SECTION 5 DISORDERS OF INTERMEDIARY METABOLISM

427 Heritable Disorders of Connective Tissue

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CLASSIFICATION OF CONNECTIVE TISSUE DISORDERS

Some of the most common conditions that are transmitted genetically in families are disorders that produce clinically obvious changes in the skeleton, skin, or other relatively acellular tissues that have been loosely defined as connective tissues. Because of their heritability, the disorders were recognized as potentially traceable to mutated genes soon after the principles of genetics were introduced into medicine. In the last several decades, many of these disorders have been linked to mutations in several hundred different genes. However, classifying the disorders on the basis of either their clinical presentations or the mutations causing them presents a challenge for both the clinician and the geneticist.

A major development in the field was made by McKusick, who suggested that a group of disorders that included brittle bones in children (osteogenesis imperfecta), hyperextensible skin (Ehlers-Danlos syndrome), and characteristic distortions of skeleton (Marfan's syndrome) be considered as "heritable disorders of connective tissue" and that mutations causing the disorders would be found in the genes coding for proteins of the tissues.

The information on the disorders has continued to develop on two levels. The initial clinical classifications suggested by McKusick, and others, had to be refined as additional patients were examined. For example, some patients had skin changes similar to those commonly seen in Ehlers-Danlos syndrome, but this feature was overshadowed by other features such as extreme hypotonia or sudden rupture of large blood vessels. To account for the full spectrum of presentations in patients and families, many of the disorders have been reclassified several times, and each has been divided into a series of subtypes. For example, a recent effort to classify all the heritable disorders that alter the skeleton defined 456 distinctive conditions that were divided into 40 major groups.

The identification of mutations causing the diseases has developed on a parallel track. The first genes cloned for connective tissues were the two genes coding for type I collagen, the most abundant protein in bones, skin, tendons, and several other tissues. Some of the first assays in patients with osteogenesis imperfecta (OI) revealed mutations in type I collagen genes. Biochemical data developed using cultures of skin fibroblasts from affected patients demonstrated that the mutations dramatically altered the synthesis or structure of collagen fibers. The results stimulated efforts to identify additional mutations in genes