17P13.3 DUPLICATION SYNDROME

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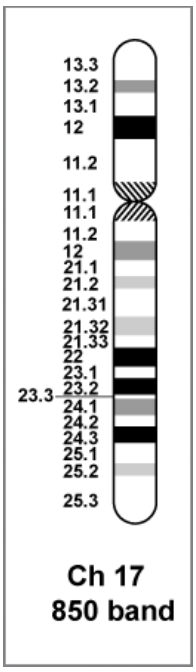
Duplication of segment p13.3 on the short arm of chromosome 17 causes a relatively rare type of limb malformations called ectrodactyly. Although rare when looking at all chromosomal disorders, ectrodactyly is quite common in individuals with duplications of 17p13.3. Ectrodactyly, also called split-hand/foot malformation (SHFM), is present when there was a failure to maintain the central portion of the apical ectodermal ridge within the developing embryo1. As a result, there may be a complete absence or under development of the central digits as well as a cleft in the hands and/or feet2. Clinically, individuals may present with features like syndactyly, clinodactyly, polydactyly, or single zeugopodial bone1.



Individuals with 17p13.3 duplication typically present with ectrodactyly in combination with long bone deficiency, usually involving the tibia and fibula. This specific grouping of malformations is called SHFM with long bone deficiency (SHFLD). In addition to any of the variety of presentations of ectrodactyly, patients with SHFLD may also present with features like a reduction defect of upper and/or lower limbs3, hemimelia, hypoplasia, aplasia, or dysplasia of the tibia or fibula4.

It is important to note that there is a great deal of heterogeneity in how individuals present with 17p13.3 duplications. The most minor of features may be something as small as a slight shortening of a central digit, while the most severe manifestations can include monodactyly2. Even within a singular family, there can be a great deal of variety in terms of presentation3. There is also an uncertain

understanding of whether or not there is a sex bias towards who presents more severely. Some studies have demonstrated a clear sex bias in Caucasians and have stated that females may present more infrequently with symptoms but tend to be more severely affected3. However, other studies have claimed there are no significant sex differences or biases in presentation5.

It is thought that ectrodactyly or SHFLD may occur due to the duplication of the gene BHLHA9, which is located in the 17p13.3 region. BHLHA9 encodes a transcription factor that is a crucial regulator in limb and finger development during embryogenesis. It is thought that this gene is dosage sensitive, providing a potential cause for the ectrodactyly seen in patients6.

Intellectual development in most affected persons in normal, although some individuals may reveal developmental delay and occasional brain malformations2. Additional abnormalities in other systems may occur if duplication involves some neighboring areas of 17p13.

Surprisingly, some individuals with 17p13.3 duplications involving BHLHA9 do not have any limb defects. It can't be excluded that some additional factors (genetic or environmental) may be necessary the pathogenic effect of this duplication to come to fruition.

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