

Genetic Testing and Your Family

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The first gene known to be associated with Cornelia de Lange Syndrome (CdLS), *NIPBL*, was discovered in 2004. Since then, four more genes have been identified:

SMC1A, *SMC3*, *HDAC8* and *RAD21*. Changes in these five genes are found in approximately 70 percent of individuals with CdLS, with mutations in *NIPBL* being identified in at least 65 percent of individuals, and the other genes being responsible, collectively, for about 5 percent. This leaves approximately 30 percent of individuals with CdLS in whom an identifiable underlying genetic etiology has not been found.

Recently a few researchers have seen children with CdLS in whom a mutation was not identified in the blood, but was found in other tissue samples, such as cheek cells. This indicates that some individuals do not have the gene change in all of their cells, but rather in a subset of cells. This is called mosaicism. It is unclear at this time what percent of individuals with CdLS have a mosaic mutation as the underlying cause. And evidence suggests there are likely additional genes to be found that cause CdLS when mutated.

Genetics 101

As a brief background on genetics, we all have around 20,000 genes. We have two copies of each gene, with one set being inherited from our mothers and the other set from our fathers. A dominantly inherited condition, like CdLS, results from a change in only one copy of a set of genes. We say the change is “dominant” to the normal functioning other copy of the gene. This means that even though you have a copy of the gene that is functioning fine, the changed (or “mutated”) copy still has an effect on that individual – and hence is dominant.

Dominant changes can happen on the sex chromosomes (X and Y chromosomes) or on the non-sex chromosomes (called autosomes). Mutations in the *NIPBL*, *SMC3*, and *RAD21* genes are associated with an autosomal dominant inheritance pattern. *SMC1A* and *HDAC8* are associated with X-linked dominant inheritance pattern. Women have two copies of the X chromosome and men have one copy each of the X and Y chromosome. Since women have two X chromosomes, the risks for future pregnancies are determined by the carrier status of the mother—although in almost all cases of CdLS caused by an X-linked gene, they have been new changes and are not carried in the mother.

Genetic testing is performed most often through a blood test and the vast majority of mutations identified are *de novo*—meaning that the mutation occurred spontaneously in the egg or sperm that went to form that child. As mentioned above, if a mutation is not identified in the blood of an individual with CdLS, it is recommended that a different tissue be tested (cheek, saliva or skin biopsy) to rule out a mosaic mutation.

Germline Mosaicism

If both parents are clinically unaffected, then the risk to have additional children with CdLS is estimated to be approximately one percent. This is due to “germline mosaicism.” In germline mosaicism, the mutation in the gene that causes CdLS arose in a precursor cell that went on to form a group of eggs or sperm. In these rare cases, the change then exists in multiple sperm or eggs (but not in other tissues of the parents, so their blood testing will be negative and they will not have features of CdLS), but are at risk (as high as 50 percent) to have other children with CdLS.

In future pregnancies, serial ultrasound examinations may be performed to follow overall growth and the development of the heart, limbs, palate and other structures affected in individuals with CdLS. In some pregnancies, the maternal serum marker, PAPP-A, may be reduced and the fetal nuchal translucency (NT) may be increased, though these findings are not specific to CdLS.

If a mutation has been previously identified, prenatal diagnosis of future pregnancies can be performed by chorionic villus sampling (at 10-12 weeks gestation) or an amniocentesis (15-18 weeks gestation). Preimplantation genetic diagnosis (PGD) is also available for families in which the causal mutation has been identified. PGD is a procedure in which embryos are created outside of the body through in vitro fertilization (IVF) and one cell (in the first few stages of division) is biopsied to determine if the genetic change is present. Then, there is implantation into the mother’s uterus of embryos that do not carry the mutation.

Second Generation CdLS

Rarely, a mildly affected individual with CdLS will have children, and in those instances the parent has a 50 percent chance of passing on the affected gene (see below).

For individuals with CdLS who are interested in having families of their own, the recurrence risk is largely dependent on the underlying gene change present in the individual. For those who have a mutation in the *NIPBL*, *SMC3*, or *RAD21* gene there is a 50 percent chance to pass on the mutation to any child. Since we all have two copies of every gene, there is a 50 percent chance to pass on the copy of the gene with the mutation and a 50 percent chance to pass on the copy of the gene without the mutation.

If a child inherits a CdLS gene mutation from a parent, the child will inherit the same mutation as the parent and will be similarly affected. For those who have mutations in either of the X-linked genes, *SMC1A* or *HDAC8*, females have a 50 percent chance to pass the copy of their X with the mutation to their children, while males will pass on the copy of their X with the mutation to all of their daughters but none of their sons (who inherit the father’s Y chromosome and not the X chromosome). Unaffected siblings of individuals with CdLS are not at an increased risk to have children of their own with CdLS.

Conclusion

For individuals interested in expanding their family or who are interested in pursuing prenatal genetic testing, it is recommended to meet with a geneticist or genetic counselor before pregnancy to discuss recurrence risk as well as the benefits, limitations, and possible uses of genetic testing for you and your family.

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