Psych 3102
Introduction to Behavior Genetics

Lecture 16
Genetics of Cognitive Disabilities
1. Mental retardation
2. Learning disabilities
3. Dementia

DSM-IV
Diagnostic and Statistical Manual of Mental Disorders Version IV
- from the American Psychiatric Association

ICD 10
International Classification of Disorders
Version 10
Mental Retardation (MR) (Intellectual disability ID)

Diagnostic criteria:
- Subaverage intellectual functioning
- Onset before age 18
- Related limitations in adaptive skills

IQ range

4 levels recognized:
- Mild: 50 – 70 (85% of retarded)
- Moderate: 35 – 50 (10%)
- Severe: 20 – 35 (3-4%)
- Profound: below 20 (1-2%)

Problems with diagnosis:
- Relies too much on IQ measurement, not enough on adaptive skills
- Little or no support that these 4 levels are actually distinct categories
Causes of mental retardation (MR)

- Cognitive ability in the normal range has been shown to have a large genetic influence.
- This does not mean that genes are a major cause of MR.
- Of the 60-70% of cases where a cause of MR is known, only 5% have a hereditary condition:

  30% have had an embryonic development problem
  10% have had pregnancy/perinatal problem
  5% have had a childhood medical problem or condition
  15-20% have had severe deprivation or disorder-induced limitation
  5% have a known hereditary condition
Problems caused by prematurity  (UK study)

- 50% chance of survival if born at 24 weeks
- <10% chance of survival at 22 weeks
- only 20% of those that survive do NOT have a disability of some kind by age 6
- cognitive disabilities are most common, cerebral palsy also common
- most cognitive disabilities are learning disorders
- ‘low IQ’ (<80) was present in 72% of survivors vs 14% prevalence
- 34% of survivors had mild problems poor eyesight
- only 4% were severely affected by cerebral palsy

several countries have policies about helping premature babies survive
eg. Netherlands – no attempt made to help babies born 25 weeks or earlier
28 other countries have LOWER infant mortality rates than the USA
Genetic causes of mental retardation (MR)

**syndromic**  MR is part of a syndrome, comes along with other behavioral, physical symptoms

**non-syndromic**  MR is the only overt symptom

Autosomal recessive conditions

~ 25% of genetic retardation  
348 genes, <2% non-syndromic

X-linked recessive conditions

~ 10% of male genetic retardation  
90 recognized diseases, 42% of these non-syndromic

~ 50% of retarded individuals have no clear etiology

**idiopathic mental retardation**  cause of retardation is unknown

25% of this might be due to unidentified autosomal recessives

estimated 2000 genes with autosomal recessive alleles causing MR
More recently discovered causes

Microdeletions and other copy number variations (CNVs)

- detected by
  - FISH assay – specific hybridization to single probe
  - CMA (chromosomal microarray) - whole genome, comparative hybridization

+10% of previously idiopathic retardation now accounted for by microdeletions

~½ of these abnormalities are inherited - making antenatal diagnosis possible

FISH
fluorescent in situ hybridization
Genetic variation for MR: Evidence from family studies

Nichols, 1984  Sibling study
Population sample of 17,000 Caucasian children
1.2% were mildly retarded
0.5% were moderately or severely retarded
Sibs of severely/moderately retarded had average IQ scores
Sibs of mildly retarded had low IQ or were also mildly retarded

• moderate/severe retardation is not due to inherited factors
• mild retardation may be heritable

Reed & Reed, 1965  Family study
80,000 relatives of 289 mildly retarded individuals
20% risk of mild retardation in offspring with 1 mildly retarded parent
50% risk of mild retardation in offspring with 2 mildly retarded parents
2% population risk
Similar pattern is NOT found for moderate/severe retardation
However, familial resemblance = genetic influence
Correlation between MR and other problems
- idiopathic syndromic MR

30% co-occurrence MR with medical problems
- seizures
- auditory/visual
- neuromuscular/cardiovascular

50% co-occurrence MR with behavioral problems
3-4 times prevalence risk of mental disorders

Assumptions: medical problems cause retardation
- eg epilepsy causes cognitive impairment, psychiatric, autistic traits
- cognitive impairment causes behavioral problems

Could be that some common factor accounts for co-occurrence

**CNVs/microdeletions** – several genes affected

some of the more common microdeletions produce both behavioral and medical problems

chr22q11.3 medical problems, learning disabilities, schizophrenia

chr15q13.3 general epilepsy, cognitive disability, increased risks for autism, schizophrenia

parents of children with both medical problems and mild retardation also show cognitive disabilities indicating genetic causes
Some of the more than 100 genetic disorders associated with cognitive impairment

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetic abnormality</th>
<th>Location</th>
<th>Gene product</th>
<th>Function</th>
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<tr>
<td>Huntington disease</td>
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<td>4p</td>
<td>Huntingtin</td>
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<td>21q</td>
<td>APP</td>
<td>Amyloid component</td>
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<td>14q</td>
<td>Presenilin 1</td>
<td>APP trafficking</td>
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<td>1q</td>
<td>Presenilin 2</td>
<td>APP trafficking</td>
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<td>Pick's disease</td>
<td>Single gene</td>
<td>17q</td>
<td>Tau</td>
<td>Microtubule protein</td>
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<td>XLMR</td>
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<td>Xq</td>
<td>GDI1</td>
<td>Rho GTPase signalling</td>
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<td>Xq</td>
<td>FMR1</td>
<td>Transcriptional regulator</td>
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<td>Duchenne muscular dystrophy</td>
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<td>Dystrophin</td>
<td>Cytoskeleton component</td>
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<td>MID1</td>
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<td>CBP</td>
<td>Transcriptional co-activator</td>
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<td>PKU</td>
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<td>PAH</td>
<td>amino acid metabolism</td>
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<td>Lesch-Nyhan syndrome</td>
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<td>X</td>
<td>HPRT</td>
<td>purine metabolism</td>
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<td>Neurofibromatosis</td>
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<td>NF1</td>
<td>tumor suppressor</td>
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<td>Williams syndrome</td>
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<td>7q</td>
<td>LIM2</td>
<td>Synapse</td>
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<td>15q</td>
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<td>UBE3A</td>
<td>protein degradation</td>
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<td>21</td>
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<td>Dyslexia</td>
<td>Quantitative trait locus</td>
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<td></td>
<td>Unknown</td>
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</table>

ATRX = -thalassaemia mental retardation X-linked syndrome; MR = mental retardation; XLMR = X-linked mental retardation  
APP = amyloid precursor protein
Molecules to behavior
lessons from the study of rare genetic disorders

Study specific rare genetic disorders
• to help locate genes affecting behavior
• to lead to understanding of role of gene action on behavior

Collectively, these disorders are not ‘rare’
1 in 20 will be affected globally
15 million in USA
Many show shared pathology mechanisms
Phenylketonuria  PKU

- causes moderate/severe retardation if untreated  IQ < 50
- variable expressivity even in untreated cases
  - variation in natural diet
  - different mutations in the same gene produce varying degrees of deficiency in the product
gene located on chr 12  PAH
phenylalanine hydroxylase

- even with diet low in phenylalanine, PKU sufferers have slightly reduced cognitive ability (mean < 100)
  - *in utero* effects
  - diet not adhered to
Fragile X syndrome  X-linked triplet repeat mutation

• accounts for 2% of males in residential special schools
• 2\textsuperscript{nd} most common genetic cause of retardation (most common inherited genetic cause)

• twice as common in males as females due to incomplete penetrance in females (50% of females with the mutation do not express any symptoms)

• causes moderate retardation in males, mild retardation in females
• premutation, genetic anticipation, imprinting
• variable expressivity, pleiotropy
  - retardation, physical and behavioral features
    large protruding ears and jaw, long face, enlarged testicles, unusual speech, flapping hands, overactive, impulsive, inattentive
fragile X mutation results in methylation of promotor region that then prevents the FMR1 gene from being transcribed

FMR1 gene product is an RNA-binding protein expressed in brain that regulates expression of other genes

- FMR1 knock-out mice show learning deficits, behavioral problems
- FMR1 mutation in Drosophila now being studied ---> treatment

One gene effected is for brain receptor mGluR5 ---> overexpression
  - treatment blocks mGluR5 activation (Sci.Transl.Med. 2011, 3, 64)
    only effective for those with fully methylated promotor

may also help with autism since some similarity in behavioral problems
  mouse model of autism mGluR5 antagonists reduce repetitive self-grooming
Duchenne muscular dystrophy (DMD)  X-linked recessive
1 in 3500 males

• 1/3 of cases are new mutations
• lethal by age 20 due to extensive muscle-wasting
• mean IQ = 85    verbal abilities especially affected
• variable expression of cognitive effects

mouse knock-out model (Mdx) shows few clinical symptoms but seems to show useful alterations in brain neurochemistry

• gene product is large protein called dystrophin (2.3 million base pairs)

Suggested roles for dystrophin in the brain:
1. Anchoring and clustering neurotransmitter receptors/stabilizing the post-synaptic membrane.
2. Involvement in stabilizing oxidative phosphorylation apparatus
Lesch-Nyhan syndrome  
X-linked lethal recessive  
1 in 20,000 males

- causes moderate to severe retardation
- compulsive, self-injuring behavior with variable age of onset (av. 2-3 years of age)
  3-8 months: motor development delays, weak muscles, involuntary movement
  2-3 years: impaired speech, self-mutilation, aggression, retardation
  early 20’s: death from pneumonia, kidney failure, uremia  
  (treatment may prolong life)

gene product is HGPRT  
(hypoxanthine-guanine phosphoribosyltransferase)
  - involved in nucleic acid production, mutation leads to uric acid build-up, overproduction, overexcretion of purines

mouse – different purine metabolism  
  self-mutilation if APRT inactivated
Neurofibromatosis Type 1 (NF1) dominant, chr 17
1 in 3000-5000

- ‘café au lait’ skin spots, freckling
- neurofibromas - Schwann cell tumors
- 40-60% have low IQ (mean=90)
- 50% have learning difficulties (impaired attention, language deficits)
- social skill, conduct, emotional, peer problems (partly due to cognitive impairment)
- variable expressivity
inherited from father 90% of cases but 50% of cases are new mutations

mouse knock-out model - learning & memory deficits
Drosophila knock-out model – used to dissect cause of cognitive deficits at cell level, possible treatment
Neurofibromin normally activates Ras pathway downregulation
Mutation leaves Ras active, increased cell proliferation leads to tumors and increased formation, migration differentiation of neurons
**Tuberous sclerosis complex**

2 autosomal dominant genes   TSC1 (chr 9)   TSC2 (chr 16)
70% is spontaneous mutation   many unique mutations
Prevalence  1 in 6000   heterozygotes only
Phenotype  - variable expression of tumor growths, tissue malformations  
cognitive and behavioral aspects

- 70-80% have epilepsy
- 20-30% very low IQ, 50% normal IQ
- 20-60% have autism
- 50% have ADHD

Psychiatric: mood, anxiety, adjustment disorders

Animal models: mouse, naturally-occurring TSC2 rat
   indicate psychiatric problems are not secondary to other symptoms
22q11.2 microdeletion syndrome (DiGeorge, velocardiofacial)

45 genes COMT PRODH others

Most common human deletion syndrome

Estimated prevalence 1 in 4000 live births

Phenotypic spectrum

40% have major heart defects
distinct facial features
abnormal CNS development
- delays, learning disabilities
seizures
60% develop a psychiatric disorder by adulthood,
20-25% schizophrenia
Williams syndrome  1 in 10000 live births

- spontaneous microdeletion on chromosome 7
- growth retardation ‘elfin’ face
- multiple medical problems
- variable expression of retardation
  IQ range 20 – 106  mean = 58
- gregarious personality
- often good language development and auditory memory (for IQ level)

% relative to norm for age

Language  
Face recognition
Musical abilities  35-98%
Social behavior
‘friendly’ personality traits
Visuo-spatial
Counting  <1%
Implicit memory
Problem solving

KBIT = Kaufman Brief Intelligence Test
~20 genes, elastin & kinase genes thought to produce most of the symptoms

LIMK1 gene thought responsible for cognitive deficits

mouse model difficult to develop since this is one region where mouse genome differs from human in order of genes present
Angelman / Prader-Willi syndromes

- spontaneous microdeletion chr 15
- region subject to imprinting

**Angelman syndrome**
- 1 in 25000
- from Mom
- seizures
- happy
- moderate retardation
- speech impairment

**Prader-Willi syndrome**
- 1 in 22-25000
- from Dad
- hormonal deficiency
- low/normal IQ (av 70)
- compulsive overeating
- life-threatening obesity
- obesity

Imprinting chromosome 15

$o =$ unknown (HBII-85 snoRNAs)

$\triangleright =$ ubiquitin-protein kinase gene

Normal | Angelman | Prader-Willi
Down syndrome spontaneous trisomy 21
- risk increases with age of mother
- most common genetic cause of retardation
- distinctive physical features
- variable expression of retardation
  mean IQ = 55
  10% in low normal range
  poor language skills
  early dementia

partial trisomies and mouse model (trisomy 16)
- useful in identifying genes responsible for cognitive impairment in Down syndrome

Down syndrome critical region – all genes responsible for syndrome, 21q
DSCR1 – gene thought to be involved in Alzheimer's
Critical genes in a critical region

Charles J. Epstein

The NFAT transcription factors activate the expression of many genes involved in the immune response and the development of a variety of tissues. They have now been implicated in Down's syndrome.

Down's syndrome is most commonly caused by the presence of an extra copy of the major portion of the human chromosome 21. But how does the presence of an extra set of the roughly 200-300 genes on the chromosome give rise to the many abnormalities that characterize the condition? Because the pattern of abnormalities is so specific, one theory is that the 1.5-fold increase in the expression of some, if not all, of these genes is responsible.

In this issue, papers by Arron et al. (page 585) and Gwack et al. (page 646) implicate two genes in the so-called Down's syndrome critical region (DSCR), a small segment of human chromosome 21, in causing the abnormalities found in Down's syndrome. Using genetically modified approaches, the groups reached this conclusion by a process thatbegan with an interest in a family of four gene products called NFATc (for nuclear factor of activated T cells).

The regulation of various developmental pathways depends on processes that are activated by the entry of calcium into the cell, and the NFAT signaling pathway mediates many of these processes. Following the influx of calcium, phosphatase-dependent dephosphorylation allows the NFAT proteins to enter the cytoplasm by the enzyme calcineurin. This allows NFATc to enter the nucleus and activate its target genes. However, once in the nucleus, NFATc can have phosphatase groups added back to it by a kinase enzyme (phosphorylation), forcing it to return to the cytoplasm and halt its effects on the genes (Fig. 1a).

Arron et al. came upon the possibility of a connection between the NFAT system and Down's syndrome by the serendipitous observation that mice lacking NFATc2 and NFATc4 have abnormalities of the skull and jawbones. These deformities are similar to those observed in Down's syndrome and in two mouse models of Down's syndrome (called T65Dn and T65C). These have an extra copy of part of the mouse chromosome most similar to human chromosome 21 (that is, they are trisomic). In addition, these and other mice lacking various NFATe proteins, either singly or in combination, display abnormalities that are highly reminiscent of Down's

Figure 1 | NFAT signaling and Down's syndrome.
Calcium signaling through the NFATc pathway mediates many developmental processes and the immune response. a. The entry of calcium ions into the cell activates the enzyme calcineurin to remove phosphate groups (P) from NFATc factors in the cytoplasm, allowing NFATc to enter the nucleus and activate its target genes. b. The genes encoding DSCR1 and DYSKJ1A are found in the 'Down's syndrome critical region' of human chromosome 21, which has an extra copy in people with Down's syndrome. The increased expression of DSCR1 and DYSKJ1A disturbs the balance of NFATc phosphorylation, so that most of the protein is found in the cytoplasm. Thus, NFATc-dependent genes will not be properly regulated, which could markedly affect development. (Modified from Arron et al., Supplementary Figure 4.)
Turner syndrome monosomy XO

- all or part of one X chromosome missing
  - 70% of cases X is maternal (paternal X or Y is missing)
  - 30% of cases X is paternal (maternal X is missing)
- infertility, short stature, webbed neck, delayed skeletal maturation
- mean IQ = 90

normal verbal ability
impaired visuo-spatial working memory & math abilities
poor social cognition & adjustment

differences between those with maternal X & paternal X would indicate effects of imprinting

poorer social cognition shown by females with maternal X compared to those with paternal X - genes for social cognition selectively inactivated as pass through female germline?

males only have one X - they always get their X from mother – does this explain higher occurrence of disorders involving social deficits?

autism ADHD Aspergers less than optimal social skills in normal males?!
Shared pathology

1. **PI3K-mTOR pathway dysregulation**

   - **PI3K** - kinases, interact w. insulin receptor to regulate glucose uptake, involved in cell growth, proliferation, cell survival
   - **mTOR** - a PI3K family kinase, regulates cell growth, proliferation, apoptosis, protein synthesis

   tuberous sclerosis, fragile X, NF1 mutations
   - gene products interact with this pathway
   - lead to mTOR dysregulation
   - all lead to mTOR overactivation

Would indicate mTOR inhibitors (eg rapamycin) might help all these conditions, both physical and cognitive problems

   clinical trials in progress

**Rapamycin** - an immunosuppressant drug used to prevent rejection in organ transplantation, also an antiproliferant
2. Dysregulation of microRNAs (miRNAs)

miRNAs - non-coding, single-stranded ~22 nucleotides long
- regulate translation of mRNA, post-transcription
  action leads to gene-silencing
target 60% of genes
encoded in mammalian genomes

Mutations in miRNA genes lead to abnormalities in brain development, cognitive impairment
Fragile X – product interacts with miRNA function, stops correct silencing
  Drosophila model
Rett syndrome – product represses transcription of several miRNAs
  including those that target BDNF
  mouse model
Down syndrome – chr 21 has 6 miRNA genes, overexpression in fetal brain and heart has been measured, could cause deficits
Use of animal models

Drosophila  
C. elegans  
zebrafish

rats  
mice

preferred when brain & behavioral phenotypes important

But:

1. proteins may not have same role in invertebrates, gene sequence not always same in rodents
2. rodents – cognitive processes may not translate well into humans

Morris water maze , radial arm maze used to indicate poor cognitive functioning in rodents but what type of cognitive impairment in humans?

3. still some major differences between rodents & human metabolism so deletion of a gene may not have same consequences in rodents

Lesch Nyhan – different purine metabolism