USA researchers discover a third gene associated with CdLS

The CdLS research team at the Children's Hospital of Philadelphia (CHoP) recently discovered a third gene involved in CdLS. The information was published in an article in the March 2007 edition of the *American Journal of Human Genetics* along with more information about the second CdLS gene.

The first gene discovered as a cause of CdLS was *NIPBL*, in 2004. The *NIPBL* gene, which is located on the 5th pair of chromosomes, has now been tested in hundreds of individuals with CdLS. Mutations (changes in the genetic code) of the *NIPBL* gene have been found in approximately 50% of individuals with CdLS. *NIPBL* changes can cause typical CdLS, with any degree of severity, from mild to severe. The *NIPBL* gene produces a protein which is involved in the "***cohesin complex***". This is a group of proteins, each coded for by a different gene, that work together. The complex has been shown to have a function in the way chromosomes behave during cell division. As cells divide and multiply during growth and development, the 23 pairs of chromosomes in each cell have to be copied and then separated equally into the dividing cells. The cohesin complex is involved in this process. It also has a role in regulating activity of other genes important in the early development of the embryo.

In 2006, a research group based in Milan, Italy identified a second gene that could be involved in CdLS. This gene, initially called *SMC1L1*, and now called *SMC1A,* also codes for another of the proteins in the cohesin complex. *SMC1A* is located on the X chromosome. CdLS caused by *SMC1A* mutations tends to be milder than CdLS cause by *NIPBL* mutations, in that no individuals have limb defects, nearly all individuals develop speech, and on average the degree of developmental disability is less. The CHoP researchers then analysed the *SMC1A* gene in 115 individuals diagnosed with CdLS, who did not have a mutation in *NIPBL.* About 10% of these individuals (thus about 5% of all people diagnosed with CdLS) turned out to have a mutation in *SMC1*A, so this is much less common than *NIPBL* mutations. Of interest, gene mutations in X chromosome genes usually cause more obvious symptoms in boys than in girls. Geneticists call this pattern called "X-linked recessive". This does not seem to be so for individuals with CdLS due to *SMC1A*. Girls can be affected as much as, or even more than boys. This type of pattern is called "X-linked dominant".

The CHoP team also analysed another gene involved in the cohesin complex, *SMC3*, in 96 individuals with CdLS. They found a mutation in *SMC3* in just one person, who also had "mild" CdLS. *SMC3* gene mutations are so far the least common cause of CdLS (about 1%). The *SMC3* gene is located on the 10th pair of chromosomes, so *SMC3* gene mutations would be expected to occur equally in males or females.

So far, whether CdLS is caused by mutation in *NIPBL*, *SMC1A* or *SMC3*, in the great majority of families the affected person is the first one in the family to have the gene mutation. This is true for many conditions that significantly affect developmental abilities, as many affected individuals do not have children. If they did, there would be a 50% chance of passing on CdLS to any child. As most parents of someone with CdLS do not have CdLS themselves, nor do they carry it genetically, their chance of having another affected child is low. Genetic testing can help to clarify that risk further.

At least 30% of individuals with CdLS so far tested still do not have an identified gene mutation, so other genes may yet be discovered. The genes coding for the other 15 or so known proteins in the cohesin complex are obviously good "candidates" to examine, but as each protein has a different function in the cohesin complex, disturbances to each might give effects other than CdLS. For example, some

individuals with mutations in cohesin complex genes might present with developmental or physical disabilities only, without the combination of features we recognise as CdLS. For those individuals who do have CdLS, but who do not have mutations in *NIPBL, SMC1A* or *SMC3* genes, the answer may turn out to be another gene in the cohesin complex, but it could be elsewhere. Active research of these possibilities continues.

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