Complex Multigene Disorders

Human Genetic Architecture

- Every individual is a carrier of ~5-8 deleterious genes; most are recessive without serious phenotypic effects.

Result of single gene mutations with large effects

Marfan Syndrome

Pleiotropism

Pathology 5: Genetic Disorders

- Manifested in heterozygous state - > 1 + one parent is affected

Disorder of connective tissue manifested by changes in skeleton, eyes, and cardiovascular system

Osteogenesis imperfecta - > defective collagen proteins

Consequences:

Characteristics:

- All sex-linked disorders are X-linked and almost all are recessive

Morphology:

- Three major subgroups

Niemann-Pick Disease (Type C) (NPC)

May also result from lack of protein necessary for lysosome function:

- Enzymes synthesized in endoplasmic reticulum - > Golgi apparatus for post-

Class A: 30-50% have mutations in COL5A1/COL5A2 genes - > defect in type V collagen; no other collagen gene abnormalities found to account for remainder of heterozygotes manifest disease despite only 50% defective strands

Arthrogryposis: mutation in COL1A1/COL1A2 - > defect in conversion of type I procollagen to collagen; no other collagen gene abnormalities

Mixed types:

- Excessive cholesterol synthesis

Characteristics:

- Cherry-red spot in macula is present in 1/3 - 1/2 of individuals

In brain, gyri are shrunk and suli widened - > leads to cell death and loss of brain substance

In 1 - 2 years, complete vegetative state is reached;

Molecular chaperone therapy provides template for

- Lack of a transport protein for egress of digested material from lysosomes

Clas s V: receptors function fully, but pH-dependent dissociation of LDL from receptor

Class II: fairly common, receptor proteins accumulate in endoplasmic

Class I: very common, receptor proteins accumulate in endoplasmic

Molecular mechanisms are different for all 3 types)

- Activity; hepatosplenomegaly present; progressive CNS involvement leads to early death

Clinical features depend on variation in penetration and

Expression of defect more uniform than autosomal dominant

MPS I:globosérine deficiency

MPS II: Hunter syndrome (MPS II): X-linked

- Histology shows distended cells with "balloon" cells; clear cytoplasm resolves into minute vacuoles

T x: replacement therapy with recombinant enzymes (very expensive); bone marrow transplant

Types II/III: CNS dysfunction, convulsions, progressive mental deterioration; liver, spleen, lymph

Increased urinary excretion of accumulated mucopolysaccharides (glycosaminoglycans; dermatan sulfate, heparan sulfate, keratan sulfate, chondroitin sulfate)

Lack of a transport protein for egress of digested material from lysosomes

Clas s III: receptor proteins reach cell surface, but fail to bind LDL well

Class I: very common, receptor proteins accumulate in endoplasmic

Molecular mechanisms are different for all 3 types)