Single-Gene Disorders

Single-gene Traits

- To date, more than 10,000 single-gene traits and disorders have been identified.
- Individually are rare, affect between 1% and 2% of the general population.

Huntington Disease (HD)

- Derives its name from Dr George Huntington, who described it in 1872.
- Progressive neurological disability one of the worst hereditary disorders in man, no effective treatment or cure.
- The prevalence is approximately 1:10,000.
- The onset is mostly between 30 and 50 years, but it can start at virtually any age.
Clinical Features of HD

- Slowly progressive movement disorder and insidious impairment of intellectual function with psychiatric disturbance.
- The mean start age is about 40, duration is approximately 15 to 20 years.
  - Chorea is the most common.
  - The gait becomes unsteady and speech unclear.
  - In the early stages, memory impairment and poor concentration span.
  - Anxiety and panic attacks, mood changes and depression.
  - Aggressive behavior, paranoia, irrationality.
- Gradual deterioration in intellectual function, leading eventually to total incapacitation and dementia.

Genetics of HD

- Autosomal dominant, variable age of onset, close to complete penetrance.
- Often shows anticipation, particularly when transmitted by a male.
- Codes for a protein known as huntingtin, 4q16.3, contain CAG repeats at 5' end.
### CAG Repeats and HD

- **Normal Alleles**: 26 or fewer CAG
- **Mutable Alleles**: 27 to 35 CAG
- **Reduced Penetrance Alleles**: 36 to 39 CAG
- **Disease Alleles**: 40 or more CAG

A Predictive genetic test is available but…

### Myotonic Dystrophy (MD)

- The most common form of muscular dystrophy seen in adults
- Overall incidence of approximately 1: 8000
- Autosomal dominant inheritance, can be congenital
- Anticipation with mother transmission

### Clinical Features of MD

- Usually present in adult life with slowly progressive weakness and myotonia
- Other clinical features include:
  - Cataracts
  - Cardiac conduction defects
  - Disturbed gastrointestinal peristalsis (dysphagia, constipation, diarrhea)
  - Increased risk of diabetes mellitus and gallstones
  - Somnolence, frontal balding
- As the age of onset becomes earlier, so the clinical symptoms increase in severity and more body systems are involved
**Genetics of MD**

- Instability in a CTG repeat, present in the 3' UTR of dystrophia myotonica protein kinase gene (DMPK), 19q13.3
- Normally the CTG consists of up to 37 repeats, affected individuals have an expansion of at least 50 copies
- Correlation between disease severity and the size of the expansion, which can exceed 2000 repeats
- Pre-symptomatic genetic testing and prenatal diagnosis are available.....

**Marfan Syndrome (MFS)**

- MFS is a disorder of fibrous connective tissue, specifically a defect in type I fibrillin, encoded by the FBN1 gene
- In the classic presentation affected individuals are:
  - Taller compared with unaffected family members
  - Joint laxity
  - Reduced upper to lower segment body ratio
  - Pectus deformity, and scoliosis
  - Connective tissue defect gives rise to ectopia lentis
  - Dilatation of the ascending aorta (some families)
**Genetics of MFS**

- **Autosomal dominant** and the majority of cases are linked to the large *FEN1* gene on 15q21.
- Most mutations are missense and have a **dominant-negative effect**.

**Cystic Fibrosis**

- One of the most common autosomal recessive disorders.
- Individuals of western European origin, incidence varies from 1 in 2000 to 1 in 3000.

**Clinical Features**

- The organs most commonly affected in CF are the **lungs** and the **pancreas**.
- Chronic lung disease caused by recurrent infection eventually leads to fibrotic changes in the lungs with secondary cardiac failure.
- In 85% of people with CF, pancreatic function is impaired.
- Cirrhosis, and diabetes mellitus are common.
- Almost all **males** with CF are **sterile** because of congenital bilateral absence of the vas deferens (CBAVD).
**Duchenne Muscular Dystrophy (DMD)**

- The most common and most severe form of muscular dystrophy.

- A similar but milder condition, Becker muscular dystrophy (BMD), is caused by mutations in the same gene.

- The incidences of DMD is approximately 1:3500 and BMD 1:20,000 males.

**Clinical Features**

- Usually present between the ages of 3 and 5 years with slowly progressive muscle weakness resulting in:
  - An awkward gait, inability to run quickly
  - Difficulty in rising from the floor
  - Most affected boys have to use a wheelchair by the age of 11 years

- Subsequent deterioration leads to lumbar lordosis, joint contractures, and cardiorespiratory failure, resulting in death at a mean age of 18 years

- One-third of boys with DMD show mild-moderate intellectual impairment
Both DMD and BMD show X-linked recessive inheritance. The *dystrophin* gene is huge in molecular terms, consisting of 79 exons and 2.3 Mb of genomic DNA.

There are two forms of hemophilia: A and B. Hemophilia A is the most common severe inherited coagulation disorder, with an incidence of 1:5000 males. Deficiency of *factor VIII*, which, plays a critical role in the pathway activation of prothrombin to thrombin. Hemophilia B affects approximately 1: 40,000 males and is caused by deficiency of *factor IX*, also known as Christmas disease.
Clinical Features

- Vary from mild bleeding following major trauma or surgery to spontaneous hemorrhage into muscles and joints.
- The degree of severity shows a close correlation with the reduction in factor VIII or IX activity.
- Levels below 1% are usually associated with a severe hemorrhagic tendency from birth.
- Hemorrhage into joints causes severe pain and swelling.

The effect of recurrent hemorrhage into the knees

Hemophilia A

- X-linked recessive inheritance, Xq28.
- Factor VIII levels are about half normal in carrier females and many are predisposed to a bleeding tendency.
Treatment

Protein Substitution
- Using plasma-derived factor VIII or factor IX
- Factor VIII has a half-life of 8 h
- Transmission of viral infection such as hepatitis B and HIV
- 10% of patients develop inhibitory antibodies

Gene Therapy
- Excellent candidates for gene therapy as only a slight increase in the plasma level of the relevant factor is of major clinical benefit.