Approach to evaluation of Children with Developmental Delay

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Specialist in Paediatric Neurology
Review Objectives

1. Introduction
2. Defining developmental delay and intellectual disability
3. Aetiology
4. Clinical evaluations
5. Early identification and intervention
6. Clinical photos
WHO description: Disability

- Disabilities is an umbrella term, covering impairments, activity limitations, and participation restrictions.
  - An impairment is a problem in body function or structure;
  - An activity limitation is a difficulty encountered by an individual in executing a task or action;
  - A participation restriction is a problem experienced by an individual in involvement in life situations.

- Complex phenomenon, reflecting the interaction between features of a person’s body and features of the society in which he or she lives.
International Classification of Functioning, Disability and Health (ICF)

Health condition
(disorder or disease)

Body Functions & Structure

Activity

Participation

Environmental Factors

Personal Factors

Contextual factors
Disability

- A disability is an impairment that may be cognitive, developmental, intellectual, mental, physical, sensory, or some combination of these.

- It substantially affects a person's life activities and may be present from birth or occur during a person's lifetime.
Developmental Trajectory

OUTCOME

Variation

Normal

Problem

Disorder

AGE

0

18

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Conceptual understanding

Spectrum:

Variations
Problems
Disorders

Causes of developmental conditions are HETEROGENEOUS and each child is UNIQUE!
• Developmental disabilities are common and were reported in 1 in 6 children in the United States in 2006 –2008.

• Prevalence of any developmental disability increased from 12.84% to 15.04% over 12 years.
Common developmental conditions

- Dyslexia
- Attention Deficit Hyperactivity Disorder
- Developmental Coordination Disorder
- Language Impairment
- Developmental delay / Intellectual Disability
- Autistic Spectrum Disorders
- Physical Impairment
- Visual Impairment
- Hearing Impairment

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<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any developmental disability</td>
<td>15956</td>
<td>13.87</td>
<td>12.84</td>
<td>13.70</td>
<td>13.98</td>
<td>15.04</td>
<td>17.1%</td>
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<tr>
<td>ADHD</td>
<td>7652</td>
<td>6.69</td>
<td>5.69</td>
<td>6.71</td>
<td>6.77</td>
<td>7.57</td>
<td>33.0%</td>
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<tr>
<td>Autism</td>
<td>537</td>
<td>0.47</td>
<td>0.19</td>
<td>0.35</td>
<td>0.59</td>
<td>0.74</td>
<td>289.5%</td>
</tr>
<tr>
<td>Blind/unable to see at all</td>
<td>360</td>
<td>0.13</td>
<td>0.11</td>
<td>0.15</td>
<td>0.12</td>
<td>0.13</td>
<td>18.2%</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>365</td>
<td>0.39</td>
<td>0.39</td>
<td>0.43</td>
<td>b</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Moderate to profound hearing loss</td>
<td>633</td>
<td>0.45</td>
<td>0.55</td>
<td>0.44</td>
<td>0.42</td>
<td>0.38</td>
<td>30.9%</td>
</tr>
<tr>
<td>Learning disability</td>
<td>8154</td>
<td>7.04</td>
<td>6.86</td>
<td>7.24</td>
<td>6.82</td>
<td>7.24</td>
<td>5.5%</td>
</tr>
<tr>
<td>Intellectual disability*</td>
<td>863</td>
<td>0.71</td>
<td>0.68</td>
<td>0.73</td>
<td>0.75</td>
<td>0.67</td>
<td>-1.5%</td>
</tr>
<tr>
<td>Seizures, past 12 months</td>
<td>792</td>
<td>0.67</td>
<td>0.66</td>
<td>0.66</td>
<td>0.72</td>
<td>0.72</td>
<td>9.1%</td>
</tr>
<tr>
<td>Stuttered or stammered, past 12 months</td>
<td>1824</td>
<td>1.60</td>
<td>1.63</td>
<td>1.40</td>
<td>1.69</td>
<td>1.68</td>
<td>3.1%</td>
</tr>
<tr>
<td>Other developmental delay</td>
<td>3870</td>
<td>3.65</td>
<td>3.40</td>
<td>3.28</td>
<td>3.67</td>
<td>4.24</td>
<td>24.7%</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention, National Center for Health Statistics, NHIS.

*Survey question asked about mental retardation, but we refer to the condition as intellectual disability.

*We excluded cerebral palsy from the analysis for 2004–2007 because of the high likelihood of interviewer error arising from a questionnaire change in 2004.


*Test of linear trend over 4 time periods, P < .05.
Prevalence of developmental conditions in Hong Kong

- 15% of preschool children are affected by developmental problems (HKU data)
- 1/7 children are affected by developmental conditions (HKSPC)
- Dyslexia: 9.6-12% (HKU)
- ADHD: 6% (CUHK)
- Autism: 0.16% (HKU)
- Intellectual Disabilities: 0.9%-1.3% (Census and Statistical Dept)
  - Male: female 3:1 (international figures 1.5:1)
- HI: 2.16% (Census and Statistical Dept)
- VI: 2.44% (Census and Statistical Dept)

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Transient

VS

Persistent
Definition
Definition

• Developmental delay is one of the commonest developmental conditions
• Significant delay in 2 or more developmental domains
  • Gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living
  • Studies showed it would predict a future diagnosis of Intellectual Disability
• **Significant delay**: scores 1.5 to 2.0 standard deviation (SD) below the mean on norm-referenced developmental tests

• **Borderline Delay**: scores 1.0 to 1.5 SD below the mean

• Griffiths Mental Developmental Scales-Extended Revised (for children < 6 years)

• Griffiths Developmental Scales-Chinese Edition (0-8 years)

• Hong Kong Wechsler Intelligence Scale for Children (for children > 5 years)
Global Developmental Delay (GDD) vs Intellectual Disability (ID)

- GDD reserved for younger children (i.e. typically younger than 5 years),

- ID is usually applied to older children for whom IQ testing is valid and reliable. (Older than ~ 5 years)
  - Present with delays in the attainment of developmental milestones at the expected age

- Implies deficits in **BOTH** learning and adaptation
## "Mental retardation" terminology used in other countries

<table>
<thead>
<tr>
<th>Country and/or language</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Australia</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Canada (English, French)</td>
<td>Mental deficiency, intellectual handicap</td>
</tr>
<tr>
<td>England</td>
<td>Learning disability*, intellectual disability,</td>
</tr>
<tr>
<td></td>
<td>developmental disability*</td>
</tr>
<tr>
<td>France</td>
<td>Mental deficiency, mental apraxia</td>
</tr>
<tr>
<td>Germany</td>
<td>Mental handicap, mental retardation</td>
</tr>
<tr>
<td>Italy</td>
<td>Mental delay, mentally deficient</td>
</tr>
<tr>
<td>Estonia</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>Mentally slowed down</td>
</tr>
<tr>
<td>Spain</td>
<td>Mental delay</td>
</tr>
</tbody>
</table>
Etiology

Genetics × Environment

- Chromosomal
- Syndromes with Mendelian Inheritance
- Syndromes with Congenital malformations
- Metabolic disorders
- Copy Number Repeat
- Single Nucleotide Polymorphism

- Toxin
  - Prenatal exposure to nicotine, alcohol, PCBs
  - Heavy Metal e.g. Lead

- Perinatal: Prematurity, Low Birth Weight, asphyxia

- Postnatal:
  - Psychosocial adversity, chronic stress, child abuse
  - Iron deficiency/iodine deficiency
Aetiological factors:
- Genetic
- Metabolic or toxic
- Teratogenic
- Idiopathic or other
- Infectious
- Hypoxic-ischaemic
- Traumatic

Environment, experiential influences

Developmental brain dysfunction

Cognitive manifestations:
- Language
- Verbal IQ
- Problem-solving
- Nonverbal IQ
- Academic achievement
- Memory

Motor manifestations:
- Volitional movement
- Involuntary movement
- Tone
- Strength
- Reflexes
- Coordination
- Graphomotor skills

Neurobehavioural manifestations:
- Attention
- Impulse control
- Activity level
- Social reciprocity
- Mood regulation
- Repetitive behaviours
- Aggression
- Self-injury
- Hallucinations
- Delusions

Neuroanatomical and neurophysiological manifestations:
- Microcephaly
- Macrocephaly
- Structural abnormalities
- Seizures
- EEG abnormalities

Clinical diagnoses
Syndromic

and

Non Syndromic
Common Genetic causes of developmental delay

- Down syndrome
- Fragile X syndrome
- Noonan syndrome
- Williams syndrome
- Prader Willi syndrome
- Angelman syndrome
- DiGeorge syndrome
Exome sequencing of extended families with autism reveals genes shared across neurodevelopmental and neuropsychiatric disorders

Holly N Cukier¹, Nicole D Dueker¹, Susan H Slifer¹, Joycelyn M Lee¹, Patrice L Whitehead¹, Eminisha Lalanne¹, Natalia Leyva¹, Ioanna Konidari¹, Ryan C Gentry¹, William F Hulme¹, Derek Van Booven¹, Vera Mayo¹, Natalia K Hofmann¹, Michael A Schmidt¹,², Eden R Martin¹,², Jonathan L Haines³, Michael L Cuccaro¹,², John R Gilbert¹,² and Margaret A Pericak-Vance¹,²*
Schizophrenia
精神分裂症

Bipolar disorder
雙相情感障礙

GDD/ ID
發展遲緩/智力障礙

Epilepsy
腦癇症

<table>
<thead>
<tr>
<th>Condition</th>
<th>Developmental delay (n=975)</th>
<th>Mental retardation (n=488)</th>
<th>Total (n=1463)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low birth weight</td>
<td>14</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>5</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Autistic spectrum disorders</td>
<td>186</td>
<td>160</td>
<td>346</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>9</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>3</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Discrepant language delay</td>
<td>459</td>
<td>84</td>
<td>543</td>
</tr>
<tr>
<td>Discrepant gross motor delay</td>
<td>69</td>
<td>37</td>
<td>106</td>
</tr>
<tr>
<td>Discrepant fine motor delay</td>
<td>32</td>
<td>20</td>
<td>52</td>
</tr>
<tr>
<td>Clinical syndromes</td>
<td>5</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Behavioural problems</td>
<td>53</td>
<td>12</td>
<td>65</td>
</tr>
</tbody>
</table>

* Each child could have none or more than one associated condition
Goals of Assessment and Investigation

● To identify aetiologies and most importantly the treatable causes
● To recognise and manage co-morbidities
● To ascertain recurrence risk for the family
● To develop the tailor-made intervention plan
Diagnostic Formulation

• History taking:
  • Good pregnancy history and birth history. (maternal health, poly or oligohydramnios, any exposure to meds/ radiation)
  • Good family history (consanguinity, history of infertility/ fetal loss, pedigree suggesting X-linked inheritance, three generations pedigree)

• Good physical examination
  • Growth parameters, head shape, unusual facial features, neurocutaneous markers, digital anomalies
Neurological abnormality

- Tone abnormality: hypotonia (generalized or truncal), spasticity
- Seizure: infantile spasms, side effects of medication/treatment
- Stereotypies (Rett’s, ASD)
- Sensory deficit: hearing, vision impairment, nerve palsy
Muscle Tone abnormalities

• **Hypotonia** – associated with many common genetic disorders including Prader-Willi syndrome, and Down syndrome, with metabolic disorders such as mitochondrial disorders, and more rare disorders including SMA, peroxisomal disorders, etc.

• Hypotonia may be short term and benign, but deserves a neurological/genetic evaluation if more pronounced.
• **Spasticity** – associated with CNS dysgenesis, brain injury from hypoxic ischemic injury, head trauma or CNS infection.

• When seen in association with delayed motor development, abnormal reflexes, persistence of primitive reflexes and delay in development of postural responses, may suggest Dx of **Cerebral palsy (CP)**.
Congenital malformations

• Skeletal dysplasia
• Connective tissue problems e.g.: Ehlers Danlos, Marfan’s
• Syndrome diagnosis e.g.: polydactyly, amniotic band syndrome
Metabolic conditions

- Storage disease
- Seizures in mitochondrial conditions
- Self-mutilation in Lesch-Nyhan syndrome
Assessment

- Perinatal and family history
- Developmental milestones, regression?
- Behavioural Questionnaire
- School reports
- Clinical Observation
- Standardized Developmental Assessment
- Home videos
- School observation
Investigation

• Paradigm shift
  – Advance in genetic studies
  – Cost drops
  – Diagnostic advantages
  – Pros and cons
Diagnostic algorithm published by the AAP Committee.
(Reprinted with permission from Moeschler JB, Shevell M, the Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics 2006;117:2304-2316.)

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Global Developmental Delay is defined as significant delay in two or more developmental domains.

Investigation should be considered only after a thorough history and examination have been performed.

These guidelines are not intended for isolated speech and language or motor problems, or for children with autism.

- If diagnosis not apparent after history and examination, proceed as follows:

  **First Line**
  - Chromosomes
  - Fragile X
  - U & E
  - Creatine kinase
  - Lead
  - Thyroid function tests
  - Urate
  - Full blood count
  - Ferritin
  - Biotinidase

  **Second Line**
  - Metabolic
    - Family history
    - Consanguinity
    - Regression
    - Organomegaly
    - Coarse features
  - Neuroimaging
    - Abnormal head size
    - Seizures
    - Focal neurology
  - EEG
    - Speech regression
    - Seizures
    - Neurodegenerative disorder
  - Genetics
    - Dysmorphism
    - Abnormal growth
    - Sensory impairment
    - Odd behaviour
    - Family history

  **Blood**
  - Lactate
  - Amino acids
  - Ammonia
  - VLCFA
  - Carnitine
  - Homocysteine
  - Disialotransferrin

  **Urine**
  - Organic acids
  - Orotate
  - Gags
  - Oligosaccharides

  **MRI**
  - (bones, calcification)
  - Consider 24 hr EEG
Figure 1   Flow chart for decision making for investigations for global developmental delay in young children.
Table 1. Table demonstrating recommendations for first-line investigations for global developmental delay from four guidelines and our proposed recommendations.

<table>
<thead>
<tr>
<th>Tests category</th>
<th>UK current McDonald et al(^6)</th>
<th>UK proposed</th>
<th>USA Moeschler and Shevell(^4)</th>
<th>Irish O’Byrne et al(^10)</th>
<th>Australian Silove et al(^9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Karyotype</td>
<td>Microarray (selected)</td>
<td>Microarray</td>
<td>Microarray</td>
<td>Microarray</td>
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<tr>
<td></td>
<td>Frag X</td>
<td></td>
<td>Frag X</td>
<td>Frag X</td>
<td>Frag X</td>
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<tr>
<td>Biochemical and metabolic</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Blood tests</td>
<td>U&amp;E</td>
<td>U&amp;E</td>
<td>TFT</td>
<td>U&amp;E</td>
<td>U&amp;E</td>
</tr>
<tr>
<td></td>
<td>CK</td>
<td>CK</td>
<td>Lead (selected)</td>
<td>CK</td>
<td>CK</td>
</tr>
<tr>
<td></td>
<td>TFT</td>
<td>TFT</td>
<td>AA</td>
<td>TFT</td>
<td>TFT</td>
</tr>
<tr>
<td></td>
<td>Lead</td>
<td>(If PICA)</td>
<td>Homocysteine</td>
<td>LFT</td>
<td>FBC</td>
</tr>
<tr>
<td></td>
<td>Urate</td>
<td>FBC</td>
<td>Acylcarnitine profile</td>
<td>FBC</td>
<td>Bone profile</td>
</tr>
<tr>
<td></td>
<td>FBC</td>
<td>Ferritin (dietary restriction)</td>
<td></td>
<td></td>
<td>Urate</td>
</tr>
<tr>
<td></td>
<td>Ferritin</td>
<td>AA</td>
<td></td>
<td></td>
<td>Glucose, lactate</td>
</tr>
<tr>
<td></td>
<td>Biotinidase</td>
<td>Homocysteine</td>
<td></td>
<td></td>
<td>Venous blood gas</td>
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<tr>
<td></td>
<td></td>
<td>Acylcarnitine profile</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Urine tests</td>
<td>OA</td>
<td>OA</td>
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<tr>
<td></td>
<td>GAG</td>
<td>GAG</td>
<td>GAG</td>
<td>GAG</td>
<td>GAG</td>
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<tr>
<td></td>
<td>Oligosaccharides</td>
<td>Oligosaccharides</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Creatine/GAA</td>
<td>Creatine/GAA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Purine and pyridinines</td>
<td>Purine and pyridinines</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

AA, amino acids; ASD, autistic spectrum disorder; CK, creatine kinase; FBC, full blood count; Frag X, fragile X; GAG, glycosaminoglycans; LFT, liver function test; OA, organic acids; TFT, thyroid function tests; U&E, urea and electrolytes.
Table 2  Table demonstrating IEM tested for by first-line metabolic investigations\textsuperscript{25}

<table>
<thead>
<tr>
<th>Test (number of conditions identified)</th>
<th>Conditions identified</th>
</tr>
</thead>
</table>
| Plasma amino acids, n=13              | Lo. arginemia, Lo. argininosuccinaciduria  
                                    | Lo. citrullinemia, Lo. citrullinemia type II  
                                    | CPS deficiency, HHH syndrome  
                                    | Maple syrup urine disease (variant)  
                                    | Lo. NAGS deficiency, OTC deficiency  
                                    | Phenylketonuria, tyrosinemia type II  
                                    | MTHFR deficiency, PDH complex deficiency |
| Plasma total homocysteine, n=7         | Cobalamin C, D, E, F and G deficiencies  
                                    | Homocystinuria, MTHFR deficiency            |
| Acylcarnitine, n=7                     | Ethylmalonic encephalopathy  
                                    | Isovaleric acidemia, tyrosinemia type II  
                                    | Cobalamin C, D and F deficiencies,  
                                    | 3-methylcrotonyl glycinuria         |
| Urine organic acid, n=22               | ß-Ketothiolase deficiency, MHBD deficiency  
                                    | Cobalamin A, B, C, D and F deficiencies  
                                    | Glutaric acidemia I, glutaric acidemia II  
                                    | HMG-CoA lyase deficiency, tyrosinemia type II  
                                    | Holocarboxylase synthetase deficiency  
                                    | 3-Methylglutaconic aciduria, 3-methylcrotonyl glycinuria  
                                    | Methylmalonic acidemia, isovaleric acidemia  
                                    | Homocystinuria, propionic acidemia mHMG-CoA synthase deficiency  
                                    | SCOT deficiency, SSADH deficiency       |
| Glycosaminoglycans, n=4                | Hunter syndrome (MPS II)  
                                    | Hurler syndrome (MPS I)  
                                    | Sanfilippo syndrome A, B, C  
                                    | Sly syndrome (MPS VII)              |
| Purines and pyrimidines, n=3           | Molybdenum cofactor deficiency type A  
                                    | Pyrimidine 5-nucleotidase superactivity  
                                    | Lesch-Nyhan syndrome               |
| Oligosaccharides, n=2                  | α-Mannosidosis  
                                    | Aspartylglucosaminuria                  |
| Urine creatine metabolites, n=3        | AGAT deficiency  
                                    | Creatine transporter defect              |
                                    | GAMT deficiency                         |
Comprehensive Evaluation of the Child With Intellectual Disability or Global Developmental Delays

abstract

Global developmental delay and intellectual disability are relatively common pediatric conditions. This report describes the recommended clinical genetics diagnostic approach. The report is based on a review of published reports, most consisting of medium to large case series of diagnostic tests used, and the proportion of those that led to a diagnosis in such patients. Chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. Fragile X testing remains an important first-line test. The importance of considering testing for inborn errors of metabolism in this population is supported by a recent systematic review of the literature and several case series recently published. The role of brain MRI remains important in certain patients. There is also a discussion of the emerging literature on the use of whole-exome sequencing as a diagnostic test in this population. Finally, the importance of intentional comanagement among families, the medical home, and the clinical genetics specialty clinic is discussed. Pediatrics 2014;134:e903–e918
Investigation

• Chromosomal Microarray Analysis (CMA)
  染色體微陣列分析
• Whole Exome Sequencing
  全基因體上定序
• Metabolic investigation
• Neuroimaging
Deoxyribonucleic Acid (DNA)

染色體

DNA 鹼基

染色體

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The comparative genomic hybridization (CGH) array compares the patient’s DNA to control DNA using 2 different fluorescent labels. Labeled control and patient DNA fragments are hybridized to an array containing oligonucleotide DNA sequences from genes throughout the human genome. Each position on the array correlates to a different part of the genome. The relative intensity of the 2 different labels indicates copy-number changes. When only the red label (control DNA) is present, it indicates an absence of patient DNA and therefore a deletion (red stars). When there is more patient than control DNA, the patient label is overrepresented (green circles) and indicates duplication. When there are no copy-number changes, there should be equal amounts of control-labeled and patient-labeled DNA (indicated with blue circles).

A single-nucleotide polymorphism (SNP) array contains small fragments of DNA from the human genome where there are known to be multiple alleles. Each allele is represented on the array and each position on the array corresponds to a genetic locus. DNA from the patient is hybridized to the array. Patients who have the A allele at a specific locus will bind to the A allele on the array. If the patient is homozygous, the sample will bind only to A or B (AA or BB). If the patient is a heterozygote, the sample will be label hybridized to A and B (AB). Copy-number changes are determined by the relative intensity of bound DNA at each allele with a relative decrease in deletions (red bar) and an increase in duplications (green bar). Consanguinity is indicated by a loss of heterozygosity over large spans of DNA.
Whole Exome sequencing

1) Collect blood
2) Extract and fragment DNA
3) Capture exome DNA with probes
4) Recover only exome DNA fragments
5) Sequence on next-generation platform

- 20,000 variants per individual
- Exome contains 85% of disease-causing mutations
<table>
<thead>
<tr>
<th>Targeted panel sequencing</th>
<th>Whole-exome sequencing</th>
<th>Whole-genome sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-400 genes</td>
<td>22,000 genes</td>
<td>All genes, translocations and non-coding DNA</td>
</tr>
<tr>
<td>High coverage</td>
<td>Intermediate coverage</td>
<td>Lower coverage</td>
</tr>
<tr>
<td>Rapid (a few days), high accuracy but small number of mutations tested</td>
<td>Slower (a few weeks), good accuracy, many mutations tested</td>
<td>Slower (several weeks), all mutations tested but lower accuracy</td>
</tr>
</tbody>
</table>
SFARI Gene 列出超過700組自閉症基因(9/8/2015)
More than 700 autism genes listed on SFARI Gene (09/08/2015)

> 1000 genes in 2018
Epigenetics
表觀遺傳學

1. EXTERNAL EXPERIENCES (e.g., stress, nutrition, toxins) spark signals between neurons
2. NEURAL SIGNALS launch production of gene regulatory proteins inside cell
3. GENE REGULATORY PROTEINS attract or repel enzymes that add or remove epigenetic markers
4. EPIGENETIC "MARKERS" control where and how much protein is made by a gene, effectively turning a gene "on" or "off," thereby shaping how brains and bodies develop

GENE – a specific segment of a DNA strand

DNA strands encircle histones that determine whether or not the gene is "readable" by the cell

NEURON (brain cell)
Developmental brain dysfunction

腦發育障礙

Currently estimated up to 40% of individuals referred for genetic testing (array/whole exome sequencing) have identifiable genetic etiology.
Identifiable genetic causes of ID

- 25% chromosomal aberrations
- 30% monogenic causes
- ~40% unknown
- <5% teratogenic exposures
- <5% perinatal complications

Hong Kong Developmental Paediatrics And Child Neurology Centre
Developmental Intervention

- Referrals for further evaluation, e.g. Child Psychiatric Centres, Paediatrics, ENT surgeons
- Referrals for training and treatment
- Counselling and psychological support for parents and child
- Review assessment for developmental progress
Treatment of abnormalities in tone

• **Management of hypotonia** — often improves over time. Physical therapy (PT) to help improve functional abilities may be helpful. Trunchal hypotonia can clearly affect fine motor development.

• **Management of hypertonia** — multidisciplinary: neurologist, orthopedics, PT/OT, orthosis

• including:
  – Medications to decrease tone including baclofen, valium
  – Botox/Phenol injections into affected muscles
  – Bracing supports
  – Surgical approaches for consequences of tone including contractures and scoliosis
Management Flow for children suspected to have special needs

1. Referral
2. Multidisciplinary Assessment (CAS/ NGO)
   - Education Placement
   - Therapy: OT, PT, ST
   - Specialist Treatment (e.g., Psychiatrist)
   - Home help, Respite care

   - Pre-school: SWD
     - EETC
     - ICCC
     - SCCC
   - School Age
     - EDB
     - SEN in mainstream school
     - Special School

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Early Identification and Intervention
Clinical photos

• For the purpose of academic knowledge sharing
Chromosomal Abnormality Syndromes

- One extra autosomal chromosome
  - Trisomy 21 syndrome (Down Syndrome)
  - 1 in 660 newborns

Other notable features:
- Fine, Soft and Straight hair
- Mental deficiency
- Hypoplasia of midphalanx of 5th finger
- Wide gap between 1st and 2nd toes

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Chromosomal Abnormality Syndromes

• One extra autosomal chromosome
  – Trisomy 18 syndrome: 2\textsuperscript{nd} most common multiple malformation syndrome
  – 0.3 per 100 newborn babies

- Clenched hand
- Tendency for overlapping of index finger over 3\textsuperscript{rd} finger, 5\textsuperscript{th} over 4\textsuperscript{th} finger
- Low arch dermal fingertips

- Narrow bifrontal diameter
- Short sternum
- Small pelvis

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Chromosomal Abnormality Syndromes

- One extra autosomal chromosome
  - Trisomy 13 syndrome
  - 1 in 5000 births
- Head: moderate microcephaly with sloping forehead
- Brain: holoprosencephaly
- Skin: capillary hemangiomata, especially forehead; scalp defects
- Ears: apparent deafness
- Eye: colobomata of iris
- Mouth: cleft lip/cleft palate
- Thin posterior ribs
- Abnormal scrotum
- Ventricular septal defect
- Abnormal septal defect
- Polydactyly
- Hyperconvex nails
- Patau syndrome
Chromosomal Abnormality Syndromes

- Partial deletion/duplication of the chromosome
  - Deletion 4p syndrome (Wolf-Hirschhorn Syndrome)

- Ocular hypertelorism
- Downturned fishlike mouth
- Broad or beaked nose
- Simple ears with preauricular dimple
- Microcephaly and/or cranial asymmetry
Chromosomal Abnormality Syndromes

- Partial deletion/duplication of the chromosome
  - Deletion 5p syndrome (Cri du Chat Syndrome)

Other notable features:
- Cat-like cry
- Slow growth
- Mental deficiency
- Hypotonia
- Simian crease
Chromosomal Abnormality Syndromes

• Williams Syndrome
  - Deletion 7p11 syndrome (Elastin gene)

  - Downward slant of the palpebral fissures
  - Microcephaly
  - Hypertelorism
  - Other notable features:
    • Long flat philtrum
    • Thick lips
    • Cardiac anomaly
    • Happy predisposition
    • Cocktail party manner
    • ADHD

Learn More at: wschanginglives.org

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Sex chromosome abnormalities

- XXY Syndrome (Klinefelter Syndrome)
- 1 in 500 males

Developmental problems:
- Most common single cause of hypogonadism and infertility
- Tendency towards behavioral problems

Features:
- Long limbs
- Small penis
Neurocutaneous Syndromes

- **Tuberous sclerosis**
  - Mutations in the TSC1 or TSC2 gene → cause cells to divide excessively

  **Facial lesions**
  - Patches of light-colored skin

  **Problems:**
  - Seizures due to lesions in brain
  - Developmental delays
  - Behavior problems
  - Risk factor for ASD
  - Lung, heart and kidney problems

Credit: American Osteopathic College of Dermatology

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Neurocutaneous Syndromes

• **Neurofibromatosis (NF): Type I, Type II, and schwannomatosis**

  - Genetic disorder of the nervous system

<table>
<thead>
<tr>
<th>Neurofibromatosis Type 1</th>
<th>Neurofibromatosis Type II</th>
<th>Schwannomatosis</th>
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<tbody>
<tr>
<td>Patches of tan/light brown skin</td>
<td>Multiple tumors on the cranial and spinal nerves</td>
<td>Lumps or swollen areas where tumors form under the skin</td>
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<tr>
<td>Neurofibromas on or under the skin</td>
<td>Hearing loss beginning in the teens</td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>Hearing loss beginning in the teens</td>
<td></td>
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<tr>
<td>Tumor in the brain</td>
<td>Vision changes</td>
<td></td>
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<tr>
<td>Learning disabilities</td>
<td></td>
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</tr>
</tbody>
</table>
Neurocutaneous Syndromes

- Sturge-Weber disease
- Hemianopsia/hemiparesis
- Port wine stain
- Microcephaly

Other Features:
- Soft-tissue hypertrophy
- ADHD/Learning problems
- Epilepsy

Credit: Medlibes (Online Medical Library)
Small Stature vs Overgrowth

- Small Stature
  - Rubinstein-Taybi Syndrome
    - Average adult height
      - M: 153 cm and F: 147 cm
    - Usually have speech difficulties and hypotonia

- Broad thumbs (and toes)
- Downward slanted palpebral fissures
- Hypoplastic maxilla with narrow palate
- Stiff, unsteady gait
- Microdeletion of CREBBP gene
Small stature vs Overgrowth

- Small Stature
  - Dubowitz Syndrome
  
  - Mild Microcephaly
  - Scalp hair
  - Short palpebral fissures
  - Eczema-like skin
Small stature vs Overgrowth

- Small Stature
  - Kabuki Syndrome

- Prominent fingertip pads
- Long palpebral fissures with eversion of the lateral portion of the lower eyelid
- Large protruding ears
- Tooth abnormalities

Mutation in KMT2D in 55-80%

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Small stature vs Overgrowth

• Small Stature
  – Noonan Syndrome
  • Autosomal dominant
  • Mutation at 12q24

Downward slanted palpebral fissures
Short or webbed neck
Pulmonic stenosis
Pectus excavatum
cryptorchidism
Overgrowth

- Fragile X Syndrome
- Sex-linked

Features:
- Mental deficiency
- ADHD/ASD
- Poor eye contact
- Mild connective tissue dysplasia
- Macro-orchidism
Small stature vs Overgrowth

• Overgrowth
  – Sotos Syndrome
    • Autosomal dominant
    • Mutation at 5q35

Features:
• Large size
• Large hands and feet
• Significant behavioral abnormalities
• Poor coordination
• Delay gross motor function
Overgrowth – Beckwith–Wiedemann Syndrome

At birth:
- Macrosomia
- Omphalocele

Linear crease on the ear lobe
Indentations on the posterior rim of the helix

macroglossia

Small stature vs Overgrowth

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Brain and/or Neuromuscular Abnormalities

• Prader-Willi Syndrome
  – Deletion at q11-q13 of chromosome 15 (mat)
  – Excessive appetite with no sense of satiation
  – Hypotonia

• Angelman Syndrome
  – Deletion at q11-q13 of chromosome 15 (pat)
  – Happy puppet
  – Ataxia
  – Epilepsy

Obesity
Small hands (and small feet)
Brain and/or Neuromuscular Abnormalities

- Rett syndrome
  - Mutation in MECP2 gene on X chromosome
  - Lethal in male, so survivors all girls
  - Severe mental retardation in most cases
  - Regression in development
  - Autistic-like behavior
  - Stereotypic hand stereotypes: midline, wringing
  - Spastic and muscle weakness
Facial Defects

- Moebius Sequence
  - 6th and 7th nerve palsy
  - Autistic features and impaired speech

- Deficient of lateral gaze
- High nasal bridge
- Small mouth with downturned corners
Facial Defects

- Cleft Lip and palate Sequence
  - A failure of lip fusion by 35 days of uterine age

Genetics + environmental
Maternal smoking and alcohol use
Folic deprivation
Maternal drug intake eg steroids, anticonvulsants
Facial Defects

• Pierre Robin Sequence
  – Small lower jaw (micrognathia)
  – A tongue which tends to ball up at the back of the mouth and fall back towards the throat (glossoptosis)
  – Breathing problems
  – Horseshoe-shaped cleft palate may or may not be present.
Facial Defects

- Melnick-Fraser Syndrome
  - Caused by a mutation of the autosomal dominant gene at 8q13.3
Facial Defects

- Treacher Collins syndrome
Limb Defects

• Grebe Syndrome
  – Disproportionate short stature with short limbs
  – Autosomal recessive mutation at chromosome 20q11.2 (responsible for CDMP-1)

Fingers replaced by globular appendages
**Limb Defects**

- **Holt-Oram Syndrome**
  - Autosomal dominant pattern with marked intra- and interfamilial variations
  - Mutations at 12q24.1 (responsible for TBX5)

Thumb anomalies (absence, hypoplasia, triphalangeal)
Severe forearm hypoplasia
Altered shoulder girdle
Metabolic Disorder - Other Treatable Disorders

• Disorders of Amino Acid and Protein Metabolism
  – Phenylketonuria (PKU)
    • Untreated: patients with PKU develop neurocognitive impairment, growth deficiency, eczema

Deficiency of phenylalanine hydroxylase
Accumulation of phenylalanine and tyrosine
Diet restricted in phenylalanine and supplemented with tyrosine
• Hunter Syndrome
  – Deficiency of iduronate sulfatase
  – Excess dermatan sulfate and heparan sulfate
  – Mutations at Xq27-28

Coarse facies

Stiff joints by 2-4 years
End