

Features of Ectodermal Dysplasia: dominance, sex and women

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There are many different types of ectodermal dysplasia. In most of these, males and females are equally likely to be affected. This is usually the situation when the gene, in which mutations cause a particular type of ED, is located on one of the autosomes (the term used to describe the chromosomes numbered 1-22, i.e. not the sex chromosomes, X and Y). Here, I will outline some differences in the way that boys and girls can be affected by any genetic condition inherited on the X chromosome. And I will try to explain why having a single altered copy of a gene can lead to features of ED even though there is another, intact, copy of the same gene in every cell of the body. My particular aim is to explain why the terms "dominant" and "recessive" simply do not apply to genes on the X chromosome.

Most genes come in matching pairs, with one gene of each pair being passed in the sperm from the father and the other of each pair coming in the egg cell from the mother. This is because the chromosomes also come in matching pairs in the egg and the sperm. A fertilised egg contains two full sets of chromosomes, two copies of each type, while an unfertilised egg and a sperm contain only one copy of each chromosome (and therefore only one copy of each gene).

The chromosomes are physical structures, sometimes visible under the microscope, which carry many hundreds or thousands of genes, which are too small to be visible under the microscope. The 22 pairs of autosomes are the same in boys and girls; the twenty-third pair of chromosomes is different - these are the sex chromosomes, X and Y. A girl has two X chromosomes and a boy has only one X chromosome, but in addition a Y chromosome. The X chromosome carries many genes involved in a wide range of body functions; the Y chromosome is much smaller and makes the boy male but seems to do little else.

If an alteration in one copy of an autosomal gene is sufficient to cause a disease or condition, then the disease gene is said to be dominant (it shows despite the other copy of the gene being intact). If no problem arises unless both copies of the same gene are affected or disrupted, then the condition is said to be recessive; the altered copy of the gene is not manifest unless a child inherits a double dose. Dominant conditions can often be passed from one generation to the next; recessive diseases can affect brothers and sisters but do not usually affect the next generation.

If a mutation in a gene on the X chromosome causes a problem, it will usually do so much more clearly in a male than a female. This is because a male has only one copy of any gene on the X chromosome, whereas a girl has two copies. Despite this, however, a mutation in a gene on the X chromosome can often show in a female because only one of the two genes will be active in any cell in the body. In fact, a female has patches where she uses the genes

on one X chromosome and other patches where she uses the genes from the other X chromosome. Just which X chromosome is active in any one area on the body is random – it is down to chance. So a girl will often show some features of an X chromosome gene disorder, especially where it affects the skin (as in the X-linked type of hypohidrotic ectodermal dysplasia), and this will depend upon which of the two copies of the gene happens to be used more than the other in the areas of skin that can easily be seen. Equally, teeth may be affected if the female happens to make use of the altered X chromosome more than the other one.

The extent to which a girl will show signs of an X chromosome disorder will depend upon a number of factors - but principally it is chance. The formal way to refer to this is as the pattern of X chromosome inactivation; this is usually random but can be skewed heavily one way or the other for a number of reasons, so that occasionally a girl will show an X chromosome condition just as severely as a fully affected male. This may be by chance or because of some other chromosome anomaly or rearrangement that alters X inactivation. Another possibility is that the condition is thought to be caused by a genetic alteration on the X chromosome, but in fact that is wrong; this can certainly happen in HED, where the X-linked type is much the commonest, but where genes on other chromosomes can occasionally be involved and can look just like the X-linked condition. In HED, for example, the gene alteration will occasionally lie on chromosome 2q instead of the X chromosome. In that case, affected girls will show it just as if they were boys with the XHED condition.

The upshot of all this is that genetic conditions can be said to be transmitted as a dominant trait, as a recessive trait or as a sex-linked trait – but one should avoid describing a sex-linked trait as being recessive or dominant because X chromosome conditions do not fall neatly into those two subcategories. It would be frankly misleading to try and categorise them in that way. Equally, the term “carrier” can be applied to someone who has one altered copy of an autosomal recessive gene – they can be said to be an unaffected, healthy “carrier” of the condition – but female “carriers” of sex-linked conditions (when the genes are on the X chromosome) may or may not be affected, so the term is misleading unless one is very careful about how it is used. In general, it is best to use the idea of the unaffected gene carrier solely in relation to autosomal recessive conditions.

We could now go into a lengthy and fascinating discussion about why a single altered copy of an autosomal gene will sometimes cause problems (when we say the mutation is dominant) and will sometimes not cause problems (when we say the mutation is recessive). This is just a taster of what is a fascinating area of biology although it can be difficult to think it through. You may need to read this more than once.

Sometimes it is just a question of whether the cell, or the body, produces enough of the protein. In such a case, as with many enzymes, there is usually a good safety margin and just one intact copy of the gene produces sufficient; the mutation will then be recessive. Examples include phenylketonuria (PKU), that is screened on a blood spot from every newborn infant because treatment is by strict diet from infancy. Sickle cell disease and cystic fibrosis are two other examples.

If a half dose of the protein (the gene product) is NOT enough, then the condition will show. It is then termed dominant (because of "haploinsufficiency", as in the blood disorders called the porphyrias). Another way in which a genetic condition may cause disease even if one copy of the gene is working normally is when the product of the mutated gene actively interferes with the protein product of the intact copy of the gene or with some other cellular processes (a "dominant negative" mechanism). This occurs over time in Huntington's disease. If mutations are likely to occur at some stage in the intact copy of a "tumour-suppressor gene", then a predisposition to tumours may be passed as a dominant condition from one generation to the next as a familial type of cancer. Whether or not a tumour or a cancer actually occurs will depend upon chance – whether the other (intact) copy of the gene mutates spontaneously so that the cell is left without either copy of the gene working to suppress tumours. Finally, for now, if the proteins produced by a gene assemble into larger molecules – perhaps into chains of a structural protein such as a collagen or a fibrillin – then having one intact copy of the gene will not be good enough. As the building blocks produced by the altered copy of the gene will not assemble properly; the larger structures assembled from both types of protein will break up too easily (as in Marfan syndrome, for example). In that case, having a complete deletion of the gene is better than having a slightly altered copy – no gene product is better than a slightly altered protein, as all the components of the larger structural protein will work well if one copy of the gene is missing but not if 50% are present but faulty; that would be like building a house from bricks when 50% of them are going to crumble in wet weather.

This area is tricky but interesting. If you have a dominant type of ED, you may be interested to find out just why the ED has developed despite the one intact copy of the gene. If you are female and show marked features of HED, you may wish to know whether you have XHED and have been unlucky or whether you have an autosomal (either dominant or recessive) type of HED. You could ask your local genetic counsellor or clinical geneticist.

Dated 10.04.07