

What is androgenetic alopecia?

Androgenetic alopecia is also called male pattern alopecia. It refers to a symptom that develops after puberty, influenced by the androgen, where thinning and/or loss of hair are seen from the vertex of the head to the frontal region. In the early stages, thick and long hair, so-called terminal hair, has been gradually replaced by thin and short hair, so-called vellus like hair. Thinning of hair therefore progresses. In other words, during the early stages, the hair becomes thin and less visible, giving the impression that hair shed. However, a decrease in the number of hair is not the major cause of alopecia. As symptoms progress, however, the hair follicle (Note 1) becomes atrophied, and the number of hair does decrease.

1. Characteristics of androgenetic alopecia

Let us compare the conditions of the head of three men in their late 30s, in order to understand the characteristics of androgenetic alopecia (AGA), or male-pattern alopecia. Figure 1 shows the condition of the heads of three men in their late 30s (one healthy subject and two with AGA). The top parts of Figure 1 shows the global hair photographs, and the middle parts shows magnified photographs of the area of thinning hair at the vertex region after it was sheared. In the photos taken immediately after the shearing and two days later, by measuring the length of each strand of hair, we can analyze the growth rate, the thickness of hair, the density, and the rate of anagen hair (the ratio of hair that grows more than 0.4 mm per day). The lower parts in Figure 1 show the analytical results.

1) Characteristics of sites of thinning and/or loss of hair (top parts, Figure 1)

Let us observe the sites of thinning and/or loss of hair, using the photos on the top parts of Figure 1, which illustrate the outer appearances including the vertex region. Appearance-wise, no thinning of hair can be detected in the healthy subject ([1]). However, subjects with AGA (subjects [2] and [3]) show thinning and loss of hair in the vertex region near the hair whorl as well as the top of the forehead on the right and left. As can be seen, with AGA, the hair thinning and loss occur only in limited sites.

2) Characteristics of hair growth (Figure 1, middle and bottom parts)

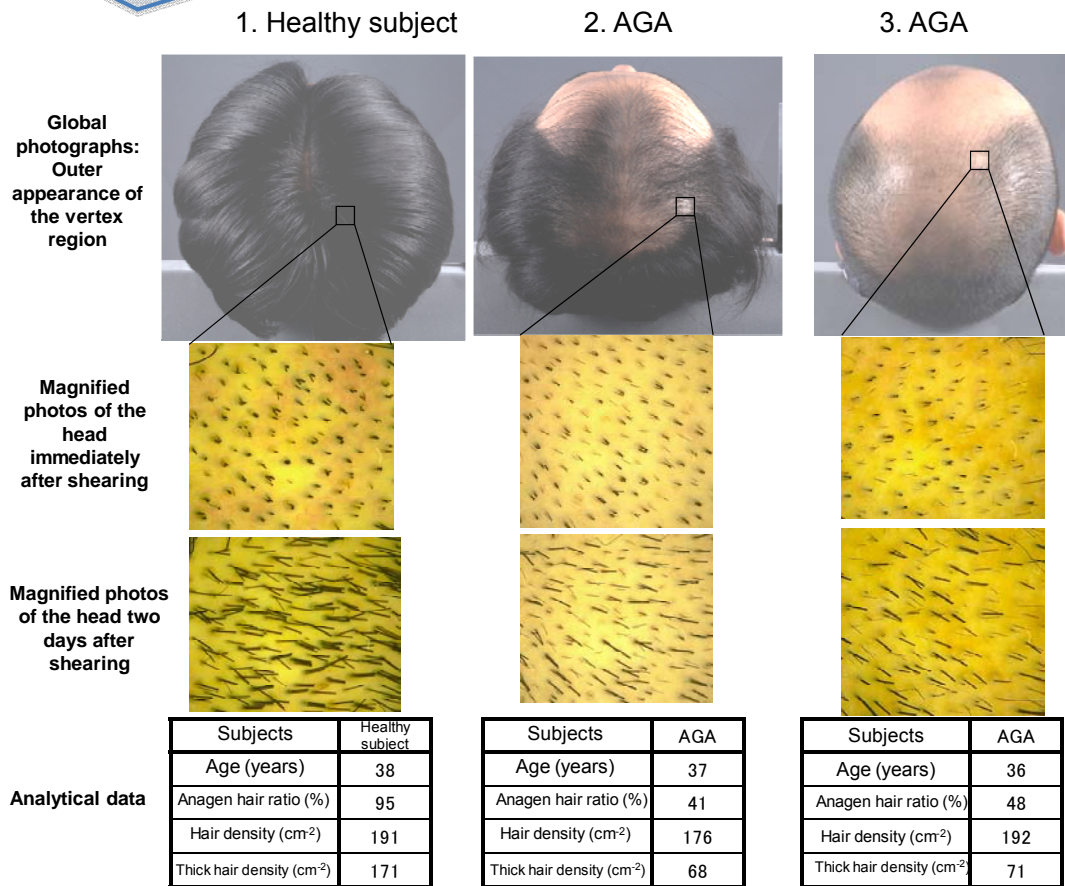
(1) Individuals with AGA have a large number of hairs that does not grow.

The photos featured in Figure 1's middle parts present a magnified view of the part in the vertex region. While the healthy subject ([1]) shows an abundance of black and thick hair, so-called terminal hair in the photos in 2 days later, the AGA subjects ([2] and [3]) show a prevalence of thin, short hair, so-called vellus like hair. There also are hairs that have not grown at all during the 2-day period. An anagen hair was defined as a hair with a growth rate of 0.2 mm per day or more. We found that the anagen hair ratio, was 95% in the healthy subject, while it was considerably low at 41% ([2]) and 48% ([3]) in AGA subjects.

(2) Even if an individual has AGA, the number of hairs does not differ sharply from that of healthy individuals.

The hair number per 1cm^2 was 191 in the healthy subject ([1]), while, in the AGA subjects, it was 176 ([2]) and 192 ([3]), respectively, showing not much of a difference.

Fig. 1. Quantitative analysis of androgenetic alopecia



Abbreviation: AGA, Androgenetic alopecia. Thick hair density is defined as a hair density with a hair diameters of 40 μm or more

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(3) AGA subjects have a fewer number of thick hairs than the healthy subject.

The number of thick hairs with a diameter of 40 μm or more was 171 in the healthy subject ([1]), while, in the AGA subjects, it was 68 ([2] and 71 ([3]), respectively, which is drastically lower.

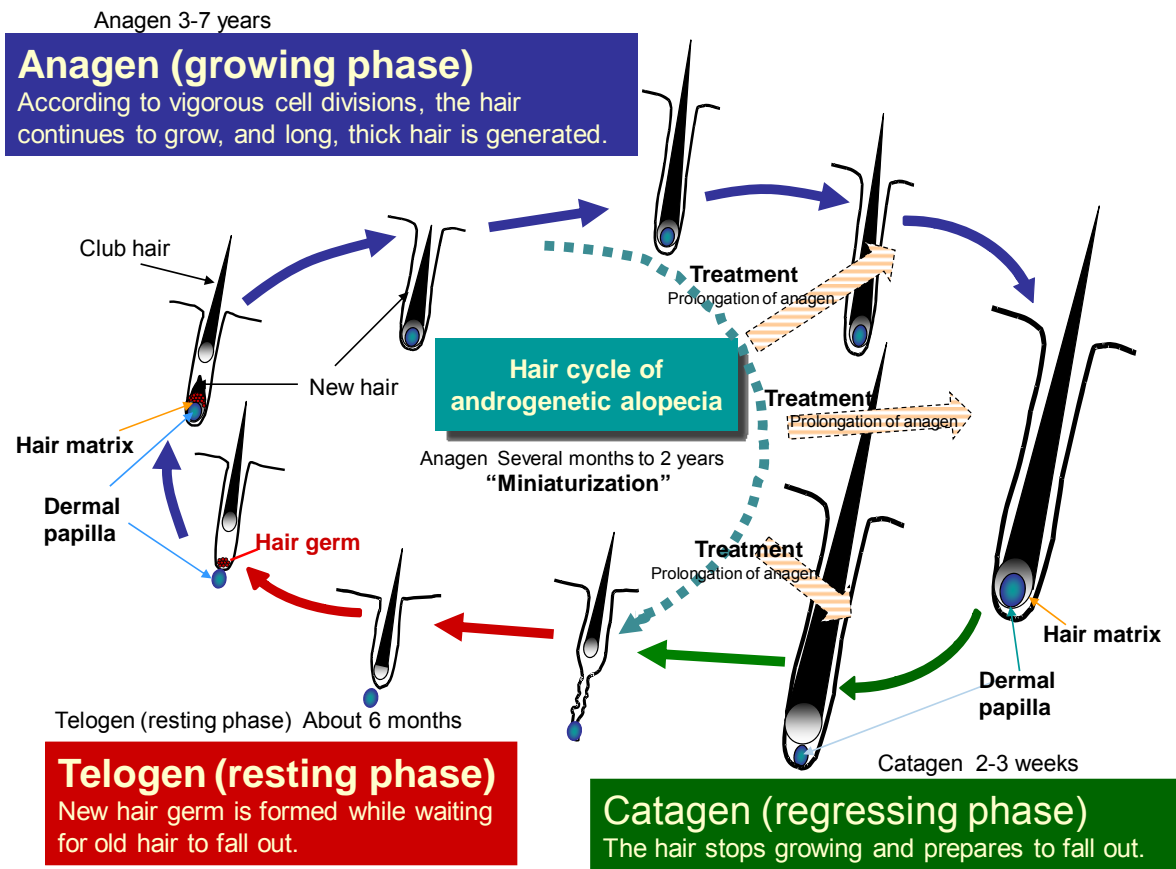
Summary

Subjects with early- to moderate-stage AGA see their hair become thinner and less visible, giving the impression that hair thinning has progressed, and that the hair has fallen out. Therefore, hair loss with the decrease of hair number is not necessarily the major reason. This phenomenon whereby hair becomes thinner and shorter is called the "miniaturization of hair follicles" (Note 2). Hair follicles refer to the part of the hair inside the scalp as shown in the diagram of the hair cycle (Figure 2). We can see that, in AGA, hair follicles have become smaller.

2. Causes of androgenetic alopecia

In AGA, the hair that grows in the area from the forehead to the vertex region becomes thin and short. This is caused by changes in the hair cycle (Note 3). In this section, we will describe the hair cycle (Figure 2) in detail.

Fig. 2 Hair cycle



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- 1) The anagen
Human hair that grows on the head falls out and regrows at a cycle of about 3 to 7 years, and becomes thick, long hair. This is called the hair cycle (Figure 2). In the thick anagen hair (terminal hair) shown on the right-hand side of the diagram (Note 4), the hair matrix (Note 5) is found around the dermal papilla where capillaries penetrate. The hair matrix is the site of vigorous cell division activity, and receives (Note 3) oxygen, nutrients and other substances from the blood vessel from the dermal papilla (Note 6) (Figure 3). The hair matrix continues to vigorously divide cells and allows the hair to keep on growing.
- 2) The catagen
After the anagen period continues for 3 to 7 years, the hair matrix stops the cell division

process. The hair enters the catagen (Note 7). The hair shaft gradually rises from inside the skin to outside the skin, and continues to grow for about 2-3 weeks although the growth rate is much slower than that in the anagen period. In AGA, the anagen is terminated and the catagen onsets in without sufficient growth of hair follicles.

3) The telogen

The condition seen after the catagen where hair growth has completely stopped is called the telogen (Note 8). After about 6 months into the telogen, the dermal papilla interacts with a second hair germ, which grows a new hair matrix (Note 9). The hair matrix cells surrounds and incorporates the dermal papilla cells to form a new hair follicle. If this hair follicle penetrates thickly and deeply into the skin (about 5-6 mm deep), a new terminal hair, is created to enter a stage of growth, anagen. Healthy subjects see their old hair (club hair) replaced by newly generated hair.

Summary

In AGA, the hair becomes thin and short (“miniaturization of follicles”). The reason is the shortening of the anagen period. If the period of growth is cut short, hair anew enters the catagen prematurely without growing thick and long. As a result, it enters the telogen while remaining thin and short. This hair cycle of AGA rotates within 2 years. the head with numerous miniaturized hairs, thus causing AGA.

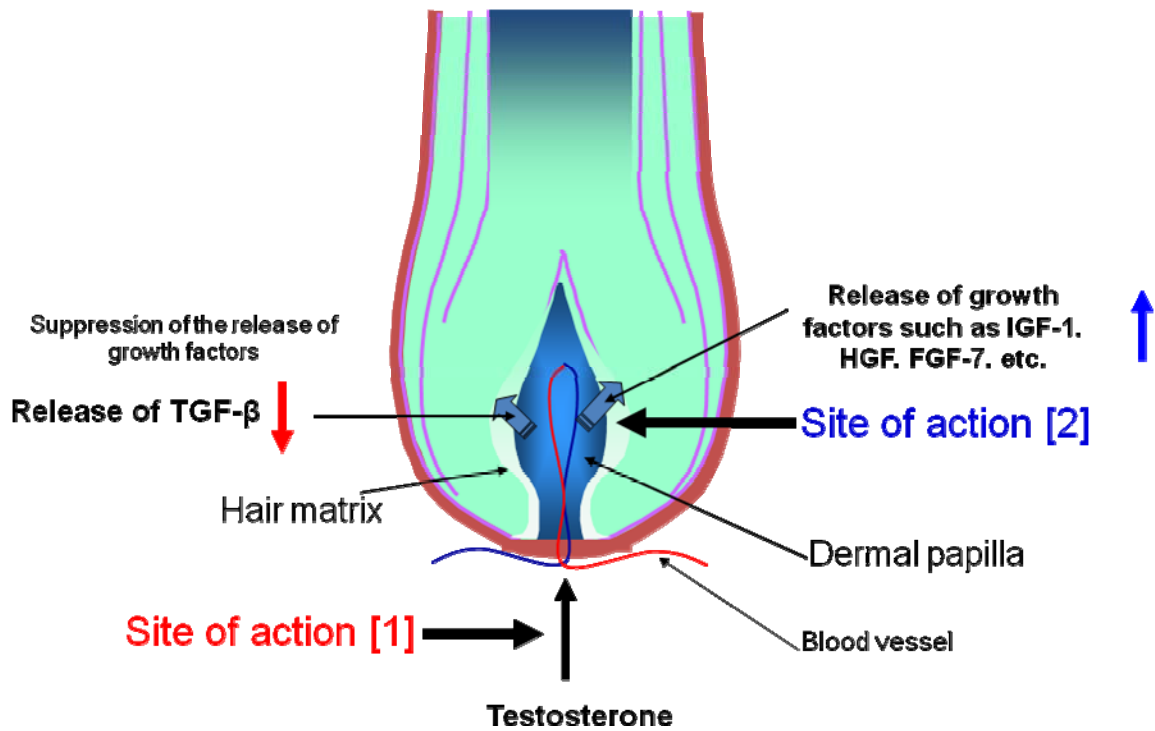
Therefore, the key to treating the symptoms of AGA is to focus on the hair cycle that has become shortened, extend the period of hair growth, and try to return it to a hair cycle length that is as close to normal as possible. (See arrow indicating “Treatment” shown in Figure 2.)

Prevention and treatment of androgenetic alopecia

With miniaturized follicles, the dermal papilla loses their vitality, preventing the hair matrix to conduct cell divisions sufficiently. Therefore, working on the dermal papilla is the key to preventing and treating AGA. In the case of healthy individuals, their dermal papilla receives oxygen, nutrients and other substances from the blood vessels to give them vitality. At the same time, they transfer these substances to the hair matrix, as well as growth factors produced by the dermal papilla, namely, IGF-1 (Note 10), HGF (Note 11), and FGF-7 (Note 12), and allow the hair matrix to continue its division process for extended periods (Figure 3). In contrast, in AGA, testosterone acts on the dermal papilla, and then TGF- β (Note 13) is released from the dermal papilla to act on the hair matrix, inducing the catagen and shortening the hair cycle as a result.

Thus, acting on the dermal papilla is the key to prevent and treat AGA. As sites of action, the two sites, shown in Figure 3, may be considered. The site of action [1] attenuates the androgen's effects on the dermal papilla, suppresses the production of TGF- β , and inhibits advancement to the catagen. The site of action [2], on the other hand, generates growth factors such as IGF-1, HGF and FGF-7, in the dermal papillae to prevent a decline in the cell division activities of the hair matrix.

Fig. 3. Sites of action of androgenetic alopecia treatment drugs



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AGA treatment drugs that are currently used throughout the world include finasteride (product name: Propecia®), which is an inhibitor of steroid 5 α reductase (Note 14), and minoxidil (product name in Japan: RiUP®). Whereas finasteride demonstrates hair growth effects mostly by working on the site of action [1], minoxidil does so by working on the site of action [2], along with blood flow promotion and other effects. Thanks to these actions, Propecia® has been proven to possess the effects and indications for “delaying advancement of AGA in men,” and RiUP, for “fostering hair growth in AGA as well as restoring hair.”

Summary:

The two sites of actions on the dermal papilla are believed to prevent and improve AGA. Propecia® works on site of action [1] to attenuate the action of androgen on the dermal papilla and inhibit advancement to the catagen. RiUP works on site of action [2], to generate growth factors in the papilla and promote cell division of the hair matrix, thus preventing the hair matrix’s cell division activities from declining.

4. Glossary

- Note 1. Hair follicle: The part of hair found inside the skin.
- Note 2. Miniaturization of hair follicles: Miniaturized hair follicles in AGA that have not grown fully as a result of a shorter anagen period.
- Note 3. Hair cycle: Cycle in which the hair repeats its process from growing to falling out.
- Note 4. Anagen: A period in the hair cycle where the hair continues to grow.
- Note 5. Hair matrix: An organ that creates hair through cell division.
- Note 6. Dermal papilla: An organ that interacts with the hair matrix cells and supplies nutrients, oxygen and other substances to the hair matrix.
- Note 7. Catagen: A period in which the end of the hair active growth arises and hair growth rate is reduce.
- Note 8. Talogen: A period in which hair growth completely stops.
- Note 9. Hair germ: The buds of new hair. A multicellular assembly that is first formed when new hair is created.
- Note 10. IGF-1: Insulin growth factor-1 (it generally promotes cell growth)
- Note 11. HGF: Hepatocyte growth factor (it generally promotes cell growth)
- Note 12. FGF-7: Keratinocyte growth factor -7 (it generally promotes cell growth)
- Note 13. TGF- β : Transforming growth factor-beta (it generally suppresses cell growth)
- Note 14. Steroid-5 α -reductase: It catalyzes the reduction of the OH in steroid's position 5.
For example, it reduces testosterone to dehydrotestosterone.

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