## Dominant Mutations

<table>
<thead>
<tr>
<th>Types of Recessive Mutations</th>
<th>Types of Dominant Mutations</th>
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<tbody>
<tr>
<td><strong>Loss of Function</strong></td>
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<tr>
<td>• amorphic</td>
<td>• amorphic</td>
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<tr>
<td>• hypomorphic</td>
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<tr>
<td>haplosufficient: less than 100% activity is sufficient to produce a wild-type phenotype</td>
<td>haploinsufficient: less than 100% activity is not sufficient to produce a wild-type phenotype</td>
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<tr>
<td><strong>Gain of Function</strong></td>
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<tr>
<td>• hypermorphic</td>
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<td>• antimorphic</td>
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<tr>
<td>• neomorphic</td>
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<tr>
<td>by increasing the normal activity of the wild-type allele</td>
<td>by interfering with the activity of the wild-type allele (= dominant negative mutation)</td>
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<tr>
<td>by conferring a new activity on the protein</td>
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### 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 normal torso 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
- limb rigidity
- personality change
- impaired cognition
- spasmodic involuntary control of limb movement
- 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 β-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
- therefore lower neuronal energy production

**Alternate Mode Of Action:**
- poly gln could tie up pools of cellular gln
  - glutamine → 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) 19q13.2-13.3  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
- reduced gonads
- heart irregular
- 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 Imperfecta (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 are major structural proteins of connective tissue
- built of triple helices of polypeptide 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

**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 relaxation and 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-hydroxyphenylpyruvic acid to a sulfur-containing cysteine resulting amino acid = hawkinsin