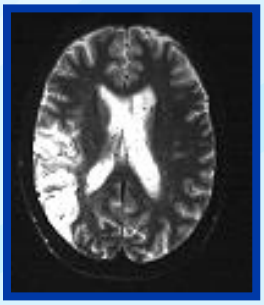
Central Nervous System

- Developmental delay
- Loss of milestones
- Intellectual disability
- Dementia
- Seizures
- Neuropsychiatric disturbances
- Cerebral palsy
- Migraines
- Stroke and stroke-like episodes
- Movement disorders: chorea, athetosis, dystonia, tremor



Developmental Delay

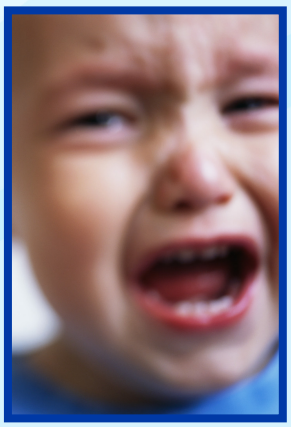
- Gross motor, fine motor, social/adaptive, visual-motor/problem solving
- Categories include
  - Intellectual disability
  - Cerebral palsy
  - Communication disorders
  - Learning disabilities
  - Pervasive developmental disorders (autistic spectrum)
  - Attention deficit hyperactivity disorder

Neurocognitive Problems

- Auditory or visual processing deficits
- Learning disabilities
- Frontal lobe symptoms
  - Neuropsychiatric
  - Executive functioning
    - Impulsivity
    - Disinhibition
    - Autistic tendencies

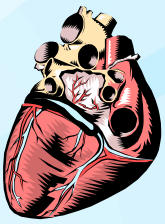
Sensory Neuropathy

- Sensory loss
- Neuropathic pain, parasthesias
- Dysautonomia
  - Temperature regulation problems
  - Abnormal sweating
  - Orthostatic hypotension
  - Bladder dysfunction
  - Gastrointestinal dysmotility
  - Fainting/syncope
- Loss of deep tendon reflexes



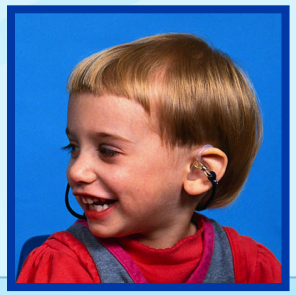
Motor Neuropathy

- Weakness and/or fatigability
- Hypotonia
- Cramping
- Eye muscle: ophthalmoplegia, ptosis
- GI dysmotility
- Cardiomyopathy



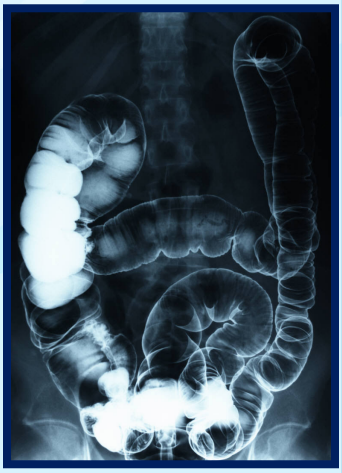
Vision and Hearing

- Visual loss, blindness
- Optic nerve changes: pallor, atrophy
- Retinal changes: retinitis pigmentosa
- Cortical visual impairment
- Hearing loss (sensorineural, high-frequency)
- Aminoglycoside sensitivity



Gastroesophageal

- Gastroesophageal reflux
- Dysmotility
- Diarrhea
- Irritable bowel syndrome
- Constipation
- Pseudo-obstruction
- Failure to thrive

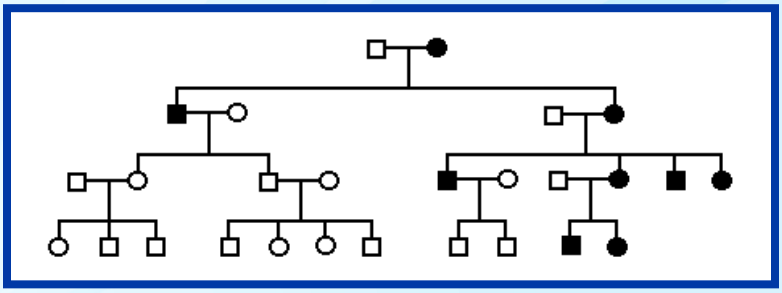


Mitochondrial Genetics

- **Inheritance of mtDNA is exclusively from the mother**
  - Eggs contain mitochondria
  - The mitochondria in sperm are in the tails, and not incorporated into the fertilized egg
- **All children of a woman with a mtDNA mutation will inherit some proportion of normal versus mutant mitochondria**
  - Each child has the potential to manifest some or all of the phenotype of a mitochondrial disorder
  - The specific phenotype will depend upon percentages of normal and mutant mitochondria within various cells and tissues

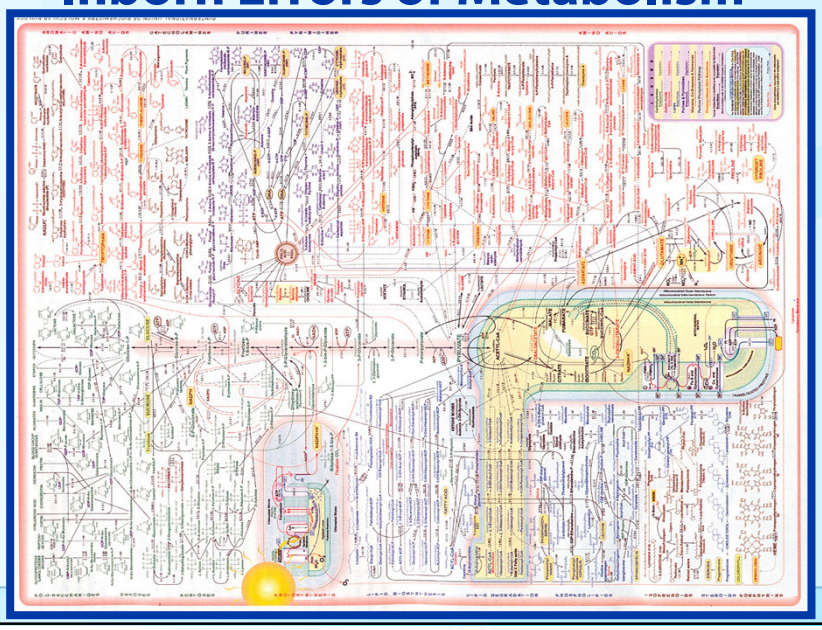
Mitochondrial Genetics

- There is no transmission of mitochondrial disorders from an affected father to his children
- Example of a pedigree manifesting mitochondrial inheritance:



Dirk brings his family tree to class

Inborn Errors of Metabolism



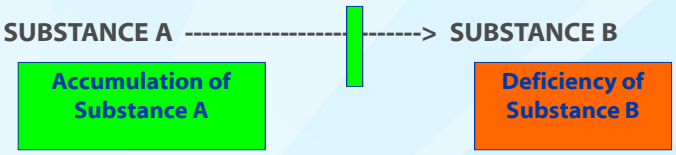
The Typical Metabolic Pathway

SUBSTANCE A ----------> SUBSTANCE B

Enzyme
Enzyme Complex
Cofactors

- **Problems arise in converting Substance A to Substance B when the enzyme and/or cofactor**
  - Are not present
  - Are present, but are not functional
  - Are present and functional, but have decreased activity

The Blocked Metabolic Pathway



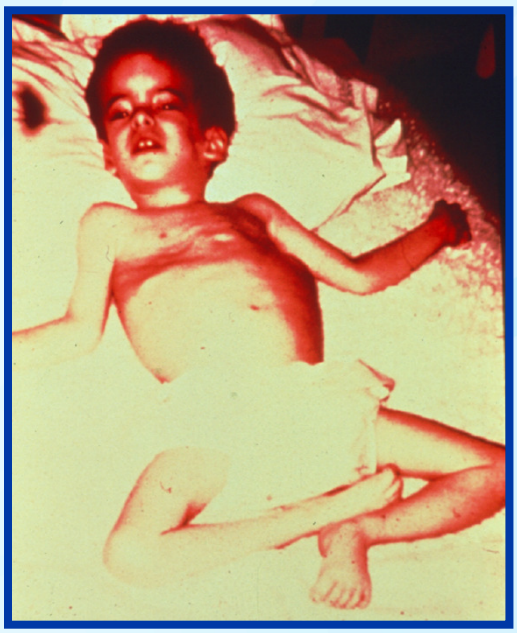
- **The consequences of being unable to convert Substance A to Substance B include**
  - Accumulation of Substance A
  - Deficiency of Substance B
  - Both accumulation of Substance A and deficiency of Substance B
  - Neither accumulation of Substance A or deficiency of Substance B are a problem

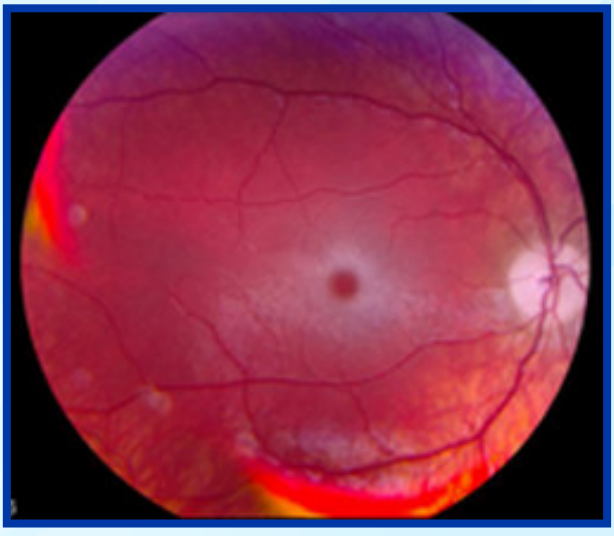
Presentations of Inborn Errors of Metabolism

- **Inborn errors of metabolism may present at any age**
- **There are often several forms of a particular disorder (neonatal, infantile, juvenile, and/or adult)**

Major Categories of Clinical Presentation

- Neonatal catastrophe
- Liver disease
- Storage disease
- Neurologic abnormalities
  - Altered muscle tone and reflexes (not focal)
  - Ataxia (unsteady movements, walking, etc.)
  - Seizure disorder
  - Developmental delay
  - Movement disorder
  - Altered state of consciousness





Tay-Sachs Disease

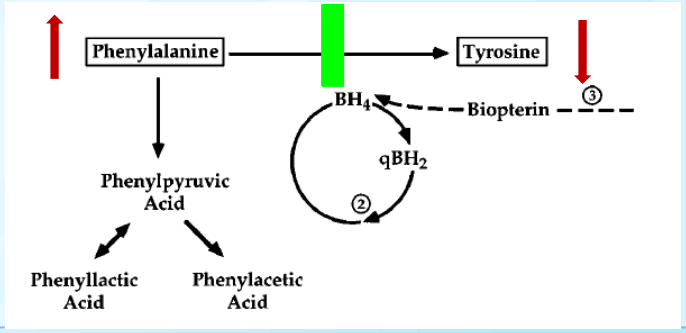
- Phenotype
  - Onset between 6-12 months
  - Loss of milestones
  - Motor weakness
  - Hyperacusis (sensitivity to loud sounds)
  - Later, seizures, blindness, spasticity
  - Death by age 2-5 years
  - Milder juvenile and adult forms exist

Tay-Sachs Disease

- Incidence--
  - 1-in-1,000,000 worldwide
  - 1-in-4000 in Ashkenazi Jews
- Inheritance--autosomal recessive
- Cause--mutation in the Hexosaminidase A (*HEXA*) gene
- Treatment--none

Phenylketonuria (PKU)

- Incidence is ~1/12,000 to 1/15,000
- Autosomal recessive condition
- Caused by mutations in the Phenylalanine Hydroxylase (*PAH*) gene

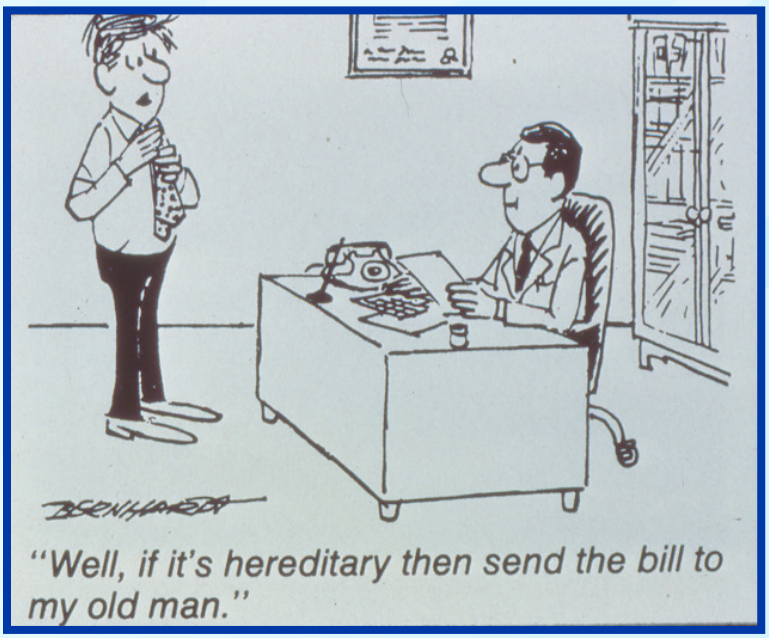


Phenylketonuria (PKU)

- Elevated phenyalanine
  - Toxic to brain and nerves
  - Causes intellectual disability, seizures, autism
- Low tyrosine
  - Tyrosine is required for making melanins (skin pigments) and dopamine and norepinephrine (neurotransmitters)
  - Partial albinism
  - Neurologic dysfunction from low neurotransmitters

Phenylketonuria (PKU)

- **Treatment**
  - Diet that restricts phenylalanine (comes from protein) and supplements tyrosine (in specialized medical formulas, capsules, or medical food bars)



Genetics of ASD

- **Does ASD have a genetic cause?**
  - **Heritability**-
    - Twin Studies: Compare the concordance rates between monozygotic (identical twins) - who share nearly 100% of their genetic information to that of dizygotic (fraternal twins) - who may share on average about 50% of their genetic information
  - **>30 twin studies to date that have consistently shown higher concordance between monozygotic (MZ) vs. dizygotic (DZ) twins – suggesting a strong genetic component**
    - Median concordance for a narrow definition of autism:
      - MZ = 76% vs. DZ = 0%*
    - Median concordance for a broader ASD definition:
      - MZ= 88% vs. DZ= 31%*

* Reviewed in Ronald and Hoekstra, 2011

Genetics of ASD

- **Does ASD have a genetic cause?**
  - Yes, genetics appears to be a significant risk factor for the development of autism

Genetics of ASD

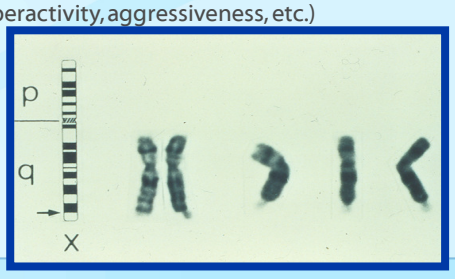
- **Certain genetic conditions have ASD as a component of the phenotype***
- **Single gene mutations**
  - **Fragile X syndrome** –caused by a mutation in the *FMR1* gene; most common known genetic cause of ASD; 25% of Fragile X patients have autistic features; 1-2% of all ASD individuals have Fragile X syndrome

* Reviewed in Abraham and Geschwind 2008

Genetics of ASD

- **Certain genetic conditions have ASD as a component of the phenotype***
- **Single gene mutations**
  - **Fragile X syndrome** phenotype:

Long face, high forehead, large mouth, large jaw, prominent chin, large ears, large testes after puberty, joint laxity, flat feet, delayed motor development, intellectual disability, speech and language deficits behavioral issues (anxiety, hyperactivity, aggressiveness, etc.)



Genetics of ASD

- **Certain genetic conditions have ASD as a component of the phenotype***
- **Single gene mutations**
  - **Rett syndrome**– vast majority caused by mutations in the *MECP2* gene (a few *CDKL5* or *FOXG1* gene mutations reported)
  - **Rett syndrome** phenotype:

Short stature, deceleration of head growth, teeth grinding, constipation, gastroesophageal reflux, spinal curvature, small feet , muscle wasting, normal development until 6-18 months of age, then reduction or loss of acquired skills, profound intellectual disability, spasticity, dystonia, seizures, gait problems, sleep disturbances, stereotypical hand movements (e.g. hand wringing)

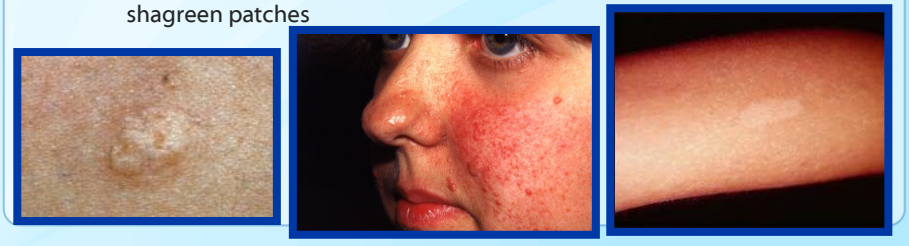
- http://www.youtube.com/watch?feature=player_detailpage&v=-coYQMSLHq8

* Reviewed in Abraham and Geschwind 2008

Genetics of ASD

- **Certain genetic conditions have ASD as a component of the phenotype***
- **Single gene mutations**
  - **Tuberous sclerosis (TS)**– caused by mutation in *TSC1* or *TSC2* gene; approximately 20% of TS patients have ASD; approximately 1% of all ASD individuals have TS
  - **Tuberous sclerosis (TS)** phenotype:

Skin anomalies: white patches (ash leaf spots), facial angiofibromas, shagreen patches



Genetics of ASD

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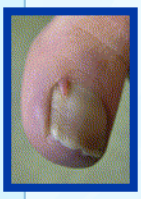
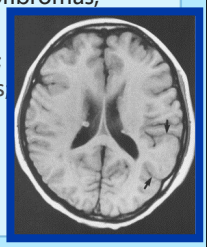


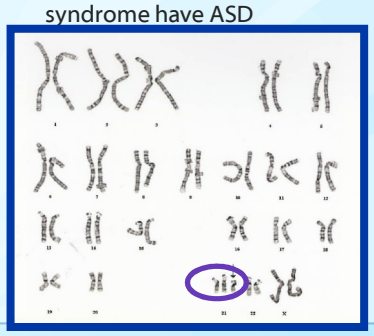
Skin anomalies: white patches (ash leaf spots), facial angiofibromas, shagreen patches

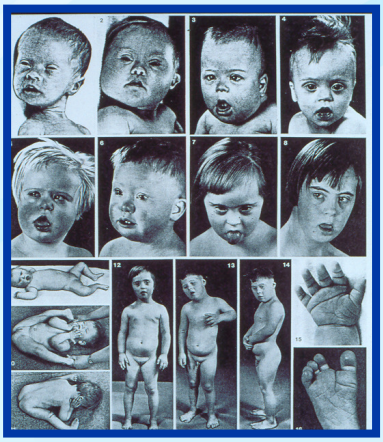
Ungual fibromas (around the edge of finger and toe nails); kidney angiomyolipomas, cysts, and renal cell carcinomas; heart rhabdomyomas and arrhythmias; subependymal nodules, cortical tubers, and vascular tumors; seizures; learning difficulties, intellectual disability, attention deficits



Genetics of ASD

- **Certain genetic conditions have ASD as a component of the phenotype***
- **Chromosome anomalies**
  - **Down syndrome** (trisomy 21)– 1-7% of those with Down syndrome have ASD





Genetics of ASD

- **Certain genetic conditions have ASD as a component of the phenotype***
- **Deletion or duplication of part of a chromosome (microdeletion or microduplication)**
  - **22q13.3 deletion** (Phelan-McDermid syndrome)**-** this deletion includes the *SHANK3* gene, which is presumed to cause much of the phenotype; approximately1% of all ASD individuals have the 22q13.3 deletion
  - **22q13.3 deletion** phenotype:

Tall stature, large head; asymmetric face, prominent brow, small pointed chin, prominent abnormally-formed ears, epicanthal folds, bulbous nasal tip, large fleshy hands, abnormal toe nails, hypotonia, developmental delay, absent or delayed speech, intellectual disability, seizures, poor social interaction and communication, aggressive behavior

* Reviewed in Abraham and Geschwind 2008

Genetics of ASD

- **Certain genetic conditions have ASD as a component of the phenotype***
- **Deletion or duplication of part of a chromosome (microdeletion or microduplication)**
  - **15q11-q13 duplication**– approximately1-2% of all ASD individuals have the 15q duplication; at least part of the phenotype is perhaps associated with a GABA receptor gene within the duplication (*GABRB3*); if the duplication is inherited from the father, the phenotype of the child is normal, but if the duplication is inherited from the mother the following phenotype emerges:
  - **15q11-q13 duplication** phenotype:

Intellectual disability; seizures; impaired social interactions, language development, use of nonverbal behaviors, and ability to form peer relationships; repetitive stereotyped behaviors; lack of spontaneous play; 4:1 male to female ratio

* Reviewed in Abraham and Geschwind 2008

Genetics of ASD

- **Certain genetic conditions have ASD as a component of the phenotype***
- **Deletion or duplication of part of a chromosome (microdeletion or microduplication)**
  - **16p11.3 deletion or duplication**– together these account for approximately1% of all ASD individuals
  - **16p11.3 deletion** phenotype:

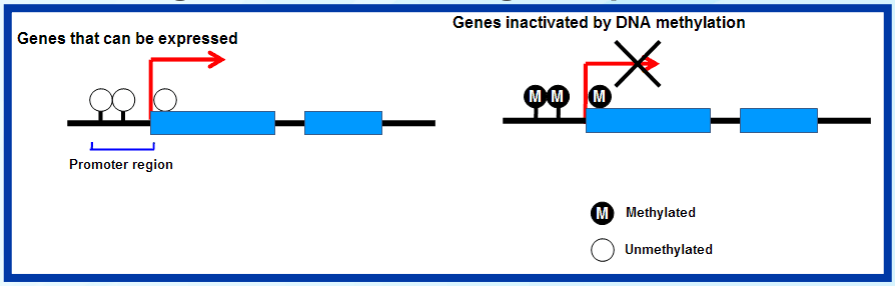
  Rarely individuals identified with the deletion have no phenotype; otherwise, the phenotype includes large head, broad forehead, widely-spaced eyes, flat face, small mouth, motor delay, seizures, speech/language delay, intellectual disability, ADHD
  - **16p11.3 duplication** phenotype:

  Small head size, other inconsistent dysmorphic features, autistic features, behavioral problems, particularly ADHD, speech/language delay, intellectual disability

* Reviewed in Abraham and Geschwind 2008

Methylation of the DNA

- **Certain sequences of the DNA can undergo the addition of a chemical, known as a methyl group ($-CH_3$)**
- **This process is called DNA methylation**
- **The addition of methyl groups can affect whether or not the gene can make its designated protein**

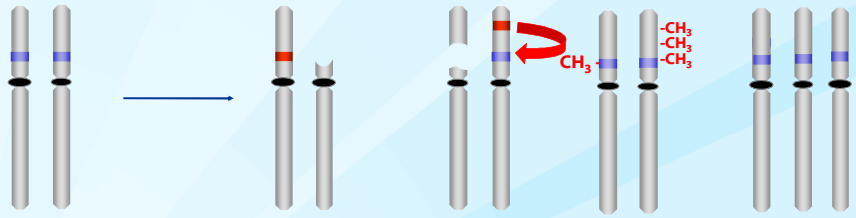


Methylation of the DNA

- DNA methylation is a normal process used by cells to "turn on" and "turn off" certain genes during specific times in development and in certain cells
- Aberrant DNA methylation leads to inappropriately "turned on" or "turned off" genes, resulting in too little or too much of certain proteins

How to Alter a Gene

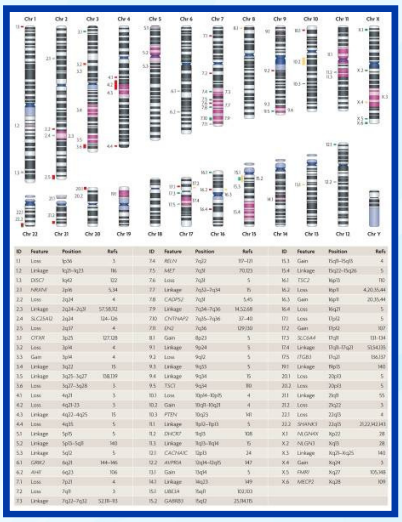
Unaffected



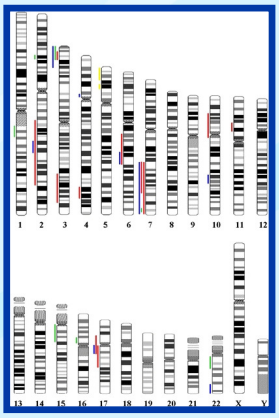
There are multiple ways to alter a gene, leading to too little or too much protein:

- mutation
- deletions -large and small
- mutation of another gene
- methylation of the gene itself or a nearby region
- another copy of the gene itself, or the whole region or chromosome
- all of these types of change have been associated with ASDs

There are many genes and genetic loci that have been associated with increased risk of ASD



Nat Rev Genet. 2008 Jun;9(6):493.



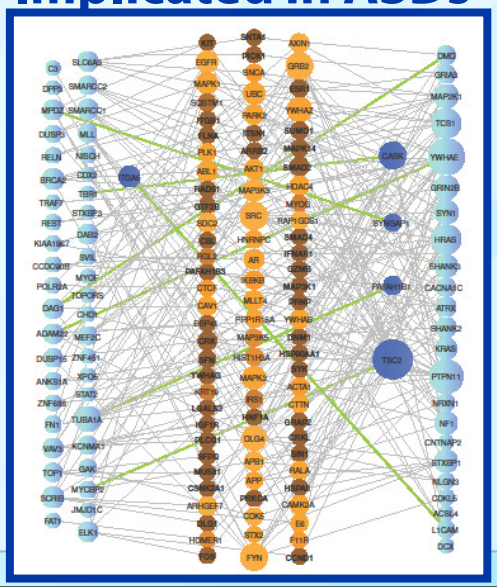
Replicated findings of linkage (*red bars*), Genome wide association (*yellow bars*), copy number variation (*green bars*) and candidate gene (*blue bars*) studies as discussed in the text.

Eur Child Adolesc Psychiatry. 2010 March; 19(3): 169-178

Genetics of ASD

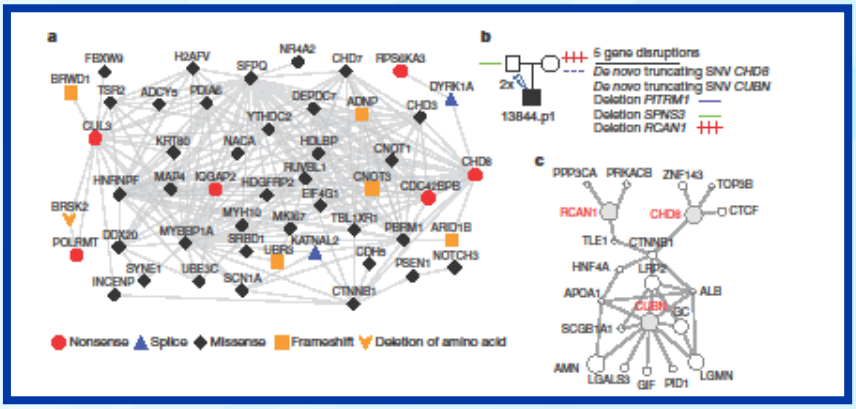
- Many of the genes implicated to date appear to interact with each other in various cellular functions
- These interactions comprise large "networks"
- Therefore, a mutation in any of the genes in the networks might increase the risk for the child developing an ASD

Networks of Gene Interactions Implicated in ASDs



Neale et al., 2012

Networks of Gene Interactions Implicated in ASDs



ORoak et al., 2012

Genetics of ASD

- The genetic changes discovered to date are present in ~10-15% of the cases of autism
- Many of the genes implicated in ASD are associated with other conditions- such as developmental delay, bipolar, schizophrenia, ADHD, speech and language delay etc…

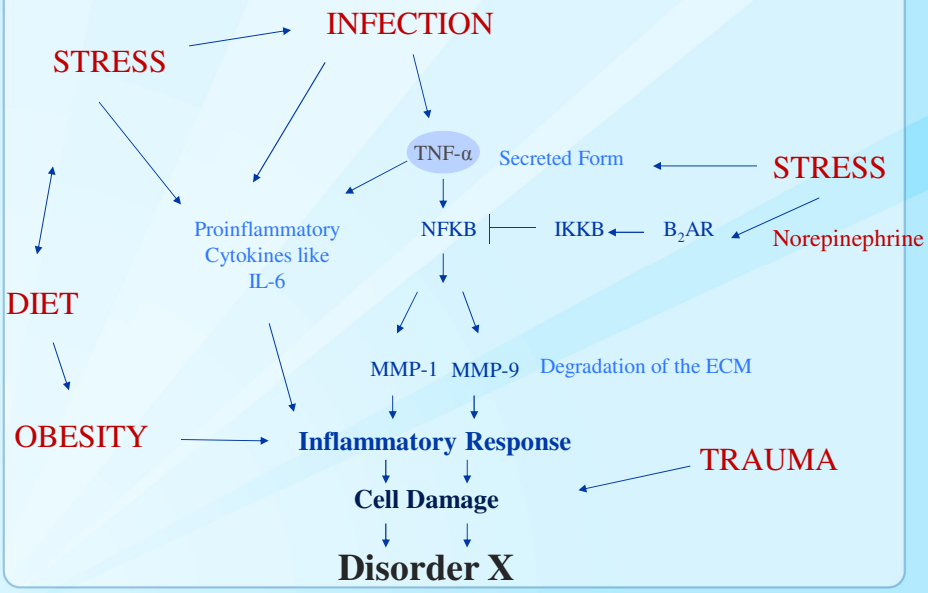
Penetrance

- Individuals who have many of these genetic changes will NOT necessarily have an ASD

Example: Only 25% of individuals with Fragile X syndrome have features of ASD or only 20% of individuals with Tuberous Sclerosis have features of ASD

- This strongly suggests:
  - Gene-gene interactions
  - Gene-environment interactions

Gene-Environment Interactions



Genetic and Gene-Environment Interactions and ASD

- Gene-Gene and Gene-Environment interactions are likely to play a prominent role in ASDs
- Single exposures (genetic or environmental) are unlikely (but possible) to be responsible for a sizable fraction of all cases of ASD in the population
- Combinatorial approaches- multiple environmental exposure and/or genetic risk factors could be explored

"Your weight problem is partly genetic and partly Boston Cream pie."