COL7A1 Gene

Subjects: Genetics & Heredity
Contributor: Vicky Zhou

collagen type VII alpha 1 chain

Keywords: genes

1. Normal Function

The *COL7A1* gene provides instructions for making a protein called pro-α1(VII) chain that is used to assemble a larger protein called type VII collagen. Collagens are a family of proteins that strengthen and support connective tissues, such as skin, bone, tendons, and ligaments, throughout the body. In particular, type VII collagen plays an essential role in strengthening and stabilizing the skin.

Three pro-α1(VII) chains twist together to form a triple-stranded, ropelike molecule known as a procollagen. Cells release (secrete) procollagen molecules, and enzymes cut extra protein segments from the ends. Then the molecules arrange themselves into long, thin bundles of mature type VII collagen.

Type VII collagen is the major component of structures in the skin called anchoring fibrils. These fibrils are found in a region known as the epidermal basement membrane zone, which is a two-layer membrane located between the top layer of skin, called the epidermis, and an underlying layer called the dermis. Anchoring fibrils hold the two layers of skin together by connecting the epidermal basement membrane to the dermis.

2. Health Conditions Related to Genetic Changes

2.1. Dystrophic Epidermolysis Bullosa

More than 700 mutations in the *COL7A1* gene have been identified in people with dystrophic epidermolysis bullosa, a condition that causes the skin to be very fragile and to blister easily. These mutations alter the structure or disrupt the production of the pro-α1(VII) chain protein, which affects the production of type VII collagen. When type VII collagen is abnormal or missing, anchoring fibrils cannot form properly. A shortage of these fibrils impairs the connection of the epidermis to the dermis. As a result, friction or other minor trauma can cause the two skin layers to separate. This separation leads to the formation of blisters, which can result in extensive scarring as they heal.

Researchers classify dystrophic epidermolysis bullosa into a few major types based on the inheritance pattern and features of the condition. The recessive types of dystrophic epidermolysis bullosa (RDEB) result from mutations in both copies of the *COL7A1* gene in each cell. The most severe, classic form of this disorder is known as recessive dystrophic epidermolysis bullosa severe generalized (RDEB-sev gen). Most of the *COL7A1* gene mutations responsible for RDEB-sev gen result in production of abnormally short pro-α1(VII) chains that cannot form type VII collagen. As a result, little type VII collagen is available to make anchoring fibrils. This lack of anchoring fibrils disrupts the connection between the epidermis and the dermis and causes the extreme skin fragility and other signs and symptoms of RDEB-sev gen.

Somewhat less severe forms of RDEB, grouped as the generalized and localized types (RDEB-gen and -loc), are caused by other types of mutations. Many of these genetic changes alter the structure of the pro-α1(VII) chain protein such that it cannot form normal type VII collagen. As a result, anchoring fibrils are reduced in number, or they are altered and cannot function normally. The small amount of normal or partially functional anchoring fibrils accounts for the less severe signs and symptoms of RDEB-gen and -loc.

A milder, dominant form of dystrophic epidermolysis bullosa (DDEB) results from mutations in one copy of the *COL7A1* gene in each cell. In many cases, these mutations alter a part of type VII collagen known as the triple helical domain. This region gives type VII collagen its usual triple-stranded structure. It is made up of a pattern of protein building blocks (amino acids) in which every third amino acid is a glycine. Mutations that substitute other amino acids for glycine in this

region can disrupt the triple-stranded structure of type VII collagen. When the abnormally shaped collagen molecules are incorporated into anchoring fibrils, they interfere with the fibrils' normal function and prevent them from effectively connecting the epidermis and the dermis. Although they are most commonly associated with DDEB, mutations that substitute glycine amino acids in the triple helical domain can also cause RDEB. DDEB can also be caused by other types of mutations, particularly changes that affect the folding of type VII collagen.

It is unclear how *COL7A1* gene mutations are associated with an increased risk of a certain cancer called squamous cell carcinoma in people with dystrophic epidermolysis bullosa, particularly RDEB-sev gen. Some research has suggested that abnormal forms of type VII collagen that retain a procollagen fragment called the NC1 domain may increase the risk of tumor formation. Other studies, however, have not found this association.

2.2. Other Disorders

Mutations in the *COL7A1* gene can also cause a rare condition called epidermolysis bullosa with congenital localized absence of skin (also known as Bart syndrome or aplasia cutis congenita type VI). Individuals with this condition have patches of missing skin at birth (aplasia cutis congenita), typically on the legs. On other parts of the body, they have the characteristic skin problems of epidermolysis bullosa. Epidermolysis bullosa is a group of conditions that cause the skin to be very fragile and to blister easily. Abnormal or absent fingernails and toenails are also common in people with epidermolysis bullosa with congenital localized absence of skin.

As in dystrophic epidermolysis bullosa (described above), *COL7A1* gene mutations impair the formation of functional anchoring fibrils. A shortage of these fibrils results in skin fragility and blistering.

Some doctors believe that the aplasia cutis congenita arises from skin fragility and blisters during birth and does not signify a condition separate from epidermolysis bullosa. It is unclear why some newborns have this feature and others do not.

3. Other Names for This Gene

- alpha 1 type VII collagen
- CO7A1_HUMAN
- collagen type VII alpha 1
- collagen VII, alpha-1 polypeptide
- collagen, type VII, alpha 1
- collagen, type VII, alpha 1 (epidermolysis bullosa, dystrophic, dominant and recessive)
- EBD1
- EBDCT
- EBR1
- LC collagen
- long chain collagen

References

1. Almaani N, Liu L, Dopping-Hepenstal PJ, Lai-Cheong JE, Wong A, Nanda A, MossC, Martinéz AE, Mellerio JE, McGrat h JA. Identical glycine substitution mutationsin type VII collagen may underlie both dominant and recessive forms of dy strophicepidermolysis bullosa. Acta Derm Venereol. 2011 May;91(3):262-6. doi:10.2340/00015555-1053.
2. Bruckner-Tuderman L, Höpfner B, Hammami-Hauasli N. Biology of anchoringfibrils: lessons from dystrophic epidermoly sis bullosa. Matrix Biol. 1999Feb;18(1):43-54. Review.
3. Chen Z, Bu W, Feng S, Wang H. Bart's syndrome in a family affected threeconsecutive generations with mutation c.600 7G>A in COL7A1. J Dermatol. 2018Aug;45(8):1000-1002. doi: 10.1111/1346-8138.14352.
4. Dang N, Klingberg S, Marr P, Murrell DF. Review of collagen VII sequencevariants found in Australasian patients with d ystrophic epidermolysis bullosareveals nine novel COL7A1 variants. J Dermatol Sci. 2007 Jun;46(3):169-78.
5. Gardella R, Castiglia D, Posteraro P, Bernardini S, Zoppi N, Paradisi M,Tadini G, Barlati S, McGrath JA, Zambruno G, Colombi M. Genotype-phenotypecorrelation in italian patients with dystrophic epidermolysis bullosa. J InvestDermatol. 2002 Dec;119(6):1456-62.
6. Han YM, Lee N, Byun SY, Cheon SJ, Ko HC. Bart's Syndrome with Novel FrameshiftMutations in the COL7A1 Gene. F etal Pediatr Pathol. 2019 Feb;38(1):72-79. doi:10.1080/15513815.2018.1543370.

7. Järvikallio A, Pulkkinen L, Uitto J. Molecular basis of dystrophicepidermolysis bullosa: mutations in the type VII collagen gene (COL7A1). HumMutat. 1997;10(5):338-47.
8. Kern JS, Kohlhase J, Bruckner-Tuderman L, Has C. Expanding the COL7A1 mutationdatabase: novel and recurrent m utations and unusual genotype-phenotypeconstellations in 41 patients with dystrophic epidermolysis bullosa. J InvestD ermatol. 2006 May;126(5):1006-12.
9. Ortiz-Urda S, Garcia J, Green CL, Chen L, Lin Q, Veitch DP, Sakai LY, Lee H,Marinkovich MP, Khavari PA. Type VII coll agen is required for Ras-driven humanepidermal tumorigenesis. Science. 2005 Mar 18;307(5716):1773-6.
10. Pfendner EG, Lucky AW. Dystrophic Epidermolysis Bullosa. 2006 Aug 21 [updated 2018 Sep 13]. In: Adam MP, Ardinge r HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): Uni versity ofWashington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1304/
11. Pourreyron C, Cox G, Mao X, Volz A, Baksh N, Wong T, Fassihi H, Arita K,O'Toole EA, Ocampo-Candiani J, Chen M, H art IR, Bruckner-Tuderman L, Salas-AlanisJC, McGrath JA, Leigh IM, South AP. Patients with recessive dystrophicepid ermolysis bullosa develop squamous-cell carcinoma regardless of type VIIcollagen expression. J Invest Dermatol. 2007 Oct;127(10):2438-44.
12. Sawamura D, Goto M, Yasukawa K, Sato-Matsumura K, Nakamura H, Ito K, Nakamura H, Tomita Y, Shimizu H. Geneti c studies of 20 Japanese families of dystrophicepidermolysis bullosa. J Hum Genet. 2005;50(10):543-546. doi:10.1007/ s10038-005-0290-4.2006;51(9):839. J Hum Genet. 2006 Sep;51(9):839.
13. Varki R, Sadowski S, Uitto J, Pfendner E. Epidermolysis bullosa. II. Type VII collagen mutations and phenotype-genoty pe correlations in the dystrophicsubtypes. J Med Genet. 2007 Mar;44(3):181-92.
