“Influencing” Cornelia de Lange Syndrome?

It has been suggested in the past, but also recently, that we should consider trying to cure Cornelia de Lange Syndrome (CdLS). Surely, if a parent would have the choice, every parent would choose to have a completely healthy child, so it is completely understandable that parents are thinking about this, and looking for every possibility to achieve it.

When discussing this it is good to know a bit about the function of the genes for CdLS. These genes are what they call developmental genes. It means each gene has an influence early during pregnancy in the formation of the body of the child. Indeed we see this already in the facial characteristics and hands etc which are influenced in their shape by the genes

Firstly, it is good to know something about the function of such genes. Take a gene that is steering the development of fingers. We have several of these genes. We know such genes, know quite a bit of what they do, and also which changes (mutations) can be present in such genes and how this can cause problems in the shape and function of the fingers. Suppose there is a mutation in one of these genes that causes your little finger not to be formed. If we see this after birth, and we know the mutation in the gene, we could try to correct that mutation (there are such techniques now; the best known of these techniques is called CRISPR-Cas9 but others are, for example, influencing the function of RNAs or proteins). The gene would then function perfectly, but we won’t get that little finger back! The gene can only do its job during a particular phase during development. If it is not doing it at that time, it won’t be able to correct that later on. In medical terms: there is a “time window” in the function of the gene. That is something that all developmental genes have.

Now back to the genes for CdLS. These genes have several functions before birth. As stated above we can see this, for instance, in the shape of the eyebrows and nose which are already abnormal at birth. Major functions of all genes that cause CdLS are in the formation of our brain. There have been extensive studies done, and we know of functions in the formation of the outer layer of the brain (called cortex) and also of several smaller parts within the brain. The CdLS genes are needed for all these parts to be formed properly. We often see that the head of a newborn child with CdLS is already small, and sometimes we can see this also on an MRI of the brain. The latter is not always the case. But please realise an MRI sees changes that are about 1mm in size, but cannot see smaller changes. An MRI does not see how a single cell is formed. So an MRI can look completely normal while under the microscope we would see many brain abnormalities.

If we make a mouse in which one of the CdLS genes is not functioning correctly, that mouse would have several brain parts not properly formed at birth. Surely we can try to correct this CdLS gene in the mouse again, but the mouse brain will remain abnormal: the abnormal brain parts can no longer be reformed correctly, as the time in which this had to be done, has passed.

This means that at birth everyone with CdLS has brain abnormalities that are the result of the abnormal functioning of the CdLS gene, and these can no longer be corrected. So in that sense curing CdLS is not possible.

Is there then nothing that can be done? Surely not! We know that developmental genes have in fact two functions: one is in the development of the human body, as described above. That is the function before birth. But they also have functions after birth, for instance in the formation of an enzyme or some other protein that is needed for an organ to function well. For CdLS genes we know for instance they have an important function in the growth of our body. So therefore most children with CdLS remain smaller than one would expect. We do not know all functions of the CdLS genes after birth yet. One can imagine that some behavioural problems can be influenced this way, as that is known for several other developmental genes as well. And maybe also the gastroesophageal reflux can be explained this way. So it is worthwhile to study this, as maybe we can influence this.

So the conclusion is that a true 'cure' of CdLS is not possible. But we can still try to influence some characteristics of the abnormal gene in someone with CdLS, not to make them function completely normally, but to allow them to have the best possible quality of life. And further studies in that respect are very useful!

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