



## **RADical new findings for some with features like CdLS**

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After several years of work, we have finally completed our first efforts to understand how changes in a gene called RAD21 cause features that overlap some seen in children with CdLS. This work was guided by our previous findings of changes in the NIPBL, SMC1A and SMC3 genes. Yes, I agree the names of these genes are a bit crazy and cryptic, but the SMC1A and SMC3 genes work together to make a bracelet like protein called cohesin that is essential to hold a chromosome together. More specifically, a chromosome is actually made up of two exact replicates, called sister chromatids, which are held together at the middle.

The cohesin ring is the structure that holds them together in the middle. Without any cohesin, a cell will die. However, we have realized that even in situations where cohesin is present, but in smaller amounts, the chromosome function is normal, but there are problems with the way genes are turned on and off. It is this problem that results in the features of CdLS.

How does RAD21 fit in here? Well, RAD21 essentially functions as a clasp for the cohesin bracelet. Because we knew how it worked in other settings (most information came from yeast), we asked whether it might play a role in causing CdLS. To check this, we tested for changes in many children with CdLS for whom we had not figured out a cause. It turns out that we did not find changes in any children with more "typical" CdLS, but found changes in this gene in three children with milder features of CdLS.

Because we found the change in so few children and we wanted to know that we were not making any mistakes, we checked how these changes affected the way cohesin works in several settings, including cells, yeast and in zebrafish. All of these tests helped to confirm that the changes we found were relevant.

One of the findings that we found to be quite interesting is that these children, while they have growth and facial features that look a bit like CdLS, their intellectual development can be normal. We are hopeful that by understanding more about RAD21, we will gain insight about how we might find an angle to improve cognitive performance for children with CdLS.

This work was published in June in the American Journal of Human Genetics. Our goal is that this will encourage other researchers who have thought about how this gene works to focus some of their attention on CdLS. As always, we could not have done this work without all of the support and participation that we receive from families. This finding belongs to you as much as it does to our team here in Philly.

