Diamond-Blackfan anemia (DBA) is caused by a mutation in a ribosomal protein gene. Ribosomal proteins build a large cellular complex called the ribosome which are the protein factories of a cell and essential for life. However, it remains to be elucidated how these mutations cause DBA exactly and why some people who carry such mutations develop the disease while others are completely healthy ("silent carriers"). One reason why silent carriers do not develop DBA could be that an additional mutation in another gene suppresses the red blood cell failure or a mutation in a gene that triggers it.

Since I joined the project two years ago I set up methods to search for mutated genes that can rescue the defective generation of red blood cells in a petri dish ("Set-up phase"). Through the establishment of specialized cell lines and techniques, I recently scanned the entire human genome to look for candidate genes that might be able to compensate for mutations that cause DBA using two different approaches ("Screening phase"). In the coming 3 years, I will investigate the relevance of the identified candidates for red blood cell production using "reprogrammed" DBA patient cells ("Follow-up phase"). To do this, I will grow red blood cells from the reprogrammed patient cells and assess if a mutation in the identified candidate genes allow the development of healthy red blood cells. The knowledge gained from these experiments could help understand why red blood cell production fails as a result of ribosomal gene mutations in some individuals but not others. Moreover, the identification of genetic factors that restore red blood cell production could suggest novel therapeutic avenues for the treatment of DBA.

Facts:

Humans are complex organisms that are comprised of billions of cells.

Each human cell contains 2 meters of DNA that is packed up in the nucleus in a very sophisticated way.

This 2 meter DNA stretch encodes over 20 thousand genes (= the blueprint for proteins) that give rise to over 300 thousand proteins (= the stuff that actually makes a human body work).

To scan the human genome for mutations that could compensate for DBA causing mutations, we mutate 120 million cells so we hit each of the over 20.000 human genes several times.

We than isolate the DNA and sequence all this 120 million mutations at the same time on a so-called next generation sequencing machine.

The generation and culturing of these 120 million cells takes several weeks, the sequencing of all the mutation in parallel is done in 24 hours.