Six Key Genes in the Ectodermal Dysplasias

EDA, EDAR, EDARADD, WNT10A, *IKBKG* (aka *NEMO*) and *TP63*

One question we are often asked is about the differences between the key genes involved in the different types of ectodermal dysplasia (ED). There are many different types of ED and many different genes can be involved. There is a small number of key genes that are most typically involved as well as many rare genes.

All these genes are present in everyone but changes in the code of that gene can cause problems if the code change alters the genetic instruction. So, when a particular gene is said to be involved in one individual with one specific type of ED, it means that a change in that gene is responsible for their form of ED. In families where more than one family member has ED they almost always share the same change in the same gene.

Genes

A gene can be thought of as an instruction – as in a recipe - for how the body should assemble itself and how it can function.

Genes consist of long runs (sequences) of the four different building blocks of DNA (Deoxyribose Nucleic Acid) A, C, G and T. The genes come in matching pairs, with one gene of each pair coming from each parent. The 20,000 or so different types of gene are all made of the DNA (those long strings of A, C, G and T) and are carried in the 23 chromosomes present in the sperm and the 23 chromosomes present in the egg that went to make each of us, with our 46 chromosomes. See the genetics section on our website https://edsociety.co.uk/what-is-ed/genetics/

Chromosomes

An important fact about genes is that this story – that we each carry two complete sets of all the genes – is only strictly true for girls and women. Twenty-two of the different types of chromosome are the same in boys and girls; they are the autosomes, 1-22. The 23rd pair are the sex chromosomes, known as X and Y. Females carry two X chromosomes (one from mother and one from father) while males have only one X chromosome (from mother) with, in addition, a much smaller chromosome known as the Y chromosome (from father). Females therefore carry two of each of the chromosomes 1-22 and two X chromosomes. Boys, however, have only one X chromosome plus one Y chromosome.

The X chromosome is an average-sized chromosome that carries many different genes important in many aspects of development and function, not only for sex and reproduction. The other sex chromosome, present in a boy, is the Y chromosome. This is important for development of male characteristics but does not have all of the other genes that are usually present on the X chromosome.

Dominant, Recessive and Sex-Linked

We must also remember that an alteration in a gene (a mutation) can be inherited or can occur, purely by chance, as a new event. The effect of a gene change depends on the exact code change and the gene involved. Sometimes, both copies of a gene need to be altered for there to be any effect: a single functioning copy of many genes is sufficient to avoid a problem. These gene alterations are known as "recessive" because they may seem to be hidden in those who carry a single alteration and are unaffected. Sometimes, gene "carriers" like this may have very mild problems.

Other genetic alterations lead to a change in the development or function of the body even when one copy of the gene is perfectly intact. With such a gene, a single altered copy is enough to cause an effect: such a gene alteration is called "dominant" and will usually show itself (its effects may be apparent at birth for some conditions or, for others, not until well into adult life).

This description of genetics misses out some of the complications - the fudges and blurring - but is broadly correct. However, we must say more about the sex chromosomes, where this distinction between dominant and recessive genetic changes is different. Because a boy has only one X chromosome, he will show any gene alteration that arises in a gene on his one and only X chromosome. A girl or woman is much less likely to show the effects of a gene alteration on the X, because she has a second copy of the same gene on her other X chromosome. However, the story gets more complicated still. Half a century ago, a genetics researcher Mary Lyon realised that only one of the two X chromosomes in a female mammal (including female humans) functions fully in any one cell (cells each contain the complete set of genes and chromosomes). Most of the genes on one of the two X chromosomes in a female are switched off – i.e. inactivated. So, as an example, a woman's skin consists of patches where her mother's X chromosome is the one that functions, and other areas of skin where it is her father's X chromosome that is working, and the decision as to which X chromosome works in which cells in her body or on her skin is random and is made in the embryo, long before birth. So a girl may still show signs of a sex-linked condition (caused by changes in a gene on the X chromosome) if the X chromosome with the intact copy of the gene is inactivated in a part of the body where the effects can be seen.

Different genes in different types of ectodermal dysplasia (ED)

So, leaving aside the sex chromosomes, we each inherit two complete sets of genes. The Human Genome Organisation (HUGO) designates an official name and symbol (an abbreviation of the name) for each known human gene.

Here, we are going to mention just six of these genes, which are often involved in some of the ED conditions. Many more are mentioned in the Tables you can find elsewhere on the EDUK website.

Hypohidrotic ectodermal dysplasia (HED): *EDA*, *EDAR*, *EDARADD* and Part One of *IKBKG* (also known as *NEMO*)

First, we will mention the most common type of ED, known as hypohidrotic ED (HED). In this condition, reduced sweating is usually a major feature as well as effects on the teeth and hair, and sometimes also the nails. A key step in development of these body structures requires a specific triggering signal to be sent and received within the developing skin. This signal is a protein molecule (ectodysplasin-A) encoded by a gene on the X chromosome (the *EDA* gene). The information encoded in the gene is used to make the protein molecule, so an alteration in the *EDA* gene alters the ectodysplasin-A protein signal and may interfere with its function. The signal is received by a signal receptor molecule embedded in the cell membrane of other cells nearby. This ectodysplasin-A receptor protein molecule is encoded by a gene (*EDAR*) and, when ectodysplasin-A binds to its receptor, it triggers the next steps in developing the affected structures (teeth, hair, sweat glands etc). This signalling step is critical for interactions between two embryonic cell layers called the ectoderm and the mesoderm. In the early embryo, these cell layers form the basis for many of the body's organs and tissues including the skin and the teeth.

Because the *EDA* gene is on the X, changes in this gene will have an effect more often and more severely in boys than in girls. Females may show no signs at all, or they may show some signs but

these will usually be less marked and often only present in some areas of the body (e.g. changes to only some teeth, patchy sweating and patchy changes to the hair on the scalp and the body).

The effects of changes in the *EDAR* gene are very similar to the effects of changes in *EDA*, because they are involved in the same step in development, but they vary in how serious they are. Some changes are rather mild and cause no problems, unless present on both copies of the gene, while others are more disruptive and having such a change in only a single copy of the *EDAR* gene will lead to clear signs of HED. In other words, the changes in *EDAR* are sometimes "recessive" and sometimes "dominant". Changes in the *EDAR* gene can affect men and women equally as this gene is situated on chromosome 2, not on the X chromosome.

Another gene, whose protein product sits close to the ectodysplasin-A receptor (the *EDAR* gene's protein product), is the *EDARADD* gene. The EDARADD protein supports the action of the ectodysplasin-A receptor, although changes in this gene are very uncommon as a cause of HED.

The fourth gene to be mentioned as important in HED, and also very rare, is the *IKBKG* or *NEMO* gene. Some changes in this gene, also on the X chromosome, will cause a very rare but unusually severe type of HED in boys, with incomplete manifestations in girls as in the usual *EDA*-type of XHED. The physical features of the condition are much the same as in the other types of HED, but this form is often complicated by a dangerous tendency to severe, sometimes life-threatening, infections. The *EDA* type of XHED can also lead to frequent chest infections, but it is especially severe in the rare, *IKBKG/NEMO* subtype of HED. Management of this condition must involve an experienced immunology specialist.

Incontinentia Pigmenti (IP): Part Two of *IKBKG* (or *NEMO*)

A different, more severe type of alteration in the *IKBKG* or *NEMO* gene just discussed causes a very different condition usually affecting girls only. In males their development is usually so severely damaged that a pregnancy with an affected male will miscarry quite early. An affected female embryo only survives to be born because half of her cells express the intact copy of the gene, as she has two X chromosomes. That allows her to survive, whereas an affected male embryo does not have even a single intact copy of the gene, as he only has one X chromosome.

This type of alteration in the gene leads, in the female, to the death of part of the outer epithelial layer (thin tissue forming the surface skin) of the affected areas of skin. These patches of skin epithelium are replaced first by angry blisters often present at birth or soon afterwards and then by pigmented tissue (coloured patches of skin). Over time, these areas of healed blistering and pigmentation are then slowly replaced by scar tissue that is pale, hairless and does not sweat; these scars can be seen as pale streaks in the skin of adult women who were affected as infants. There can also be damage to certain other body structures where this gene is important in early development, including the eyes and the teeth. It is of great importance that newborns with IP have their eyes examined before they leave hospital and then have eye checks every 3 months until one year of age, every 6 months until 3 years of age and annually thereafter.

TP63 gene: ED plus Limbs, Palate, Eyes, …

The protein produced by the *TP63* gene is a transcription factor: it sits in the cell nucleus (the separate part of the cell where the chromosomes are found) acting on other genes to control how they are expressed. It is involved in the development of many different parts of the body, not only those involved as key features of an ectodermal dysplasia (like hair, teeth, nails and sweat glands).

Other parts of the body that can be involved include the palate and the developing limb buds, so that patients where this gene has a problem may have a cleft palate and syndactyly (fusion of the fingers or toes) or ectrodactyly (split hand and/or split foot). Development of the breasts may also be disturbed, and the lacrimal glands of the eye and more generally the tissues around the eyes. The exact pattern of problems that can be caused varies with the particular change in the gene, so different changes in *TP63* can lead to a number of different "syndromes" including EEC syndrome, AEC syndrome, Rapp-Hodgkin syndrome, ADULT syndrome and Limb-Mammary syndrome. These could all be regarded as, at root, different expressions of the same condition - or else as distinctly different conditions but where different changes in the same gene happen to be responsible for causing them all.

The *WNT10A* Gene

Finally, we come to *WNT10A*. The protein product of this gene is another signalling molecule that influences the expression of other genes within the cell nucleus. It is involved in a different developmental pathway from either *EDA*, *EDAR*, *EDARADD* and *IKBKG / NEMO* or from *TP63*. However, it also influences the *EDA* gene pathway so that changes in *WNT10A* cause slightly different features of ED from XHED or EDAR. The protein produced from the *WNT10A* gene plays a role in the development of many parts of the body. However, the *WNT10A* protein is particularly important for the formation and shaping of both baby (primary) teeth and adult (permanent) teeth, which tend to be more evenly affected than in XHED. The teeth tend to be a bit small but evenly spaced and without being so misshapen as in XHED. Effects on the hair and nails are often less marked than in *EDA* and there may be variable sweating problems. This is sometimes recognised by researchers as a "mild variant HED".