Genetic Syndromes in Developmental Disabilities

Dr. Kerry Boyd, MD.
Psychiatrist
Chief Clinical Officer
Bethesda

Associate Clinical Professor
Department of
Psychiatry and Behavioural Neurosciences
McMaster University

Outline

- Introduction
- Overview of Genetics/Definitions
- Specific Syndromes
  - Down syndrome
  - Fragile X
  - 22q11 Deletion
  - Smith-Magenis

- Conclusion and Question Period

Overview of Genetics

- DNA basics
- Genetic Disorders

What Can Go Wrong?

- Chromosomal Problems
  - Too much (e.g. trisomy 21 Down)
  - Too little (e.g. monosomy, Turner)
  - Structural abnormalities/mutations
    - Deletions
    - Translocations
    - Mosaicism
Transmission Patterns

- Dominant
- Recessive
- X-Linked
- Multifactorial
- Sporadic
- Family history important

Genetic Syndromes, Phenotypes and Dual Diagnosis

Genetic Syndrome
An aggregation of signs and symptoms that together make up a recognizable condition with a known genetic cause

Basic Genetic Concepts

- Genotype
  - the genetic composition of an individual, referring specifically to the alleles at a particular locus
- Physical Phenotype
  - physical expression of a specific genotype
- Behavioural Phenotype
  - pattern of behaviour that is consistently associated with a specific genotype
Why Is Diagnosis of a Genetic Syndrome Important?

- Predicts:
  - Medical and psychiatric disorders
  - Abilities and disabilities (cognitive, physical)
  - Behavioural phenotype

- Offers:
  - Appropriate treatment and management
  - Genetic counselling/family planning
  - Explanation

Benefits of Genetic Diagnosis

<table>
<thead>
<tr>
<th>Bio</th>
<th>Psych</th>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome delineation and research</td>
<td>Behavioural phenotypes</td>
<td>Answers</td>
</tr>
<tr>
<td>Specific therapies</td>
<td>Cognitive features</td>
<td>Information</td>
</tr>
<tr>
<td>Screening/Tx</td>
<td>Learning profiles</td>
<td>Genetic counselling</td>
</tr>
<tr>
<td>Guides medical care</td>
<td>Intangible benefits (reduce blame)</td>
<td>Care planning</td>
</tr>
<tr>
<td>Psychiatric Dx/Mx</td>
<td>Mental Health Vulnerabilities</td>
<td>Assoc. &amp; supports</td>
</tr>
<tr>
<td>Develop info. &amp; tx recommendations</td>
<td>Sensitivities</td>
<td>Contribute</td>
</tr>
</tbody>
</table>

What’s New in Genetics

- Fluorescent In Situ Hybridization (FISH)
- structural abnormalities (Williams, DiGeorge syndromes)
- Imprinting
- parental (Prader-Willi, Angelman)
- Expansion
- trinucleotide repeats (Fragile X)
- Microarray
- Genetics of Autism Spectrum Disorders
- Copy number variants

Syndromes from Area Resource Team Database (total 488 Cases)

- Down Syndrome 35
- Cornelia DeLange 5
- PKU 4
- 22 q Deletion (VCF) 4
- Williams 4
- Smith Magenis 2
- Prader Willi 2
- Angelman 2
- Tuberous Sclerosis 2
- Fragile X 1
- F.A.S. 1
- Chromosome 18 deletion 1
- 12 deletion 1
- Inverted dup 8p 1
- Mucopolysaccharidosis 1
- XYY 1
Down Syndrome

- Prevalence - 1/700 to 1/1000 live births
- Diagnosed by karyotype
- Trisomy 21
- Transmission
  - Sporadic
  - 3 to 4% translocation
  - mosaicism

Down Syndrome: Physical Phenotype
- Small head
- Flat-looking face
- Broad neck
- Small ears and mouth
- Protruding tongue
- Upward slanting eyes
- Inner epicanthal folds

Down Syndrome: Medical Issues
- Congenital heart defects
- Hearing loss
- Ophthalmic conditions
- Dental conditions
- Endocrine conditions
- Obesity
- Orthopedic anomalies
- Skin conditions
**Down Syndrome: Cognitive**

- Intellectual disability
- Developmental delay (sensory-motor skills)
- Strength - visual-spatial tasks
- Weakness - language (expressive > receptive)

**Down Syndrome: Behavioural Phenotype**

- Amiable nature, some obstinacy
- A keen sense of the ridiculous
- Excellent memory
- Positive affect and highly sociable
- Less persistence at a task
- Stubborn/some obstinancy

**Down Syndrome: Psychiatric**

- ADHD, oppositional defiant disorder, conduct disorder (15-25%)
- ↑ Depression (6-11% higher) very rarely mania
- Anxiety very rare in literature
  - Underreported, esp. OCD
- ↑ Alzheimer’s disease (nearly all have plaques by 40) but only 15-40% have symptoms

**Down Syndrome: Interventions**

**Biopsychosocial**

- Attend to medical issues – Practice parameters available
  - yearly medical review, treat specifically
- Tailored school curriculum (e.g. sign language)
- Recreation and self esteem building
- Social skills and employment
- Residential living
C.A.R.E.
“Managing the Manageable”

Communication  Enhanced via attention to hearing, familiar carers, family visits…
Assessment       Psychology and psychiatry evaluations, regular medical and dental exams…
Respect          Personal care, mutual enjoyment…
Environment      Housing modifications, adaptation as needed…

Fragile X Syndrome

Fragile X Syndrome

- Estimated prevalence: 1/1,500 males
  1/2,500 females
- Most common hereditary cause of M.R.
- X-linked
- FMR 1 gene identified 1991
- New genetic mechanism - gene expansion
  - ‘CGG’ repeats: normal 6-50 repeats
  - Premutation carrier 50-230
  - Full mutation >230, up to 3000
- Decreased F.M.R.P.
- Variable expression

FMR1 Related Disorders

- Fragile X Syndrome
- Fragile X – Associated Tremor/Ataxia Syndrome (FXTAS)
- FMR1 – Related Primary Ovarian Insufficiency (POI)
### FXS: Physical/Medical

- ‘Normal’
- Increased head circumference
- Facial: long narrow face, prominent ears
- Connective tissue abnormalities
  - ‘loose joints’, hyperextensible fingers
  - Pectus excavatum
  - Knee dislocations
  - Orthopedic problems (flat feet, club feet, scoliosis)
  - Soft skin
  - Increased risk of hernias
  - M.V.P.

- Large testicles
- High arched palate, ± cleft lip/palate
- Ophthalmological features
  - Strabismus, myopia/hyperopia, nystagmus, ptosis, epicanthal folds
- Hypotonia, failure to thrive, motor delays, gait problems
- Seizures > 20%

### FXS: Cognitive

- Males: almost all some degree I.D.
- About 30% severe/profound range
- Can perform better than IQ suggests
- Specific strengths (eg. memory, imitation)
- Speech/Language
  - Failure/slow to develop
  - Cluttering 46%
  - Poor pragmatics
  - Poor topic maintenance
  - Perseverance
  - Echolalic

- ADHD: up to 80%, especially in childhood
- Autistic features - P.D.D. > 30%
  - Socially interested but ‘aversion’ (‘over stimulated)
  - Averted gaze
  - Tactile defensiveness
  - Stereotypies, hand flapping, hand biting
  - Resistance to change
  - Outbursts (?hyperarousal)
- Anxiety: mild to severe
- O.C.D.
- Emotional lability
- Tics
- Other
FXS: Interventions

- **Bio**
  - Medical problems
    - Eye care
    - Ear infections, hearing test
    - Cardiac
    - Seizures
    - Feet
  - Psychiatric (symptomatic)
- Future
  - Gene therapy
  - Protein replacement therapy
  - Pharmacotherapy

FXS: Interventions

- **Psycho/Social**
  - Development - computers, use strengths
  - ‘Calm’
  - Speech/Language
  - Behavioural
  - O.T., P.T.
  - Family supports
  - Resources

---

22q11 Deletion Syndrome

- **Velocardiofacial Syndrome (VCF)**
- **Conotruncal Anomaly Face Syndrome (CTAF)**
- **Sedlackova Syndrome**
- **Shprintzen Syndrome**
- **Cayler Cardiofacial Syndrome**
- **Autosomal Dominant Opitz G/BBB Syndrome**
22q11 Deletion Syndrome

- Estimated prevalence 1/4,500
- Much higher in developmentally delayed, psychotic population
- Diagnosed by F.I.S.H.
- Most cases sporadic; minority autosomal dominant
- Phenotypic variability

22q11 Deletion Syndrome: Physical

- Palatal anomalies (cleft palate, velopharyngeal insufficiency)
- Cardiac defects
- Facial elongation, prominent nose, malar hypoplasia, retrognathia, minor ear anomalies
- Slender hands, tapered fingers
- Other congenital anomalies

22q11 Deletion Syndrome: Medical

- Congenital heart defects
- Palate abnormalities
- Immune deficiencies
- Endocrine problems – hypocalcemia, hypothyroidism
- Other – e.g. skeletal, renal, seizures, gastrointestinal, hearing

22q11 Del Syndrome: Cognitive

- Learning disabilities
- Variable degrees of developmental delay
**22q11 Del Syndrome: Psychiatric/Behavioural**

- Higher incidence psychotic disorders
- Temper outbursts
- Other - variable

**22q11 Del Case Study: Female in her 20’s**

- Born with cleft palate, early feeding problems
- Nasal voice
- ‘slow learner’, special education
- Between 13-15 y.o. behavioural changes (eg distress, yelling, self-talk, outbursts)
- ‘cyclic vomiting’
- Psychiatric admissions/medical workups
- Trials of antipsychotic medications
- Family stress

**22q11 Del Case Study: Female in her 20’s**

- Assessed by Clinical Genetics twice
- Genetics testing in 1989 was negative
- Retested in 1995 looking for 22q11 D.S. and tested positive

**22q11 Del: Interventions**

- Bio
  - Repair cleft
  - GI workups repeated
  - Echocardiogram, renal u/s
  - Annual thyroid tests, calcium

- Psycho
  - Psychometric testing
  - Speech and language assessment
  - Mx psychosis
  - Mx anxiety
### 22q11 Del: Interventions

- Social
  - Individualized programming
  - Family meetings
  - Behaviour therapy input
  - Sexuality issues

### Smith Magenis Syndrome

- First Publication 1986
- Syndrome well studied and described
- Research and understanding is ongoing

<table>
<thead>
<tr>
<th>Anne Smith</th>
<th>Ellen Magenis</th>
</tr>
</thead>
</table>

- Estimated prevalence 1/25,000
- Growing number identified
- Dx by F.I.S.H. - deletion chromosome 17
- Virtually all de novo
- Phenotype well-described
**SMS: Physical Features**

**Frequent**
- Brachycephaly
- Prominent forehead
- Flat midface
- Broad nasal bridge
- Brachydactyly
- Short stature

**Variable**
- Synophrys
- Epicanthal folds
- Ocular pathology
- Down-turned mouth
- Prominent jaw (prognathism)
- Ear anomalies

**SMS: Medical - E.N.T.**

- Recurrent ear infections
- Conductive and sensorineural hearing deficits
- Cleft lip/palate
- Velopharyngeal incompetence
- Nasal voice
- Deep, hoarse voice
- Increase laryngeal polyps, nodules, edema

**SMS: Medical Issues**

- Signs of peripheral neuropathy
- Congenital heart defects
- Renal anomalies
- Scoliosis
- Thyroid abnormalities

**SMS: Psychological Profile**

- Cognitive delay - can vary
- Speech delay - with or without hearing loss
- Language - receptive > expressive
- Cognitive & Behavioural Profiles of 10 pts
  - Weaknesses: sequential processing
  - Strengths: L-T memory, expressive vocabulary
  » Dykens et al, 1997
**SMS: Behavioural Features**

- Over/hyperactivity
- Attention deficits
- Impulsivity
- Attention-oriented
- “Outbursts”
- Emotional lability
- Self-injury
  - Head banging, handbiting, pick/pull off finger/toe nails (onychotillomania), foreign object insertion in body orifices (polyembolokoilomania)

**SMS: Behavioural Features 2**

- Stereotypies
  - Oral (hands/objects in mouth), upper body squeeze/’self-hug’ (auto-amplexation)
- Sleep disturbance
- Enuresis/encopresis

**SMS: Features**

Many Positive Attributes!

- Engaging
- Great sense of humour
- True helpers
- Inquisitive
- Interested & interesting

**SMS: RAI 1 gene mutation**

- 95% of the cases deletion detected by F.I.S.H.
- 15 cases with single gene mutation (2007)
- RAI 1 SMS individuals are larger
- Higher functioning
- No syndromic medical features
- Active area of research
**SMS: Features**

Biggest predictor of behaviour is sleep!

“The SMS Perfect Storm”

- daytime melatonin
- stressors
- Behaviours
- Tantrums
- sleep deprivation

Dr. W. Duncan, NIMH

**SMS: Implications for Management - Medical**

- Echocardiogram
- Renal U/S
- Ophthalmological exam
- Hearing evaluation
- ENT
- Scoliosis
- Thyroid function tests
  - Greenberg et al, 1996

**SMS: Implications for Management - Psychological**

- Parent support
- Educational input
- Speech and language therapy
- Behavioural therapy

**SMS: Implications for Management - Pharmacological**

- Limited or preliminary success
  - Case reports
SMS Case Study: 47 y.o. Female

◆ Cognitive profile
  – Severe M.R. attributed to ‘birth trauma’
  – Receptive > expressive language ability
  – Repetitive speech

◆ Behaviours
  – ADHD
  – Abrupt mood swings (esp. irritability)
  – Aggressive outbursts
  – Stereotypies
  – Self-injury: picked skin/nails, object insertion, body squeeze
  – Sleep disturbance

◆ Physically
  – Short stature, fingers/toes
  – Malar hypoplasia
  – Flat nose
  – Hoarse, deep, nasal voice

◆ Medically
  – Seizure disorder
  – Chronic constipation
  – P.M.S.

SMS Case Study: Genetics

◆ Genetics
  – No prior testing
  – Chromosome analysis
  – Metabolic screen, plasma A.A., fragile X, 7-DHCholesterol
  – Positive F.I.S.H. for S.M.S.

SMS Case Study: Management

◆ Bio
  – Medical evaluation(s)
  – Carbamazepine (Tegretol) for seizures and mood stabilization
  – Taper Nozinan
  – Ritalin for ADHD
  – Mx of P.M.S.
  – Sleep monitoring
SMS Case Study: Management

- Psycho
  - Positive outlets for energy and need for attention
  - ‘Space’ to settle
- Social
  - Consistent staff
  - Behaviour therapy

Williams Syndrome

- Estimated prevalence 1/20,000
- Now diagnosed by F.I.S.H.
  - Deletion chromosome 7
- Most sporadic; 50% transmission

Facial Features

- Short, upturned nose
- Long philtrum
- Broad forehead
- Puffy under eyes
- Full cheeks
- Prominent earlobes
- Dental malocclusion and crowding
Williams Syndrome - Medical: A Multisystem Disorder

- **Cardiac**
  - Supravalvular aortic stenosis
  - Peripheral pulmonary stenosis
  - Risk of hypertension
  - Mitral valve prolapse

- **Musculoskeletal**
  - Short stature
  - Hyperextensible
  - Hypotonic

Williams Syndrome – Medical 2

- **Endocrine**
  - Hypercalcemia (15%)
  - Hypothyroidism (10%)
  - Diabetes in adults

Williams Syndrome - Medical 3

- **Gastrointestinal/Renal**
  - Colic, feeding problems, F.T.T.
  - Abdominal pain
  - Constipation, diverticulitis, P.U.D.
  - Renal anomalies, U.T.I.’s, enuresis

Williams Syndrome - Medical 4

- **Vision**
  - Strabismus
  - Far-sighted

- **Hearing**
  - Hyperacusis
  - Ear infections
  - Musical abilities
## Williams Syndrome: Cognitive Profile

- Typically
  - Mild - moderate M.R.
    - Range from average to severe
  - Pattern of strengths
    - Vocabulary
    - Expressive
    - Empathetic
    - musical
- Pattern of weaknesses
  - Adaptive behaviour
  - Fine motor
  - Visual-spatial construction
  - Perceptual planning

## Williams Syndrome: Behavioural/Psychiatric

- Emotional lability
- Aggression
- Anxiety (phobias, generalized, OCD traits)
- Somatization
- Other

## Williams Syndrome: Case Study

- Teenaged boy, facial features of Williams
- S.V.A.S.
- No hypercalcemia
- GI reflux, pain
- Indiscriminately friendly
- Sexuality
- Destructive outbursts
- Extreme mood lability
- Anxiety

## Williams Syndrome: Case Study Interventions

- Bio
  - Annual Px, ECHO, Calcium, TSH
  - GI workup
  - Renal ultrasound
- Psycho
  - Manage anxiety
  - SSRIs, lorazepam p.r.n.
  - Monitor response
- Social
  - Behaviour therapy
  - Own space
  - Protected environment
  - Positive interests encouraged
Conclusion

Benefits of a Genetic Diagnosis

- Anticipating medical problems
- Understanding learning strengths and weaknesses
- Looking at behaviour patterns in the syndrome context
- Intangible benefits – relief and support for families
- Genetic information & counselling
- Targeted interventions
- Contribute to research

Resources

Books
- Genetics and Mental Retardation Syndromes; *A new look at Behaviours and Intervention*, Dykens, Hodapp and Kincaide
- Demystifying Syndromes, Dorothy M. Griffiths MD & Robert King, Ph.D.

Websites
- National Organization for Rare Disorders (NORD)
- Human Genome Project multiple websites
- GeneClinics, GeneReviews, GeneTests Website
- InfoAbility (through Our Gov’t) [www.infoability.org](http://www.infoability.org)

Disorder-Specific Website Resources

**Down Syndrome**
- Canadian Down Syndrome Society

**Fragile X**
- National Fragile X Foundation
- Research Foundation of Canada
- Fraxa Research

**22q11 Deletion Syndrome**
- VCFS Educational Foundation
- 22q11 Group

**Smith Magenis Syndrome**
- "Parents & Researchers Interested in Smith-Magenis Syndrome (PRISMS)"

**Williams Syndrome**
- Williams Syndrome Association
Acknowledgements

- Ann Bassett and her team, CAMH
- Ann Smith and PRISMS
- Area Resource Team & Students
- All of the people who’s lives are touched by these genetic syndromes