SINGLE GENE DISORDERS

Dr. Abhi Veerakumarasivam
(2011)
• Genetic Diseases

• Monogenic disease

• Autosomal Dominant Disorder

• Autosomal Recessive Disorder

• X-linked Dominant Disorder

• X-linked Recessive Disorder

• Learning Outcomes
Genetic Diseases

Occurs in 14% general population

Usually a cosmetic issue rather than a functional problem...

What about diseases that are not obvious at birth or early stages of life?
Macroglossia
Clinodactyly
Polydactyly
Skin Tag
Alien Child?
Harlequin-Type Ichthyosis

- Skin disease
- Most severe form of congenital ichthyosis
- Thickening of the keratin layer in skin
- Due to the mutation in the *ABCA12*; for transport of lipids to epidermis.
- Frequency: 1/300,000 births, both genders affected
- Consanguinity and occurrence of harlequin ichthyosis in siblings suggest an **autosomal recessive** pattern of inheritance
1% of general population

Defects code for protein with functional significance
Encephalocele
Cleft Lip & Palate
Ectrodactyly
Bilateral Clubfoot
Famous People & Genetic Diseases

**Dyslexia**
- Language based learning disorder
- Grounded in the neurobiology of the brain.
- Many dyslexics are left-handed
- Gene affected: **DCDC2**, Chr 6
- Highly unlikely a monogenic disease.

**Marfan Syndrome**
- Inherited disorder of the connective tissue
- Mistake in the gene that makes fibrilin; **FBN1** Chr 15
- Affects heart, bones & eyes
- Autosomal dominant disease

**Parkinson’s Disease**
- Degenerative disorder of CNS
- Motor symptoms, mood, behaviour, cognition, sensation.
- Many causes (toxin, head trauma, drugs), one of them is genetic.
- Genes affected: **LRRK2, SNCA**
Genetic Diseases

Definition: **A disease caused by abnormal expression of one or more genes in a person that result in a clinical phenotype**

- Causes for genetic defects:
  - Chromosomal
  - Mitochondrial
  - Mutation in a gene, affecting the protein function/availability
    - Multifactorial/Polygenic
    - Monogenic (Single Gene)

- **Hereditary disease: defective genes inherited from parents**

- Not all of the genetic diseases are inherited

- More than 4,000 genetic disorders are known
  - Most are quite rare, 1:thousands/millions
Aneuploidy: abnormal chromosome number

- Changes not inherited
- Occur randomly during the formation of ova and sperm cells
- Error in cell division (non-disjunction)
- Examples:
  - Trisomy (Down Syndrome)
  - Monosomy (Turner Syndrome)

Rearrangement of pieces of DNA within chromosome or transferred between two or more chromosomes

- Example: Cancer
Y-linked chromosomal micro-deletion

- Affects male only.
- Example: **Male infertility**
- Large terminal deletions of the long arm (Yq) in men with azoospermia
- Designated as “azoospermia factor” (AZF) region.
Caused by mutations in the non-chromosomal DNA of mitochondria

Mitochondrion may contain 5-10 circular pieces of DNA

Maternally inherited only

Example:
- Mitochondrial Encephalopathy (MELAS)
- Leber’s Hereditary Optic Neuropathy (LHON)
Multifactorial & Polygenic Disorders

• Combination of environmental factors and mutations in multiple genes (polygenic)

• Multifactorial
  • Example:
  • Heart disease
  • High blood pressure
  • Diabetes
  • Cancer,
  • Obesity

• Polygenic
  • Example:
  • *Breast cancer* susceptibility genes found on chromosomes 6, 11, 13, 14, 15, 17 and 22.
For any condition, the **overall balance** of genetic and environmental determinants can be represented by a point somewhere within the triangle.
Continuum of penetrance in determining a person’s susceptibility to a disease:

- from fully penetrant conditions, where other genes and environmental factors have no effect
- to low-penetrance genes that simply play a small part, along with other genetic and environmental factors,

Example *Multiple sclerosis*

- Multifactorial condition
- Genetic factors play a major part in determining susceptibility
- Current research: Each individual factor has a very low penetrance.
The contributions of **genetic** and **environmental** factors to human diseases:

- **Rare**
  - Genetics simple
  - Unifactorial
  - High recurrence rate

- **Common**
  - Genetics complex
  - Multifactorial
  - Low recurrence rate
Age of Expression of Major Genetic Diseases

- Chromosomal
- Single Gene Mendelian
- Multifactorial

Age of Expression (Incidence)
Genetic Jargons

- **Autosome**: Any of the 22 non-sex chromosomes
- **Sex chromosomes**: Chromosomes responsible for sex determination
- **Locus**: The site of a gene on a chromosome
- **Allele**: Alternative form of a gene found at the same locus on homologous chromosome
- **Homozygote**: Individual who possesses *two identical alleles* at one particular locus on a pair of homologous chromosome
- **Heterozygous**: The state of having *different alleles* at a locus on homologous chromosome.
- **Dominant**: A trait which is expressed in individuals who are *heterozygous* for a particular allele.
- **Recessive**: A trait which is expressed in individuals who are *homozygous* for a particular allele but not in those who are heterozygotes.
Pedigree charts show a record of the family of an individual.

They can be used to study the transmission of a hereditary condition ethically.

They are particularly useful when there are large families and a good family record over several generations.

Allow inferences concerning genotypes and predictions concerning phenotypes of offspring (genetic counseling).

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<th>Symbol</th>
<th>Unaffected Male</th>
<th>Unaffected Female</th>
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<td>unaffected male</td>
<td>unaffected female</td>
<td>affected male</td>
<td>affected female</td>
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(genetic counseling)
Most common signs and symbols used in pedigree analysis

Symbols

- Male
- Female
- Mating
- Parents and children: 1 boy; 1 girl (in order of birth)
- Dizygotic (nonidentical twins)
- Monozygotic (identical twins)
- Sex unspecified

- Number of children of sex indicated
- Affected individuals
- Heterozygotes for autosomal recessive
- Carrier of sex-linked recessive
- Death
- Abortion or stillbirth (sex unspecified)
- Propositus
- Method of identifying persons in a pedigree: here the propositus is child 2 in generation II, or II-2
- Consanguineous marriage
Single Gene Disorders

Definition: Disease caused by mutations in 1 gene

- Genes code proteins - perform most of the life functions, make up the majority of the cell structure

- Gene mutates → protein no longer able to carry its job = disorder!!

- Not all are lethal (eg. color blindness)

- Carrier advantages:
  - CF resistant to cholera
  - Sickle cell anemia & thalassemia resistant to malaria
• **Sickle-cell disease** occurs more commonly in people (or their descendants) from parts of the world such as **sub-Saharan Africa**

• Where **malaria** is or was common, but it also occurs in people of other ethnicities.

• This is because those with one or two alleles of the sickle cell disease are resistant to malaria since the red blood cells are not conducive to the parasites.

• In areas where malaria is common there is a survival value in carrying the sickle cell genes.
Biochemical and molecular basis of single-gene disorders

- **Enzyme** defects and their consequences
- Defects in **receptors** and **transport** systems
- Alterations in structure, function or quantity of **non-enzyme** proteins
- Genetically determined **adverse reactions to drugs**
Single mutated gene can be passed on to subsequent generation

Transmission of single gene disorders
  - Autosomal Dominant
  - Autosomal Recessive
  - X-linked Dominant
  - X-linked Recessive

The division between recessive and dominant is not clear cut
  - Genotype vs. Phenotype

Achondroplasia is typically considered a dominant disorder, but children with two mutated alleles for achondroplasia have a severe skeletal disorder that achondroplasics could be viewed as carriers
  - Sickle cell anemia = recessive, but carriers have resistance to malaria. Is it dominant then?
Definition: **Only one mutated copy of the gene is needed for a person to be affected.**

- Each affected person usually has one affected parent.
- There is a 50% chance that a child will inherit the mutated gene.
- Deleterious disease, wiped out by natural selection?
  - **Late onset**
  - **Variable expressivity** (different individuals with the same mutation will develop different degrees of the disorder due to difference in environment and the modifying effects of other genes)
  - **Incomplete penetrance** (although only one mutated copy is needed, a relatively small proportion of those who inherit that mutation do not develop the disease) (All or none)

- Example: Neurofibromatosis 1, Hereditary Breast Ovarian Cancer syndrome (HBOC), Hereditary nonpolyposis colorectal cancer, Huntington’s disease.
The affected parent has a single defective gene (D), which dominates its normal counterpart (d).

Each child has a 50 percent risk of inheriting the faulty gene and the disorder.
Autosomal Dominant

- Vertical Transmission
- Equal frequency of affected males & females
- Advanced paternal age associated with sporadic cases
- Variable expression
- Reduced penetrance (in some disorders, non-penetrance)
AD: Achondroplasia

- It is the most common form of **short-limb dwarfism**
- Developmental disorder: bone tissue does not develop properly in the long bones of the arms and legs.
- Affects about 1 in 25,000 individuals of all ethnic groups.
- Cannot be cured
- Symptoms can be treated with surgery.
- Mutations of the **FGFR3** gene
- Growth factors: proteins that control cell growth and behaviour
- In order to work they must bind to receptors on the surface of responding cells.
- When absent/not working properly, the growth factors cannot carry out their normal functions.
- FGFR3 protein is concentrated in the **cartilage** and the **central nervous system**, so mutations in the FGFR3 gene predominantly affect these parts of the body.
Progressive degenerative disorder of the central nervous system

Frequency: 8/100,000

Pathology
- Neuronal loss with gliosis in striatum and cortex.
- Slow progressive selective cell death in the CNS.

Clinical features
- Dementia, choreic movement (involuntary) [facial grimacing, twitching of limbs & face], emotional & cognitive impairment, hallucination, paranoia, agitation, personality changes
- Onset in middle age, death within 15-20 yrs
- **Juvenile HD:** 10% cases the disorder presents before 20 yrs
HD Genetics

- **HTT** (Huntingtin) gene located at 4p16.3
  - 67 exons, 10,366 bp size, 348 kDa cytoplasmic protein (Huntingtin)
  - 5’ end of HD gene has a sequence of 3 DNA bases, CAG (glutamine), that is repeated multiple times (trinucleotide repeat).
  - In normal people, repeat size is 6-35
  - In intermediate HD, repeat is 30-38; full HD repeat is 35-120

- Genetic Anticipation & Dynamic mutation – Trinucleotide Repeat Expansion

- When gene has more than 35 copies of the CAG sequence, DNA replication loses its fidelity = number of repeat changes in successive generation

- If mutated allele comes from mother = count is usually similar

- If mutated allele comes from father = repeat increases = disease tends to increase in severity and have earlier onset in successive generation

- Inverse relationship between the length of repeat and onset of disease

- Why only trinucleotide repeats?
**HD Mechanism & Management**

**Mechanism**

- Huntingtin acts as a transcription factor for brain-derived neuropathic factor (BDNF).
  - Low Huntingtin = Low BDNF
  - Low BDNF linked with clinical depression, obsessive compulsive & dementia
  
  *Direct causation still unclear!*

- Abnormal Huntingtin molecules become aggregated in neurons - causes cell death

**Management**

- 1. Antidepressants/ antipsychotics/ sedatives to control chorea
- Nutrition. HD patients need more calories
- Speech therapy and swallowing techniques
- **No treatment**
- Future possible treatments: Stem cells therapy, gene therapy, protein therapy, Omega-III EPA
Half the people in the Venezuelan village of Barranquitas are affected.

A large-scale pedigree analysis was conducted including 10,000 people.

Example for one particular family:
Definition: **Two copies of the gene must be mutated for a person to be affected.**

- Affected person usually has unaffected parents who each carry a single copy of the mutated gene (carrier)
- There is a 25% chance that a child will be affected by the disorder.
- Usually the disease is due to a defective enzyme in a biochemical pathway
  - If one functional copy is present, then it’s ok.
  - If both non-functional, manifestation of the disease

Example: **Sickle cell anemia, Tay-Sachs disease, Spinal muscular atrophy, muscular dystrophy, Cystic Fibrosis.**
1 chance in 4

- Both parents carry a single defective allele (d) but are protected by the presence of a normal allele (N), which is generally sufficient for normal function.

- Two defective copies of the gene are required to produce a disorder.

- Each child has a 50 percent chance of being a carrier like both parents and a 25 percent risk of inheriting the disorder.
Autosomal recessive diseases often appear as sporadic cases
Problem of small families
Autosomal recessive diseases often appear as sporadic cases
Problem of small families

Problems in Determining Pattern of Inheritance

0 affected

1 affected

2 affected

3 affected

3/4*3/4*3/4

(1/4*3/4*3/4)3

(1/4*1/4*3/4)3

(1/4*1/4*1/4)

27/64 = 42%

27/64 = 42%

9/64 = 14%

1/64 = 2%
Autosomal recessive diseases often appear as sporadic cases
Problem of small families

Problems in Determining Pattern of Inheritance

\[
\frac{3}{4} \times \frac{3}{4} \times \frac{3}{4} \times \frac{3}{4} = \frac{27}{64} = 42\%
\]

\[
\left(\frac{1}{4} \times \frac{3}{4} \times \frac{3}{4} \times \frac{3}{4}\right)^3 = \frac{27}{64} = 42\%
\]

\[
\left(\frac{1}{4} \times \frac{1}{4} \times \frac{3}{4} \times \frac{3}{4}\right)^3 = \frac{9}{64} = 14\%
\]

\[
\left(\frac{1}{4} \times \frac{1}{4} \times \frac{1}{4}\right) = \frac{1}{64} = 2\%
\]
Accumulation of thick mucus secretions which lead to blockage of the airways and secondary infection

Frequency: 1/2000 in Caucasians, 1/15,000 in African Americans, 1/30,000 in Asian-Americans. 1/25 is a carrier.

Pathology

- Primary defect in chloride secretion by epithelial glands leading to abnormally viscous mucus
- Affects the lungs, intestines, pancreas, liver, vas deferens

Clinical Features

Meconium ileus (infancy), pancreatic exocrine failure, cough due to bronchopulmonary infection, bronchiectasis, hepatic cirrhosis.

Associated lung disease is the major cause of morbidity and mortality in CF
CF Genetics

- CF gene located at 7q31.
- 27 exons, 250kb size, 1480 amino acid, 168kDa
- **CF Transmembrane Conductance Regulatory (CFTR)** protein.

- Two transmembrane domains, two nucleotide binding folds (NBF), regulatory domain (R domain)
- Acts as a chloride channel.

In normal individuals:
- Activation: Phosphorylation at R-domain, followed by binding of ATP at NBF.
- Channels open = the protein moves Cl⁻ out of an epithelial cell to the covering mucus
- Results in an electrical gradient being formed and in the movement of Na⁺ in the same direction as the Cl⁻
- Due to this movement, the water potential of the mucus is reduced, resulting in the movement of water here by osmosis and a more fluid mucus.
**Mechanism**

- Defected CFTR gene in CF individuals (*5 classes of mutations*) = CF symptoms
  - Defect in protein synthesis
  - Defect in protein trafficking to the cell membrane
  - Defect in regulation of the ion channel (does not respond to phosphorylation)
  - Defect in conductance properties (reduced Cl⁻ current)
  - Reduced in functional CFTR protein on the membrane

- Over 1500 mutations of CFTR gene have been identified

- The most common one is deletion of 3bp at the 508th codon resulting in the loss of phenylalanine residue (**ΔF508**)

**Genotype/phenotype correlation**

- Level of severity linked with the activity of the CFTR
- Less than 3% = severe; 3%-8% = milder form; 8%-12% = the mildest (only male infertility)

**Management**

- Increase the patients’ life quality (No cure for the disease)
- Antibiotics, DNase, diet, pancreatic enzymes, physiotherapy, vitamins, lung transplants.
- Future: Gene therapy
Definition: *A single dose of the mutant allele in X-chromosome will affect the phenotype.*

The chance of passing on an X-linked dominant disorder differs between men and women.

A woman with an X-linked dominant disorder has a 50% chance of having an affected daughter or son with each pregnancy.

Some X-linked dominant conditions, such as Aicardi Syndrome, are fatal to boys, therefore only girls have them (and boys with Klinefelter Syndrome).

The sons of a man with an X-linked dominant disorder will not be affected, and his daughters will all inherit the condition.

Females are more frequently affected than males.

Examples: Hypophosphatemia, Aicardi Syndrome.
A rare congenital disorder characterised by absence of the corpus callosum, retinal abnormalities, and seizures (infantile spasms)

Frequency: 500 cases worldwide

Pathology
- Absence of the corpus callosum, either partial or complete
- Lesions or "lacunae" of the retina of the eye that are very specific to this disorder
- Microcephaly, (small brain); porencephalic cysts (a gap in the brain where there should be healthy brain tissue)

Clinical Features
- Infantile spasm, lacunae, moderate to profound mental retardation.
- Children are most commonly identified between the ages of three and five months.
- Spasm around the age of three months due to closure of the final neural synapses in the brain, a stage of normal brain development.
Genetics
• Aicardi gene located at Xp22
• Fatal *in utero* for male, female affected mostly

Mechanism
• The precise mechanism for the disease is still unknown

Treatment
• Management of seizures
• Early/continuing intervention programs for developmental delays
X-linked Recessive

Definition: Two doses of the mutant allele to affect the female phenotype, one for male phenotype.

• The chance of passing on an X-linked recessive disorder differs between men and women.

• The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene.

• With each pregnancy, a woman who carries an X-linked recessive disorder has a 25% chance of having sons who are affected and a 25% chance of having daughters who carry one copy of the mutated gene.

• Males are more frequently affected than females.

Examples: Duchenne muscular dystrophy, Color blindness, Turner Syndrome, Haemophilia.
Inherited blood clotting or coagulation disorder.
Frequency: 1/10,000 males affected
The most common severe inherited coagulation disorder

Pathology
Factor VIII, together with Factor IX, play a role in activation of prothrombin to thrombin.
Thrombin converts fibrinogen to fibrin which form the structural framework for clotted blood.

Individuals affected with haemophilia are deficient in Factor VIII = fibrin production affected.

Clinical Features
Severely increased risk of bleeding from common injuries.
The sites of bleeding are: joint, muscles, digestive tract, brain.
• *Factor VIII* gene located at the last megabase of the X-chromosome.
• 186 kb, 26 exons, 9 kb mRNA transcript.
• 5% deletion - complete absence of Factor VIII
• Flip inversion - 50% of haemophilia A cases = less than 1% Factor VIII activity.
• Factor VIII level below 1% associated with severe haemorrhagic tendency dating from birth.

**Flip inversion**
• Intra-chromosomal recombination between homologous sequence in Factor VIII gene
• Inversion disrupts the Factor VIII gene
• Flip inversion more common in male
• Long arm of X chromosome does not pair with homologous chromosome during male meiosis
• Greater chance for intra-chromosomal recombination via distal end looping
Haemophilia A: Famous Pedigree

The British Haemophilia Line

Queen Victoria XX  Albert of Saxe-Coburg-Gotha XY

Victoria XX  King Edward VII XY  Alice Xx

Victoria XX  Elisabeth Xx  Irene Xx  Henry of Prussia XY

Grand Duke Louis IV of Hesse XY  Alfred XY  Helena Xx? Louise Xx? Arthur XY

Frederick XxY  Olga Xx? Tatiana Xx? Marie Xx? Anastasia Xx?

Emperor Nicholas II of Russia Xx  Alexei XxY

Helene of Waldeck Xx  Beatrice Xx

Henry of Battenberg XY

Waldemar xY  Sigismund XY  Henry xY

Alexander Cambridge, 1st Earl of Athone XY

May XX  Rupert XxY  Maurice xY

May XX

Alexandar Mountbatten, 1st Marquess of Carrickfergus XY

Victoria Eugenie Xx

King Alfonso XIII of Spain XY

Alfonso xY  Jaime XY  Beatriz Xx  Cristina Xx  Gonzalo xY

Kev
X: Unaffected X-chromosome
Y: Y-chromosome
k: Affected X-chromosome
1. Intravenous supplementation of recombinant or plasma derived factor VIII. Repeated infusion of Factor VIII from plasma is necessary as it has a half-life of 8 hours.

2. Desmopressin promotes the release of Factor VIII for mild cases.

3. Future: Gene therapy for Haemophilia A.

Gene therapy shows promise for haemophilia

Scott Gottlieb, New York

A new type of gene therapy boosted levels of factor VIII clotting factor in a small number of people with haemophilia, allowing two severely ill patients to go for 10 months without spontaneous bleeding, a new study says.

These results are far from the proof needed to bring the treatment to market. In particular it is not clear if the effect lasts long enough to make the procedure practical, but the finding revives hopes that gene therapy, written off by many scientists as a failure, may yet work.

Researchers used a factor VIII gene transfer method that avoided the traditional viral vectors (New England Journal of Medicine 2001;344:1735-42). Instead, Dr David Roth from Beth Israel Deaconess Medical Center in Boston, Massachusetts, and colleagues used a non-viral somatic cell, gene therapy system, which they call transkaryotic implantation, in six patients with severe haemophilia. The procedure involved isolating dermal fibroblasts from a full thickness skin biopsy.

These were then transfected by electroporation with a plasmid containing the gene for factor VIII; the cells that expressed factor VIII were cloned, propagated, and laparoscopically implanted into the omentum of the patients.

According to the report, there were no significant adverse events related to the procedure in any patient, and none of the patients developed antibodies against factor VIII or a cellular immune response to the implanted transfected fibroblasts.

Concern over the safety of gene therapy has lingered since the death in 1999 of an 18 year old patient at the University of Pennsylvania. Since then, however, preliminary successes have been found in treating children with a rare immune system disorder and in some forms of cancer.
Single-gene disorders with nonclassic inheritance

- **Diseases caused by triplet-repeat mutations** (Fragile X chromosome syndrome): The mutation which is characterized by a long repeating sequence of three nucleotides CGG. It is the second most common genetic cause of mental retardation after Down’s. The affected males are mentally retarded (IQ 20-60) with a long face and large mandibule, large everted ears, and large testicles (macro-orchidism). 50% of affected females have mental retardation.

- **Diseases caused by mutations in mitochondrial genes** (leber hereditary optic neuropathy)

- **Diseases associated with genomic imprinting** (Prader-Willi syndrome)

- **Diseases associated with gonadal mosaicism** (germ line mosaicism, gonadal mosaicism)
Prader-Willi & Angelman Syndromes

- Both of these genetic disorders are caused by deletion of a region of chromosome 15q11 (2 genes closely located)
- This region is differently imprinted in maternal and paternal chromosomes, and both imprintings are needed for normal development.
- In a normal individual, the one allele is methylated, while the other allele is unmethylated.
- If an individual fails to inherit a properly imprinted 15q11 from one parent, as a result either of deletion of the 15q11 region from that parent's chromosome 15 or, less frequently, of uniparental disomy.

- If neither copy of 15q11 has paternal imprinting:
  **Prader-Willi Syndrome (PWS)**
  - obesity, mental retardation, short stature,
  - hypotonia, hypogonadism
- If neither copy of 15q11 has maternal imprinting
  **Angelman Syndrome (AS)**
  - uncontrollable laughter, jerky movements,
  - and other motor and mental symptoms.
- Syndrome that develops depends upon the parent that provided the mutant chromosome
Prader-Willi Syndrome

- Maternal gene is normally inactivated – imprinted
- Both maternal and paternal *SNRPN* genes are inactivated in PWS patients
Illustration of post-zygotic event by which mosaicism arises

Key:
- ▨ = cell with 2 normal alleles
- ▨ = cell with 1 mutated allele

Fertilized egg (zygote)

Post-zygotic event* (mutation in one allele of a pair of genes in one cell)

Proliferation of cell line containing mutation

Proliferation of normal cell line

*Note: A spontaneous mutational event in a single cell that proliferates to form a population of cells with that abnormality can occur at any point in an individual's lifetime. The sooner the mutation occurs after fertilization, the more cells will be affected.
Mosaicism

Key

- Cells without the mutation
- Cells with the mutation

Mutation in:

1) Single germline cell
2) Somatic cells only
3) Some germline and some somatic cells
4) All cells

Spontaneous new mutation in a single sperm; may be transmitted to offspring
Mutations confined to a tumor
Mosaicism for mutation affecting multiple somatic cells including all or some of germline
Mutation inherited at conception contained in virtually every cell of the body

Mutations in germline cells, whether present or not in somatic cells, can be passed to offspring.
Phenotypic female with a chromosomal genotype of 46,XY
Affordable ‘Exomes’ Fill Gaps in a Catalog of Rare Diseases

Mystery solved. Exome sequencing found the mutation that led to blindness in three children in the Lidsky family of Miami. The approach is uncovering the cause of other single-gene disorders.

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<th>MENDELIAN DISORDERS</th>
<th>Number</th>
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<tr>
<td>Gene unknown</td>
<td>1771</td>
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<td>Suspected disorders</td>
<td>1977</td>
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<td>Total</td>
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</table>
Exome sequencing identifies *MLL2* mutations as a cause of Kabuki syndrome

Sarah B Ng1,7, Abigail W Bigham2,7, Kati J Buckingham3, Mark C Hannibal2,7, Margaret J McMillin5, Heidi I Gildersleeve3, Anita E Beck2,7, Holly K Tabor2,7, Gregory M Cooper1, Heather C Mefford2, Choli Lee1, Emily H Turner1, Joshua D Smith1, Mark J Rieder1, Koh-ichiro Yoshiura6, Naomichi Matsumoto6, Tohru Ohta6, Norio Niikawa6, Deborah A Nickerson1, Michael J Bamshad1,7 & Jay Shendure1

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**LETTERS**

WDR62 is associated with the spindle pole and is mutated in human microcephaly

Adeline K Nicholas1,2, Maryam Kharshidi1,2, Julie Desta1,2, Odilia F Carvalho3, Janet J Cox3, Gemma Thornton1, Rassveta Katsar4, Muhammad Ansar5, Wastim Ahmad3, Alain Verlouw6, Sandrine Fuzeretides6, Jean-Paul Mosset6, Susan Lindsay7, Pavel Zegzhevsky8, William B Dobyns6, Emma Roberts9, Marc Abramowicz6 & C Geoffrey Woods1

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Whole-exome sequencing identifies recessive WDR62 mutations in severe brain malformations

Kaya Bilgürar1,2,3, Ali Kemal Öztürk1,2,4, Angeliki Louvi1,2,3, Kenneth Y. Kwan2,3, Murim Choi4, Burak Tath5, Dilek Yalınçoğlu6, Beyhan Tüysüz7, Ahmet Okay Çağlayan8, Sarenur Gölben8, Hande Kaymakçalan9, Tanyeri Barak1,2, Mehmet Bakiroğlu1,2,3, Katsuhiro Yasuno1,2,3, Winson Ho1,2,3, Stephen Sanders1,2,3, Ying Zhu1,2,3, Sanem Yilmaz2, Alp Dincer1, Michele H. Johnson1,2,3, Richard A. Bronen1,2,3, Richard A. Bronen1,2,3, Naci Koçer1, Hüseyin Per1, Shrikant Mane3,4, Mehmet Necmettin Pamir3, Cengiz Yalçınkaya3, Sefer Kumandag1, Meral Topçu5, Meral Özmen6, Nenad Šestan7,8, Richard P. Lifton9,2,1, Matthew W. State3,5,1,2,3 & Murat Günel1,2,3
Pedigree analysis: Case 1

- Two children, one of each sex, show the trait but trait was not shown in the parents
- Conclusions:
  - must be **autosomal recessive** trait (example: PKU)
  - parents must be **heterozygous** (Pp)
Pedigrees: Case 2

I

1
A/a

2
a/a

II

1
A/a

2
a/a

3
a/a

4
a/a

5
A/a

6
a/a

7
a/a

8
A/a

III

1
A/a

2
a/a

3
a/a

4
a/a

5
a/a

6
A/a

7
a/a

8
A/a

9
a/a
Learning Outcomes

1. What is a genetic disease?
2. What are the types of genetic diseases?
3. What is a monogenic disease?
4. How are these diseases transmitted?
5. And the example of the diseases associated with the type of transmission?
6. The molecular/genetic basis behind each of the disease?

Things to ponder
1. Why do we have these diseases?
2. Advantage during human evolution? Natural selection?
3. Why are fatal genetic diseases rare?
"... AND YOU CANNOT CHANGE A THING, AS YOU ARE COMPLETELY CONTROLLED BY YOUR GENES."