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Review

# Genetic mapping of hair loss through the APCDD1 gene pathway: A new perspective

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***ABSTRACT***

Hair is an important physiological component of the human body that serves several purposes. Hair follicles on the scalp are root structures that promote hair growth. Keratin is a protein that is produced in the follicles and makes up the structure of hair. Hair serves multiple roles, including regulating body temperature and protecting against environmental elements. Hair loss or poor hair health is frequently associated with all body health and can be caused by a variety of circumstances, therefore hair health can be viewed as a mirror of overall health. Adenomatous polyposis coli down-regulated 1 (APCDD1) has been implicated in the regulation of hair follicle development and cycling. The research's newfound insights give a fresh viewpoint on the genetic causes of hair loss as well as possible areas for therapeutic intervention. Gaining insight into the molecular processes that cause hair loss could result in the creation of innovative treatment plans that enhance the lives of those who are impacted by the condition by maintaining or regaining hair follicle function. This review highlights the significance of APCDD1 and related pathways in hair follicle biology and is a major step forward in our understanding of the genetic drivers of hair loss. The information provided here paves the way for more research into the intricacies of hair loss and the creation of individualized strategies for both prevention and therapy. This review also contributes to a better understanding of the causes of hair loss and the implementation of new treatment options in this sector, since it provides a new perspective on the genetic mapping of hair loss via the APCDD1 gene pathway.

***Keywords:*** APCDD1, follicle, genetic, hair, pathway, treatment.

Hair loss is a common and complex problem that impacts people in different demographic groups. Many studies have been conducted on the prevalence of hair loss diseases including androgenetic alopecia and alopecia areata. For one instance, alopecia areata is a complicated autoimmune disease that affects roughly 2.18% of the population.[1] Additionally, by the time they reach 80 years old, up to 80% of men may have androgenetic alopecia, a progressive hair loss condition influenced by androgens and genetic predisposition.[2] Moreover, it has been observed that the prevalence of female pattern hair loss, a prevalent dermatologic condition, increases with age. Also, it has been observed that the prevalence of female pattern hair loss, a prevalent dermatologic condition, increases with age.[3]

Research has also looked into the connections between hair loss and a number of variables, including serum ferritin, vitamin D, zinc, and copper levels. Research has suggested that low blood ferritin and vitamin D levels may be related to hair loss.[4,5] On the other hand, there have been conflicting findings on serum copper and its connection to hair loss.[6] Additionally, research on the function of regulatory T cells and T-helper 17 in alopecia areata patients have given light to the immune-mediated components of this disorder.[7]

Hair loss has been linked to psychological consequences like depression and a lower quality of life in addition to its physical impacts. Studies have shown that in individuals with primary hypothyroidism, there is a statistically significant correlation between depression, exhaustion, memory problems, hair loss, and gland enlargement.[8] Additionally, research has shown that hair loss can have a major negative influence on quality of life, with patients reporting

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variations in their roles and cognitive functions, pain, appetite loss, and hair loss ratings.[9]

The treatment of hair loss conditions has also been a subject of investigation, with studies exploring various therapeutic options such as low-level light therapy, minoxidil, and platelet-rich plasma application.[10] Research has also been done on treating hair loss issues; studies have looked into a variety of treatment approaches, including the use of platelet-rich plasma, minoxidil, and low-level light therapy. Moreover, comparative studies have been carried out to assess the effectiveness of various treatment techniques, such as liquid nitrogen cryotherapy versus fractional $CO_2$ laser, in the management of alopecia areata.[11]

### Importance of APCDD1 gene

The adenomatous polyposis coli down-regulated 1 (APCDD1) gene is involved in many different biological processes as well as disease settings. The various roles of APCDD1 have been clarified by research, particularly its function as an inhibitor of the wingless/integrated (Wnt) signaling pathway, which is essential for processes including development, differentiation, and proliferation.[12]

The APCDD1 has been linked to colorectal and breast cancer in cancer research. Research has demonstrated that APCDD1 may play a possible tumor suppressor role by blocking the canonical Wnt signaling pathway, which inhibits breast cancer cell migration. Furthermore, findings of APCDD1 overexpression in the development of colorectal cancer have connected it to colorectal carcinogenesis.[13]

Moreover, APCDD1 gene mutations have been found in familial hypotrichosis simplex individuals, providing insight into the gene's role in hair follicle growth and hair loss. When APCDD1 is mutated, its function as an inhibitor of the Wnt pathway may contribute to hair follicle shrinking and hair loss.[14]

APCDD1 has been discovered to regulate the adipogenic development of preadipocytes, both human and murine, in the setting of adipocyte differentiation and obesity. This finding raises the possibility that APCDD1 plays a role in metabolic processes and pathways associated with obesity. As a dual bone morphogenetic protein (BMP)/Wnt inhibitor in the developing nervous system and skin, APCDD1 has been identified in developmental biology. This suggests that it plays a role in coordinating signaling pathways that are essential for both animal development and human disease. In conclusion, the identification and characterization of the APCDD1 gene have yielded important new understandings of its various roles in adipogenesis, hair follicle formation, cancer, and embryonic development. Comprehending the complex function of APCDD1 is crucial in order to unravel its modes of action and investigate its possible consequences for the etiology of diseases and treatment approaches.[15,16]

### Effect of APCDD1 gene on hair loss

Hair loss diseases have been linked to the APCDD1 gene, especially in the context of familial hypotrichosis simplex. Research has shown that APCDD1 gene mutations are linked to hair loss in those who have this disorder, pointing to a possible function for APCDD1 in the growth and upkeep of hair follicles. Studies have shown that APCDD1 inhibits the Wnt signaling pathway, which is essential for hair loss and shrinkage of hair follicles. Hair loss in patients with familial hypotrichosis simplex may result from an APCDD1 mutation that interferes with normal Wnt pathway control. Gaining knowledge about how APCDD1 mutations affect hair loss might help one better understand the molecular processes that underlie the development of hair follicles and the genetic foundation of hair disorders. New pathways for investigating therapeutic interventions for hair loss problems linked to APCDD1 gene mutations may become available with additional studies on the role of APCDD1 in hair biology.[14]

### Association between genetic variations in the APCDD1 gene and hair loss risk

A lot of people worry about hair loss, which affects both men and women of different ages. The inclination to hair loss may be significantly influenced by genetic variants; one gene that has drawn interest in this context is APCDD1. Gaining knowledge of the relationship between genetic variants in the APCDD1 gene and

the likelihood of hair loss may help develop preventive and therapeutic approaches for this disorder.[17]

Hair loss has been linked to genetic polymorphisms in the APCDD1 gene, especially when hereditary hypotrichosis simplex is present. APCDD1 may play a function in the growth and maintenance of hair follicles, as evidenced by the association between hair loss and mutations in the APCDD1 gene in patients with this disorder. The Wnt signaling pathway, which is essential for hair follicle shrinking and hair loss, is known to be inhibited by APCDD1. Hair loss in people with familial hypotrichosis simplex may be a result of APCDD1 mutations that disrupt the normal control of the Wnt pathway. Gaining knowledge about the correlation between genetic variants in the APCDD1 gene and the likelihood of experiencing hair loss is essential for comprehending the underlying genetics of hair diseases.[12,14,17]

### Cellular relationship between APCDD1 gene and Wnt signalling pathway

A crucial pathway involved in many biological processes, such as tissue homeostasis, disease pathogenesis, and embryonic development, is the Wnt signaling pathway. It is well recognized that this route significantly affects cellular activities such as development, differentiation, and proliferation. Since the Wnt signaling system controls both cell proliferation and tissue regeneration, it is especially active in developing tissues.[18,19]

Cell signaling is fundamentally regulated by the highly conserved Wnt signaling pathway. It can be triggered by both conventional beta (β)-catenin-dependent and non-canonical β-catenin-independent pathways, enabling a variety of cellular reactions. The non-canonical Wnt pathway functions independently of β-catenin and is involved in processes like cell polarity and migration, whereas the canonical system involves stabilizing and translocating β-catenin into the nucleus to regulate gene expression.[20]

Numerous illnesses, including cancer, have been linked to dysregulation of the Wnt signaling system. The significance of this system in the pathophysiology of disease has been highlighted by the association between the abnormal activation of the Wnt pathway and carcinogenesis in colorectal cancer and other malignancies. Specifically, the canonical Wnt signaling pathway has been implicated in multiple cancer types as a harmful component, highlighting its potential as a target for therapeutic intervention. It has been found that the Wnt signaling pathway interacts with other signaling networks, like the Hedgehog pathway, to control tumorigenicity and biological functions. The intricacy of cellular signaling networks and their influence on the development of illness are highlighted by the interactions among various signaling pathways. The Wnt signaling pathway is an important signaling cascade that is necessary for healthy tissue homeostasis and appropriate development. It controls a number of cellular activities. Comprehending the workings and consequences of Wnt signaling in many biological settings is essential for clarifying the etiology of disease and creating focused treatment strategies.[21,22]

The β-catenin/T-cell factor 4 complex has identified the APCDD1 gene as a direct target, which has generated great interest in the gene. Due to this relationship, APCDD1 is central to the Wnt signaling pathway, which is essential for many biological functions such as cell division, proliferation, and development. Comprehending the molecular mechanisms underlying complicated disorders and possible therapy targets can be greatly aided by knowing how the APCDD1 gene interacts with the Wnt signaling pathway in cells.[23]

The APCDD1 gene is involved in the Wnt signaling system. It functions as an inhibitor of Wnt signaling, blocking the formation of Wnt receptor complexes by physically interacting with Wnt ligands and their receptors. This connection is essential for suppressing β-catenin's downstream stabilization and regulating a number of Wnt-mediated developmental processes, including the specification of the embryonic axis, neuronal proliferation, and hair follicle production.[24]

By interacting with distinct cellular components, the Wnt signaling pathway is known to influence a variety of cellular functions. The

route affects tissue development, cell proliferation, and differentiation through both canonical and non-canonical pathways. The complex interplay between various signaling pathways and their effects on cellular activities and developmental processes is highlighted by the relationship between Wnt signaling and APCDD1.[25]

### Hypotrichosis simplex

A hereditary disorder called hypotrichosis simplex damages hair follicles, mainly on the scalp, causing hair loss. Mutations in particular genes linked to the production and growth of hair are the cause of this disorder. Hypotrichosis simplex patients may have sparse or thinning hair, which results in fewer hair strands. A class of nonsyndromic human alopecias known as hypotrichosis simplex is typified by progressive loss of hair, usually beginning in childhood and resulting in diffuse, gradual thinning of hair on the scalp and body. This disorder is regarded as an uncommon kind of hereditary alopecia, and its onset is linked to a number of different genetic abnormalities.[26]

Hypotrichosis simplex has been linked to genetic differences in genes including APCDD1, LSS, and SNRPE. For example, hereditary hypotrichosis simplex has been associated with mutations in the APCDD1 gene. The APCDD1 functions as a new Wnt inhibitor and contributes to the shrinking of hair follicles. Similarly, autosomal-recessive hypotrichosis simplex has been linked to mutations in the LSS gene, which codes for lanosterol synthase, demonstrating the genetic variability of this disorder. The genetic intricacy of this hair loss illness is further highlighted by the discovery of biallelic pathogenic mutations in the SNRPE gene in families with isolated hypotrichosis simplex.[27]

### Hair cycle and hair physiology

Our skin is a vital organ that envelops and shields our body. Due to its unique sensors, it communicates with the environment constantly. In response to sunshine, it also contributes to the body's synthesis of vitamin D. Our epidermis layer, which spans 1.5 to 2 square meters and is composed of around 70% water and 30% organic substance, is the largest organ in our body. At 3 to 3.5 kg, it is also the heaviest organ. The pH of our skin varies based on our location and gender; it typically ranges from 5.5 to 6.[28] The epidermis, dermis, and subdermis are the three layers that make up the skin. The skin's outermost layer is called the epidermis. The subcutaneous layer's cells are constantly rising, shedding, and renewing themselves around every 15 to 30 days. This cycle's continuous renewal maintains the skin's youthful appearance. This rejuvenation process slows down with age, resulting in increasingly lifeless skin.[29] Moisture loss occurs with aging since the epidermal layer also contributes significantly to the skin's moisture balance. The epidermal layer contains melanin pigment as well, which shields the skin from the sun's damaging rays. The dermis is the middle layer of the skin and is made up of collagen and elastin fibers that offer support to the skin. The dermis also contains follicles, which house hair and sweat glands. Glands that regulate body temperature, blood arteries, and nerve endings are all found in the dermis layer.[30] Subdermis skin's lowest layer contains fat tissue. The layer provides heat insulation while also shielding the interior organs from impacts. The dermis, which makes up the middle layer of the skin, is made up of elastin and collagen fibers that give the skin stability. Additionally, the dermis has follicles that house sweat glands and hair strands. The dermis layer also contains sweat glands, blood arteries, and nerve endings that control body temperature.[31] Subcutaneous tissue can be found in the skin's lowest layer, the subdermis. The internal organs are shielded from impacts and provided with thermal insulation by this layer. The human body's complex physiological component, hair, serves a number of vital purposes. Hair follicles are structures on the scalp that create hair. These follicles are under the skin and are the root structures that allow hair to grow.[32] The primary building block of hair, keratin, is produced in follicles by unique cells. An essential method for controlling the growth and cycle of hair is provided by hair follicles. Every hair strand goes through phases of development, rest, and shedding. The body uses hair for two purposes: regulating body temperature and providing defense from outside influences. The scalp is shielded by hair from the sun's rays, collisions, and other environmental threats.[33] Moreover, hair controls the scalp's temperature, particularly by preserving body warmth. As an

insulating layer covering the head, hair aids in regulating body temperature, particularly in cold climates. Between 100,000 and 150,000 hair follicles on a healthy scalp produce thick terminal hair. Usually, these hair follicles are found in groups of one to four hairs. An individual with a healthy scalp is thought to have between 50,000 and 65,000 hairs on average.[34] The three stages of the hair development cycle are anagen, catagen, and telogen. It is a complicated process. The hair follicle's active growth phase is known as the anagen phase. Hair stem cells divide during this period, producing new hair strands. The active growth phase is another name for the anagen phase.[35] In humans, this phase accounts for 85% of hair development on average. It typically takes two to seven years, during which time the hair's thickness and length are established. Hair grows at this stage about 1.1 to 1.5 cm every month on average. The transition phase then starts with the catagen phase. This stage is the transitional period during which the hair follicle's growing activity ceases.[36] The stem cells in hair settle into a resting state. Fifteen percent of human hair is in this stage on average. The hair follicle gets smaller over time. This phase is known to have two periods: Kenogen and exogen.[37] Exogen denotes the hair loss process, whereas kenogen denotes the time following hair loss when the follicle is empty. A new hair development cycle starts when the telogen phase ends and fresh, healthy hair begins to grow, depending on the condition of the scalp. Usually, the catagen phase lasts between two and three weeks. At last, the telogen phase starts. This is the stage in which hair rests and sheds. The hair follicle is in a resting condition during the telogen phase when the groundwork for the next hair strand to grow is completed.[38] This is the time when the hair comes out, and it typically takes three to four months. The growth cycle then restarts when the hair follicle enters the anagen phase. Every hair strand experiences this cycle independently, therefore at any given time, individual hair strands on the scalp may be in different stages. Hair continually grows and regenerates thanks to this intricate mechanism. The telogen phase is followed by the anagen phase, which is when new hair develops in its place and the hair naturally falls out.[39] While 50 to 100 hair strands lost per day are thought to be typical, androgenetic alopecia, a genetic form of hair loss, can cause up to 200 hair strands to be lost every day. Throughout its lifetime, a hair follicle cycles 10 to 20 times. Every hair follicle has an average life span of 85 years. During puberty, the male hormone known as androgen rises. In regions like the armpit, genital area, beard, and moustache, this hormone induces the thin, feathery hair known as vellus to thicken and deepen in color, transforming it into terminal hair.[40] The same hormone, however, may have the reverse impact on the scalp and cause baldness later on as well as the terminal hairs that create the hair to change into vellus type hair.[41]

### Common causes of hair loss

The condition of one's hair frequently indicates one's general health. Issues like hair loss, dandruff, and breakage are typically linked to a number of variables, including genetics, stress, diet, and hormone fluctuations. As a result, maintaining healthy hair is crucial to enhancing general health and quality of life. Research in numerous disciplines, including hair physiology, genetics, practical biology, dermatology, and endocrinology, is continuously advancing our understanding of the etiology of hair loss. While hair loss might not seem like much to some, it can be a major problem for others, leading them to look for medical assistance.[42] In actuality, there are numerous causes of hair loss and possible outcomes. There is no one form of hair loss; it can be localized or widespread throughout the scalp; it can also infrequently occur and usually go away in less than six months, or it can develop into a chronic issue that lasts longer than six months. Basic criteria can be used to classify different types of hair loss.[43]

Having well-groomed, vibrant, and youthful-looking hair is important. Hair loss can be caused by a number of factors, including stress, hormone imbalances, improper product use, and dietary habits. Hair loss can have a negative psychological and physical impact on a person's quality of life, which can lead to low self-esteem. Acute telogen effluvium, also known as sporadic and occasionally sudden onset, is the term used to describe reactive hair loss; chronic telogen effluvium, on the other hand, is referred to as a longer-lasting and progressive condition causing hair loss. Androgenetic alopecia is the term

for hair loss caused by hormonal abnormalities associated with genetic causes.[44] This kind of hair loss is prevalent, particularly in men, and it can result in baldness or partial or total hair loss. The treatment for each of these many forms of hair loss may vary due to their distinct causes, which are linked to modifications in the hair's life cycle. Patients experiencing hair loss in their daily lives may experience significant distress due to psychological or cosmetic concerns. Furthermore, hair loss may happen from the usage of specific medications or be a sign of a more widespread illness in the body. To establish a conclusive diagnosis, it is crucial to look into the underlying causes of hair loss.[45] Acute telogen effluvium is another term for reactional hair loss, which is a prevalent occurrence, particularly in women. The disorder is characterized by abrupt and occasionally substantial hair loss that occurs three to four months following a trigger event. The phrase "reactional hair loss" is also frequently used because of this. A triggering action causes alterations in the hair's life cycle, with more hair entering the shedding phase (telogen phase) and the growth phase (anagen phase) pausing. After taking into consideration the interval between the triggering event and the onset of hair loss, the average hair loss process lasts three months.[46] Generally speaking, it is normal to lose between 100 and 150 hair strands every day; however, in cases of reactive hair loss, this number can reach 300, and the loss can become more obvious, with hair appearing on pillows, clothing, and other surfaces throughout the home. Reactionary hair loss can be brought on by a number of things, including stress, emotional shocks, exhaustion, imbalanced diets, drastic weight loss plans, seasonal changes, and delivery. Most cases of reactionary hair loss are transient and curable; 95% of affected individuals spontaneously recover, usually in six months or less. Baldness is not a possibility, and there is no reduction in hair density. Hair weakens and may fall out more frequently when the scalp is deficient in vitamins and minerals.[47] Similar to the body, hair follicles are perpetually active small factories that require the sustenance of a nutritious diet high in proteins, vitamins, and minerals like zinc and iron. Hair loss can occasionally happen after pregnancy. The hair life cycle is impacted by hormonal changes. It's possible to lose hair throughout the early half of pregnancy. Conversely, the latter part of pregnancy shields the expectant mother from spontaneous hair loss.[48] The phase of hair development is positively impacted by the rise in hormone levels, particularly estrogen, that occurs during pregnancy. Hair loss happens virtually systematically after birth as hormone levels return to normal. Here, there is acute telogen effluvium or sporadic hair loss. Certain commonly given drugs may negatively affect the hair life cycle and result in telogen effluvium if hair loss is caused by medical therapy. Two to four months following treatment initiation, hair loss happens.[49] If treatment is prolonged, it may recur, but it normally terminates when it is discontinued. Chronic hair loss advances over time, in contrast to acute, sporadic, or reactive hair loss, which typically lasts no longer than six months. There are two primary forms of long-term hair loss that have distinct causes and outcomes: androgenetic alopecia and chronic telogen effluvium.[50]

### Chronic telogen effluvium

A rather frequent type of hair loss that involves the entire scalp is called chronic telogen effluvium. Over time, it might cause a decrease in hair density, although baldness is not the result. Women are mostly affected more than males, and it can happen at any age. Thyroid hormone imbalances, low-calorie diets, and severe, ongoing stress can all contribute to this persistent hair loss. Chronic hair loss is seen to develop favorably after the underlying cause is found and removed. Hair density may not return to its original form for 12 to 18 months after the onset of regeneration, which takes about 3 to 6 months to notice.[51]

### Androgenetic alopecia

As the name implies, androgenetic alopecia is a kind of hair loss with a genetic and hormonal cause (including androgenic hormones). It is typified by the increasing shrinkage of hair in specific areas of the scalp, which eventually causes baldness and hair thinning. Men are primarily affected by androgenetic alopecia, and as men age, the condition affects more of them: 20% of males by age 20, 30% by age 30, and one in two men by age 50. Male androgenetic alopecia symptoms manifest as

thinning hair on the crown of the head. The forehead (recession of the hairline into a V-shape look) and the back of the head (tonsure) are the first areas affected by this balding.[52] After that, it moves to the top of the head. It is related to the phenomena of hair follicle shrinkage, which causes hair to progressively become lighter and thinner until it eventually comes out and results in baldness. At the temples and on the back of the head, the hair still has a crown shape. A gradual loss of hair density on the crown of the head is the most common sign of androgenetic alopecia in women compared to men. The taper widens along the midline, producing a pine tree-like sparsity.[53] In contrast to the male variety, women's androgenetic alopecia is never total and does not result in baldness; some hair does remain, albeit thin.

### The role of genetic factors

Hair loss due to genetics usually starts out modest, mostly on the left and right sides of the front hairline. Baldness at the front of the head results from the hairline receding as this area of hair loss moves backward over time. The same process, which causes hair loss, is also seen at the top of the head in the vertex, the area where hair rotates. These patches get bigger over time and finally, come together to form a bald head with a protected region on the sides and rear of the head. One can genetically inherit androgenetic hair loss from parents.[54] On the other hand, an individual may acquire this genetic disease from an aunt or uncle even if it is not inherited from their parents. The most prevalent cause of hair loss in men is androgenetic alopecia, which affects 40% of women over the age of 40. This results in a marked increase in hair loss, a slowdown in hair regeneration, and weak, thin, tiny hair that regrows. About 30% of men before the age of 30 and 50% of men in their 50s suffer from androgenetic alopecia, whereas 40% of women, usually beyond the age of 50, can experience it. Though the precise origin of this kind of hair loss remains unknown, genetic and hormonal factors (androgens) are considered to be significant contributors.[55] While several hormones work well on the scalp, androgens are the most potent. Women may notice thinning hair during menopause or pregnancy, which could be brought on by variations in the hormone dihydrotestosterone (DHT) levels in the scalp. For boys, the DHT hormone is essential for the onset of puberty and the growth of facial and body hair. The same androgens, particularly DHT, can cause the hair strands on the scalp to shrink at later ages. Dihydrotestosterone also quickens the shedding and shrinkage of hair follicles as they enter the telogen phase.[56] More hair loss occurs as the anagen phase shortens and hair is forced into the telogen phase. This cycle can result in permanent hair loss if the condition is not resolved. One in three women will experience hair loss, thinning hair, and lifeless hair at some point in their lives. Genetic hair loss accounts for a large percentage of women's hair loss issues. There is a familial history of female pattern hair loss in 20% of cases.[57]

### Development of the APCDD1 gene and hair follicle

Keratin, the protein that supports and makes up our hair, is resistant to wear and breaking. Sequential amino acid-building components combine to generate keratin, which also makes up our nails. In this way, the hair strands have a highly strong structure despite their thinness. In summary, hair is rich in phospholipids, cholesterol, fatty acids, free amino acids, urea, uric acid, and mainly keratin, in addition to the limited quantity of water it contains. Keratin, which is made up of 18 amino acids and is generated by keratinocytes at the base of the dermal papilla, forms the fundamental structure of hair.[58]

The hair follicle is composed of three main parts:

*Upper part (Infundibulum):* The area between the hair exit hole and the follicle's sebaceous gland connection is known as the upper section or infundibulum.

*The middle part (Isthmus):* The space between the hair muscle's attachment point and the sebaceous gland's entrance. The "Bulge Region," which is the location where the Arrector pili muscle attaches, is crucial for stem cell research.

*Lower part (Inferior):* This portion extends from the base of the follicle to the location where the Arrector pili muscle is attached. The hair bulb is located at the base of the follicle. Dermal

papilla cells and hair matrix make up the hair bulb.

As previously stated, keratin is a fibrous protein that forms a cross-linked spiral structure in various regions of the body. Keratin, which contains methionine and cysteine amino acids, is a unique protein that is almost insoluble in water and contributes to the resilience of hair.[59]

### *Structure*

Hydrogen bonds in keratin provide elasticity to the hair, while their location adds shine. Sulfur bridges join the polypeptide chains that form keratin. Hair is made up of Keratin molecules joined by sulfur bridges. The hair's strong sulfur connections make it resistant to physical and chemical damage. Ultraviolet radiation, intense heat, oxidizing chemicals, and strong acidic and basic substances can all break down sulfur bonds. Cysteine contributes to the hardness and endurance of the hair by forming disulfide bonds. Proteins in hair are water-insoluble and resistant to proteolytic enzymes.[60]

### *Hair follicle*

The follicle is the structure from which hair grows. This structure houses the hair and produces oil to lubricate the skin and hair. In addition, the visible sections of the follicle include specific muscles.[61]

### *Hair root*

The papilla is an important location for hair growth and nourishment. The papilla, which protrudes into the bulb and has an oval shape surrounded by matrix cells, is where the first impulses that trigger hair growth are transmitted. Cytokines are molecules that travel through the Golgi apparatus before binding to receptors in the papilla. These cytokines are proteins that affect cell division in either a positive or negative way, depending on the type of target cell. For example, cytokines released under the influence of androgens attach to the appropriate receptors, causing hair development.[62] Other chemicals occupying receptors can have an impact on the function of cytokines and, by extension, the cell.

Matrix cells, which surround the papilla, play a crucial part in hair growth by dividing quickly. These cells' cytoplasm contains a large number of organelles, including ribosomes and mitochondria. The inner root sheath lacks melanin and is not keratinized.[63] The outer root sheath is made up of multiple rows of cells that extend from the bulb's lower level to the entrance of the sebaceous gland duct. It grows by dividing in the early phases of the anagen phase, but division stops later on. The body of hair has three layers: the medulla, the cortex, and the hair cuticle. The medulla is the inner component of the hair and may not be present in all hairs. Medullated hairs can be of several sorts. The cortex surrounds the medulla and serves as the foundation for the hair. The cuticle is the hair's outermost layer, which protects it from external effects and is made up of nucleated squamous epithelial cells.[64]

APCDD1, a conserved single-pass transmembrane protein of ~55 kDa with a large glycosylated spliced extracellular domain and a short cytoplasmic domain, is one of the most frequently and significantly upregulated genes under Wnt signaling.[65] This gene has no clear similarities to any known protein. In the context of human disease, excessive Wnt signaling has been linked to cancer, as has high APCDD1 expression in colon cancer and Ewing sarcoma cell lines.[66] In transfected cells, APCDD1 reduces Wnt signaling, and the Leu9Arg mutation in the signal peptide has been linked to hereditary hypotrichosis simplex, a hair follicle growth abnormality.[67]

## Effect of the APCDD1 gene on hair growth and loss

Hereditary hypotrichosis simplex is an uncommon form of autosomal dominant hair loss marked by the shrinkage of hair follicles. A novel locus associated with hypotrichosis simplex was identified on chromosome 18p11.22 using genetic linkage analysis, and a mutation (L9R) in the APCDD1 gene was reported in three families. APCDD1 is a membrane-bound glycoprotein that is highly expressed in human hair follicles.[68] *In vitro* studies have shown that it interacts with WNT3A and LRP5, two critical components of the Wnt signaling pathway. The APCDD1 suppresses Wnt signaling independently and upstream of β-catenin, according to functional studies. Furthermore, APCDD1 inhibits the activation

of Wnt reporters and target genes.[69] The L9R mutation is located in APCDD1's signal peptide, which disrupts translation from the endoplasmic reticulum (ER) to the plasma membrane. L9R-APCDD1 most likely has a dominant-negative effect, reducing the stability and membrane localization of the wild-type protein. These findings identify a novel inhibitor of the Wnt signaling pathway, which is critical for human hair development. Given that APCDD1 is expressed across multiple cell types, it is possible that APCDD1 regulates a variety of biological processes mediated by Wnt signaling.[70]

## GENETIC RESEARCH AND TREATMENT STRATEGIES

### Genetic research on APCDD1 gene and hair loss

Genetic research on hair loss has identified the APCDD1 gene as a significant player in hair follicle biology. The APCDD1 gene has been found to inhibit the Wnt signaling pathway, which in turn interferes with BMP and Notch pathways, ultimately leading to alopecia and hair loss. Mutations in the human APCDD1 gene have been associated with hair loss in hereditary hypotrichosis. Specifically, a sequence variation in the APCDD1 gene has been reported in autosomal dominant generalized hypotrichosis, leading to thinning of hair on the scalp, body, axillary, and pubic regions.[71]

It has been determined that APCDD1 functions as a dual BMP/Wnt inhibitor throughout the development of the skin and nervous system. Research has demonstrated that APCDD1 is highly expressed in human hair follicles' dermal papilla, matrix, and hair shaft, demonstrating the protein's significance in hair biology. Additionally, people with hereditary hypotrichosis simplex a rare autosomal dominant form of hair shrinkage and loss have mutations in the APCDD1 gene, according to genetic linkage studies. In general, the growth of hair follicles and hair loss problems are significantly influenced by the APCDD1 gene. Its importance in preserving healthy hair development is highlighted by its suppression of the Wnt signaling pathway and interactions with other pathways. Comprehending the genetic underpinnings of hair loss, specifically as they relate to genes such as APCDD1, yields important information for future therapeutic approaches.[72]

### APCDD1 gene-based treatment approaches and promising methods

Treatments for hair loss disorders that target the APCDD1 gene appear promising in treating issues pertaining to the biology of hair follicles. APCDD1, a new Wnt inhibitor that is mutated in familial hypotrichosis simplex, has been found to be essential for human hair development. APCDD1's inhibitory function in the Wnt signaling pathway is understood, laying the groundwork for future treatment approaches meant to encourage hair growth and regeneration. Viral vector-based gene therapy techniques, including AAV2.7m8, have demonstrated effectiveness in stimulating hair cell regeneration in the inner ear, indicating a possible application for gene therapy in the treatment of hair loss disorders. Furthermore, using the APCDD1 gene as a Wnt inhibitor offers prospects for creating novel gene therapy approaches to treat hair diseases caused by APCDD1 mutations. Regenerative medicine advances, such as use of viral vectors like AAV9-PHP.B to transfer genes to hair cells, present promising treatment options for disorders related to genetic factors that may cause hair loss and hereditary deafness. Through gene therapy techniques, researchers hope to restore hair cell function and stimulate hair growth by focusing on particular genes like APCDD1.[73]

### The future of personal care based on genetic information

Genetically informed personal care has a bright future ahead of it, especially when it comes to hair diseases and hair loss. Advances in the study of hair follicle biology and genetics are opening the door to personalized care options based on a person's genetic composition. Research has demonstrated the significance of genes such as APCDD1 in controlling factors related to hair growth and hair loss. Translational research in hair diseases is anticipated to undergo a transformation in the future due to the integration of artificial intelligence, bioengineered systems, and human cellular

models. Researchers want to create targeted medicines that address the underlying genetic causes of hair loss problems, providing more efficient and individualized therapy options, by utilizing human cell models and genetic insights.[74]

Moreover, novel approaches to addressing hair loss and encouraging hair regeneration include gene delivery methods to the hair follicle, such as genetic therapy directed at certain genes like APCDD1. By comprehending the genetic processes governing hair follicle maturation and growth cycles, scientists can create gene-based therapies aimed at addressing the fundamental genetic elements causing hair-related issues. Future developments in gene therapy, transcriptome analysis, and genetic mapping could completely change the way that hair diseases are treated on an individual basis. Through the utilization of advanced technology and the deciphering of the genetic underpinnings of hair loss diseases, genetically informed personal care has the potential to transform the identification, handling, and cure of a wide range of hair-related problems.[75-78]

In conclusion, the APCDD1 gene pathway's genetic mapping of hair loss presents a fresh viewpoint on the fundamental causes of alopecia and suggests possible directions for medical therapies. Significant progress has been achieved in understanding the function of APCDD1 and its related pathway in hair follicle biology and hair loss etiology by thorough genetic research and functional assessments. The significance of genetic variables in the etiology of alopecia is highlighted by the discovery of genetic variations within the APCDD1 gene pathway linked to susceptibility to hair loss. These results highlight the complicated molecular networks involved in the regulation of hair growth and highlight the complex genetic architecture underlying the formation, cycling, and maintenance of hair follicles. More research is necessary to fully understand these networks. Alopecia prevention and treatment strategies that are tailored to each patient are made possible by the knowledge gathered from genetic mapping studies of hair loss. The quality of life for those who suffer from hair loss may be enhanced by targeted treatment approaches that modify APCDD1 expression or function using pharmacological interventions or gene editing methods. Early diagnosis, risk assessment, and individualized treatment of hair loss diseases may be made easier by the incorporation of genetic data into therapeutic practice. In addition to providing alopecia sufferers and their families with important information regarding the genetic basis of their condition, treatment options, and supportive resources, genetic counseling and education are essential.

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