PRIMEVIEW

THE EHLERS–DANLOS SYNDROMES

nature reviews disease primers

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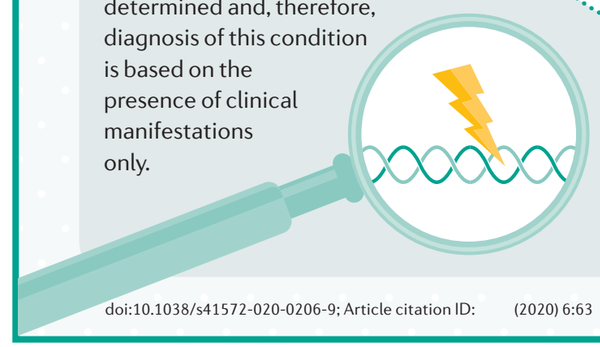
The Ehlers–Danlos syndromes (EDS) are a group of connective tissue disorders caused by alterations in genes encoding fibrillar collagens, collagen modifying or collagen-processing enzymes, or enzymes that modify glycosaminoglycans within the extracellular matrix (ECM).

DIAGNOSIS

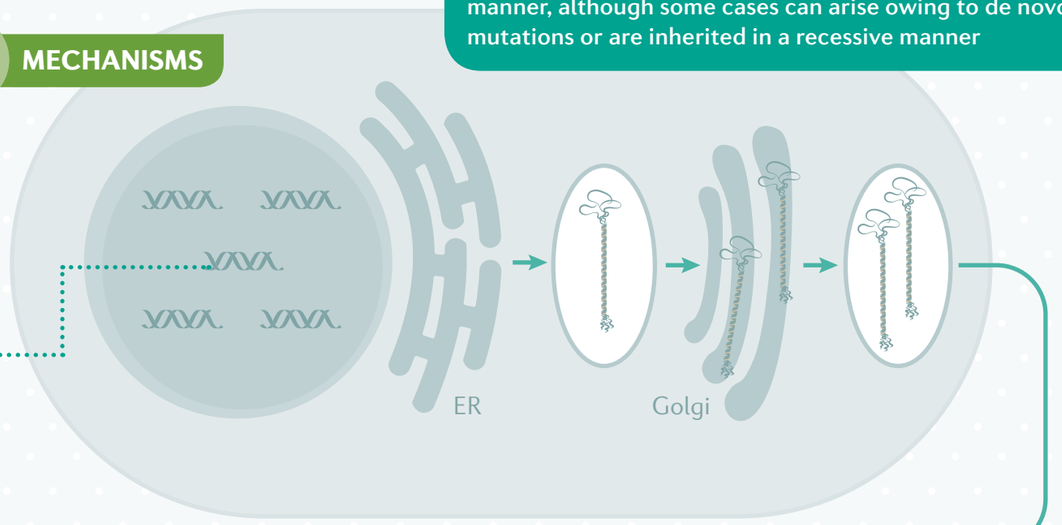
The symptoms of EDS are diverse and differ between subtypes. Symptoms that are found in multiple EDS subtypes include joint hypermobility, soft and hyperextensible skin, poor wound healing, pain and easy bruising. Vascular and musculoskeletal symptoms are present in some subtypes. Diagnostic work-up comprises clinical examination, followed by genetic testing in individuals who fulfil the clinical criteria for an EDS subtype. Genetic testing can include targeted analysis in those with a family history of EDS caused by a known genetic variant or, more frequently, next-generation sequencing using multi-gene panels. Genetic diagnosis should lead to family testing to enable detection of EDS in family members and, for patients with a recessive form of EDS, carrier testing in their partners to evaluate the risk of transmission to offspring. Of note, the genetic cause of hypermobile EDS has not been determined and, therefore, diagnosis of this condition is based on the presence of clinical manifestations only.



Variants in genes encoding the fibrillar procollagens I, III and V, or in genes encoding enzymes responsible for cleaving procollagen to mature collagen, lead to collagen fibrils with an abnormal structure or composition

MECHANISMS

Most types of EDS are inherited in an autosomal dominant manner, although some cases can arise owing to de novo mutations or are inherited in a recessive manner



Accurate data on the prevalence and incidence of EDS are not available

Variants in genes encoding ECM bridging molecules or in enzymes that modify ECM proteoglycans can interfere with the organization of collagen fibrils

Variants in genes involved in collagen crosslinking and collagen folding causes impaired collagen crosslinking

Other variants, such as those in the complement pathway and in genes of unknown intracellular function, can cause rarer forms of EDS

MANAGEMENT

All patients with EDS should receive multidisciplinary care and, if available, be part of a patient advocacy community. The precise treatment depends upon the subtype of EDS and its manifestations. Physiotherapy is essential for patients with musculoskeletal alterations. Helmets and/or skin protection, or joint protection, braces or splints can be used to reduce the risk of injury in patients with skin fragility or joint hypermobility. In addition, low-resistance exercise (such as walking or swimming) can improve joint stability, although exercise that place considerable strain on the joints (such as gymnastics or weight lifting) should be avoided. Monitoring for cardiovascular alterations using non-invasive procedures is recommended in patients at risk of adverse cardiovascular events.

OUTLOOK

Despite improvements in genetic testing, some forms of EDS (hypermobile EDS) and some patients with other forms of EDS have no identified genetic cause, which can hinder diagnosis of these conditions. Large-scale international studies are underway to address this issue. Genotype–phenotype correlations for EDS are only starting to emerge; additional correlations may be identified by ongoing research.

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