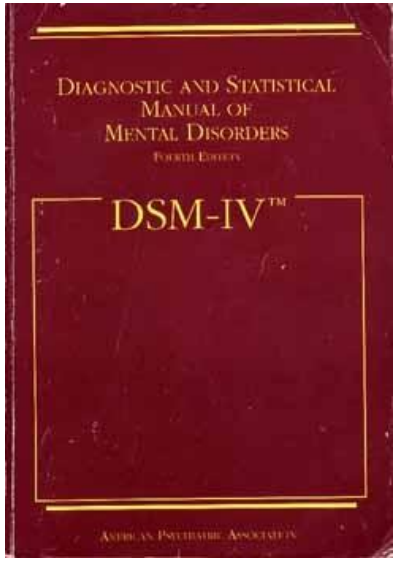
Psych 3102
Introduction to Behavior Genetics

Lecture 16

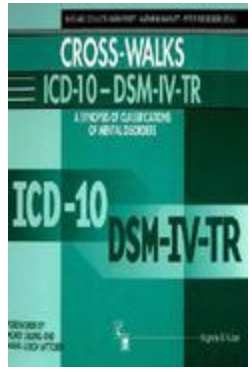
Genetics of Cognitive Disabilities

1. Mental retardation
2. Learning disabilities
3. Dementia



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

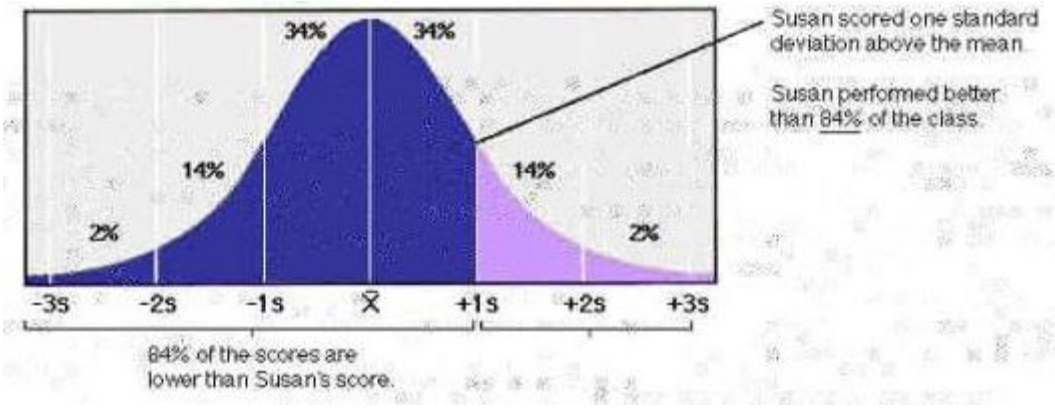
ICD 10
International Classification
of Disorders
Version 10



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%



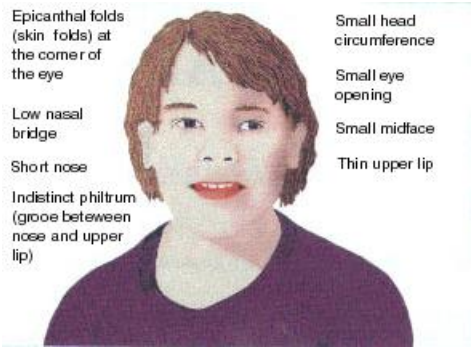
Problems with diagnosis:

- 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

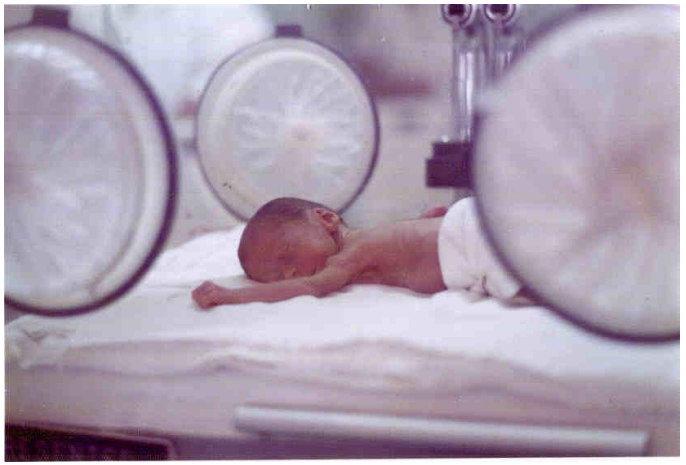
Problems caused by prematurity (UK study)

- 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

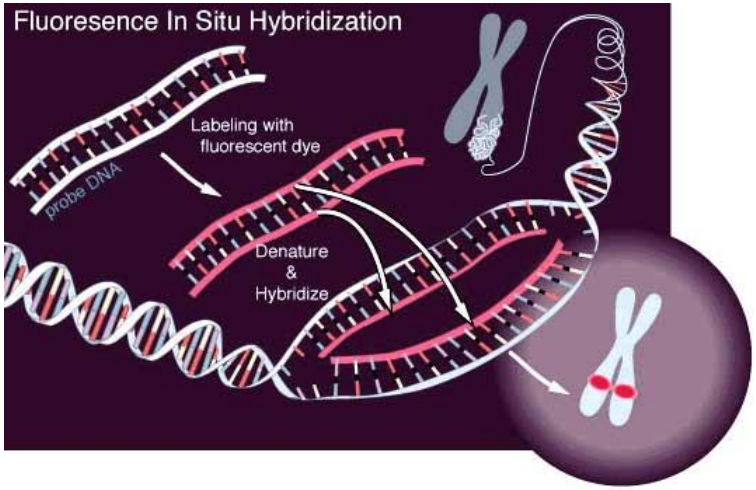
More recently discovered causes

Microdeletions and other copy number variations (CNVs)

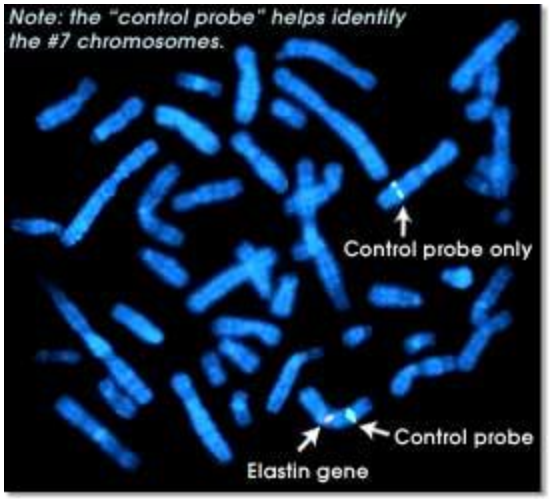
- detected by
  - FISH assay – specific hybidization to single probe
  - CMA (chromosomal microarray) - whole genome, comparative hybridization

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

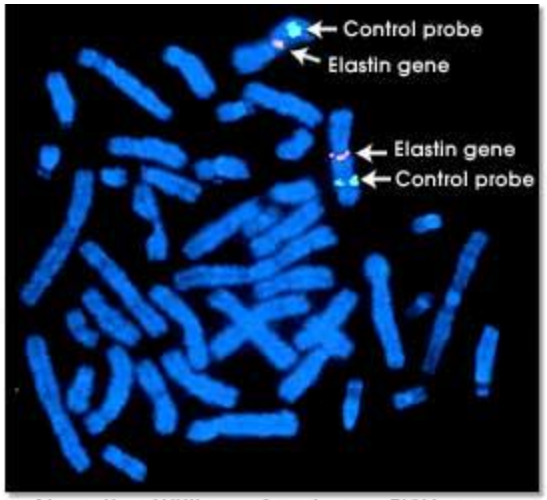
~½ of these abnormalities are inherited - making antenatal diagnosis possible



FISH
fluorescent in situ hybridization



Positive Williams Syndrome FISH assay
(*Chromosome 7*)
The elastin gene is found on only one chromosome. The other copy carries an elastin gene deletion.



Negative Williams Syndrome FISH assay
(*Chromosome 7*)
The elastin gene is found on both chromosomes. This individual does not have Williams Syndrome.

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

Disorder	Genetic abnormality	Location	Gene product	Function
Huntington disease	Single gene	4p	Huntingtin	Unknown
Alzheimer's disease	Single gene	21q	APP	Amyloid component
Alzheimer's disease	Single gene	14q	Presenilin 1	APP trafficking
Alzheimer's disease	Single gene	1q	Presenilin 2	APP trafficking
Pick's disease	Single gene	17q	Tau	Microtubule protein
XLMR	Single gene	Xq	GDI1	Rho GTPase signalling
XLMR	Single gene	Xq	PAK3	Rho GTPase signalling
XLMR	Single gene	Xq	Oligophrenin	Rho GTPase signalling
XLMR	Single gene	Xq	FMR2	Unknown
Fragile X syndrome	Single gene	Xq	FMR1	Transcriptional regulator
ATRX syndrome	Single gene	Xq	ATRX	Transcriptional regulator
Duchenne muscular dystrophy	Single gene	Xp	Dystrophin	Cytoskeleton component
OpitzG/BBB	Single gene	Xq	MID1	Transcriptional regulator
Rubinstein–Taybi syndrome	Single gene	16p	CBP	Transcriptional co-activator
PKU	Single gene	12	PAH	amino acid metabolism
Lesch-Nyhan syndrome	Single gene	X	HPRT	purine metabolism
Neurofibromatosis	Single gene	17	NF1	tumor suppressor
Williams syndrome	deletion	7q	LIM2	Synapse
Prader–Willi syndrome	imprinted deletion	15q		
Angelman syndrome	imprinted deletion	15q	UBE3A	protein degradation
Down syndrome	trisomy	21	Multiple genes	
Turner syndrome	monosomy	X	Multiple genes	
Dyslexia	Quantitative trait locus	6p	Unknown	

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

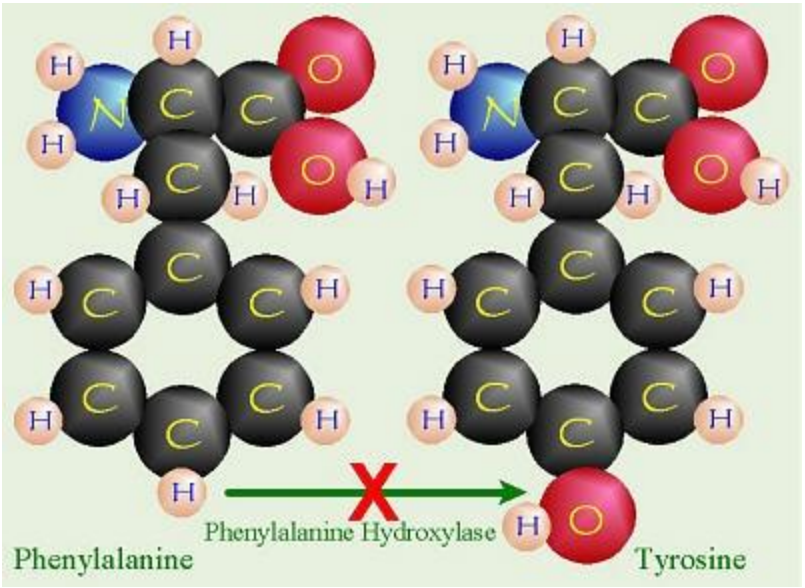
Many show shared pathology mechanisms

Phenylketonuria PKU single-gene recessive
1 in 10,000 live births

- 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
- 2nd 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

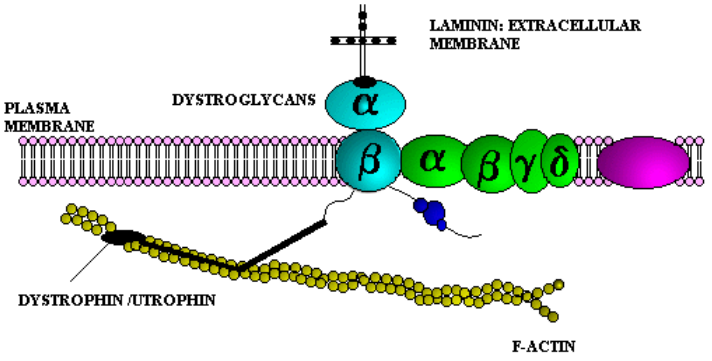
- gene product is large protein called dystrophin (2.3 million base pairs)

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)

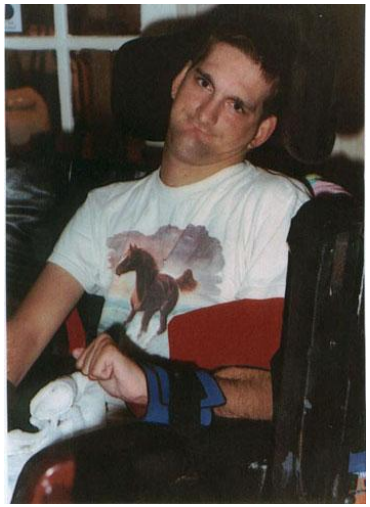
gene product is HGPRT

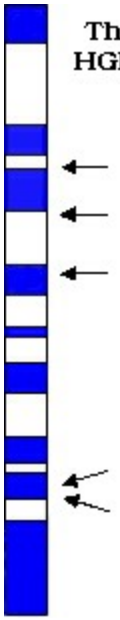
(hypoxanthine-guanine phosphoribosyltransferase)

- 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





mutations at these positions in gene have been found

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

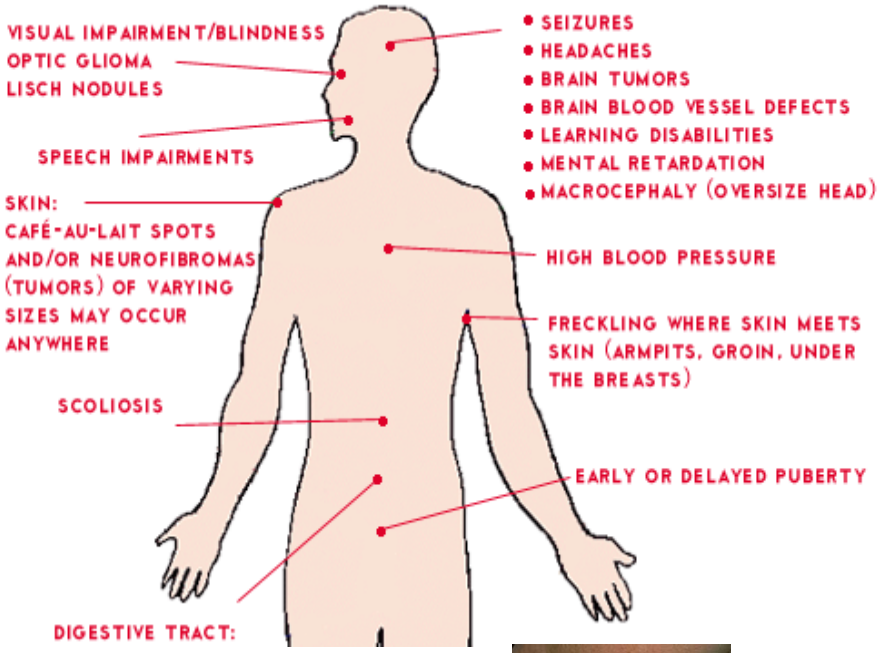
but 50% of cases are new mutations

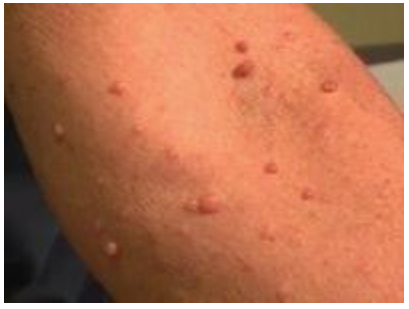
mouse knock-out model - learning & memory deficits

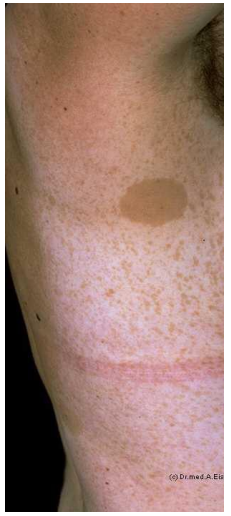
Drosophila knock-out model – used to dissect cause of cognitive deficits at cell level, possible treatment

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)

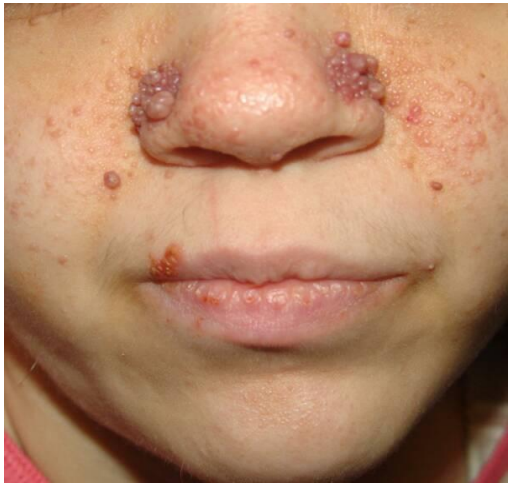
70% is spontaneous mutation many unique mutations

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

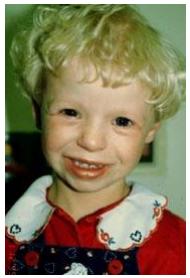
Estimated prevalence 1 in 4000 live births

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

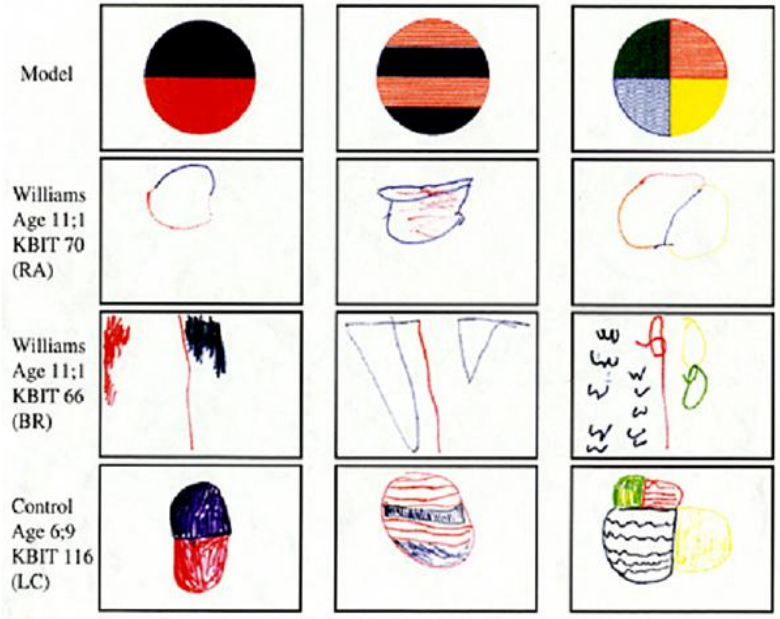
often good language development and auditory memory (for IQ level)

% relative to norm for age

Language
Face recognition
Musical abilities
Social behavior
‘friendly’ personality traits — 35-98%

Visuo-spatial
Counting
Implicit memory
Problem solving — <1%

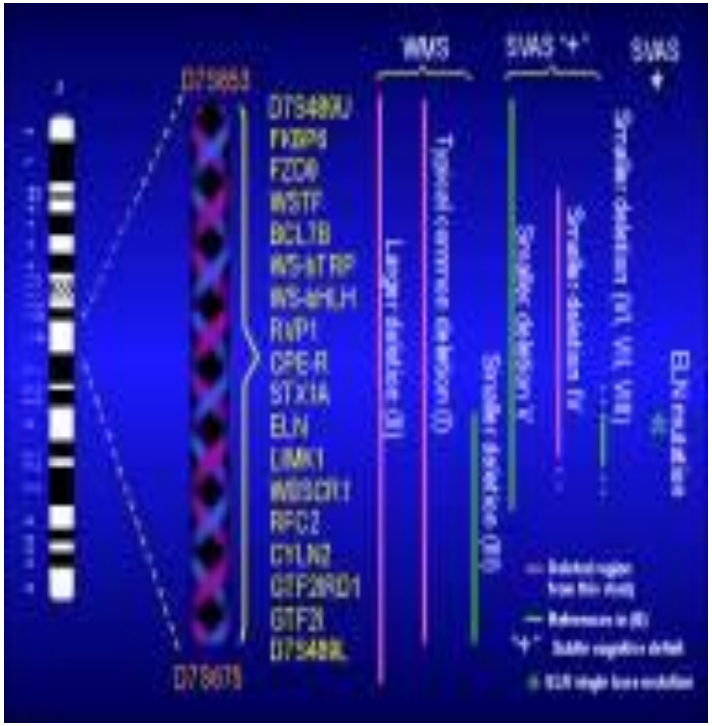
KBIT = Kaufman Brief Intelligence Test

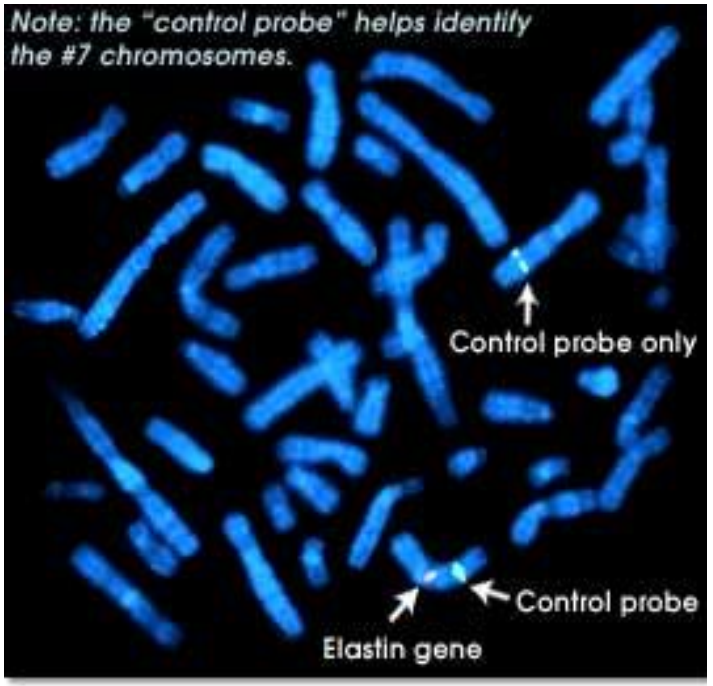


~20 genes, elastin & kinase genes thought to produce most of the symptoms

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





Positive Williams Syndrome FISH assay

(Chromosome 7)

The elastin gene is found on only one chromosome. The other copy carries an elastin gene deletion.

Angelman / Prader-Willi syndromes

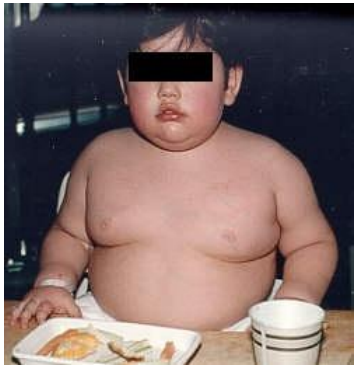
- spontaneous microdeletion chr 15
- region subject to imprinting

Angelman syndrome
1 in 25000
from Mom

seizures
happy
moderate retardation
speech impairment

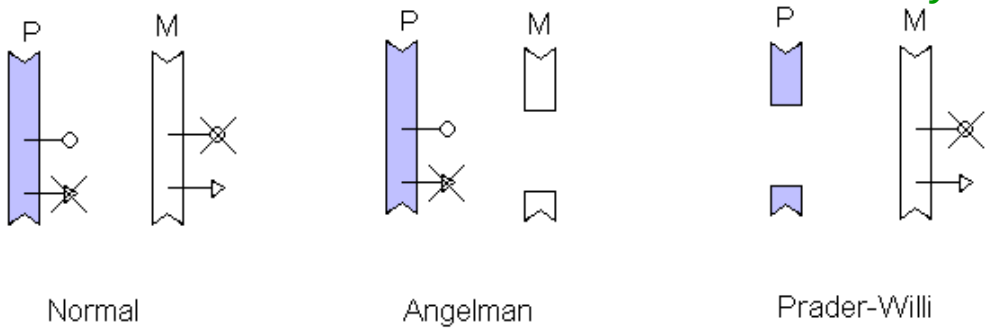
deletion on chr 15

from Dad
1 in 22-25000
Prader-Willi syndrome

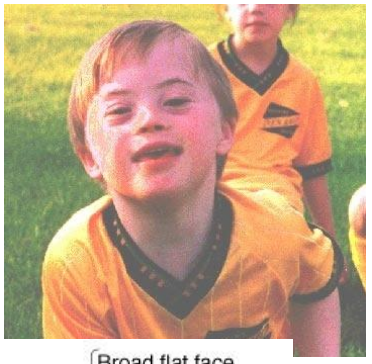


hormonal deficiency
low/normal IQ(av70)
compulsive overeating
life-threatening obesity

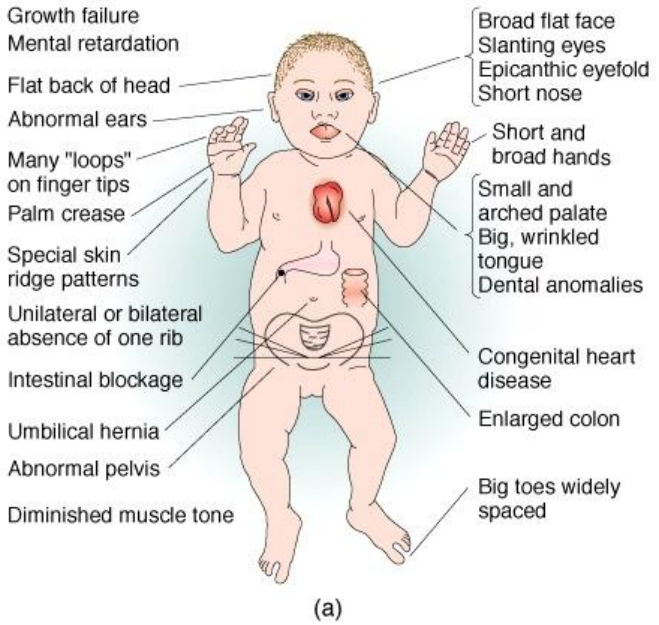
Imprinting chromosome 15
o = unknown(HBII-85 snoRNAs)
▷ = ubiquitin-protein kinase gene



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 Alzheimers

retrovirus (MLV), further indicating that the replication defect is specific to HIV-1 and not due to a widespread disruption of the normal cell physiology. Replication of MLV required BAF and LAP2α, but not emerin[1,8]. So it would seem that, although both retroviruses recruit BAF, each virus also enlists different LEM-domain proteins.

What is the viral replication defect in cells depleted of either emerin or BAF? In these cells, viral DNA was synthesized at normal levels but failed to integrate into the cellular genome. Biochemical subcellular fractionation experiments indicated that depletion of emerin or BAF did not prevent the viral DNA from entering the nucleus, but that the viral DNA became associated with different nuclear fractions from normal. In control macrophages, most of the viral DNA was associated with the soluble chromatin fraction, whereas in cells depleted of BAF or emerin it was mainly in the insoluble nuclear-matrix fraction. The identical infectivity defects caused by depletion of either emerin or BAF suggest that these proteins have a cooperative role in HIV-1 infection, consistent with the known interaction between BAF and the LEM domain of emerin.

The mechanism by which emerin and BAF facilitate the proper nuclear localization of the HIV-1 PICs remains unknown. The association of emerin with the PIC depends on BAF, which probably interacts with the viral DNA. But how does emerin then influence the association of the HIV-1 PIC with the host chromatin? It may be that the work required to answer this question will also uncover other features of nuclear architecture. Although the organization of chromatin has been extensively studied at the level of the nucleosome (the smallest unit of DNA packaging), the global organization of chromatin within the nucleus is not well understood. However, the nucleus is clearly both highly compartmentalized and dynamic, and chromatin is intimately associated with the nuclear envelope. Perhaps we should not be surprised that there is more to accessing chromatin than simply crossing the nuclear envelope. ■

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DOWN'S SYNDROME

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 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[1].

In this issue, papers by Arron *et al.* (page 595)[2] and Gwack *et al.* (page 646)[3] 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 diametrically opposed approaches, the groups reached this conclusion by a process that began with an interest in a family of four gene-regulatory factors called NFATc (for 'nuclear factor of activated T cells').

The regulation of various developmental pathways and of the immune response relies on processes that are activated by the entry of calcium into the cell, and the NFAT signalling pathway mediates many of these processes. Following the influx of calcium, phosphate groups are removed from NFATc factors in 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 phosphate groups added back to it by a kinase enzyme (phosphorylation), forcing it to return to the cytoplasm and halting its effects on the genes (Fig. 1a).

Arron *et al.*[2] 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 jawbone. These deformities are similar to those observed in Down's syndrome and in two mouse models of Down's syndrome (called Ts65Dn and Ts1Cje) that have an extra copy of part of the mouse chromosome most similar to human chromosome 21 (that is, they are trisomic)[4]. In addition, these and other mice lacking various NFATc family members, either singly or in combination, display abnormalities that are highly reminiscent of Down's

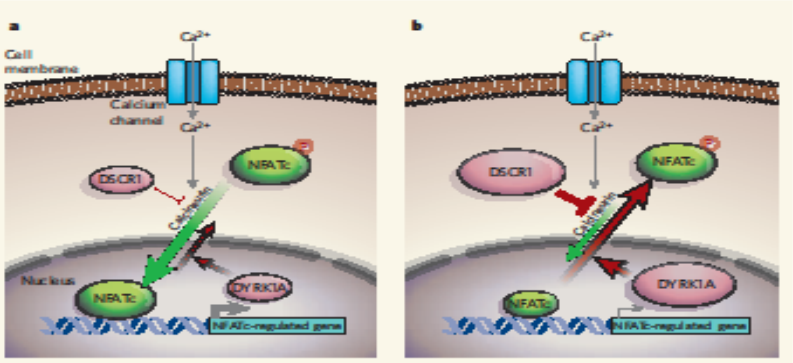

Figure 1 | NFAT signalling and Down's syndrome. Calcium signalling through the NFATc pathway mediates many developmental processes and the immune response. **a**, The entry of calcium ions into the cell activates the enzyme calcineurin to remove phosphate groups (P) from NFATc factors in the cytoplasm, allowing NFATc to enter the nucleus and activate its target genes. However, once in the nucleus, the NFATc can be phosphorylated, and so returns to the cytoplasm. Arron *et al.*[2] and Gwack *et al.*[3] implicate the DSCR1 and DYRK1A proteins in regulating the levels of NFATc phosphorylation. **b**, The genes encoding DSCR1 and DYRK1A 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 *DYRK1A* disturbs the balance of NFATc phosphorylation, so that most of the protein is found in the cytoplasm[2,3]. Thus, NFATc-dependent genes will not be properly regulated, which could markedly affect development. (Modified from Arron *et al.*[2], Supplementary Figure 1.)

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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
} used as molecular and cellular models

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