

Baldness genetics – more than skin deep.

Stephen B Harrap

The condition male pattern baldness is common, estimated to be present in 50% of white males by 50 years of age. It is characterized by the loss of hair from the scalp in a defined pattern and, although there are no serious direct health consequences, the loss of scalp hair can be distressing. Understanding male pattern baldness might also reveal some fundamental secrets of biology.

Hair follicles on the scalp seem to be pre-programmed to undergo a transformation from the normal long growing phases and short resting phases to cycles of long rest and short growth periods. This process is coupled with progressive miniaturization of the follicle.

Unusual postulated causes have ranged from an old idea that baldness was the result of wearing hats and depriving the scalp of sunlight and air, to more recent suggestions of skull expansion.ⁱ However, the factors that determine male pattern baldness appear to be genetic predisposition coupled with the presence of sufficient circulating androgens. Evidence in support of androgenic influence comes from the fact that eunuch's do not go bald. For this reason male pattern baldness is also known as androgenetic alopecia.

The mystery, and the potential for fundamental biological discovery, is why front hair should vanish, while that at the back of the head should flourish. Presumably genetic predisposition alters expression of key genes in a regionally specific manner to cause patterned hair loss. But what genes are involved and how are they affected?

Prime candidates for baldness are genes encoding enzymes and receptors involved in sex steroid metabolism. Key enzymes include 5 α -reductase that converts testosterone (T) to the more active dihydrotestosterone (DHT) and aromatase that converts estrogen to T. Both T and DHT exert their effect by binding to the androgen receptor (AR), a member of the steroid-thyroid hormone nuclear receptor superfamily. In balding scalp there are observed high levels of T, DHT and AR.

In 2001, we were the first to identify the AR gene was significantly associated with male pattern baldness.ⁱⁱ This finding has now been replicated by at least 5 other independent studies. The presence of the AR gene on the X chromosome, which men inherit from their mother, is consistent with the popular belief that baldness is inherited from the maternal grandfather.

However, the observed patterns of inheritance are not simply consistent with an X-linked recessive condition. For example, one often sees fathers and sons who are bald. Indeed, it has postulated for some time that male pattern baldness best fits a polygenic pattern.ⁱⁱⁱ

Consistent with the polygenic concept, more recent genome wide association analyses have identified another locus on chromosome 20.^{iv,v} This locus seems to be independent of the AR gene in its association with baldness and the identity of the gene and the mechanisms of action are not yet clear. Nevertheless, the AR appears to be significantly stronger in its association with baldness and fits nicely with the known role of androgens in this condition.

The mystery remains as to the precise DNA variant in or around the AR gene that explains its role in baldness. We know that there are no variants in the coding sequences of the gene and so it is more likely that there are variants in regulatory regions within and outside the AR gene that control the time and tissue-specific nature of its expression. The challenge in identifying the precise variant is the fact that it might be anywhere within approximately 1 million base pairs of DNA.

The search is now underway around the AR gene to check the many hundreds of polymorphisms to see whether any might be in critical sequences that control gene expression. This is a difficult task, as current knowledge is limited and many such sequences are not recognisable.

However, the study of male pattern baldness offers an advantage over many other common conditions in that it is possible to obtain fresh tissue for detailed analyses of gene expression patterns. We are pursuing a complementary and promising approach that involves looking at the AR gene from balding and non-balding scalp of volunteers. This might reveal differences in the expression of the AR gene related to chemical modification of the DNA, such as methylation. Differences in methylation patterns across the AR gene might provide insights into the so-called epigenetic mechanisms that control gene expression and in this case might predispose to male pattern baldness.

Androgenetic alopecia is a condition that might not be life threatening in itself, but might offer insights into basic molecular mechanisms that underpin many of the more serious diseases of middle age.

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