Clinical Genomics of Neuropsychiatric Illnesses

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Figure 4. NAT activity of recombinant hNaa10p WT or p.Ser37Pro towards synthetic N-terminal peptides. A) and B) Purified MBP-hNaa10p WT or p.Ser37Pro were mixed with the indicated oligopeptide substrates (200 µM for SESSS and 250 µM for DDDIA) and saturated levels of acetyl-CoA (400 µM). Aliquots were collected at indicated time points and the acetylation reactions were quantified using reverse phase HPLC peptide separation. Error bars indicate the standard deviation based on three independent experiments. The five first amino acids in the peptides are indicated, for further details see materials and methods. Time dependent acetylation reactions were performed to determine initial velocity conditions when comparing the WT and Ser37Pro NAT-activities towards different oligopeptides.

C) Purified MBP-hNaa10p WT or p.Ser37Pro were mixed with the indicated oligopeptide substrates (200 µM for SESSS and AVFAD, and 250 µM for DDDIA and EEEIA) and saturated levels of acetyl-CoA (400 µM) and incubated for 15 minutes (DDDIA and EEEIA) or 20 minutes (SESSS and AVFAD), at 37°C in acetylation buffer. The acetylation activity was determined as above. Error bars indicate the standard deviation based on three independent experiments. Black bars indicate the acetylation capacity of the MBP-hNaa10p wild type (WT), while white bars indicate the acetylation capacity of the MBP-hNaa10p mutant p.Ser37Pro. The five first amino acids in the peptides are indicated.

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UF
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STANLEY INSTITUTE FOR COGNITIVE GENOMICS
COLD SPRING HARBOR LABORATORY

illuminar
Illumina

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Kristen Brennan
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our study families

Barry Moore
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Michael Schatz
Giuseppe Narzisi
Dick McCombie

Kai Wang

Tina Hambuch
Erica Davis
Dawn Barry
Ogden Syndrome

I

II

III

1 mt/

2 +/mt

3 +/-

4 mt/

5 +/-

6 mt/

7 mt/

8 +/
These are the Major Features of the Syndrome.

<table>
<thead>
<tr>
<th>Table 1. Features of the syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth</strong></td>
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<tr>
<td><strong>Development</strong></td>
</tr>
<tr>
<td><strong>Facial</strong></td>
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<td></td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Skeletal</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Integument</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Cardiac</strong></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Genital</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
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<td></td>
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</tbody>
</table>

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
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.
Walter Frank Raphael Weldon Vs. William Bateson

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.
Clinical genetics of neurodevelopmental disorders

Gholson J Lyon and Jason O'Rawe

*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

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

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
A little booklet was distributed among their members and other British families, appealing for children seeking refuge from Hitler-occupied Europe. My photograph, at age 7, had been among those in the booklet.

Twenty-nine years later, Professor Penrose and his visitors recognized my somewhat uncommon name and realized that I had been among the hundreds of children for whom a British home had been found during World War II and whose lives they had helped to save.

Lionel Sharples Penrose was born on June 11, 1898, the second of four brothers. His father was an artist (a portrait painter); one of his brothers was a sailor, and another, Roland, was also an artist and, according to family legend, introduced Britain to the work of Picasso. Lionel, the most academically minded of the four, studied the Moral Sciences Tripos (mathematics, philosophy, and psychology) at Cambridge; later, after spending a year in Vienna where he met and explored the work of Freud, Wagner-Jauregg, and others, he became interested in the psychology of mental illness and mental deficiency. However, to learn more thoroughly about brain physiology, Penrose realized that he needed to obtain a degree in medicine.

He returned to Cambridge in the late twenties. His subsequent M.D. thesis and interest in psychiatry resulted in an appointment in 1930 to the position of Research Medical Officer at the Royal Eastern Counties Institution, a residential facility for what was then called the "mentally defective" population. Penrose's charge was to study the causes of mental retardation, with funding provided by the Medical Research Council and the Darwin Trust.

In answer to the Prof's rather diffident question, he announced that he had lived in the house for over two weeks. He had met Mrs. Penrose in the street one night and inquired about an address in the neighborhood where a room was available for rent. Rather than give him the complicated directions he was looking for, she invited him to stay at Rodborough Road. In the Prof's study, someone wanted to meet me. As I entered, he introduced me simply by my first name. A tall, slender woman came toward me with outstretched arms and, with tears in her eyes, embraced me warmly. I knew him never before, nor did I recognize formation that he contained. I knew him now.

The trivial matter of informing her husband had slipped both of her two male companions. "So fortunate, dear," she said, noticing my completely bewildered facial expression, "that Lionel has such a good memory. You see, I remembered the 'Replete and contributed an enormous amount to knowledge about multiple aspects of mental retardation, most of which applies to this day. The work was done pre-

The Colchester Survey, 1931–38: The Royal Eastern Counties Institution was located in Colchester in southern England, and Penrose's work there culminated in the incomparable classic, The Colchester Survey: An Etiological Study of 1280 Cases of Mental Defect (Penrose 1933a) and later three editions of The Biology of Mental Defect (Penrose 1972), which are unsurpassed in their time for the knowledge, research, and edited superintendence of Margaret's mind.

On another evening during that same fall, the Prof knocked on the door of our room and invited me to his study. Someone wanted to meet me, he said. As I entered, he introduced me simply by my first name. A tall, slender woman came toward me with outstretched arms and, with tears in her eyes, embraced me warmly. I knew him never before, nor did I recognize formation that he contained.

The work was done pre-

The Colchester Survey included evaluations not only of the residents of the institution but of both parents and siblings whenever available. It took 7 years to complete the Colchester Survey, which was dominated by Penrose and one co-worker, Miss D. A. His basic concept was that mental retardation (MR) and mental illness are biologically, not socially, determined. Hence, of course, it had to be you!"

I learned that the three visitors, like Lionel, his parents, and his family, were Newlyn; it was prepared for publication by his devoted, loyal, erstwhile secretary, typist of manuscripts, later co-worker, editor, and Cerberus of the office, Miss Helen...
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.
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 1889 aged 20.

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.

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

*Private Photograph – Do not further distribute.
Current Diagnoses under Evaluation (DSM IV-TR)

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

Assessment Procedures:
- Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Wide Range Achievement Test 4th Edition (WRAT-4)
- Test of Memory and Learning 2 (TOMAL, 2)
- 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
Dysmorphic
Mental Retardation
“autism”
“ADHD”
Hearing difficulties
Figure 4. NAT activity of recombinant hNaa10p WT or p.Ser37Pro towards synthetic N-terminal peptides. A) and B) Purified MBP-hNaa10p WT or p.Ser37Pro were mixed with the indicated oligopeptide substrates (200 µM for SESSS and 250 µM for DDDIA) and saturated levels of acetyl-CoA (400 µM). Aliquots were collected at indicated time points and the acetylation reactions were quantified using reverse phase HPLC peptide separation. Error bars indicate the standard deviation based on three independent experiments. The five first amino acids in the peptides are indicated, for further details see materials and methods. Time dependent acetylation reactions were performed to determine initial velocity conditions when comparing the WT and Ser37Pro NAT-activities towards different oligopeptides. C) Purified MBP-hNaa10p WT or p.Ser37Pro were mixed with the indicated oligopeptide substrates (200 µM for SESSS and AVFAD, and 250 µM for DDDIA and EEEIA) and saturated levels of acetyl-CoA (400 µM) and incubated for 15 minutes (DDDIA and EEEIA) or 20 minutes (SESSS and AVFAD), at 37°C in acetylation buffer. The acetylation activity was determined as above. Error bars indicate the standard deviation based on three independent experiments. Black bars indicate the acetylation capacity of the MBP-hNaa10p wild type (WT), while white bars indicate the acetylation capacity of the MBP-hNaa10p mutant p.Ser37Pro. The five first amino acids in the peptides are indicated.