

MHE Meeting: Overview

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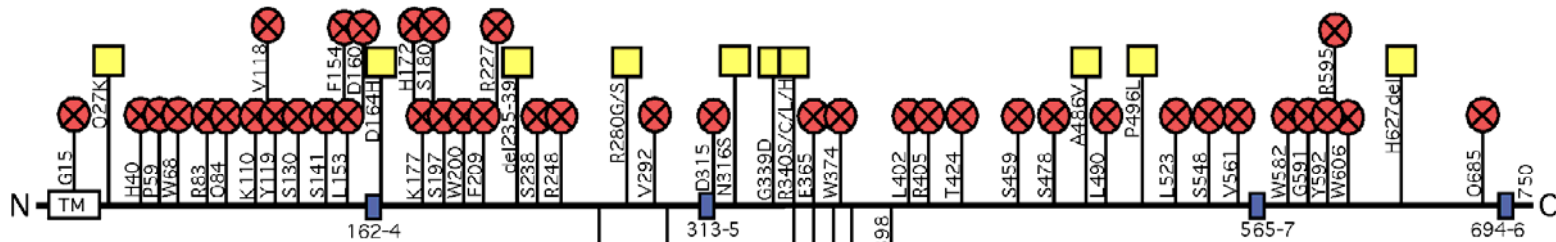
University of Minnesota, Minneapolis

MHE

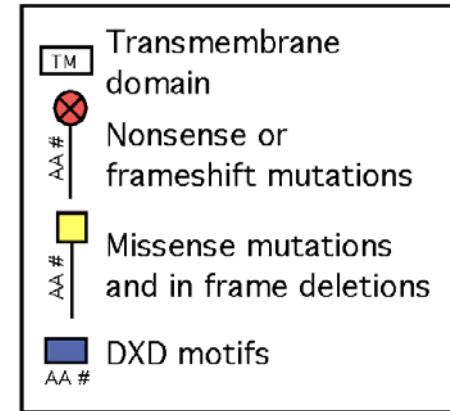
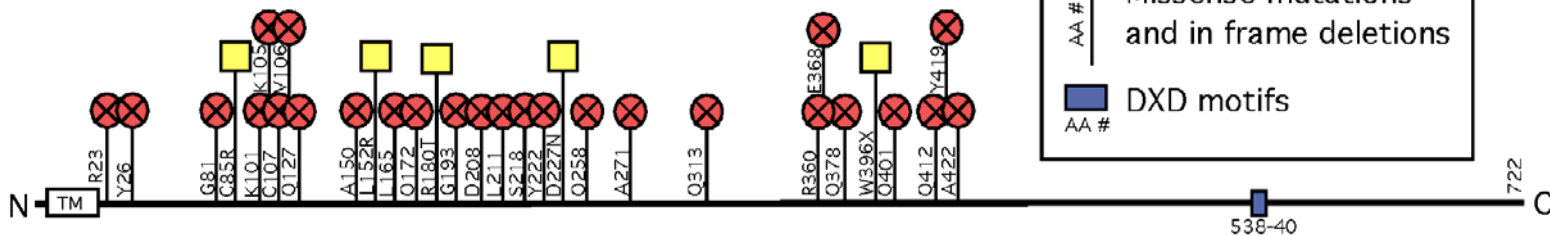
- **Multiple Hereditary Exostosis (MHE) is a heritable disorder, but exostoses can occur spontaneously**
- **Genetic mutation that affects the formation of a polysaccharide called heparan sulfate**
- **Heparan sulfate is found everywhere, but the disease seems to preferentially affect bones**
- **Dominant - Only one copy of the gene is mutated**
- **Enormous variation in severity of disease. Why?**
- **No pharmacological treatment is available**
- **Need more information about how the mutation affects bone development**
- **Information comes from many sources, sometimes from simple organisms like worms, flies, birds and fish**

I. Orthopedics and Clinical Genetics

EXT1



EXT2



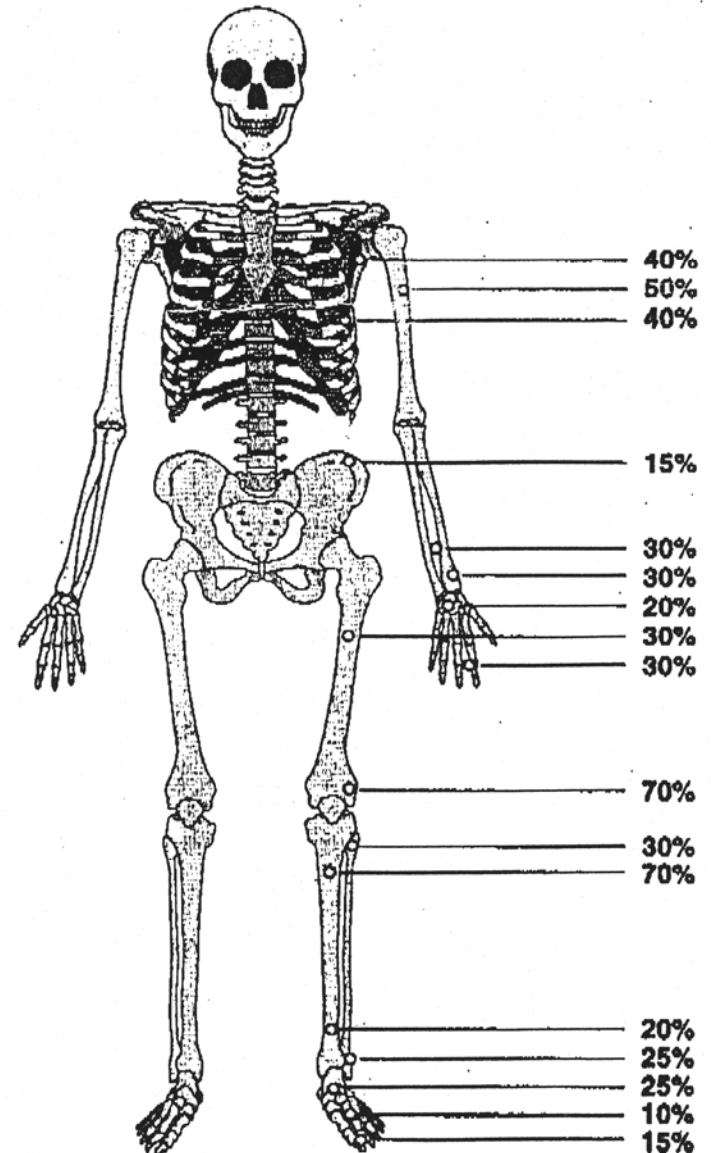
Very large number of mutations are known

Orthopedics and Clinical Genetics

Investigators are working on rapid methods to determine the types of mutations that occur

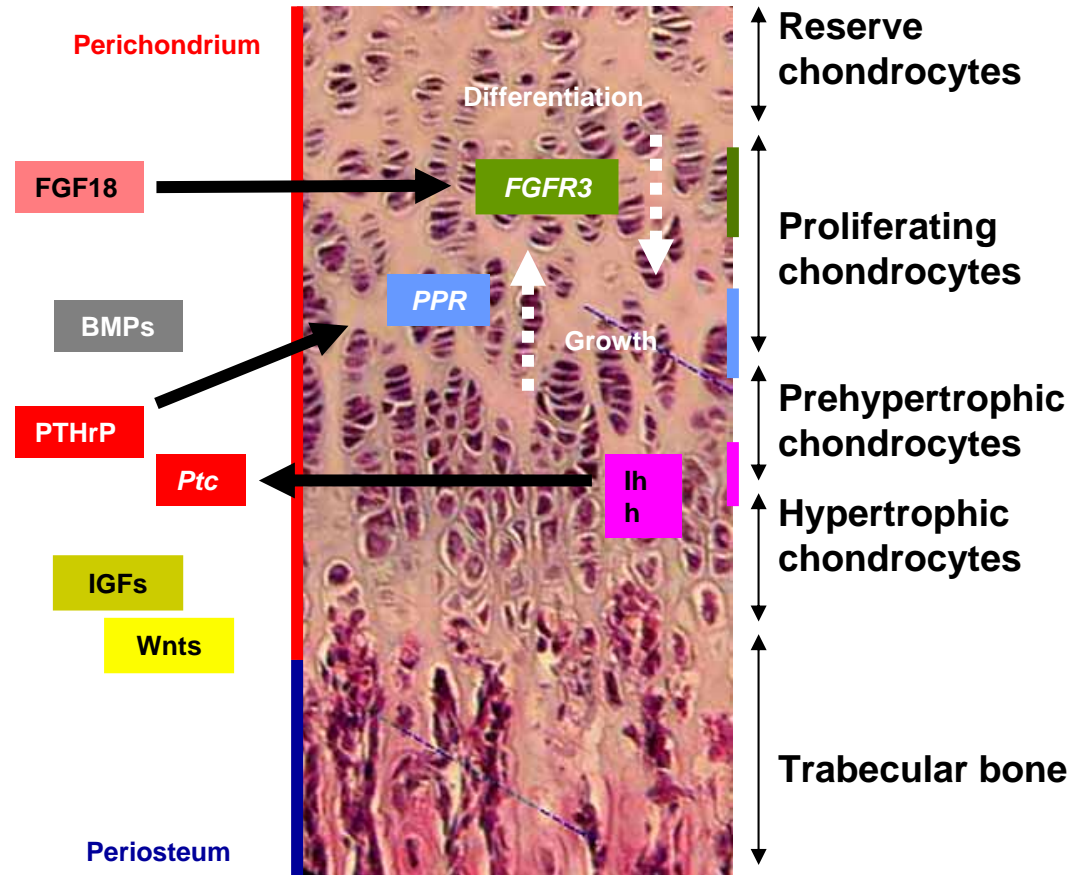
Exostoses appear on numerous bones, including spine and pelvis

Does a correlation exist between genotype (the type of mutation) and the location and severity of disease?



II. Bone Development

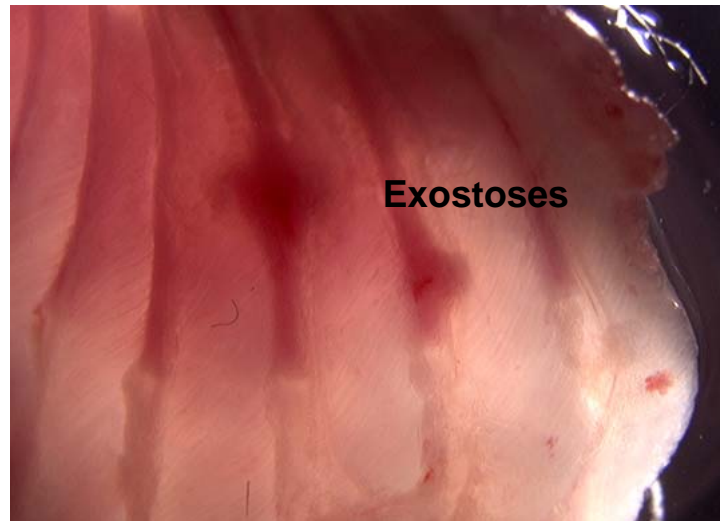
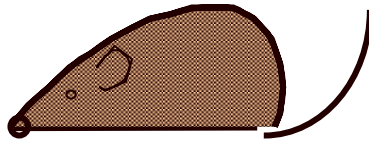
- Many growth factors are involved in cartilage and bone formation.
- Many of these factors depend on heparan sulfate
- Investigators are still working out how the system works
- This kind of work requires a combination of genetics and biochemistry



III. Exostoses/Development

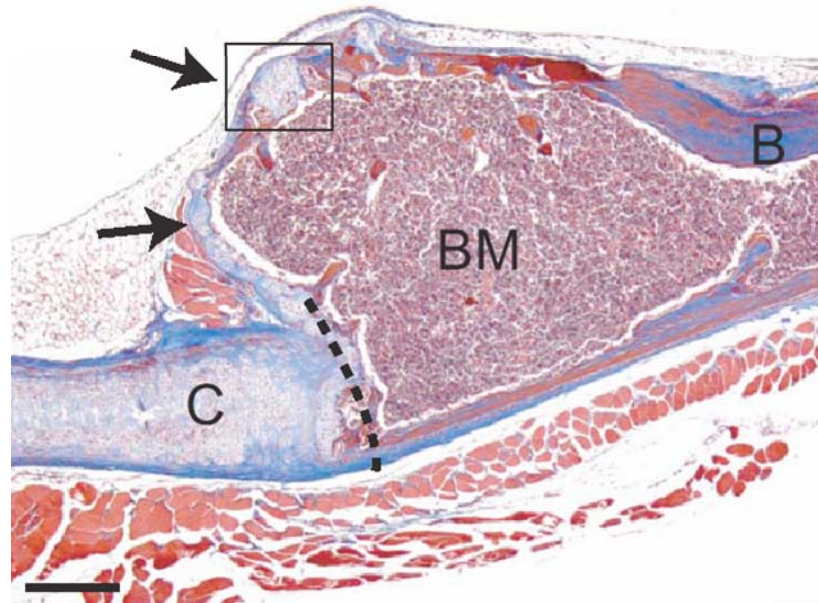
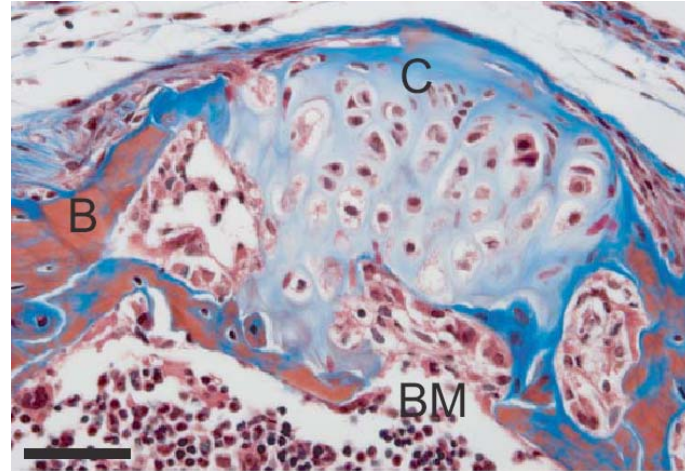
- **Mice have been created with mutations in EXT1 and EXT2**
- **Extostoses arise in EXT deficient mice that resemble exostoses in humans**
- **But in mice the exostoses only occur on the ribs**

Back-lighting rib mice cage shows irregular contours of exostoses

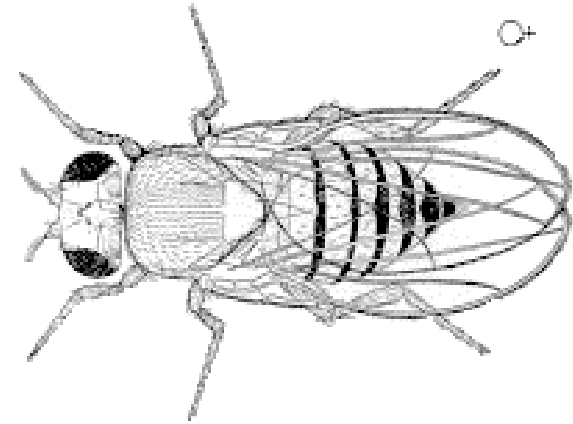
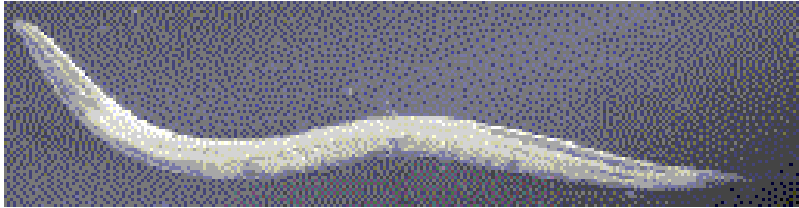


III. Exostosis/Development

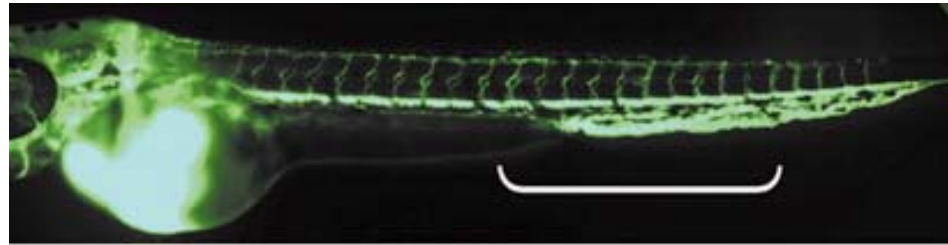
- **Clusters of special types of chondrocytes arise in the tissue surrounding the bone, which may be the source of exostoses**
- **Mutations in other genes can increase the frequency and severity of exostoses**



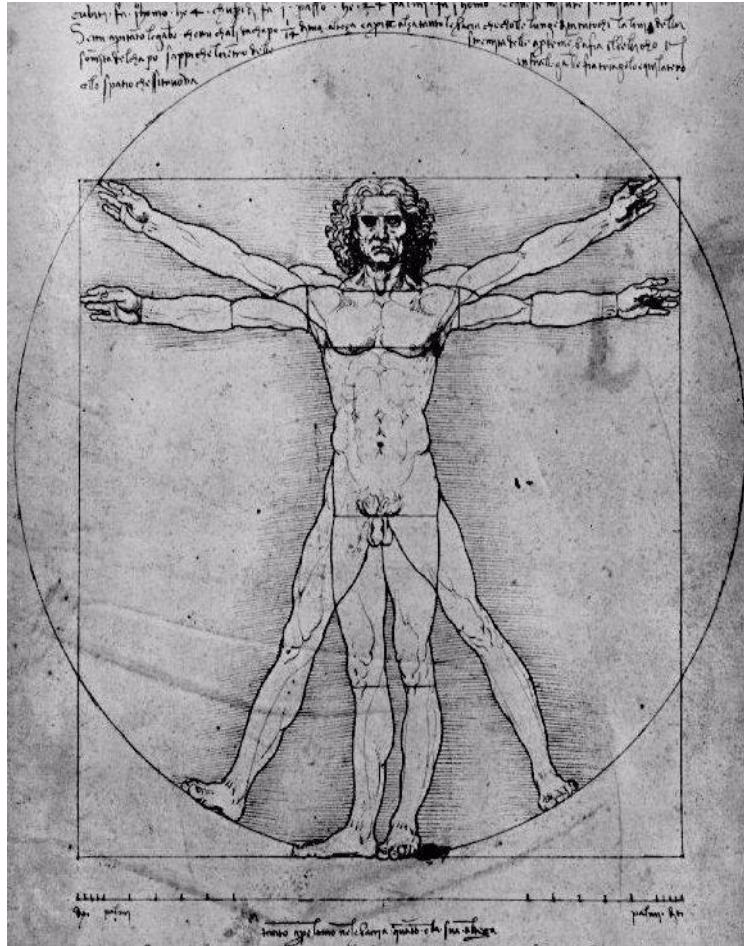
IV. EXT Function and Non-mammalian models



EXTs are being studied in model organisms, including the worm, fruitfly and zebrafish



V. Non-bone Phenotypes



- **Other tissues may be affected by EXT mutations**
- **The effect of altered heparan sulfate in other tissues such as the brain is under study using mouse models**
- **Scarring**
- **Insights into the formation of exostoses could come from studies of other cartilage and bone diseases.**