Genetics of ehlers-danlos syndrome

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Abstract. Ehlers-Danlos Syndrome (EDS) is a genetic condition characterized by joint hypermobility, skin hyperextension, and tissue fragility that affects the connective tissue and collagen structures in the human body. The prevalence has been reported as in 1 in 5000 births and affects equally in both sexes. EDS has no racial proportions. There are several types of EDS, that are based on the 2017 International Ehlers-Danlos Syndrome Classification. Thin and fragile mucosa, bleeding tendency, periodontal tissue injuries, and also tongue ghorlin syndrome has been reported as the intraoral manifestations in EDS. Another manifestation is hypermobile temporomandibular joint with high incidence of subluxation and dislocation. The mechanism of Ehlers-Danlos Syndrome is connected to collagen biosynthesis, originating with nucleus transcription to aggregate collagen heterotrimers into large fibrils. Mutations have been found in collagen-encoding genes for several of these forms, or in genes encoding collagen-modifying enzymes. One of the most common type of EDS is classical EDS which is having type V collagen deficiency. This is caused by mutation in type V collagen-encoding gene, COL5A1 dan COL5A2. Type V collagen is a regulatory collagen fibril that forms the basis of the fibrils in bony, cartilaginous, fibrous, and tubular structures. The majority of mutations have been reported are nonsense mutations; splice site mutations leading to exon skips, missense mutations causing glycine substitutions, and frameshift mutation. As a clinician, the knowledge about the etiology, clinical sign, oral manifestation, and the genetic aspect of this syndrome is crucial for making correct diagnoses and proper treatment planning. In this review, the author will explain further about the genetic aspects of Ehlers-Danlos Syndrome.

1. Introduction
Ehlers-Danlos Syndrome (EDS) is a genetic condition characterized by joint hypermobility, skin hyperextension, and tissue fragility that affects the connective tissue and collagen structures in the human body. [1,2]. The prevalence of EDS is measured at 1 in 5000 births and affects both sexes also has no racial predisposition. There are 13 subtypes of EDS, according to the 2017 international classification for the Ehlers–Danlos syndromes: Classical EDS, Classical-like EDS, Cardiac-valvular, Vascular EDS, Hypermobile EDS, Arthrochalasia EDS, Dermatosparaxis EDS, Kyphoscoliotic EDS, Brittle Cornea syndrome, Spondylodysplastic EDS, Musculocontractural EDS, Myopathic EDS, Periodontal EDS[1]. Most of these subtypes are due to genetic defects in the genes encoding or modifying enzymes of fibrillar collagens.[3] Oral health can be impaired by collagen defects, including vascularity, bone, teeth, gum tissue, nerve tissue, and tendons, ligaments, and temporomandibular joint (TMJ) that maintain maxillofacial structures. Thin and high fragile mucosa are included in the intraoral manifestation, so it is easy to injure and has a propensity to bleed,
recurrent periodontal tissue injuries, tongue with a Gorlin sign evident in almost 50 percents of EDS patients, hypermobile TMJ with a high incidence of subluxation or dislocation.[2,4].

The mortality rate of Ehlers-Danlos Syndrome is known to be not affected by the disease itself, but there is one of the subtypes of disease named kyphoscoliotic EDS is likely to be significantly affected by it, in this type of EDS patient, vascular insults and even restrictive lung disease are encountered, which may decrease life expectancy.[5] In this review, the author will explain further about the genetic aspects of Ehlers-Danlos Syndrome.

2. Clinical sign of ehlers-danlos syndrome
Classical EDS is the most common form of Ehlers-danlos syndrome. The classical EDS is characterized by hyperextensibility of the skin, delicate and soft skin, delayed wound healing with atrophic scar formation, quick bruising and joint hypermobility.[6]

![Figure 1 a. Skin hyperextensibility, b. atrophic scar scars and c. hypermobility of the join][3]

Classical ehlers-danlos syndrome caused by COL5A1 and the COL5A2 gene mutations encoding the type V collagen α 1 and the α 2-chain. This mutation causes the development defect of type V collagen to occur [6].

3. Function and structure of collagen
Collagen is a major molecule of the extracellular matrix (ECM that facilitates cell growth, and is responsible for connective tissues mechanical durability and contributes in preserving their structural and biological integrity [7].

![Figure 2.a. Structure of molecule collagen b. Hydrogen bond within the triple helix][7]
4. Collagen biosynthesis

The collagen biosynthesis starts with the transcription within nucleus for aggregating heterotrimers of collagen into large fibrils. Numerous growth factors and cytokines regulated the transcription activities. The mature mRNA is transported to cytoplasm after transcription and coverted into preprocollagen molecules at the rough endoplasmic reticulum. With the N terminus, the preprocollagen molecules enter the lumen of endoplasmic reticulum first, which is converted by the elimination of the signal peptide into procollagen. After removal of the signal peptide by a signal peptidase, posttranslational modifications include hydroxylation and glycosylation of procollagen molecules. Proline and lysine residue hydroxylation catalyzed by prolyl hydroxylase and lysyl hydroxylase and glycosylation processes catalyzed by galactosyltransferase and hydroxylysyl and galactosyltransferase enzymes [7,8].

The formation to triple helices is followed by the alignment of three a-chains between the C-terminal domains. Enzymes such as PPI (peptidyl-prolyl cis-trans-isomerase) and collagen-specific chaperones like HSP47 helo to shape and fold the procollagen chain and PDI (protein disulphide isomerase) enzyme is also involved in the formation of intra- and inter-chain disulphide bonds in the proco-chain disulphide chain. After that, inside the Golgi compartment, the triple-helix molecules are packaged and released into the extracellular space. N¬ and C¬ propeptides are extracted enzymatically by the procollagen N-proteinase and the procollagen C-proteinase in the extracellular space, resulting in the triple helices of collagen (also known as tropocollagen) that shape collagen fibrilase [7,8].

![Figure 3. Steps in Collagen Synthesis.](image-url)
prolyl hydroxylase; OTC: oligosaccharyl transferase complex; PDI: protein disulphide isomerase; PPI: peptidyl-prolyl cis-trans-isomerase; NP: procollagen N-proteinase; CP: procollagen C-proteinase; LO: lysyl oxidase; HSP47: heat shock protein 47)

5. Type V collagen

Type V collagen (COLV) is a regulatory fibril-forming collagen that is necessary for the type I and III collagen fibrillation and consequently, for optimum fibrillar formation and consistency of the tissue. With about ninety percent of the total collagen forming the basis of the fibrils in bony, cartilaginous, fibrous and tubular structures, fibril-forming collagen are the most widespread family of the collagens. V collagen dysregulation that causes connective diseases as a result of decreased matrix quality. Type V collagen-encoding gene mutation, COL5A1 and COL5A2, which causes the classical ehler danlos syndrome [9].

![Figure 4. Multiple collagen fibrils form the collagen fibres.](image10)

COLV consists of combinations of three separate polypeptide chains, namely α1(V), α2(V), and α3(V), offering a special chains composition for each isoform and producing three distinct molecular isoforms, a1(V)2a2(V), a1(V)3, and a1(V)a2(V) a3(V). The c a1(V)2a2(V) heterometric chains are widely distributed in tissues and are most commonly referred to as COLV. A1(V)3, known as A1(V) homotrimer, was first observed in cultured Chinese hamster lung cells (Haralson et al., 1980) which occurs in the skin dermis as microfilaments of 5–10 nm in diameter. The heterotrimer a1(V)a2(V)a3(V), was identified in the placenta and other tissues: uterus, skin and synovial membranes [9,11].

![Figure 5. Schematic diagram of the chain composition of the fibril-forming collagens](image12)
6. Mutation in COL5A1 and COL5A2 Gene

Approximately 90% of classical EDS patients are responsible for the COL5A1 and COL5A2 genes encoding the type V collagen proalpha-1 and proalpha-2 chains.[13] COL5A1 cytogenic locations: 9q34.3, which is the long q) arm of chromosome 9 at position 34.3 and COL5A2 cytogenic location: 2q32.2, which is the long (q) arm of chromosome 2 at position 32.2.

![Figure 6. Cytogenic location of COL5A1](image)

![Figure 7. Cytogenic location of COL5A2](image)

Nonsense mutations; splice site mutations leading to exon skips; missense mutations causing glycine substitutions; and frameshift mutations are the majority of mutations identified. The majority of mutations result in a non-functional COL5A1 allele that results in haploinsufficiency of collagen type V.[3,14] A nonsense mutation is a shift in DNA that causes a protein to terminate or end its translation earlier than expected, or its synonym, a stop mutation. The nonsense mutation that results in the translation of an al-chain that can not be assembled into a triple helix decreases the total amount of tissue collagen [14].

![Figure 8. Nonsense mutation](image)
7. **Missense mutation**
A missense mutation is the modification of a single base pair that allows the resulting protein to substitute a different amino acid. The substitution of glycine for arginine has been documented in Ehlers Danlos syndrome [15].

![Missense mutation](image)

**Figure 9.** Missense mutation

8. **splice site mutation**
An important step in the expression of most human genes is RNA splicing. In ehlers-danlos syndrome, the splice site mutations resulting in exon skips have been identified. This will lead to the production of a protein that does not work properly [3].

![Splice site mutation](image)

**Figure 10.** Splice site mutation leading to exon skipping[16]

9. **Frameshift mutation**
A specific type of mutation involving either insertion or deletion of extra DNA bases is the Frameshift mutation. This mutation causes premature termination codon (PTC) to be produced.[17]
Figure 11. Frameshift mutation

10. Conclusion
Ehlers-Danlos Syndrome (EDS) is a genetic condition characterized by joint hypermobility, skin hyperextension, and tissue fragility that affects the connective tissue and collagen structures in the human body. There are many type of EDS with different symptom for each type. As a clinician, the knowledge about the etiology, clinical sign, oral manifestation and the genetic aspect of this syndrome is crucial for making correct diagnoses and proper treatment planning so that clinician can properly plan the treatment for each patient. The genetic mutation hopefully can be well known and used as one of the further biomarkers in this rare disease.

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