Multiple Hereditary Exostoses: Genetic Overview

About 90% of cases of MHE/HME/MO are caused by mutations in one of two genes:

- ***EXT1*** (chromosome 8q24.11) resulting in MHE type 1 (OMIM: 133700)
- ***EXT2*** (chromosome 11p11.2) resulting in MHE type 2 (OMIM: 133701)

These genes produce enzymes that help make heparan sulfate (HS), a molecule that regulates bone growth and cartilage development. Mutations disrupt HS production, leading to abnormal cartilage growth.

Genotype–Phenotype Patterns

General trends observed in research include:

- ***EXT1***: Tends to be more severe, with more growths, higher deformity scores, more severe forearm drift, higher lifetime surgeries, and higher risk of malignant transformation.
- ***EXT2***: Usually milder on average, though variability is high.

These trends have been documented in literature, with Kim et al. (2022) finding that **people with *EXT1* mutations have more growths overall**, particularly in the forearm and lower limbs, and more angular deformities compared to *EXT2*. Matsumoto et al. (2020) linked *EXT1* mutations to more severe forearm deformity, ulnar shortening, and radial head dislocation. Even within one family, severity of how MHE presents can range from mild to severe.

Research and Future Treatments

Right now, there is no cure that can stop osteochondromas from forming, so **treatment is focused on surgery and symptom relief.** A pediatric trial of palovarotene (RARγ agonist, NCT03442985) for MHE was terminated early, and no interventional pharmacologic trials are currently active specifically for MHE.

Family Planning and Genetic Counseling

A parent with MHE has a 50% chance of passing on the gene change that causes MHE to each child. Genetic testing can confirm a diagnosis and inform reproductive planning. Early diagnosis and genetic counseling support monitoring and intervention. Genetic testing should encompass both point mutations and large deletions/insertions (Figure 3 Bukowska-Olech et al. 2021).

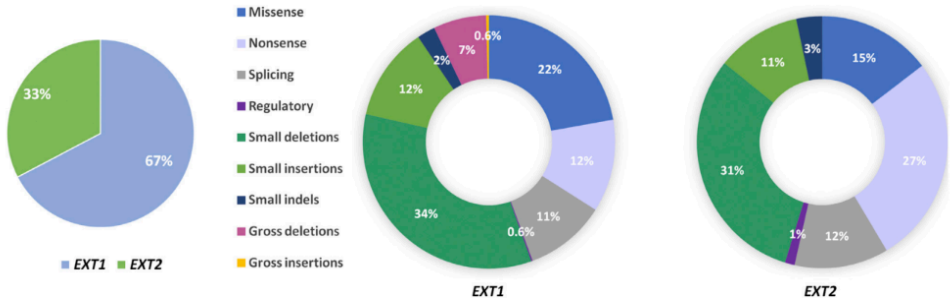

FIGURE 3 | Pie charts showing the percentage of mutation types found in the *EXT1* and *EXT2* genes in patients affected with hereditary multiple exostoses (HMEs). Data were obtained from Human Gene Mutation Database (HGMD v.2021.1; accessed on 25th of May).

References

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