

Germ-line Mosaicism in Osteogenesis Imperfecta

Germ-line mosaicism is the presence of more than 1 population of germ cells within a gonad. It is suspected when multiple children affected with an autosomal dominant disorder or a disorder that results from a new mutation of an X-linked gene are born to normal parents. Although evidence for such mosaicism is usually circumstantial, Cohn et al document the phenomenon in a family with lethal osteogenesis imperfecta (OI) type II. Two affected sons were born to an "unaffected" father by 2 separate wives. Electrophoretic abnormalities typical of OI type II were detected in type I collagen synthesized by skin fibroblasts from both affected infants, but not from the father or from 2 unaffected sisters of the second son. Further analysis pointed to an abnormality in the $\alpha 1(I)$ collagen chain; ultimately, a single nucleotide change resulting in a substitution of aspartic acid for glycine at position 883 of the triple helix was detected. Since the base change disrupted a restriction endonuclease cleavage

site, it allowed the normal gene to be distinguished from the mutant gene, which was exploited to search for the mutation in the germ cells and somatic cells of the father.

A small (225 base pair) fragment containing the exon harboring the mutation was amplified by polymerase chain reaction from genomic DNA isolated from the father's sperm, white blood cells, and hair root bulbs. The mutation was found in approximately 12% of sperm and in about 40% of the somatic cells. Thus, in addition to germ-line mosaicism, the father exhibited somatic mosaicism for the mutation, despite being clinically unaffected. The authors mention that they are aware of several other cases of undocumented germ-line mosaicism in OI type II and point out that it appears to be more common in OI type II (estimated 6% to 7%) than in most other genetic conditions. They con-

clude that the clinical phenotypes produced in genetic disorders reflect not only the qualitative effects of the mutation but also quantitative effects determined by the abundance and distribution of the cells expressing the mutation.

Cohn DH, Starman BJ, Blumberg B, et al. Recurrence of lethal osteogenesis imperfecta due to paternal mosaicism for a dominant mutation in a human type I collagen gene (COL1A1). *Am J Hum Genet* 1990; 46:591-601.

Editor's Comment—Determining recurrence risks for Mendelian (single gene) disorders, such as OI type II, used to be simple and straightforward. Standard risk figures are given in any genetics textbook. However, there are a growing number of

phenomena that complicate such calculations. Germ-line mosaicism is a good example. In the past, the father in the above case would have been given a negligible recurrence risk considering his normal clinical phenotype and especially his normal collagen electrophoretic studies. However, as demonstrated, his actual risk was substantially higher. Uniparental disomy, in which a child receives 2 copies of a particular chromosome from 1 parent and none from the other, and genomic imprinting, in which the expression of a mutation (and the disease phenotype) is influenced by which parent transmitted the mutation, are 2 other examples. It seems likely that more will be heard about these phenomena that distort Mendelian risk figures as their investigation receives more attention.

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