Genotype-Phenotype Correlations in Cornelia de Lange Syndrome

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Our bodies are made up of billions of cells and within each cell there are chromosomes which are the structures that hold all of our approximately 20,000 genes and genetic information. Genes function as the body's instruction manual telling our body how to grow and develop. We have two copies of each gene as we get one set from our mothers and one set from our fathers. Genes are made up of genetic material, called DNA, and they serve as the blueprint from which proteins are made. Proteins are the basic building blocks of the human body performing specific functions so that our bodies work properly controlling everything from our heartbeat to determining our eye color (Figure 1).

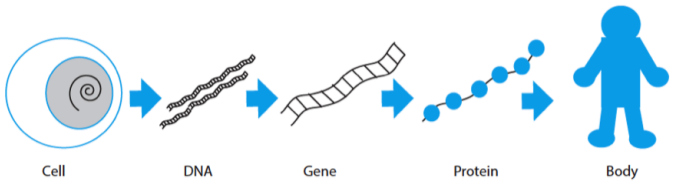

Figure 1. Cells contain DNA material which is organized into genes. Genes make proteins which are the basic building blocks of the body responsible for making our bodies work properly.

Sometimes changes (or mutations) spontaneously occur in genes that prevent them from working properly altering the proteins that are made. As a result, this affects various bodily functions including growth and development. Currently, mutations in five different genes, *NIPBL, SMC1A, SMC3, HDAC8* and *RAD21*, have been associated with Cornelia de Lange Syndrome (CdLS) (and several others, such as *AFF4, TAF1* and *TAF6* that have been associated with clinical pictures similar to CdLS). The association between the presence of a certain mutation or mutations in a specific gene (genotype) and the resulting presence, absence or severity of symptoms or clinical features (phenotype) is called a "genotype-phenotype correlation".

Now that there are five genes known to be involved in CdLS certain genotype-phenotype correlations have been observed for each of the genes. Changes in these five genes are found in approximately 65 percent of individuals with a clinical diagnosis of CdLS, with the vast majority being caused by mutations in *NIPBL*.

NIPBL

Individuals with classic findings of CdLS, including characteristic facial features and limb

anomalies, are likely to have a change identified in the *NIPBL* gene. However, changes (or mutations) in *NIPBL* have been found in individuals with both classic and mild presentations. The degree of severity depends on the specific type of mutation that occurs and where the mutation falls within the *NIPBL* gene.

A truncating (or frameshift) mutation is one type of mutation that tends to have a more significant effect on the gene that can ultimately block protein production. Therefore individuals with truncating mutations typically present with a more classic or severe form of CdLS.

Missense mutations are a different type of mutation which generally only slightly changes the protein. Therefore, individuals with missense mutations typically present with milder forms of CdLS, since their proteins likely retain some residual function.

SMC1A and *SMC3*

Individuals with *SMC1A* or *SMC3* mutations typically have fewer structural differences, such as a limb difference or heart difference. Such individuals also tend to present with less significant growth restriction than those with *NIPBL* mutations. However, individuals with *SMC1A* or *SMC3* mutations will still typically have intellectual disability that can range from moderate to severe [Deardorff et al 2007].

Subtle facial features in individuals with *SMC1A* or *SMC3* mutations may differ than those observed in "classic" CdLS caused by *NIPBL* mutations and can include slightly flatter and broader eyebrows with a broader and longer nasal bridge [Rohatgi et al 2010]. Specifically, individuals with *SMC3* mutations often have subtle or absent synophyrs (connecting eyebrows), wider nose with a rounder tip, and a well-formed philtrum (vertical groove between the base of the nose and upper lip).

RAD21

Individuals with mutations in *RAD21* typically do not have major structural differences. Individuals with *RAD21* mutations have milder cognitive impairment compared to those with "classic" CdLS. These individuals typically display growth retardation, minor skeletal anomalies, and facial features that overlap with CdLS. [Deardorff et al 2012].

HDAC8

Individuals with mutations in *HDAC8* have facial features which overlap with CdLS but typically display delayed closure of the anterior fontanel (the opening or "soft spot" on the top of the head in babies which typically closes around one year of age), hooded eyelids, a wider nose, varying pattern of skin pigmentation, and friendly personalities. Growth restriction also tends to be less significantly affected with this gene and a lower frequency of microcephaly (small head circumference) is reported.

In females, the severity of clinical presentation caused by mutations in *HDAC8* is variable, since this gene is on the X chromosome and females have two X chromosomes while males have only one X chromosome and a Y chromosome. Since women have two X chromosomes in every cell, they randomly shut off one copy of the X chromosome (called X-inactivation). Therefore, depending on how many X chromosomes with the mutation versus those without the mutation are inactivated will directly influence the severity of their clinical presentation. (Though *SMC1A* is also located on the X chromosome this X-inactivation process does not apply to the *SMC1A* gene).

NIPBL mosaicism

A recent study led by Dr. Raoul Hennekam in the Netherlands [Huisman et al 2013] has found that mosaicism for *NIPBL* mutations may be found in up to 30 percent of individuals with CdLS who have tested negative in the blood for mutations in the known CdLS genes. Mosaicism means that an individual has a change in a gene which is present in only some but not all of the cells in their body. If an individual is mosaic for a change in *NIPBL*, we may not be able to identify this change by testing only their blood; instead, we may need to test other cells from other tissues such as cheek cells, also called buccal cells.

Depending on the number of cells carrying the mutation and the tissues involved, an individual with *NIPBL* mosaicism can theoretically present with a more mild form of CdLS. However, additional research is needed in this area since only a few patients with *NIPBL* mosaicism have been identified thus far.

What it all means

While clinicians and researchers have reported these genotype-phenotype correlations (summarized in Figure 2) it is important to note that they are generalities and are often true but these "rules" are also frequently broken. We have seen children with severe (truncating or frameshift) mutations in *NIPBL* who have a mild clinical picture (phenotype) and conversely also seen children with mild (missense) mutations in *NIPBL* who have a very severe clinical picture.

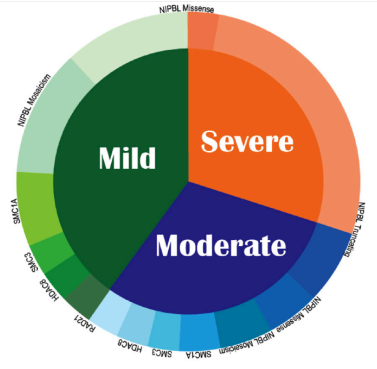

Figure 2. With five genes known to be involved in CdLS certain genotype-phenotype correlations have been observed for each of the genes.

There is still much work to be done to fully understand the correlations between the genotype and phenotype in individuals with CdLS, but there are general principles emerging and clinicians are getting better at using this information to help provide some guidance and prognostic information to families.

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