Neuromuscular disorders

- Muscular Dystrophies
- Charcot-Marie-Tooth disease
- The Myotonic dystrophies
- Spinal muscular atrophy
- Periodic Paralyses

Floppy infant

- Prader Willi syndrome
- SMA
- Congenital myotonic dystrophy
- Congenital myopathy
- Congenital muscular dystrophy

Spinal muscular atrophy (SMA)

- SMA 1- the patients die by two years of age
- SMA 2-the patients achieve the ability to sit
- SMA 3- slowly progressive form of the disease
- All patients with SMA share clinical features: symmetrical muscle weakness and muscle atrophy as well as decreased or absent deep tendon reflexes

Molecular genetics of SMA

- SMA types I, II and III were all mapped to chromosome 5q11.2-13.3
- Approximately 95% of individuals with SMA lack both copies of SMN1 exon 7.
- In the remaining 5% of SMA patients missense, nonsense or splice site mutations in the SMN1 gene are present.

Prenatal diagnostics in SMA

- Possible by chorionic villus sampling (CVS) at 11 weeks gestation
- Carrier testing

Duchenne muscular dystrophy

DMD/BMD

- DMD is a severe X-linked disease occurring in 1 out of 3500 live male births.
- Disease occurs in early childhood, causing bilateral weakness in the proximal muscles of the hip girdle and legs.
- Loss of ambulation in the patients with DMD at age 11.

DMD/BMD

- DMD is caused by mutations in the dystrophin gene that change the reading frame of the transcript (60% of these mutations are large deletions, 35% of mutations are point mutations or small insertions, 5% of mutations are dupliactions)
- BMD results from mutations maintaining the reading frame of the transcript.

Molecular diagnostics in Duchenne dystrophy

- Major deletion testing by multiplex PCR
- DHPLC, DGGE or SSCP to screen for mutations
- Direct sequencing
- Duplication testing

The myotonic dystrophies

- Progressive muscle wasting and weakness
- Myotonia
- Cardiac effects
- The cataract

Genetics of myotonic dystrophies

- The genetic cause of DM1 is mutation (CTG)n repeat in the 3’-untranslated region of the protein kinase gene DMPK

CTG number in healthy individuals ranges from 5 to 37

Premutation-the number of CTG ranges from 38 to 49

Protomutation CTG ranges from 50 to 80

Mutation- more than 200 CTG

Charcot-Marie-Tooth disease

- Autosomal dominant Charcot-Marie-Tooth disease (CMT1A, CMT1B, CMT1C, CMT2A)
- CMTX disease
- Autosomal recessive CMT

Fabry's disease

- Males present in late childhood with burning pain in the palms and soles, precipitated by stress, alcohol, exercise or heat.
- A neuropathy affecting small fibers develops
- Is caused by mutations in the alpha-galactosidase A gene on chromosome Xq22

Ornithine transcarbamylase deficiency (OTC)

- Occurs both in males and females
- Is characterized by the onset in neonatal period usually with coma and convulsions
- Is inherited in X- dominant trait
- Is characterized by elevated plasma ammonia
- Phenotype of OTC depends on degree of X chromosome inactivation

Warburg micro syndrome

- Is inherited in autosomal recessive trait
- Is caused by mutations in RAB3GAP1 gene
- Is characterized by coexistence of microcephaly, microcornea and mental retardation
- Often occurs in the families with consanguinity