



Help Me Understand Genetics

Genetics and Human Traits

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Genetics and Human Traits

1 Are fingerprints determined by genetics?

Each person's fingerprints are unique, which is why they have long been used as a way to identify individuals. Surprisingly little is known about the factors that influence a person's fingerprint patterns. Like many other complex traits, studies suggest that both genetic and environmental factors play a role.

A person's fingerprints are based on the patterns of skin ridges (called dermatoglyphs) on the pads of the fingers. These ridges are also present on the toes, the palms of the hands, and the soles of the feet. Although the basic whorl, arch, and loop patterns may be similar, the details of the patterns are specific to each individual.

Dermatoglyphs develop before birth and remain the same throughout life. The ridges begin to develop during the third month of fetal development, and they are fully formed by the sixth month. The function of these ridges is not entirely clear, but they likely increase sensitivity to touch.

The basic size, shape, and spacing of dermatoglyphs appear to be influenced by genetic factors. Studies suggest that multiple genes are involved, so the inheritance pattern is not straightforward. Genes that control the development of the various layers of skin, as well as the muscles, fat, and blood vessels underneath the skin, may all play a role in determining the pattern of ridges. The finer details of the patterns of skin ridges are influenced by other factors during fetal development, including substances taken during pregnancy and the environment inside the womb. These developmental factors cause each person's dermatoglyphs to be different from everyone else's. Even identical twins, who have the same DNA, have different fingerprints.

Few genes involved in dermatoglyph formation have been identified. Rare diseases characterized by abnormal or absent dermatoglyphs provide some clues as to their genetic basis. For example, a condition known as adermatoglyphia is characterized by an absence of dermatoglyphs, sometimes with other abnormalities of the skin. Adermatoglyphia is caused by mutations in a gene called *SMARCAD1*. Although this gene is clearly important for the formation of dermatoglyphs, its role in their development is unclear.

Scientific journal articles for further reading

Burger B, Fuchs D, Sprecher E, Itin P. The immigration delay disease: adermatoglyphia-inherited absence of epidermal ridges. *J Am Acad Dermatol*. 2011 May;64(5):974-80. doi: 10.1016/j.jaad.2009.11.013. Epub 2010 Jul 8. PubMed: 20619487.

Nousbeck J, Burger B, Fuchs-Telem D, Pavlovsky M, Fenig S, Sarig O, Itin P, Sprecher E. A mutation in a skin-specific isoform of *SMARCAD1* causes autosomal-dominant adermatoglyphia. *Am J Hum Genet*. 2011 Aug 12;89(2):302-7. doi: 10.1016/j.ajhg.2011.07.004. Epub 2011 Aug 4. PubMed: 21820097. Free full-text available from PubMed

Central: PMC3155166.

Warman PH, Ennos A.R. Fingerprints are unlikely to increase the friction of primate fingerpads. *J Exp Biol.* 2009 Jul;212(Pt 13):2016-22. doi: 10.1242/jeb.028977. PubMed: 19525427.

Sudha PI, Singh J, Sodhi GS. The Dermal Ridges as the Infallible Signature of Skin: An Overview. *Indian J Dermatol.* 2021 Nov-Dec;66(6):649-653. doi: 10.4103/ijd.ijd_1123_20. PubMed: 35283510. Free full-text available from PubMed Central: PMC8906331.

To find out more about the influence of genetics on the formation of fingerprints:

The Washington State Twin Registry has an FAQ about the fingerprints of identical twins (<https://wstwinregistry.org/2015/10/01/do-identical-twins-have-identical-fingerprints/>).

OMIM.org provides more detailed genetic information about dermatoglyphs (<http://omim.org/entry/125590>) and adermatoglyphia (<http://omim.org/entry/136000>).

2 Is eye color determined by genetics?

A person's eye color results from pigmentation of a structure called the iris, which surrounds the small black hole in the center of the eye (the pupil) and helps control how much light can enter the eye. The color of the iris ranges on a continuum from very light blue to dark brown. Most of the time eye color is categorized as blue, green/hazel, or brown. Brown is the most frequent eye color worldwide.

Eye color is determined by variations in a person's genes. Most of the genes associated with eye color are involved in the production, transport, or storage of a pigment called melanin. Eye color is directly related to the amount of melanin in the front layers of the iris. People with brown eyes have a large amount of melanin in the iris, while people with blue eyes have much less of this pigment.

A particular region on chromosome 15 plays a major role in eye color. Within this region, there are two genes located very close together: *OCA2* and *HERC2*. The protein produced from the *OCA2* gene, known as the P protein, is involved in the maturation of melanosomes, which are cellular structures that produce and store melanin. The P protein therefore plays a crucial role in the amount and quality of melanin that is present in the iris. Several common variations (polymorphisms) in the *OCA2* gene reduce the amount of functional P protein that is produced. Less P protein means that less melanin is present in the iris, leading to blue eyes instead of brown in people with a polymorphism in this gene.

A region of the nearby *HERC2* gene known as intron 86 contains a segment of DNA that controls the activity (expression) of the *OCA2* gene, turning it on or off as needed. At least one polymorphism in this area of the *HERC2* gene has been shown to reduce the expression of *OCA2* and decrease P protein production, leading to less melanin in the iris and lighter-colored eyes.

Several other genes play smaller roles in determining eye color. Some of these genes are also involved in skin and hair coloring. Genes with reported roles in eye color include *ASIP*, *IRF4*, *SLC24A4*, *SLC24A5*, *SLC45A2*, *TPCN2*, *TYR*, and *TYRP1*. The effects of these genes likely combine with those of *OCA2* and *HERC2* to produce a continuum of eye colors in different people.

Researchers used to think that eye color was determined by a single gene and followed a simple inheritance pattern in which brown eyes were dominant to blue eyes. Under this model, it was believed that parents who both had blue eyes could not have a child with brown eyes. However, later studies showed that this model was too simplistic. Although it is uncommon, parents with blue eyes can have children with brown eyes. The inheritance of eye color is more complex than originally suspected because multiple genes are involved. While a child's eye color can often be predicted by the eye colors of his or her parents and other relatives, genetic variations sometimes produce unexpected results.

Several disorders that affect eye color have been described. Ocular albinism is characterized by severely reduced pigmentation of the iris, which causes very light-

colored eyes and significant problems with vision. Another condition called oculocutaneous albinism affects the pigmentation of the skin and hair in addition to the eyes. Affected individuals tend to have very light-colored irises, fair skin, and white or light-colored hair. Both ocular albinism and oculocutaneous albinism result from mutations in genes involved in the production and storage of melanin. Another condition called heterochromia is characterized by different-colored eyes in the same individual. Heterochromia can be caused by genetic changes or by a problem during eye development, or it can be acquired as a result of a disease or injury to the eye.

Eye anatomy (Figure 1)

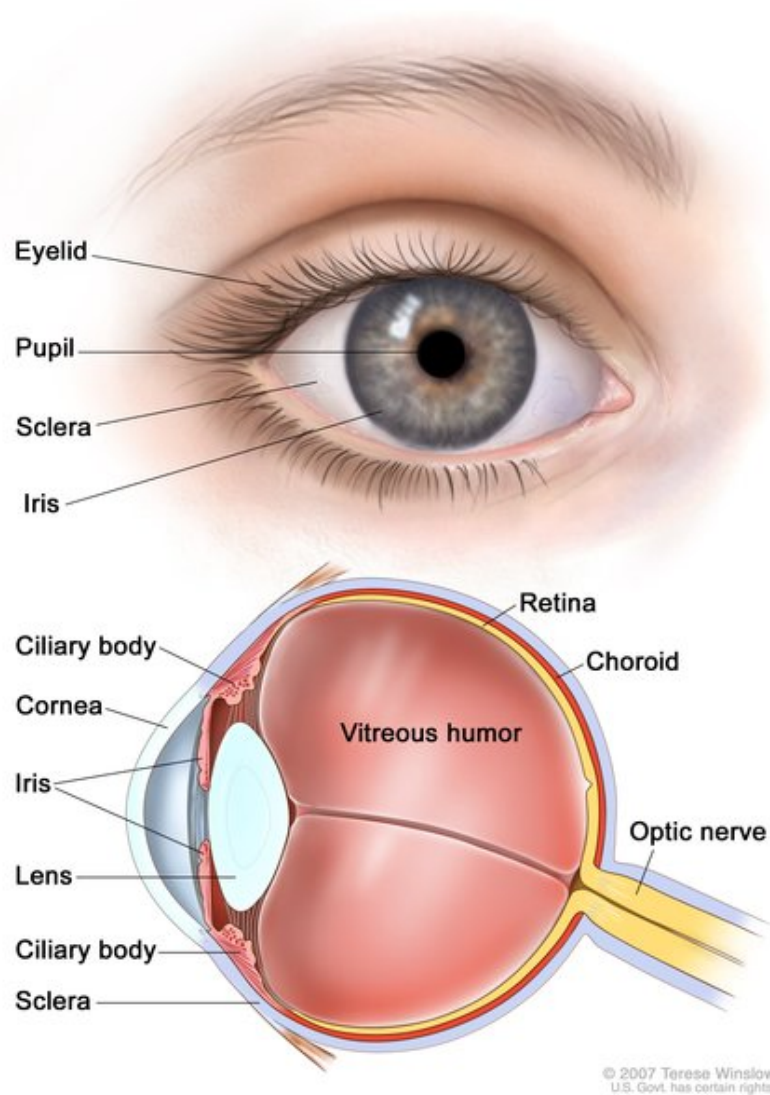


FIGURE 1: Two-panel drawing shows the outside and inside of the eye. The top panel shows outside of the eye including the eyelid, pupil, sclera, and iris; the bottom panel shows inside of the eye including the cornea, lens, ciliary body, retina, choroid, optic nerve, and vitreous humor.

To learn more about the genetics of eye color:

The Tech Museum of Innovation at Stanford University provides a Q&A explaining how brown-eyed parents can have blue-eyed children (<https://genetics.thetech.org/ask-a-geneticist/brown-eyed-parents-blue-eyed-kids>).

More detailed information about ocular albinism (<http://omim.org/entry/300500>) and oculocutaneous albinism (<http://omim.org/entry/203100>), as well as the genetics of eye, hair, and skin color variation (<http://omim.org/entry/227220>), is available from OMIM.org.

Additional information from MedlinePlus provides a brief description of heterochromia (<https://medlineplus.gov/ency/article/003319.htm>). Further information about this condition is provided by the American Academy of Ophthalmology (<https://www.aao.org/eye-health/diseases/what-is-heterochromia>).

3 Is intelligence determined by genetics?

Like most aspects of human behavior and cognition, intelligence is a complex trait that is influenced by both genetic and environmental factors.

Intelligence is challenging to study, in part because it can be defined and measured in different ways. Most definitions of intelligence include the ability to learn from experiences and adapt to changing environments. Elements of intelligence include the ability to reason, plan, solve problems, think abstractly, and understand complex ideas. Many studies rely on a measure of intelligence called the intelligence quotient (IQ).

Researchers have conducted many studies to look for genes that influence intelligence. Many of these studies have focused on similarities and differences in IQ within families, particularly looking at adopted children and twins. Other studies have examined variations across the entire genomes of many people (an approach called genome-wide association studies or GWAS) to determine whether any specific areas of the genome are associated with IQ. Studies have not conclusively identified any genes that have major roles in differences in intelligence. It is likely that a large number of genes are involved, each of which makes only a small contribution to a person's intelligence. Other areas that contribute to intelligence, such as memory and verbal ability, involve additional genetic factors.

Intelligence is also strongly influenced by the environment. During a child's development, factors that contribute to intelligence include their home environment and parenting, education and availability of learning resources, and healthcare and nutrition. A person's environment and genes influence each other, and it can be challenging to tease apart the effects of the environment from those of genetics. For example, if a person's level of intelligence is similar to that of their parents, is that similarity due to genetic factors passed down from parent to child, to shared environmental factors, or (most likely) to a combination of both? It is clear that both environmental and genetic factors play a part in determining intelligence.

Scientific journal articles for further reading

Plomin R, Deary IJ. Genetics and intelligence differences: five special findings. *Mol Psychiatry*. 2015 Feb;20(1):98-108. doi: 10.1038/mp.2014.105. Epub 2014 Sep 16. Review. PubMed: 25224258. Free full-text available from PubMed Central: PMC4270739.

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individuals identifies new loci and genes influencing human intelligence. Nat Genet. 2017 Jul; 49(7):1107-1112. doi: 10.1038/ng.3869. Epub 2017 May 22. Erratum in: Nat Genet. 2017 Sep 27;49(10):1558. PubMed: 28530673. Free full-text available from PubMed Central: PMC5665562

Sternberg RJ. Intelligence. Dialogues Clin Neurosci. 2012 Mar;14(1):19-27. Review. PubMed: 22577301. Free full-text available from PubMed Central: PMC3341646

To find out more about the influence of genetics on intelligence:

The Tech Museum of Innovation at Stanford University provides a Q&A about the influence of genes and environment on IQ (<https://genetics.thetech.org/ask-a-geneticist/intelligence-and-genetics>).

Cambridge Brain Sciences discusses a recent research study that identified 22 genes that have been linked to intelligence (<https://www.cambridgebrainsciences.com/more/articles/22-genes-have-been-linked-to-intelligence>). (See Sniekers, et al (2017) in the 'scientific journal articles for further reading' list in the main summary to read the full research study.)

The Cold Spring Harbor Laboratory offers an interactive tool called Genes to Cognition (<https://dnalc.cshl.edu/view/2251-Thinking-.html>) that provides information about many aspects of the genetics of neuroscience.

4 Is handedness determined by genetics?

Like most aspects of human traits, handedness is complex and appears to be influenced by multiple factors, including genetics and environment.

Handedness, or hand preference, is the tendency to be more skilled and comfortable using one hand instead of the other for tasks such as writing and throwing a ball. Although the percentage varies worldwide, in Western countries, 85 to 90 percent of people are right-handed and 10 to 15 percent of people are left-handed. Mixed-handedness (preferring different hands for different tasks) and ambidextrousness (the ability to perform tasks equally well with either hand) are uncommon.

Hand preference becomes increasingly apparent in early childhood and tends to be consistent throughout life. However, little is known about its biological basis. Hand preference probably arises as part of the developmental process that differentiates the right and left sides of the body (called right-left asymmetry). More specifically, handedness appears to be related to differences between the right and left halves (hemispheres) of the brain. The right hemisphere controls movement on the left side of the body, while the left hemisphere controls movement on the right side of the body.

It was initially thought that a single gene controlled handedness. However, more recent studies suggest that multiple genes, perhaps up to 40, contribute to this trait. Each of these genes likely has a weak effect by itself, but together they play a significant role in establishing hand preference. Studies suggest that at least some of these genes help determine the overall right-left asymmetry of the body starting in the earliest stages of development. So far, researchers have identified only a few of the many genes thought to influence handedness. Studies suggest that other factors also contribute to handedness. The prenatal environment and cultural influences may play a role.

Like many complex traits, handedness does not have a simple pattern of inheritance. Children of left-handed parents are more likely to be left-handed than are children of right-handed parents. However, because the overall chance of being left-handed is relatively low, most children of left-handed parents are right-handed. Identical twins are more likely than non-identical twins (or other siblings) to both be right-handed or left-handed, but many twins have opposite hand preferences.

Scientific journal articles for further reading

Armour JA, Davison A, McManus IC. Genome-wide association study of handedness excludes simple genetic models. *Heredity (Edinb)*. 2014 Mar;112(3):221-5. doi:10.1038/hdy.2013.93. Epub 2013 Sep 25. PubMed: 24065183. Free full-text available from PubMed Central: PMC3931166.

Brandler WM, Morris AP, Evans DM, Scerri TS, Kemp JP, Timpson NJ, St Pourcain B, Smith GD, Ring SM, Stein J, Monaco AP, Talcott JB, Fisher SE, Webber C, Paracchini S. Common variants in left/right asymmetry genes and pathways are associated with relative hand skill. *PLoS Genet*. 2013;9(9):e1003751. doi: 10.1371/journal.pgen.1003751. Epub 2013 Sep 12. PubMed: 24068947. Free full-text available from PubMed

Central: PMC3772043.

Brandler WM, Paracchini S. The genetic relationship between handedness and neurodevelopmental disorders. *Trends Mol Med*. 2014 Feb;20(2):83-90. doi: 10.1016/j.molmed.2013.10.008. Epub 2013 Nov 23. Review. PubMed: 24275328. Free full-text available from PubMed Central: PMC3969300

de Kovel CGF, Francks C. The molecular genetics of hand preference revisited. *Sci Rep*. 2019 Apr 12;9(1):5986. doi: 10.1038/s41598-019-42515-0. PubMed: 30980028; Free full-text available from PubMed Central: PMC6461639.

McManus IC, Davison A, Armour JA. Multilocus genetic models of handedness closely resemble single-locus models in explaining family data and are compatible with genome-wide association studies. *Ann N Y Acad Sci*. 2013 Jun;1288:48-58. doi:10.1111/nyas.12102. Epub 2013 Apr 30. PubMed: 23631511. Free full-text available from PubMed Central: PMC4298034.

To find out more about how handedness is determined:

General information about left-handedness, including its causes, is available from the Better Health Channel (<https://www.betterhealth.vic.gov.au/health/healthyliving/left-handedness>) (Australia).

The Washington State Twin Registry has an FAQ about hand preference in identical twins (<https://wstwinregistry.org/2015/10/01/do-identical-twins-always-have-the-same-hand-preference/>).

5 Is the probability of having twins determined by genetics?

The likelihood of conceiving twins is a complex trait, meaning that it is affected by multiple genetic and environmental factors, depending on the type of twins. The two types of twins are classified as monozygotic and dizygotic.

Monozygotic (MZ) twins, also called identical twins, occur when a single egg cell is fertilized by a single sperm cell. The resulting zygote splits into two very early in development, leading to the formation of two separate embryos. MZ twins occur in 3 to 4 per 1,000 births worldwide. Research suggests that most cases of MZ twinning are not caused by genetic factors. However, a few families with a larger-than-expected number of MZ twins have been reported, which indicates that genetics may play a role. It is possible that genes involved in sticking cells together (cell adhesion) may contribute to MZ twinning, although this hypothesis has not been confirmed. Most of the time, the cause of MZ twinning is unknown.

Dizygotic (DZ) twins, also called fraternal twins, occur when two egg cells are each fertilized by a different sperm cell in the same menstrual cycle. DZ twins are about twice as common as MZ twins, and they are much more likely to run in families. Compared to the general population, having DZ twins is about two times more likely if a close relative (for example, a sister) has had DZ twins.

DZ twinning is thought to be a result of hyperovulation, which is the release of more than one egg in a single menstrual cycle. To explain how DZ twinning can run in families, researchers have looked for genetic factors that increase the chance of hyperovulation. However, studies examining the contributions of specific genes have had mixed and conflicting results. Few specific genes in humans have been definitively linked with hyperovulation or an increased probability of DZ twinning.

Other factors known to influence the chance of having DZ twins include the mother's age, ethnic background, diet, body type, and number of other children. Assisted reproductive technologies such as in vitro fertilization (IVF) are also associated with an increased frequency of DZ twins.

Scientific journal articles for further reading

Hoekstra C, Zhao ZZ, Lambalk CB, Willemsen G, Martin NG, Boomsma DI, Montgomery GW. Dizygotic twinning. *Hum Reprod Update*. 2008 Jan-Feb;14(1):37-47. Epub 2007 Nov 16. Review. PubMed: 18024802.

Machin G. Familial monozygotic twinning: a report of seven pedigrees. *Am J Med Genet C Semin Med Genet*. 2009 May 15;151C(2):152-4. doi: 10.1002/ajmg.c.30211. PubMed: 19363801.

Mbarek H, Steinberg S, Nyholt DR, Gordon SD, Miller MB, McRae AF, Hottenga JJ, Day FR, Willemsen G, de Geus EJ, Davies GE, Martin HC, Penninx BW, Jansen R, McAloney K, Vink JM, Kaprio J, Plomin R, Spector TD, Magnusson PK, Reversade B,

Harris RA, Aagaard K, Kristjansson RP, Olafsson I, Eyjolfsson GI, Sigurdardottir O, Iacono WG, Lambalk CB, Montgomery GW, McGue M, Ong KK, Perry JR, Martin NG, Stefánsson H, Stefánsson K, Boomsma DI. Identification of Common Genetic Variants Influencing Spontaneous Dizygotic Twinning and Female Fertility. *Am J Hum Genet*. 2016 May 5;98(5):898-908. doi: 10.1016/j.ajhg.2016.03.008. Epub 2016 Apr 28. PubMed: 27132594.

Monden C, Pison G, Smits J. Twin Peaks: more twinning in humans than ever before. *Hum Reprod*. 2021 May 17;36(6):1666-1673. doi: 10.1093/humrep/deab029. PubMed: 33709110. Free full-text available from PubMed Central: PMC8129593.

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Shur N. The genetics of twinning: from splitting eggs to breaking paradigms. *Am J Med Genet C Semin Med Genet*. 2009 May 15;151C(2):105-9. doi: 10.1002/ajmg.c.30204. PubMed: 19363800.

To learn more about the genetics of twinning:

Information about factors influencing MZ and DZ twinning is available from the Washington State Twin Registry:

- Twins run in my family. Do I have an increased chance of having twins? (<https://wstwinregistry.org/2015/10/01/twins-run-in-my-family-do-i-have-an-increased-chance-of-having-twins/>)
- I am a twin. Do I have an increased chance of having twins? (<https://wstwinregistry.org/2015/10/01/i-am-a-twin-do-i-have-an-increased-chance-of-having-twins/>)
- Does identical (MZ) twinning run in families? (<https://wstwinregistry.org/2015/10/01/does-mz-twinning-run-in-families/>)
- What factors are related to fraternal (DZ) twinning? (<https://wstwinregistry.org/2015/10/01/what-factors-are-related-to-dz-twinning/>)

The Tech Museum of Innovation at Stanford University offers a discussion of why twins can run in families (<https://genetics.thetech.org/ask-a-geneticist/twin-genetics>).

A brief overview of the factors that influence twinning (<https://www.nhs.uk/conditions/pregnancy-and-baby/twins-healthy-multiple-pregnancy/>) is available from the UK National Health Service.

More detailed information about genetic factors related to MZ twinning (<http://www.omim.org/entry/276410>) and DZ twinning (<http://www.omim.org/entry/276400>) is available from OMIM.org.

6 Is hair texture determined by genetics?

Genetic factors appear to play a major role in determining hair texture—straight, wavy, or curly—and the thickness of individual strands of hair. Studies suggest that different genes influence hair texture and thickness in people of different ethnic backgrounds. For example, normal variations (polymorphisms) in two genes, *EDAR* and *FGFR2*, have been associated with differences in hair thickness in Asian populations. A polymorphism in another gene, *TCHH*, appears to be related to differences in hair texture in people of northern European ancestry. It is likely that many additional genes contribute to hair texture and thickness in various populations.

Several genetic syndromes are characterized by unusual hair texture. These syndromes are caused by variants in genes that play roles in hair structure and stability, including genes associated with specialized cell structures called desmosomes that hold hair cells together, proteins called keratins that provide strength and resilience to hair strands, and chemical signaling pathways involving a molecule called lysophosphatidic acid (LPA), which promotes hair growth. Genetic syndromes that feature altered hair texture include:

- Autosomal recessive hypotrichosis (caused by variants in the *DSG4*, *LIPH*, or *LPAR6* gene)
- Keratoderma with woolly hair (caused by variants in the *JUP*, *DSP*, *DSC2*, or *KANK2* gene)
- Monilethrix (caused by variants in the *DSG4*, *KRT81*, *KRT83*, or *KRT86* gene)
- Uncombable hair syndrome (caused by variants in the *PADI3*, *TCHH*, or *TGM3* gene)

Researchers speculate that the genes associated with these disorders probably also contribute to normal variations in hair texture and thickness.

Factors other than genetics can also influence hair texture and thickness. Hormones, certain medications, and chemicals such as hair relaxers or perms can alter the characteristics of a person's hair. These changes can be temporary or permanent. Hair texture and thickness can also change with age.

Scientific journal articles for further reading

Fujimoto A, Kimura R, Ohashi J, Omi K, Yuliwulandari R, Batubara L, Mustofa MS, Samakkarn U, Settheetham-Ishida W, Ishida T, Morishita Y, Furusawa T, Nakazawa M, Ohtsuka R, Tokunaga K. A scan for genetic determinants of human hair morphology: *EDAR* is associated with Asian hair thickness. *Hum Mol Genet*. 2008 Mar 15;17(6):835-43. Epub 2007 Dec 8. PubMed: 18065779.

Fujimoto A, Nishida N, Kimura R, Miyagawa T, Yuliwulandari R, Batubara L, Mustofa MS, Samakkarn U, Settheetham-Ishida W, Ishida T, Morishita Y, Tsunoda T, Tokunaga K, Ohashi J. *FGFR2* is associated with hair thickness in Asian populations. *J Hum Genet*. 2009 Aug;54(8):461-5. doi: 10.1038/jhg.2009.61. Epub 2009 Jul 10. PubMed:

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Medland SE, Nyholt DR, Painter JN, McEvoy BP, McRae AF, Zhu G, Gordon SD, Ferreira MA, Wright MJ, Henders AK, Campbell MJ, Duffy DL, Hansell NK, Macgregor S, Slutske WS, Heath AC, Montgomery GW, Martin NG. Common variants in the trichohyalin gene are associated with straight hair in Europeans. *Am J Hum Genet.* 2009 Nov;85(5):750-5. doi: 10.1016/j.ajhg.2009.10.009. Epub 2009 Nov 5. PubMed: 19896111. Free full-text from PubMed Central: PMC2775823.

Shimomura Y, Christiano AM. Biology and genetics of hair. *Annu Rev Genomics Hum Genet.* 2010;11:109-32. doi: 10.1146/annurev-genom-021610-131501. Review. PubMed: 20590427.

To find out more about the influence of genetics on hair texture:

The Tech Museum of Innovation at Stanford University provides a Q&A on the differences in hair texture among ethnic groups (<https://genetics.thetech.org/ask/ask107>) and another on the inheritance of hair texture (<https://genetics.thetech.org/ask/ask368>).

More detailed information about the genetics of hair thickness (<http://omim.org/entry/612630>) and hair texture (<http://omim.org/entry/139450>) is available from OMIM.org.

7 Is hair color determined by genetics?

Hair color is determined by the amount of a pigment called melanin in hair. An abundance of one type of melanin, called eumelanin, gives people black or brown hair. An abundance of another pigment, called pheomelanin, gives people red hair.

Black. Large amount of eumelanin

Brown. Moderate amount of eumelanin

Blond. Very little eumelanin

Red. Mostly pheomelanin with a little eumelanin

The type and amount of melanin in hair is determined by many genes, although little is known about most of them. The best-studied hair-color gene in humans is called *MC1R*. This gene provides instructions for making a protein called the melanocortin 1 receptor, which is involved in the pathway that produces melanin. The melanocortin 1 receptor controls which type of melanin is produced by melanocytes. When the receptor is turned on (activated), it triggers a series of chemical reactions inside melanocytes that stimulate these cells to make eumelanin. If the receptor is not activated or is blocked, melanocytes make pheomelanin instead of eumelanin. Many other genes also help to regulate this process. Most people have two functioning copies of the *MC1R* gene, one inherited from each parent. These individuals have black or brown hair, because of the high amount of eumelanin. It is estimated that more than 90 percent of people in the world have brown or black hair.

Some people have variations in one copy of the *MC1R* gene in each cell that causes the gene to be turned off (deactivated). This type of genetic change is described as loss-of-function. For these individuals, eumelanin production is lower, while pheomelanin production is higher, so they have strawberry blond, auburn, or red hair. In an even smaller percentage of people, both copies of the *MC1R* gene in each cell have loss-of-function changes, and the melanin-production pathway produces only the pheomelanin pigment. The hair of these individuals is almost always very red. Even when the melanin-production pathway is making eumelanin, changes in other genes can reduce the amount of eumelanin produced. These changes lead to blond hair.

Hair color ranges across a wide spectrum of hues, from flaxen blond to coal black. Many genes other than *MC1R* play a role in determining shades of hair color by controlling levels of eumelanin and pheomelanin. Some of these genes, including *ASIP*, *DTNBP1*, *GPR143*, *HPS3*, *KITLG*, *MLPH*, *MYO5A*, *MYO7A*, *OCA2*, *SLC45A2*, *SLC24A5*, *TYRP1*, *TYR*, *ERCC6*, *GNAS*, *HERC2*, *IRF4*, *OBSCN*, *SLC24A4*, *TPCN2*, and *MITF*, are involved in the production of melanin in hair. Some of these genes are associated with gene transcription (which is the first step in protein production), DNA repair, the transport of substances (such as calcium) across cell membranes, or the structure of hair follicles. Several of these genes contribute to eye and skin color, but

the exact role they play in determining hair color is unknown.

Hair color may change over time. Particularly in people of European descent, light hair color may darken as individuals grow older. For example, blond-haired children often have darker hair by the time they are teenagers. Researchers speculate that certain hair-pigment proteins are activated as children grow older, perhaps in response to hormonal changes that occur near puberty. Almost everyone's hair will begin to turn gray as they age, although when it happens and to what extent is variable. Gray hair is partly hereditary and may vary by ethnic origin; it is also somewhat dependent on external factors such as stress. Hair becomes gray when the hair follicle loses its ability to make melanin, but exactly why that occurs is not clear.

Scientific journal articles for further reading

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Tobin DJ. Human hair pigmentation--biological aspects. *Int J Cosmet Sci.* 2008 Aug;

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To find out more about the influence of genetics on hair color:

The Tech Interactive at Stanford University provides a Q&A page about hair color. (<https://www.thetech.org/ask-a-geneticist/hair-color-genetics>)

KidsHealth from Nemours explains why hair turns gray (<https://kidshealth.org/en/kids/gray-hair.html?ref=search&WT.ac=msh-p-dtop-en-search-clk>).

8 Is height determined by genetics?

Scientists estimate that about 80 percent of an individual's height is determined by the DNA sequence variations they have inherited, but which genes these changes are in and what they do to affect height are only partially understood. Some rare gene variants have dramatic effects on height (for example, variants in the *FGFR3* gene cause achondroplasia, a rare condition characterized by short stature). For most individuals, though, height is controlled largely by a combination of genetic variants that each have more modest effects on height, plus a smaller contribution from environmental factors (such as nutrition). More than 700 such gene variants have been discovered and many more are expected to be identified. Some of these variants are in genes that directly or indirectly affect cartilage in growth plates, which are areas in the long bones of the legs and arms where new bone is produced, lengthening the bones as children grow. The function of many other height-associated genes remains unknown.

In addition to the *FGFR3* gene, researchers have identified hundreds of other genes involved in rare disorders that have an extreme effect on height. These genes (and the conditions they are associated with) include *FBN1* (acromicric dysplasia, geleophysic dysplasia, Marfan syndrome), *GH1* (isolated growth hormone deficiency), *EVC* (Ellis-van Creveld syndrome), Weyers acrofacial dysostosis, and *GPC3* (Simpson-Golabi-Behmel syndrome). By studying the dramatic effect that altered versions of these genes have on height, scientists hope to better understand the complex interactions among genes that contribute to normal height. Some genes, such as *ACAN*, contain rare variants that cause severe growth disorders, and also other variants with milder effects on height in individuals without a related health condition. Identifying other height genes, and variants with large or small effects, is an active area of genetic research.

Because height is determined by multiple gene variants (an inheritance pattern called polygenic inheritance), it is difficult to accurately predict how tall a child will be. The inheritance of these variants from one's parents helps explain why children usually grow to be approximately as tall as their parents, but different combinations of variants can cause siblings to be of different heights. Height is influenced by other biological mechanisms (such as hormones) that may also be determined by genetics, although the roles of these mechanisms are not fully understood.

In addition to genetic and biological determinants, height is also influenced by environmental factors, including a mother's nutrition during pregnancy, whether she smoked, and her exposure to hazardous substances. A well-nourished, healthy, and active child is likely to be taller as an adult than will be a child with a poor diet, infectious diseases, or inadequate health care. Socioeconomic factors such as income, education, and occupation can also influence height. In some cases, ethnicity plays a role in adult height, but studies on immigrant families have shown that moving to a country with better access to nutritious food, healthcare, and employment opportunities can have a substantial influence on the height of the next generation; this suggests that some differences in height between ethnicities are explained by non-genetic factors.

Scientific journal articles for further reading

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Perola M. Genome-wide association approaches for identifying loci for human height genes. *Best Pract Res Clin Endocrinol Metab*. 2011 Feb;25(1):19-23. doi: 10.1016/j.beem.2010.10.013. PubMed: 21396572.

To learn more about the genetics of height:

The Broad Institute of the Massachusetts Institute of Technology and Harvard University published a press release about the Genetic Investigation of Anthropometric Traits (GIANT) study (<https://www.broadinstitute.org/news/giant-study-reveals-giant-number-genes-linked-height>), which greatly expanded understanding of the role of genetics in height determination.

OMIM.org provides a list of genes that are associated with height (<https://www.omim.org/search/?index=geneMap&search=stature+height+shortness+tallness&start=1&limit=10>).

9 Are moles determined by genetics?

Moles are very common, especially in people with fair skin. Moles are overgrowths of skin cells called melanocytes, but the genetic factors involved in their development are not well understood. Although moles, like tumors, are an overgrowth of cells, moles are almost always noncancerous (benign). Perhaps because most moles are benign, scientists have not studied them extensively, and not much is known about their genetics. Similar numbers of moles seem to occur on individuals of different generations of a family, so a tendency to develop moles seems to be inherited, but the inheritance pattern is not well understood. Most moles occur on parts of the body that are exposed to the sun (ultraviolet radiation), and the number of moles an individual has may increase after extended time in the sun. Moles usually begin to occur in childhood. These moles are called acquired melanocytic nevi (and include the subtype epidermal nevus). It is common for new moles to appear during times when hormone levels change, such as adolescence and pregnancy. During an individual's lifetime, moles may change in appearance; hair may grow out of them, and they can change in size and shape, darken, fade, or disappear. Infants and the elderly tend to have the fewest moles.

Sometimes, moles are present at birth or develop during infancy. These moles, which are called congenital nevi, are almost always benign. Rarely, a very large mole, called a giant congenital melanocytic nevus, is present at birth. In rare cases, the most serious type of skin cancer (called melanoma) may develop in this type of mole. Large, irregularly shaped and colored moles called dysplastic nevi or atypical moles can occur at any age. Although not common, they tend to be numerous, and they increase a person's risk of melanoma. Heredity contributes to the development of dysplastic nevi and to having a higher-than-average number of benign moles. Spending a lot of time in the sun can also increase the number of moles a person has. However, moles are often found on areas of the body that are not exposed, which suggests that factors other than ultraviolet radiation from the sun, perhaps hormones or other biologic processes, are involved in triggering the development of acquired melanocytic nevi and dysplastic nevi.

Although the genetics of melanoma has been widely studied, much less is known about genes involved in the development of benign moles. Variations in several genes, including *FGFR3*, *PIK3CA*, *HRAS*, and *BRAF*, are involved with benign moles. The most-studied of these is the *BRAF* gene. A variant in *BRAF* leads to the production of an altered protein that causes melanocytes to aggregate into moles. This altered protein also triggers the production of a tumor-suppressor protein called p15 that stops moles from growing too big. In rare cases, *BRAF* gene variants together with loss (deletion) of the *CDKN2A* gene causes a lack of p15, which creates the potential for mole cells to grow uncontrollably and become cancerous (malignant). The formation of cancer is increasingly likely when combined with environmental factors, such as cell damage caused by ultraviolet radiation exposure. In susceptible individuals (those with fair skin, light hair, skin that burns instead of tans, a family history of melanoma, and genetic risk factors such as deletion of or variants in the *CDKN2A* gene), ultraviolet radiation from repeated sun exposure can damage existing moles, increasing their risk of becoming

malignant. Research has shown that individuals who have an abundance of moles are at an increased risk of melanoma. However, some people who are diagnosed with melanoma have few moles, and melanoma often develops in areas of the body that are not exposed to the sun. Researchers are working to identify additional susceptibility genes to better understand the genetics of moles and their relationship with cancer.

Scientific Journal articles for further reading

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Roh MR, Eliades P, Gupta S, Tsao H. Genetics of melanocytic nevi. *Pigment Cell Melanoma Res.* 2015 Nov;28(6):661-72. doi: 10.1111/pcmr.12412. PubMed: 26300491. Free full-text available from PubMed Central: PMC4609613. Silva JH1, Sá BC, Avila AL, Landman G, Duprat Neto JP. Atypical mole syndrome and dysplastic nevi: identification of populations at risk for developing melanoma - review article. *Clinics (Sao Paulo).* 2011;66(3):493-9. PubMed: 21552679. Free full-text available from PubMed Central: PMC3072014.

To learn more about the genetics of moles:

MedlinePlus offers additional resources (<https://medlineplus.gov/moles.html>) to learn more about moles.

A University of Pennsylvania press release describes *BRAF* and p15, factors that keep moles from turning into melanoma (<https://www.pennmedicine.org/news/news-releases/2015/august/penn-scientists-identify-key-g>).

10 Are facial dimples determined by genetics?

Dimples—indentations on the cheeks—tend to occur in families, and this trait is assumed to be inherited. Dimples are usually considered a dominant genetic trait, which means that one copy of the altered gene in each cell is sufficient to cause dimples. However, some researchers say that there is no proof that dimples are inherited. Little research has been done to explore the genetics of dimples and it is not known which gene or genes may be involved.

A dimple is an anomaly of the muscle that causes a dent in the cheek, especially when the individual smiles. Some people have dimples in both cheeks, others in just one cheek. Babies are likely to have dimples caused by baby fat in their cheeks. When they lose their baby fat as they get older, their dimples disappear. Other children do not have them at birth but may develop them later in childhood. In some people, dimples last only until adolescence or young adulthood, while in others they are a lifetime trait.

Dimples that have a similar appearance can occur in successive generations of a family. For example, in one family, it was observed that the siblings, their father, uncles, grandfather, and great-grandfather all had similar-looking dimples in both cheeks. In other families, dimples may occur in a child but are not seen in more than one generation.

Scientific articles for further reading

OMIM: Dimples, Facial (126100)

Wiedemann HR. Cheek dimples. *Am J Med Genet.* 1990 Jul;36(3):376. PubMed: 2363446.

To find out more about the influence of genetics on dimples:

Stanford at the Tech: Genetics of Dimples (<https://genetics.thetech.org/ask/ask47>)

Genetic Science Learning Center at the University of Utah: Observable Human Characteristics (<https://learn.genetics.utah.edu/content/basics/observable/>)

11 Is athletic performance determined by genetics?

Athletic performance is a complex trait that is influenced by both genetic and environmental factors. Many physical traits help determine an individual's athletic ability, primarily the strength of muscles used for movement (skeletal muscles) and the predominant type of fibers that compose them. Skeletal muscles are made up of two types of muscle fibers: slow-twitch fibers and fast-twitch fibers. Slow-twitch muscle fibers contract slowly but can work for a long time without tiring; these fibers enable endurance activities like long-distance running. Fast-twitch muscle fibers contract quickly but tire rapidly; these fibers are good for sprinting and other activities that require power or strength. Other traits related to athleticism include the maximum amount of oxygen the body can deliver to its tissues (aerobic capacity), muscle mass, height, flexibility, coordination, intellectual ability, and personality.

Studies focused on similarities and differences in athletic performance within families, including between twins, suggest that genetic factors underlie 30 to 80 percent of the differences among individuals in traits related to athletic performance. Many studies have investigated variations in specific genes thought to be involved in these traits, comparing athletes with nonathletes.

The best-studied genes associated with athletic performance are *ACTN3* and *ACE*. These genes influence the fiber type that makes up muscles, and they have been linked to strength and endurance. The *ACTN3* gene provides instructions for making a protein called alpha (α)-actinin-3, which is predominantly found in fast-twitch muscle fibers. A variant in this gene, called R577X, leads to production of an abnormally short α -actinin-3 protein that is quickly broken down. Some people have this variant in both copies of the gene; this genetic pattern (genotype) is referred to as 577XX. These individuals have a complete absence of α -actinin-3, which appears to reduce the proportion of fast-twitch muscle fibers and increase the proportion of slow-twitch fibers in the body. Some studies have found that the 577XX genotype is more common among high-performing endurance athletes (for example, cyclists and long-distance runners) than in the general population, while other studies have not supported these findings. The 577RR genotype is associated with a high proportion of fast-twitch fibers and is seen more commonly in athletes who rely on strength or speed, such as short-distance runners.

The *ACE* gene provides instructions for making a protein called angiotensin-converting enzyme, which converts a hormone called angiotensin I to another form called angiotensin II. Angiotensin II helps control blood pressure and may also influence skeletal muscle function, although this role is not completely understood. A variation in the *ACE* gene, called the ACE I/D polymorphism, alters activity of the gene. Individuals can have two copies of a version called the D allele, which is known as the DD pattern, two copies of a version called the I allele, known as the II pattern, or one copy of each version, called the ID pattern. Of the three patterns, DD is associated with the highest levels of angiotensin-converting enzyme. The DD pattern is thought to be related to a higher proportion of fast-twitch muscle fibers and greater speed.

Many other genes with diverse functions have been associated with athletic performance. Some are involved in the function of skeletal muscles, while others play

roles in the production of energy for cells, communication between nerve cells, or other cellular processes.

Other studies have examined variations across the entire genomes (an approach called genome-wide association studies or GWAS) of elite athletes to determine whether specific areas of the genome are associated with athleticism. More than 150 different variations linked to athletic performance have been identified in these studies; however, most have been found in only one or a few studies, and the significance of most of these genetic changes have not been identified. It is likely that a large number of genes are involved, each of which makes only a small contribution to athletic performance.

Athletic performance is also strongly influenced by the environment. Factors such as the amount of support a person receives from family and coaches, economic and other circumstances that allow one to pursue the activity, availability of resources, and a person's relative age compared to their peers all seem to play a role in athletic excellence. A person's environment and genes influence each other, so it can be challenging to tease apart the effects of the environment from those of genetics. For example, if a child and his or her parent excel at a sport, is that similarity due to genetic factors passed down from parent to child, to similar environmental factors, or (most likely) to a combination of the two? It is clear that both environmental and genetic factors play a part in determining athletic ability.

Scientific journal articles for further reading

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12 Is longevity determined by genetics?

The duration of human life (longevity) is influenced by genetics, the environment, and lifestyle. Environmental improvements beginning in the 1900s extended the average life span dramatically with significant improvements in the availability of food and clean water, better housing and living conditions, reduced exposure to infectious diseases, and access to medical care. Most significant were public health advances that reduced premature death by decreasing the risk of infant mortality, increasing the chances of surviving childhood, and avoiding infection and communicable disease. Now people in the United States live about 80 years on average, but some individuals survive for much longer.

Scientists are studying people in their nineties (called nonagenarians) and hundreds (called centenarians, including semi-supercentenarians of ages 105-109 years and supercentenarians, ages 110+) to determine what contributes to their long lives. They have found that long-lived individuals have little in common with one another in education, income, or profession. The similarities they do share, however, reflect their lifestyles—many are nonsmokers, do not have obesity, and cope well with stress. Also, most are women. Because of their healthy habits, these older adults are less likely to develop age-related chronic diseases, such as high blood pressure, heart disease, cancer, and diabetes, than their same-age peers.

The siblings and children (collectively called first-degree relatives) of long-lived individuals are more likely to remain healthy longer and to live to an older age than their peers. People with centenarian parents are less likely at age 70 to have the age-related diseases that are common among older adults. The brothers and sisters of centenarians typically have long lives, and if they develop age-related diseases (such as high blood pressure, heart disease, cancer, or type 2 diabetes), these diseases appear later than they do in the general population. Longer life spans tend to run in families, which suggests that shared genetics, lifestyle, or both play an important role in determining longevity.

The study of longevity genes is a developing science. It is estimated that about 25 percent of the variation in human life span is determined by genetics, but which genes, and how they contribute to longevity, are not well understood. A few of the common variations (called polymorphisms) associated with long life spans are found in the *APOE*, *FOXO3*, and *CETP* genes, but they are not found in all individuals with exceptional longevity. It is likely that variants in multiple genes, some of which are unidentified, act together to contribute to a long life.

Whole genome sequencing studies of supercentenarians have identified the same gene variants that increase disease risk in people who have average life spans. The supercentenarians, however, also have many other newly identified gene variants that possibly promote longevity. Scientists speculate that for the first seven or eight decades, lifestyle is a stronger determinant of health and life span than genetics. Eating well, not drinking too much alcohol, avoiding tobacco, and staying physically active enable some individuals to attain a healthy old age; genetics then appears to play a progressively important role in keeping individuals healthy as they age into their eighties and beyond.

Many nonagenarians and centenarians are able to live independently and avoid age-related diseases until the very last years of their lives.

Some of the gene variants that contribute to a long life are involved with the basic maintenance and function of the body's cells. These cellular functions include DNA repair, maintenance of the ends of chromosomes (regions called telomeres), and protection of cells from damage caused by unstable oxygen-containing molecules (free radicals). Other genes that are associated with blood fat (lipid) levels, inflammation, and the cardiovascular and immune systems contribute significantly to longevity because they reduce the risk of heart disease (the main cause of death in older people), stroke, and insulin resistance.

In addition to studying the very old in the United States, scientists are also studying a handful of communities in other parts of the world where people often live into their nineties and older—Okinawa (Japan), Ikaria (Greece), and Sardinia (Italy). These three regions are similar in that they are relatively isolated from the broader population in their countries, are lower income, have little industrialization, and tend to follow a traditional (non-Western) lifestyle. Unlike other populations of the very old, the centenarians on Sardinia include a significant proportion of men. Researchers are studying whether hormones, sex-specific genes, or other factors may contribute to longer lives among men as well as women on this island.

Scientific journal articles for further reading

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To learn more about the genetics of longevity:

Boston University School of Medicine provides a description of the New England Centenarian Study (<http://www.bumc.bu.edu/centenarian/>).

The Institute for Aging Research at Albert Einstein College of Medicine describes the Longevity Genes Project (<https://www.einsteinmed.edu/centers/aging/longevity-genes-project/about-the-study/>).

The Duke University Center for Population Health & Aging provides descriptions of studies of long lives (<https://cpha.duke.edu/life-course-studies>).

The National Institute on Aging offers a video about the Baltimore Longitudinal Study of Aging (<https://www.nia.nih.gov/research/labs/blsa/about>).

The SardiNIA Project has several pages describing research investigating longevity genes (<https://sardinia.irp.nia.nih.gov/index.html>) among Italians living on the Mediterranean island of Sardinia.

The Okinawa Centenarian Study (<https://orcls.org/>) describes the genetics, healthy aging, and longevity of Japanese living on the island of Okinawa.

13 Is temperament determined by genetics?

Temperament includes behavioral traits such as sociability (outgoing or shy), emotionality (easy-going or quick to react), activity level (high or low energy), attention level (focused or easily distracted), and persistence (determined or easily discouraged). These examples represent a spectrum of common characteristics, each of which may be advantageous in certain circumstances. Temperament remains fairly consistent, particularly throughout adulthood.

Similar temperaments within a family may be attributable to shared genetics and to the environment in which an individual is raised. Studies of identical twins (who share 100 percent of their DNA) and their non-twin siblings (who share about 50 percent of their DNA) show that genetics play a large role. Identical twins typically have very similar temperaments when compared with their other siblings. Even identical twins who were raised apart from one another in separate households share such traits.

Scientists estimate that 20 to 60 percent of temperament is determined by genetics. Temperament, however, does not have a clear pattern of inheritance and there are not specific genes that confer specific temperamental traits. Instead, many (perhaps thousands) of common gene variations (polymorphisms) combine to influence individual characteristics of temperament. Other DNA modifications that do not alter DNA sequences (epigenetic changes) also likely contribute to temperament.

Large studies have identified several genes that play a role in temperament. Many of these genes are involved in communication between cells in the brain. Certain gene variations may contribute to particular traits related to temperament. For example, variants in the *DRD2* and *DRD4* genes have been linked to a desire to seek out new experiences, and *KATNAL2* gene variants are associated with self-discipline and carefulness. Variants affecting the *PCDH15* and *WSCD2* genes are associated with sociability, while some *MAOA* gene variants may be linked to introversion, particularly in certain environments. Variants in several genes, such as *SLC6A4*, *AGBL2*, *BAIAP2*, *CELF4*, *L3MBTL2*, *LINGO2*, *XKR6*, *ZC3H7B*, *OLFM4*, *MEF2C*, and *TMEM161B* contribute to anxiousness or depression.

Environmental factors also play a role in temperament by influencing gene activity. In children raised in an adverse environment (such as one of child abuse and violence), genes that increase the risk of impulsive temperamental characteristics may be turned on (activated). However, a child who grows up in a positive environment (for example a safe and loving home) may have a calmer temperament, in part because a different set of genes is activated

Scientific journal articles for further reading

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To find out more about the role of genetics in temperament:

The Dana Foundation. One of a Kind: The Neurobiology of Individuality (<https://www.dana.org/article/one-of-a-kind-the-neurobiology-of-individuality/>).