Dominant Mutations

Types of Recessive Mutations

Loss of Function

- amorphic — haplosufficient: less than 100% activity is sufficient to produce a wild-type phenotype
- hypomorphic

Types of Dominant Mutations

Loss of Function

- amorphic — haploinsufficient: less than 100% activity is not sufficient to produce a wild-type phenotype
- hypomorphic

Gain of Function

- hypermorphic — by increasing the normal activity of the wild-type allele
- antimorphic — by interfering with the activity of the wild-type allele (= dominant negative mutation)
- neomorphic — by conferring a new activity on the protein

Amorphic Mutation (haploinsufficiency)

Supravalvular Aortic Stenosis **7q11.2 MIM 185500**

Affected Gene: ELN = elastin

Incidence:

Symptoms: narrowing of aorta just above heart

Normal Function: elastic tissue (skin, lung, blood vessels)

Mode Of Action: heterozygous → for most part elastic tissues work normally
but: aorta is highly elastic tissue – shows some narrowing above the heart → may require surgery

Hypermorphic Mutation

***Achondroplasia*:** **4p16.3 MIM 100800**

Affected Gene: FGFR3 = fibroblast growth factor receptor 3

Incidence: 1/15,000 to 1/40,000

Symptoms:

short limb bones	prominent forehead
normal torso	short hands
large head	fingers in trident or vVulcan position

Normal Function: transmembrane protein → growth factors bind to receptor & transmit signals into cell
FGFR3 involved in development & maintaince of bone & brain tissue
regulates bone growth → inhibits proliferation of chondrocytes → limits formation of bone fromcartilage (ossification) esp in long bones

Nature of Mutation: one of two mutations: both cause same change → G380R = gly380arg

inherited as autosomal dominant, but 80-90% of cases = new mutations, particularly during spermatogenesis of ♂ over 35 yrs old

bones of achondroplastic children have growth plates only fraction of normal size → have far fewer dividing chondrocytes than normal

Mode Of Action: increases rate of ossification, leads to reduction in long bone growth → growth plate cartilage converted to bone too early in development

Antimorphic Mutations (= dominant negative mutations)

Huntington Disease (HD) **4P16.3 MIM 14310**

Affected Gene: HD = huntingtin protein
Incidence: 1/24,000; most common in N European descent
rare in Asians and African ancestry

Symptoms:
- progressive dementia
- personality change
- spasmodic involuntary control of limb movement
- limb rigidity
- impaired cognition
- extreme psychiatric destabilization

Normal Function: huntingtin → binds/associated with
- huntingtin – associated protein 1 (HAP-1): assoc with cytoskeleton proteins
- huntingtin-interactive protein 1 (Hip-1) " " " "
- cystathionine b-synthetase

Nature of Mutation: Trinucleotide Expansion Disease (within coding sequence)
trinucleotide repeat CAG = glutamine
normal = 9 - 35 repeats affected = 40 - 121 repeats

Mode Of Action: polyGln – may bind more HIP1 & HAP1
remove from site of action
therefore disrupt function (loss of function)

also abnormal binding of polygln of important cell proteins:
calmodulin
glyceraldehyde-3-phosphate dehydrogenase → lower neuronal energy production

Alternate Mode Of Action: poly gln could tie up pools of cellular gln

glutamine →→→→→→→ to glutamate
glutaminase A

therefore drop in glutamate = loss of neurons with glutamate receptors
35% of all CNS neurons use glutamate as neurotransmitter

Myotonic Dystrophy (MD) **19q132.2-13.3 MIM 160800**

Affected Gene: DMPK = dystrophia myotonia protein kinase

Incidence: 1/8000 age of onset under 10 to age 50; average 20 yrs

Symptoms:
- muscle rigidity
- muscle loss
- heart irregular
- reduced gonads
- frontal baldness

Normal Function: phosphorylates proteins – precise function unknown
affects motor & sensory nerves, cerebral corex

Nature of Mutation: Trinucleotide Expansion Disease (outside coding region)
trinucleotide expansion = CTG in 3' untranslated region
expanded CTG = CUG in mRNA
normal = 5-37 repeats affected = >2000 repeats

Mode Of Action: may lead to inappropriate binding of CUG binding protein to CUG track
CUG binding protein involved in mRNA processing: interferes with translation
no production of DMPK; dominant negative mutation

Osteogenesis imperficta* (*Brittle Bone Disease) types I – IV **17q22 (COL1A1) or 7q22.1 MIM16220, 166210, etc**

Affected Gene: COL1A1 = α1 or
COL1A2 = α2

Incidence: type I 1 in 15,000- 20,000
type II 1 in 20,000 – 60,000

Symptoms: fragile bones, easily broken
8 types of OI → 4 involve COL1A1 and/or COL1A2
different types range from mild to moderate to severe

Normal Function: fibrillar collagens = major structural proteins of connective tissue
built of triple helices of plypeptide chains (some = homotrimers, others = heterotrimers)
assemble into close-packed crosslinked arrays to form rigid fibrils

type I collagen fiber = trimer of 2 α1 chains + 1 α2 chain

Nature of Mutation: missense mutation in COL1A1 leads to amino acid substitution that interferes with assembly

null mutation in COL1A1 leads to fewer fibrils, but all are normal

Mode Of Action: incorporation of mutant chain into trimer leads to defective fibril
substitutions close to NH3 terminus are mild (minor disturbance of packing)
substitutions close to COOH terminus are severe (major disturbance of packing)

Hypokalemic Periodic Paralysis (hypoKPP) **1q31-32 MIM 114208**

Affected Gene: CACNA1S = α1 subunit of L-type voltage-dependent calcium channel

Incidence:

Symptoms:
episodic weakness → proximal more than distal limb muscles
respiratory muscle weakness → may prove fatal
onset at adolescence
as weakness develops during attacks, reflexes become hypoactive
low serum potassium levels provoke paralytic attack

attacks triggered by
- strenuous exercise followed by rest
- high carbohydrate meals
- meals w/ high sodium conent
- sudden changes in temp
- excitement → noise, flashing lights

weakness may be limited to certain muscle groups or severe full body paralysis
attacks may last few hours to several days
recovery is usually sudden when it occurs

Normal Function: forms channel in sarcolemma and regulates uptake of calcium into muscle cells

Nature of Mutation: missense mutation in α1 subunit

Mode Of Action: increases intracellular level of calcium in muscle cells, preventing muscle relaxationand leading to paralysis

Neomorphic Mutation

***Hawkinsinuria*: 12q24 – qter MIM 140350**

Affected Gene: HPD = 4 hydroxyphenylpyruvic acid dehydrogenase

Incidence:

Symptoms: appearance of a hawkinsin, a novel sulfur containing amino acid in the urine
"swimming pool" odor to urine
failure to thrive

Normal Function: converts 4-hydroxyphenylpyruvic acid to homogenistic acid

Nature of Mutation: missense mutation

Mode Of Action: novel enzyme activity attaches 4-hydroxyphenlpyruivic acid to a sulfur-containing cysteine resulting amino acid = hawkinsin