Ectodermal Dysplasias:

Why they are so diverse and how that can benefit us

Almost two hundred different types of ectodermal dysplasia (ED) and ED syndromes are estimated to exist, indicating that ED-associated disorders are extremely diverse. This diversity involves differences in several respects: which ectodermal structures are affected, how severely they are affected and whether this occurs in conjunction with other abnormalities.

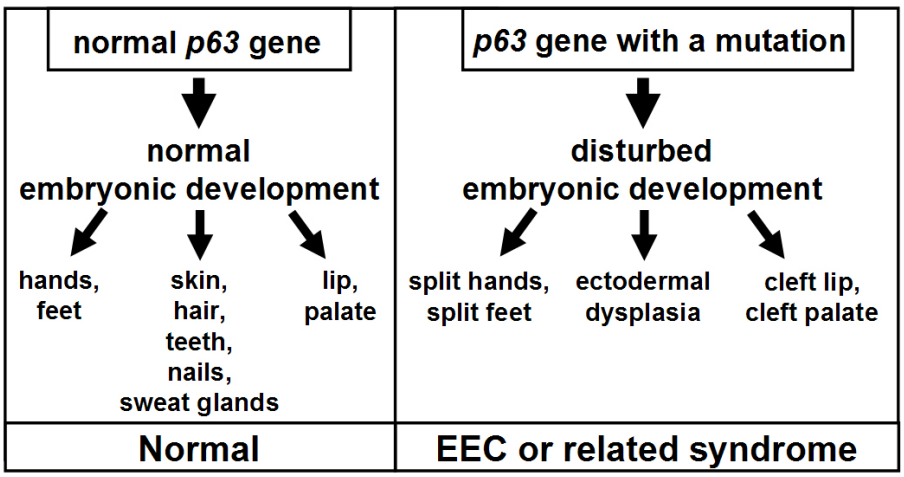
Why are ectodermal dysplasias so diverse? To answer that question, we need to go back to how EDs develop. Briefly, the development of ectodermal structures (hair, nails, teeth and several glands, including sebaceous, sweat, mammary and saliva glands) involves many different genes. Early during embryonic development, these genes are implicated in complex interactions between the ectoderm (the future skin of the embryo) and the underlying tissue, which ultimately results in the development of an ectodermal structure. Since the development of all these structures is initially very similar, many of the same genes are involved in the development of several different ectodermal structures. This explains why a mutation in one of these genes frequently gives rise to ectodermal defects affecting multiple ectodermal structures.

Other critical factors that contribute to the variability of ED include the nature of a mutation and its location within the gene. Some mutations disturb only part of the function of a gene, whereas others abolish it completely. Yet, again others may even cause a gene to acquire functions that it normally does not have. Often, a gene has multiple functions, which are each executed by distinct parts (or domains) of the gene. Hence, two very similar mutations can have completely different consequences if they are located in different domains within the same gene (see below for examples).

Many genes that are required for the development of ectodermal structures are also important for the development of other organs or parts of our body. Therefore, ED is often part of a syndrome, meaning that it is associated with other clinical problems. This adds another level of diversity to the heterogeneity of EDs.

I will illustrate how the aforementioned factors contribute to the variability of ED using several examples of common ED syndromes. The first is Ectrodactyly, Ectodermal dysplasia, Cleft lip/palate (EEC) syndrome. EEC syndrome is caused by mutations in the *p63* gene. Similar to the development of all ectodermal structures, development of our hands, feet, lip and palate also involve interactions between the ectoderm and underlying tissue. Because the *p63* gene plays an important role in all of these processes (left side of the figure below), *p63* mutations cause abnormalities that affect all of the abovementioned structures. Specifically, *p63* mutations cause malformations of the hands and feet, also known as split hand/foot malformation or ectrodactyly, ED, and clefting of the lip and/or palate (see figure, right side). Several EEC-related syndromes are also caused by mutations in the *p63* gene. Interestingly, depending on the type and location of the mutation, these syndromes affect only the limbs, as in isolated Split Hand/Foot Malformation (SHFM), or variable combinations of ED with SHFM and/or cleft lip/palate, as in EEC syndrome, limb-mammary syndrome, AEC/Hay-Wells syndrome, Rapp-Hodgkin syndrome and acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome.

A similar phenomenon is seen for mutations in the *NEMO* gene in X-linked forms of hypohidrotic ectodermal dysplasia (HED). *NEMO* plays an important role in the immune system as well in ectodermal development. The most dramatic type of *NEMO* mutations cause Incontinentia Pigmenti (IP), which, in addition to ED (mostly affecting hair



and teeth), is characterized by severe inflammation of the skin. Milder mutations in the *NEMO* gene give rise to immunodeficiency (ID) only, to anhidrotic ectodermal dysplasia with ID (EDA-ID), or to EDA-ID in combination with skeletal abnormalities.

How can we benefit from the fact that EDs are so diverse? For obvious reasons, the high degree of clinical variability will complicate clinicians in diagnosing patients. However, there is also an upside. In order to facilitate diagnosis, genetic counselling, clinical management and treatment of ED patients, it is important to gain more insights into the normal and disturbed development of the skin and ectodermal structures. Discovery of the genetic mutations that cause ED are a crucial aspect of that and it is precisely here where clinicians and geneticists benefit from the fact that EDs are so diverse. How they do may best be illustrated using examples of how ED mutations have been discovered in the past. Now almost a decade ago, researchers discovered that the *p63* gene was crucial for ectodermal appendage, limb and craniofacial development in mice. Since EEC syndrome does not only involve ED, but also limb malformations and clefting of the lip and/or palate, the *p63* gene became an obvious candidate for harbouring EEC mutations (also because of its genetic location). Indeed, causative *p63* mutations were identified thereafter.

The significance of *NEMO* in the development of ED was discovered in a different way. Before the identification of *NEMO* mutations in IP and EDA-ID patients, the *NEMO* gene was known to play an important role in the immune system. The severe skin inflammations and defects in the innate immune response in these patients, respectively, suggested that *NEMO* might be involved. Yet, that the *NEMO* gene is also important for development of ectodermal structures only became apparent after the discovery of *NEMO* mutations as those were associated with ED as well. These examples show that the abnormalities that ED patients may have in addition to ED can greatly facilitate the discovery of causative mutations.

In conclusion, the significant degree of clinical variability among EDs and ED syndromes is a consequence of the fact that many genes implicated in these disorders are important for the development of multiple – ectodermal and/or non-ectodermal – structures. In addition, the difference in nature and location of mutations in these genes often significantly contributes to the diversity of EDs. While a high degree of variability complicates diagnosis, the presence of abnormalities in addition to ED can aid in the discovery of causative mutations and therefore ultimately facilitate diagnosis, genetic counselling, clinical management and treatment of ED patients.

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