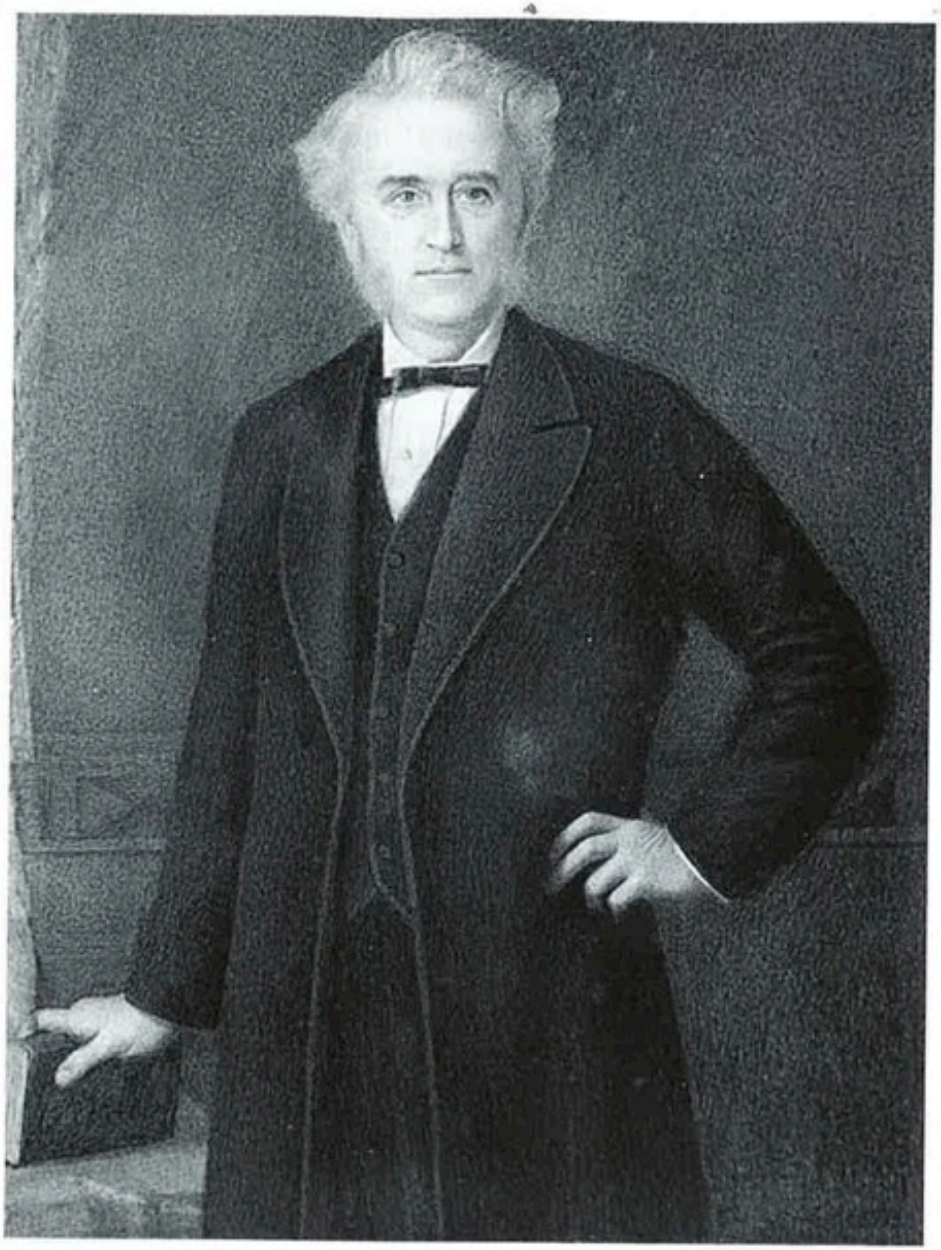


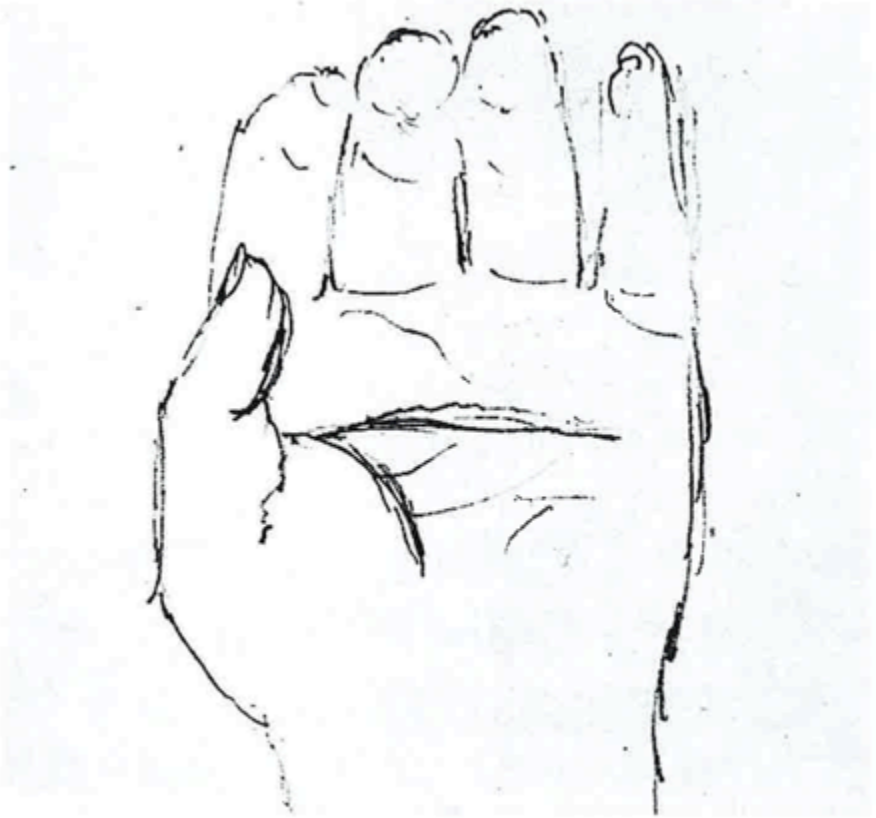
Figure 1.—Lionel Sharples Penrose, photograph about 1971. Photo by Godfrey Argent.



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

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.

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

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.

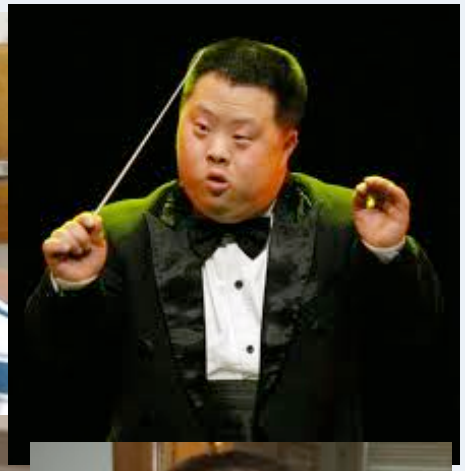
Dr Percival Langdon Down with his wife and children. His son Norman, was to be the last Langdon Down superintendent of Normansfield, ending a family connection that had lasted for 102 years. The elder daughter, Molly, was also a doctor and worked in Normansfield.

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

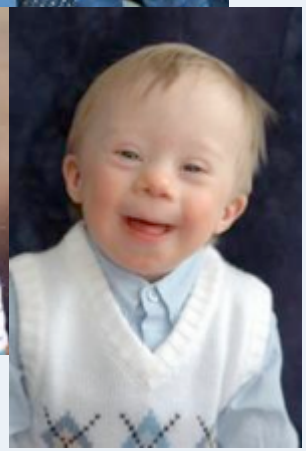








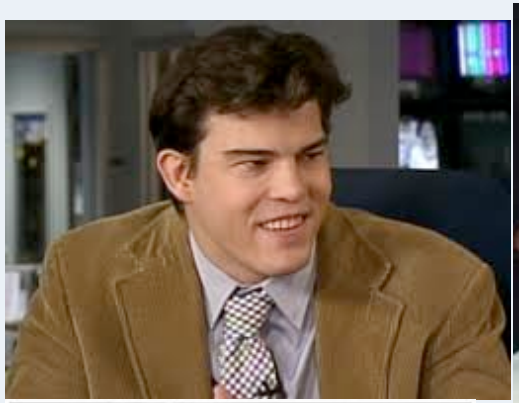



Down Syndrome

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














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

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”.

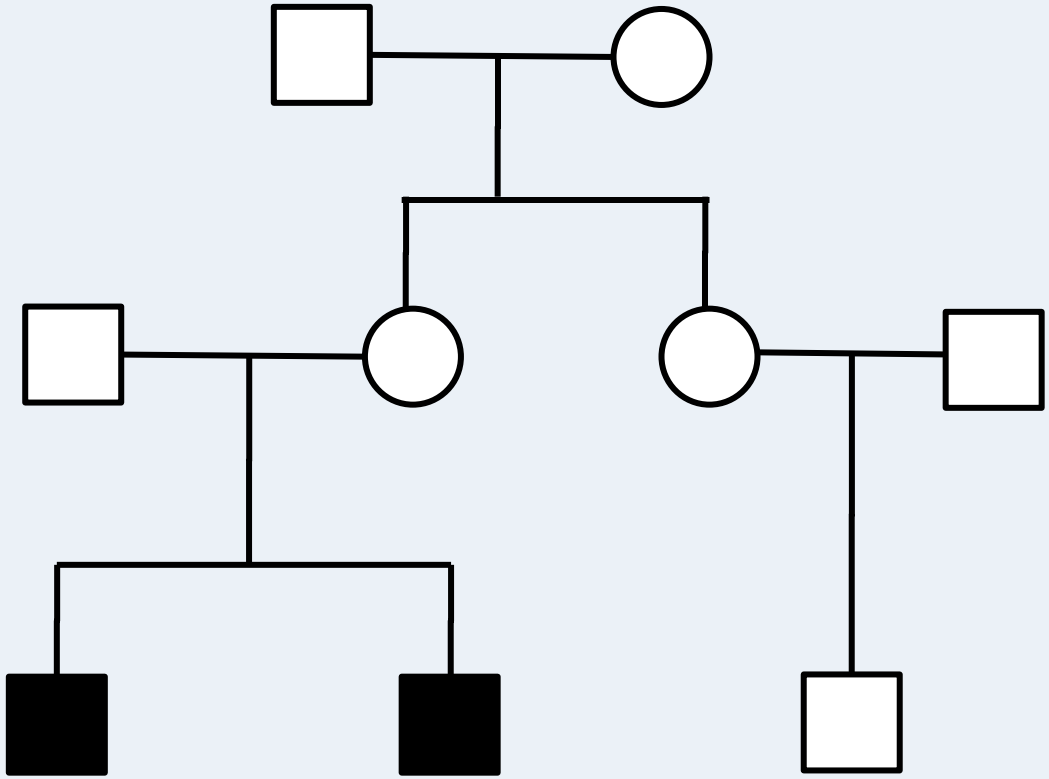
Current Diagnoses under Evaluation (DSM IV-TR)

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

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

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