Genetics Research Update

Researchers in Italy identify a second genetic cause of Cornelia de Lange syndrome

A team of clinicians and researchers from Italy has recently published their findings of a new gene involved in CdLS. This research was published in the May 2006 issue of the journal *Nature Genetics.* The article, called **"X-linked Cornelia de Lange syndrome owing to *SMC1L1* mutations",** was from a research group based in Milan, Italy. The group was led by Dr Antonio Musio, a research scientist, and Dr Angelo Selicorni, a clinician well known to the CdLS group.

Previously, in 2004, researchers from the USA and UK had identified the first gene known to be involved in CdLS, called *NIPBL.* DNA studies show that mutations in *NIPBL*, located on chromosome 5, can be found in around 50% of individuals with CdLS. That left a lot of people for whom the cause of CdLS was unknown. Researchers knew this must be because there were other, as yet unknown gene(s), in which mutations could lead to CdLS. The question was: how to identify them?

Genes are DNA recipes, each located at a particular address on a particular chromosome. Genes code for proteins that the cell makes, each of which has a function. The insulin gene, for example, makes a protein that works as a hormone, controlling the use of glucose by our cells. Some genes, such as collagen genes, produce proteins that are used like building materials, in the structure of various tissues in our body, such as skin and ligaments. Other genes make proteins that first need to join up with other proteins, to make *complexes*. The protein complex then has a function in the cell. In those complexes, disruption of any one of the component parts could lead to a problem with the function of the whole complex.

NIPBL has a number of functions, but one function is as part of a protein complex. So one idea to follow was whether there were known genes that worked in the same complex as *NIPBL*, and whether any of these could be involved in the cause of CdLS in some people.

It was known that *NIPBL* gene has some function in chromosome cohesion (which means sticking together). Chromosomes are constantly unwinding and rewinding sections as genes are needed. Before cells multiply, chromosomes need to copy themselves, and then separate into different cells, and re-arrange themselves tidily, all of which involves control of cohesion (and lots of other things too). Chromosome cohesion problems do not usually show up on chromosome tests unless cohesion is extremely severely disrupted. One example where we can see cohesion problems with a chromosome test is a condition called Roberts syndrome. This is a very severe genetic condition which has limb abnormalities very similar to what we see in CdLS, but looks quite different otherwise.

It turns out that chromosome cohesion is controlled by a "cohesion complex", which includes at least 7 proteins, coded for by 7 different genes. Within the last 2 years, problems in two of these genes have been linked to human genetic conditions. The first was in fact *NIPBL,* reported in June 2004*,* which is involved in many individuals with CdLS*.* The other is *ESCO2*, reported in December 2005, which is involved in Roberts

syndrome. However, researchers knew that *NIPBL* has *other* functions apart from its involvement in the cohesion complex –it's a gene with multiple roles. One other gene involved in producing a protein for the cohesion complex, called *SMC1L1*, is also thought to have multiple roles. So, the researchers decided to investigate this gene in 33 individuals with CdLS who did not have *NIPBL* mutations.

These 33 patients studied included one remarkable family where there were 4 affected relatives with a diagnosis of CdLS, including 2 brothers, their very mildly affected mother, and her nephew. They found mutations in the *SMC1L1* gene in all 4 individuals and one other unrelated boy. The 4 boys with mutations in *SMC1L1* all had moderate to severe mental retardation, facial features that looked like CdLS, feeding problems in childhood, and small hands. Some had reflux, and some had epilepsy as well. The mother of the two brothers really had very few differences, only slight problems with learning and some slight facial similarities. Her sister (mother of her affected nephew) and her mother were both also found to carry the same mutation in *SMC1L1* but they had no features of CdLS. The other affected boy, unrelated to that family, was the first person in his family to have a mutation in *SMC1L1* – his mother did not carry the mutation.

The explanation of why the boys were more severely affected and the women were only very mildly affected, or not at all, is because *SMC1L1* is an ***X-linked*** gene. This means it is located on the X chromosome. Of the total of 46 chromosomes in every cell, women have two X chromosomes (46,XX) whereas men only have one, paired with a Y chromosome (46,XY). There are hundreds of different important genes on the X chromosome. If men have a mutation (mistake) in a gene on the X, it will always cause a problem, as there is no back-up gene on the Y. Women only use one of their X chromosomes in every cell, so if they have a mutation on one X, the problem often will not show up, especially if most of their cells work from the normal copy of the X. Or if there is a condition, it will usually be much milder than it is for a male. Haemophilia is an example of another X-linked condition, which is why it usually only affects males.

How important is this finding for CdLS? X-linked CdLS due to mutations in the X-linked *SMC1L1* gene is probably uncommon, especially compared to *NIPBL.* CdLS is not significantly more frequent overall in males than females (which it would be if *SMC1l1* was a more common cause). But X-linked CdLS due to mutations in *SMC1L1* could be the cause of CdLS in a small proportion of boys who do not have mutations in *NIPBL*. It would be particularly important to check for in any families who have more than one affected boy. As we learn more about X-linked CdLS, we may be able to recognise that there are differences in the overall appearance or features of boys with X-linked CdLS compared to others with CdLS due to mutation in *NIPBL*. *SMC1L1* might also turn out to be an important gene to check in boys whom we think look a bit like they have CdLS, but are not quite typical.

Is there another gene or even genes involved in CdLS? The answer is, almost certainly yes! Many people with CdLS, male and female, will not have mutations in either of these first two discovered genes. The next gene discovery will, we hope, be just around the corner….