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on the notion of tall

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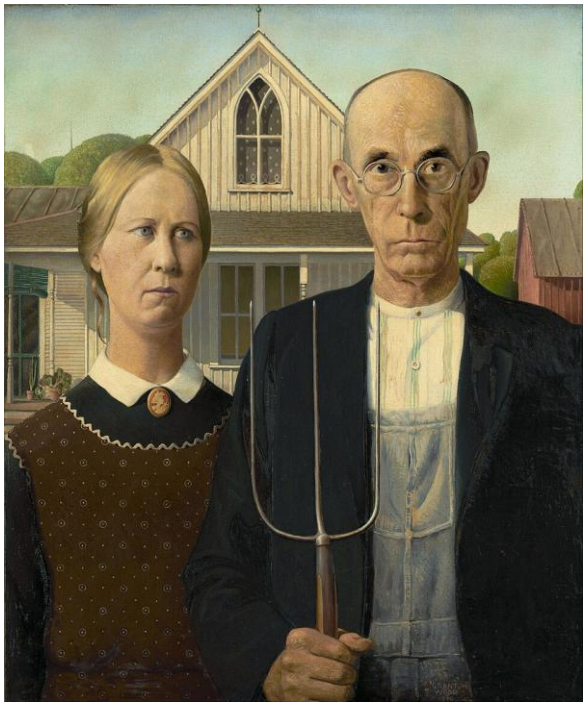
Take a child. Show it two toy animals that differ in height and ask which is the mum and which is the dad. The youngster will probably point to the tallest and say: "That's the dad". Because that is what we see in real life. It is also the way humans, like animals, are usually depicted in children's books and films. Remember "Goldilocks and the three bears"? The bigness of Dad, the 'mediumness' of Mum and the littleness of Baby bear? It's not only fiction, though. On an average, men are indeed taller than women. Why? Undoubtedly, natural selection will have played a role. Tall men are imposing, and hence instinctively sensed as dominant figures that can offer protection. Over the course of time, female humans will have been attracted to them for status as well as to ensure their progeny's safety and, who knows, inheritance of the trait. But this doesn't explain the underlying biology that makes a man taller than a woman. Recently, an intriguing explanation emerged. We know that the SHOX protein is involved in bone growth and elongation. What was discovered is that the protein is less expressed in women than it is in men because of the chromosomal location of its gene.



American Gothic (1930)

by Grant Wood (1891-1942)

Nature has distributed obvious sexual attributes to male and female humans, but there are other differences related to biological sex such as height, muscular mass and hairiness – to name but three. This is called sexual dimorphism. Traits defined by sexual dimorphism are frequently (but not only) the result of genes that are located on our sex-determining chromosomes, in other words our X and Y chromosomes. Biological women carry two copies of these X chromosomes in their cells (XX), while biological men carry one sex-determining X chromosome and one Y chromosome (XY) in theirs. Besides observing the patent visual differences in humans, scientists have long wondered how such traits are defined on the molecular level.

The study of height came as a natural choice for understanding sexual dimorphism. In developing countries, humans are measured by medical staff from the very minutes they enter our world to when they reach adolescence, at least. This has provided exceptional data and, in the UK for instance, scientists have been able to state confidently that men are generally 13cm taller than women. Such a difference is due to a variety of factors, whose effects overlap. There are growth hormones, naturally. But there are also factors such as the SHOX protein which is involved in bone growth and maturation. According to scientists, the SHOX protein accounts for one quarter of the difference between a man and a woman's height, while hormones would provide most of the remaining three quarters.

SHOX is an abbreviation for "Short stature HOmeoboX"-containing gene. Why 'short' when we

are talking about 'tall'? This is because, like many genes and proteins, SHOX was discovered while studying diseases which cause humans to be under tall – where tallness is defined by the average height of a male or female human individual at a certain age. Typically, people suffering from Leri-Weill syndrome or Turner syndrome are of short stature. This is directly caused by mutations in the SHOX gene. The SHOX protein belongs to the homeodomain protein family whose members bind DNA (genes) via their homeodomain – a stretch of about 60 amino acids. Homeodomain proteins are commonly transcription factors, and often play fundamental roles during embryogenesis and development by binding to specific domains on genes to either activate or repress their transcription and hence activate or repress their protein products.

SHOX proteins are about 300 amino acids long. Their N-terminal contains the homeodomain which is composed of three helices. It is this part of the protein that makes direct contact with the DNA to activate or repress gene expression by binding to palindromic motifs such as 5'-TAATNNNATTA-3'. The C-terminal portion of SHOX also harbours an OAR region, which is about 14 to 15 amino acids long and necessary for the protein's transcriptional activity. Indeed, SHOX is known to act as a transcriptional activator. Consistently, it is found in the cell nucleus of chondrocytes, cells that are critical for bone maturation. The SHOX protein targets a variety of genes, all of which are involved in limb development by way of various molecular pathways ultimately leading to chondrocyte proliferation, differentiation and apoptosis.

How can SHOX provide an explanation for the difference in height between men and women? The SHOX gene is found on the short arm of both the X and the Y chromosomes. In females, one of the sex-determining X chromosomes is always (randomly) inactivated, or silenced. This would leave women with only one copy of the SHOX gene, while men have two. This is not the case, however, because one part of the female X chromosome is never silenced, the pseudoautosomal region 1 or PAR1. This happens to be where the SHOX gene is situated. So, if we do our mathematics, male and female humans both have two copies of the SHOX gene. The thing is, PAR1 is unable to avoid a little bit of inactivation – a bit like when you spread icing over the top of a cake and it drips down the sides. Genes on this part of the X chromosome seem to undergo a bit of inactivation, nevertheless. As a result, women express a little less of the SHOX protein than men do, and this would partly explain the constant difference in height between women and men, and the fact that women are usually less tall.

Understanding the molecular intricacies of the SHOX protein may provide alternative ways of dealing with short stature in young adults, which is currently mainly treated with growth hormones. It could also provide therapeutic solutions for patients suffering from the Leri-Weill or Turner syndromes, or indeed other syndromes, that are caused by mutated SHOX proteins. Depending on where the mutation occurs, the SHOX protein may not be able to reach the cell nucleus or may be dysfunctional. In both occurrences, it is unable to function correctly as a transcription activator, which ultimately affects the patient's stature. Certainly, how the genetics surrounding one protein can affect what has become a characteristic trait between men and women is profoundly intriguing and reminds us once again that biology is not an exact science. Pathways overflow and overlap, easing things onto unsuspected paths.

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