WHY DO SO MANY INDIAN MEN HAVE HAIRY EARS?

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Like the beard, hairy ears are rarely if ever seen in women. Unlike the beard, only a small minority of men have hairy ears. Many of these men are from India. Why is this so? And how is this trait inherited? How do scientists investigate such questions?

It is not uncommon to see men with hair growing from the fleshy part of their outer ears (or pinnae). While the amount and quality of this hair growth can vary, the presence of excessively coarse and long black ear hair is known medically as hypertrichosis pinnae auris (see **Fig. 1**). This trait or distinguishing feature is most common in men from India and Sri Lanka. In fact, the record for the longest ear hair is currently held by Anthony Victor, a retired school headmaster, from Madurai, Tamil Nadu. Why is this so? This question has captured the attention of many scientists.

Early hypotheses

Interestingly, hairy ears, like beards, are rarely if ever seen in women. For example, as far back as 1907, the Italian physician C Tomassi documented the occurrence of hairy ears through five generations of an Italian family (see **Fig. 2**). His pedigree chart showed that **only men** have hairy ears, that **all sons** of hairy-eared men have hairy ears, and **none** of their **daughters** do. This suggested that the trait had a genetic basis and that it was passed only from father to son, and all sons, but not to daughters.

As other such pedigrees were described, the internationally-known geneticist JBS Haldane, who was born in England but later became an Indian citizen, first sketched a hypothesis of Y-linked inheritance for hairy ears in 1936 (see **Box 1**). He ascribed hairy ears to a mutation in a gene (or an allele) on the Y chromosome. Since only men have this chromosome and receive it from their fathers, the trait was expressed only in men and was transmitted to them from their fathers.

Box 1. The genetic basis of hairy ears:

Tomassi made his observations shortly after Mendel's laws of inheritance were rediscovered in 1900. Those laws said that traits such as seed colour or shape in peas were determined by pairs of factors (now called **alleles**), one inherited from each parent. The combination of alleles that the offspring inherited (genotype) determined the nature of the trait they expressed (phenotype). Alleles are different forms of the same **gene**. Typically, one of the two alleles for any gene is expressed if it is present in either one or two copies in the offspring. This is called the dominant allele. The other allele, which is expressed only if present in two copies, is called the recessive allele.

What does this have to do with hairy ears and beards? As you know, genes are located on chromosomes. Males and females have 22 pairs of identical chromosomes, one inherited from each parent. These are called autosomes. Although Mendel's Laws explained the behaviour of typical genes, it turns out that they do not apply to all genes or traits. In humans and other mammals, sex is determined by a pair of non-identical chromosomes, called X and Y, a fact recognized by WE Castle in 1922 (These are just names, and not descriptions of what these chromosomes look like under the microscope. For example, a Y chromosome is not an X chromosome missing one leg). Females are XX—they have two X chromosomes. Each female receives one of these X chromosomes from her father, and another from her mother. Males are XY—they have one X and one Y. Each male receives the X chromosome from his mother and the Y chromosome from his father. Alleles of genes on the X and Y chromosomes are said to be sex-linked. In XX females, sex-linked alleles behave like the alleles on autosomes. In XY males, whichever allele is present on the single X chromosome determines what trait is expressed. Genes on the Y chromosome determine sex. In particular a gene called SRY (Sex-determining region Y) triggers differentiation of male from female development in the early embryo. Every male inherits his Y chromosome from his father. It is due to the presence of the Y chromosome that he develops as a male, and exhibits male traits, such as beard growth.

What about traits like hairy ears, that occur only in males, and only in a few males? This is where it gets interesting. Let's suppose that the inheritance of hairy ears is determined by a single gene with two alleles—call them H and h, where H is the allele for non-hairy ears, and h the allele for hairy ears.

Let's also suppose that this gene lies on the Y chromosome. Then, Tomassi's pedigree is easily explained. The great-grandfather II-3, with hairy ears, has five sons and two daughters (by two wives). All five sons have hairy ears, while the two daughters do not.

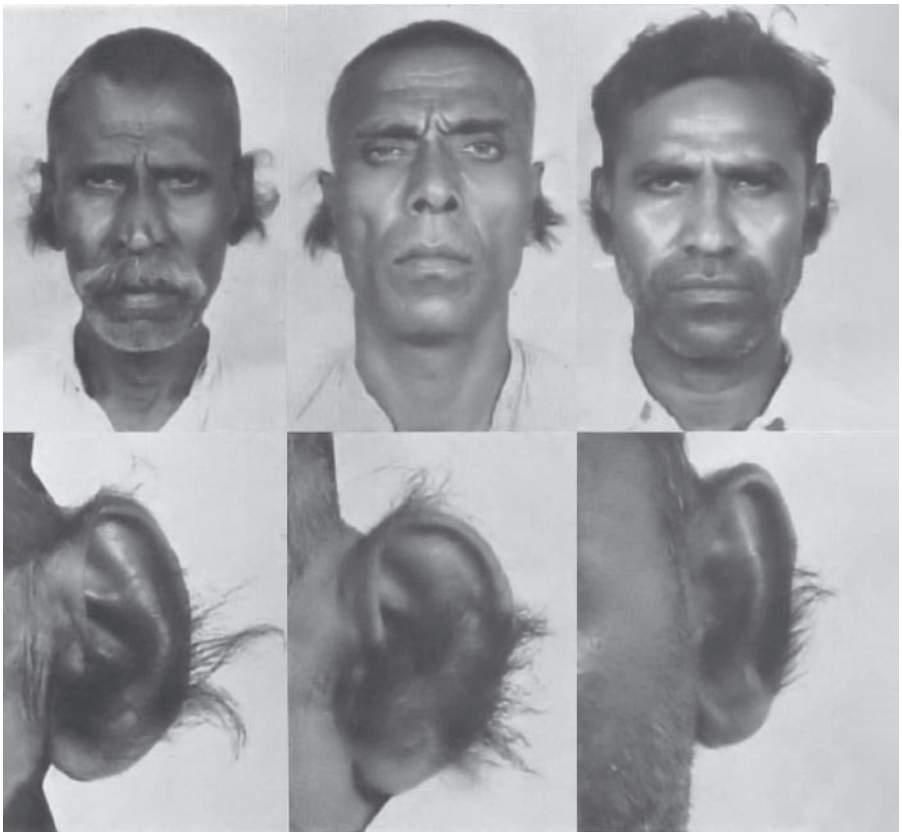


Fig. 1. Hypertrichosis in three men from the southern Indian city of Vellore. Slightly modified from Figure 1 of Stern et al. (1964). The caption of their image reads: *"Vellore. Three Muslim brothers. ± 60, 50-55, and 45-50, with grades of hairiness 5, 5, and 4, respectively,"* based on the system of Slatis and Apelbaum (1963).

One of the first modern experimental investigations of Haldane's hypothesis was by the Indian scientist KR Dronamraju. In 1960, Dronamraju simply counted the occurrence of hairy ears among 400 persons traveling on public buses in Andhra Pradesh. Among 345 men, 21 had hairy ears to some degree; none of the 55 women did. When Dronamraju looked at the pedigrees of three of the men with hairy ears, he found that **all** of their sons above age 17 (when the trait becomes apparent) also had hairy ears, but **none** of their daughters had any. Further, **none** of the affected sons had affected daughters. Haldane used statistical calculations to show that the Y-linkage hypothesis best explained Dronamraju's pedigrees (see **Box 2**).

Curt Stern, another eminent geneticist, and his colleagues had also reviewed pedigree data for several cases of hairy ears. In 1957, they suggested that this data *"... did not permit unequivocal discrimination between the hypotheses of Y-linked and autosomal inheritance"*. In 1961, Stern, Sarkar, and their

The fifth son (III-8) has two affected sons, and one unaffected daughter. His sons (IV-2 and IV-4) have multiple unaffected daughters between them. One of his sons (IV-2) has three sons, of which only one (V-4) had, at the time when this pedigree was being prepared, reached the age when hairy ears first begin to be seen. Prove this to yourself—simply write down h next to I-1, his sons, their sons, and so on, and the pedigree is exactly what you would expect for a Y-linked gene. Case closed, right?

Not really. Is it possible that the allele for hairy ears is not Y-linked, but instead an autosomal h recessive to a dominant H? Go back now and add a second h to every male h you wrote in before, and write one H next to every mother of an affected son. Now add an h to every one of these mothers, making them Hh. You will see that it is just possible to explain the pedigree by chance. How? Imagine the possibility that every son gets an h from his mother and an h from his father; every daughter gets an H from her mother and an h from her father; and this happens in every case. Then, all hairy-eared sons would be hh and all daughters would be Hh, with H dominating h.

Another alternative is that hypertrichosis is due to an autosomal H dominant to a recessive h, with sex-limited expression. This would mean that even if women had the genotype for the trait, the trait would be expressed exclusively in men, like male pattern baldness. Try this out for yourself. Get a clean copy of Tomassi's pedigree, but this time let H be the allele for hairy ears, h for non-hairy ears, and let Hh individuals have hairy ears. What do you get? What assumptions must be made?

How do we decide which of these three possibilities is most plausible? Let us do what we do in science, and look at some more evidence.

colleagues published a pedigree of a South Indian man with hairy ears. The man had three sons, all of whom were well past the typical age of onset for hairy ears. Yet, only one of them had hairy ears; the other two did not. Stern, Sarkar, and their colleagues claimed that this unusual pattern could be explained by autosomal inheritance of the trait (mutations of genes on autosomes, not sex chromosomes) and incomplete penetrance (see **Box 3**).

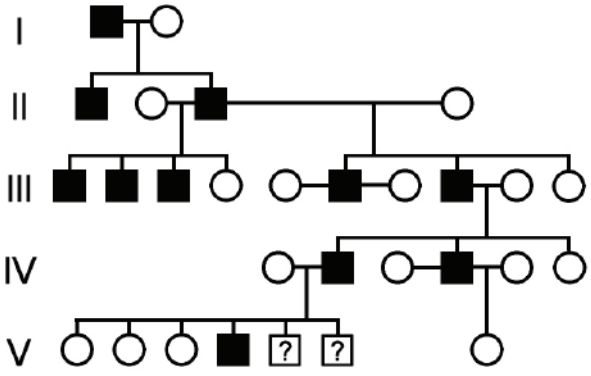


Fig. 2. Occurrence of hypertrichosis in an Italian family. Redrawn from Figure 8A of Stern (1957), after C Tomassi (1907): *Ipertricosi auricolare famigliare*. Giorn Pysch Clin Tech Manic 35: 1-21. Circles are women, squares are men; filled-in squares are affected men. Individuals are identified by generation (Roman numerals) and left-to-right order in each line. In the fifth generation, V-4 was 19 years of age at onset; V-5 and V-6 died before the expected age of onset.

In 1962, Dronamraju and Haldane suggested that the inconsistency between the results predicted by the Y-linked hypothesis and the results that Stern, Sarkar, and their colleagues had documented in their pedigree could be explained by *"illegitimacy"* in the *"lower-caste"*. The two sons who did not have hairy ears may have the **same mother** as the son with hairy ears but might have a **different, unaffected father**. This, they implied, **could not** (of course) happen in the *"upper-caste"* pedigrees studied by Dronamraju. That such discriminatory arguments made it to the scientific literature of the time shows us the distance that we have travelled since then.

Dronamraju and Haldane also countered Stern's claim that this pedigree challenged the possibility of Y-linked inheritance of hairy ears. What would be required to disprove Y-linked inheritance, they suggested, was to identify an **affected man** (or a man with hairy ears) whose father was **unaffected** but whose **maternal** grandfather **was** affected. In such a case, the trait would be 'skipping a generation' because it would be transmitted to a man from his mother's side. Since the man would only receive an X chromosome from his mother, such a case would show that the transmission of hairy ears could occur without the transmission of a Y chromosome (see **Fig. 3**).

Finding such a specific case was admittedly difficult. In the event, it has not yet been reported. As an example of the way science works, note Dronamraju and Haldane's assumption that the Y-linked hypothesis was now, by default, the 'correct' explanation; and that any alternative hypothesis required a higher standard of proof to be accepted.

Box 2. What statistical calculations did Haldane use?

Let us go back to Tomassi's pedigree. The probability that any one daughter would get an H allele from an Hh mother is 1/2. That all six daughters of affected hh men in the pedigree would inherit H from an Hh mother is $(1/2)^6 = 1/64$. This makes an autosomal recessive model pretty unlikely. It is also pretty unlikely that every hh man in the pedigree just happened to marry an Hh woman. This calculation is further complicated when an affected father has daughters but no sons (which proves nothing either way).

Once Haldane had shared these calculations, hairy ears began to be used as a standard example of Y-linked inheritance, alongside the four standard modes expected in classical genetics (autosomal dominant or recessive, and X-linked dominant or recessive).

In 1964, Stern and his colleagues objected to Dronamraju and Haldane's suggestion that the unusual pattern in their pedigree chart could be explained by illegitimacy. They also pointed to a 1963 study by the geneticists HM Slatis and A Apelbaum that showed that the degree of ear hair growth varied greatly (variable penetrance again) among Israeli men, and was often delayed until advanced age. This age-related pattern, Stern and his colleagues suggested, would explain at least some cases of the absence of the trait in men in whom it would otherwise be expected.

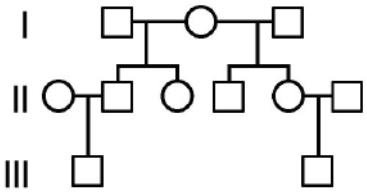


Fig. 3. A theoretical test of Y-linked inheritance of hypertrichosis. JBS Haldane suggested that the Y-linked model for the inheritance of hairy ears could be disproved by a pedigree of an affected man whose maternal grandfather was also affected. If an affected man's father and paternal grandfather were both affected, it would support the Y-linked hypothesis. Fill in the appropriate boxes in the pedigree above to show these two possibilities. Explain why the two scenarios disprove and support the Y-linked hypothesis, respectively.

Box 3. What does incomplete penetrance mean?

Incomplete penetrance occurs when individuals with the same genotype (genetic makeup) do not all express the same phenotype (trait characteristics)—the genotype fails to 'penetrate' through to the phenotype. This may be due to differences in environment or the influence of other genes. For example, a genotype predisposing to lung cancer may not be expressed in a non-smoker, and a genotype predisposing to breast cancer is more likely to be expressed in women than men. Because facial hair is strongly associated with male hormones, hairy ears might be a good candidate for this explanation.

Despite lingering doubts, Haldane's argument established the transmission of hairy ears as a textbook example of Y-linked inheritance. Dronamraju's pedigree chart even appeared in Stern's standard textbook on human genetics (3rd edition, 1973). There things sat until the new era of molecular genetics (see **Box 4**).

More recent advances

In 2004, the scientist AC Lee and his colleagues brought molecular thinking to bear on the Y-linked model for hairy ears. Previous classical studies had looked at pedigrees of hairy ears within a single family. Lee and his colleagues looked at the yDNA haplotypes of 50 men with hairy ears from across southern India (see **Box 5**). These men were deliberately chosen from multiple families. For their control group, they looked at the yDNA haplotypes from a matched sample of 50 men without hairy ears, who were deliberately chosen from the same geographic area as the affected men. The yDNA haplotypes that they examined were not known to be associated with hairy ears. They were just representative samples of the whole Y chromosome sequence in these 100 men.

Box 4. The era of molecular genetics:

That genes on chromosomes were made of Deoxyribonucleic Acid (DNA) was not discovered until 1953, and the Genetic Code that determines how any sequence of DNA's four bases A, C, G, and T are expressed as a protein was not 'cracked' until 1965. Methods for routine and rapid determination of the base sequences of DNA molecules did not become widespread until the late 1980s, and accelerated rapidly in the 1990s. Identification of the exact chromosomal locations of the DNA sequences responsible for many genes of interest had to wait till the Human Genome Organization (HuGO) was started in 1990 and the epoch-making Human Genome Project (HGP) was completed in 2003.

Box 5. What does a yDNA haplotype mean?

Classical genetics had assumed that there were typically only two alleles for any gene—the 'wild type' for the trait as it was usually seen; and a variant or a 'mutant' (changed) type that was typically rare and often harmful. It recognised that some genes were more variable, with multiple favourable alleles that allowed humans to artificially select for better breeds of plants and livestock, but these were considered the exception.

As DNA sequencing began, it became apparent that most genes comprised multiple molecular alleles. These could be recognized by numerous small variations in their DNA sequence (or single nucleotide polymorphisms, referred to as SNPs or 'snips'), each of which had originated by single mutations (one base pair becomes different) in single individuals, and which were now widespread in populations. These SNPs allowed the construction of molecular pedigrees, in which individual gene changes could be tracked in the same way as phenotypic traits. This means that if a man carried a certain mutation, one could use sequencing to see which of his children inherited this mutation.

The DNA sequence of any gene is multiple thousands of bases long. It includes dozens of SNPs that, when taken together, could define hundreds of alleles. The combination of SNPs on any single chromosome is called a haplotype. Each Y chromosome is unique because it acts like a single yDNA haplotype in being inherited as a unit, present only in males, and in only one copy for each male. This means that all the mutations in the Y chromosome of a man, however minor, will be inherited by all his sons.

If hairy ears were caused by a single allele on the Y chromosome, a single haplotype (equivalent to an allele) would have been found in the yDNA of all the men with hairy ears. Further, this haplotype would have been missing from the yDNA of the men who did not have hairy ears. However, Lee and his colleagues found that the yDNA of affected men occurred in several different extended families as distinct haplogroups (related lineages of haplotypes). In other words, two unrelated men with hairy ears need not carry the same mutations in their Y chromosomes. This ruled out the single-allele model. It remained possible that the different haplotypes that were responsible for hairy ears had diverged from a single original mutation that was inherited from a recent common ancestor. However, the data showed that the affected men had last shared a common ancestor more than 68,000 years ago, well before the arrival of the various peoples that now make up the population of the Indian subcontinent. Finally, the range of yDNA haplotypes in affected men was not very much different from that in the control group. In other words, the DNA sequences of the Y chromosome of men with hairy ears were not very different from those of unaffected men from the same geographic area. Taken together, these data indicated that the possibility that any gene responsible for hypertrichosis could be Y-linked was very slim. For it to be possible, the same mutation would need to have occurred on multiple occasions in haplotype lineages that were otherwise distinct.

The final nail in the Y-linked hairy ears hypothesis comes from our increased knowledge of the gene content of individual chromosomes, including the Y chromosome. The locations of all 20,050 human genes across 22 autosomes and the X and Y chromosome are stored in a free online library called GenBank. A search of the complete DNA sequence of the Y chromosome does not suggest any candidate genes for hypertrichosis anywhere on the Y chromosome.

Box 6. Our hypothesis:

It is so tempting to speculate. When asked to review the question of hairy ears, we discussed some of the newer options in genetics. One of these is epigenesis. Unlike a mutation, an epigenetic modification does not change the DNA sequence, but makes small chemical modifications that affect gene expression. Such changes are usually reversed ('reset') during the formation of sperm and eggs for the next generation. One form of epigenetic modification is paramutation, where one of the two alleles of a gene changes the expression of the other.

Paramutation at an autosomal gene might mimic Y-linkage. How? Imagine a paramutagenic allele h* received by both a son and a daughter from their hairy-eared father, along with an h from their unaffected mother. Both have the hh* genotype. In the son, after the fusion of egg and sperm, the h* allele paramutates the h allele (h → h*)—his 'molecular' phenotype is now h*h* and his 'ear' phenotype is hairy. In the daughter, during development of her eggs, the h* is reset (h* → h)—her molecular and genetic phenotypes are the same (hh), and her ear phenotype is unaffected. The bottom line is that h always paramutates to h* in male zygotes, and h* is always reset to h in developing eggs. Consequently, the epigenetic condition will persist in men between generations, and will never show up in women, mimicking Y-linked inheritance.

If this seems confusing, it may be because we are still working on it. Let us know what you think.

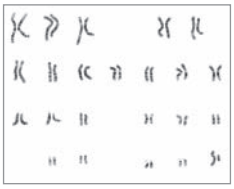
Parting thoughts

Attempts to explain the genetic basis of hypertrichosis have now completed their centenary. The inheritance of this trait is among the earliest research problems in human genetics. It has been vetted throughout the period of classical genetics, tested in the molecular era, and remains unresolved down to the present. JBS Haldane, asked why there are so many competing ideas in this investigation, might have smiled and replied, *"We have an inordinate fondness for hypotheses".*

While hypertrichosis is not a medical concern, and the extra hair can easily be trimmed or shaved off, understanding its genetic basis might provide us with broader insights into more medically important traits. For example, it may help us understand why many neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD) are, like hairy ears, more common in boys than in girls. But, ultimately, understanding the inheritance of hypertrichosis is a matter of simple curiosity. Scientists like to observe differences among peas, pachyderms, and people, and come up with explanations for these differences (see **Box 6**).

Given that Y-linkage is ruled out and evidence for autosomal dominant sex-limited inheritance has not been forthcoming, have we reached a dead-end in the search for an explanation for inheritance of hairy ears? Hardly. This may be one of those instances where Nature yields her secrets slowly.

Key takeaways



- The presence of excessively coarse and long black hair on the fleshy part of our outer ears is called hypertrichosis. This condition is most common in men from India and Sri Lanka.
- In 1907, the Italian physician C Tomassi published a pedigree chart documenting the occurrence of hairy ears through five generations of men in an Italian family. This suggested that the trait had a genetic basis and that it was passed only from father to son, and all sons, but not to daughters.
- Later pedigrees showed that while all the sons of a hairy-eared man may inherit the trait, the amount of hair growth and the age at which it appears may vary within the same family.
- The transmission pattern of the trait lent itself to two competing possibilities in classical genetics—the allele for hairy ears was either Y-linked or autosomal recessive.
- The eminent Indian geneticist JBS Haldane attributed hairy ears to a mutant allele on the Y chromosome. His hypothesis was supported by evidence from a study of hairy ears from southern India by the Indian scientist KR Dronamraju.
- Curt Stern, another eminent geneticist, argued that the available evidence did not unequivocally support the Y-linked inheritance of hairy ears. Autosomal recessive inheritance remained a plausible alternative explanation.
- In 2004, the scientist AC Lee and his colleagues used molecular evidence to show that it is extremely unlikely that this trait is caused by a single allele or is Y-linked. The genetic basis of this trait remains a mystery.
- While hairy ears are not a medical concern, the genetic basis for this trait has for long captured the curiosity of many scientists. Understanding it may give scientists broader insights into more medically important traits that are more common in men than in women.

Acknowledgements: We thank S Giridhar for the invitation to submit this review. Steven M Carr thanks Durgadas P Kasbekar for his generous offer to co-author this article, and remembers with fondness Profs. Herman Slatis and Curt Stern for their excellence in teaching and contributions to classical genetics. Durgadas P Kasbekar held the first Haldane Chair at CDFD—both authors hold JBS Haldane in high esteem.

Note: Source of the image used in the background of the article title: Karyotype of a human male. Credits: Talking Glossary of Genetics, National Human Genome Research Institute, Wikimedia Commons. URL: https://en.wikipedia.org/wiki/File:NHGRI_human_male_karyotype.png. License: Public Domain.

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