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The role of CBX2 in human sex development

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Sex development is a complex and fundamental process and is required for the continued existence of most multicellular organisms. Human sex development can be subdivided into two separate and distinct processes: sex determination, which encompasses all events that drive the commitment of the bipotential gonad in the direction of either the male or female pathway, and sex differentiation, the subsequent maturation of the body through hormones, leading to sexual male/female dimorphism. Variants in genes important for human sex development can lead to Differences of Sex Development (DSD). Currently, it is estimated that in about 50% of DSD cases in humans, the underlying genetic cause remains unknown.

One of the recently identified factors important in human sex development is CBX2. It has been shown that the isoform 1 of CBX2 (CBX2.1) is necessary for male human sex development, by studying a 46,XY DSD case with loss-of-function variants. In order to clarify the mechanism of disease, we proceeded to identify direct and indirect targets of CBX2. To gain insights into the CBX2-dependent transcriptional landscape, RNA-Sequencing from Sertoli-like testicular cells was performed, with either CBX2 overexpression or downregulation. Additionally, a complete CBX2 knockout Sertoli-like cell line was created using CRISPR/Cas9. These experiments lead to the identification of around 2'000 direct and indirect targets of CBX2.
Furthermore, two 46,XY DSD patients with mutations in isoform 2 of CBX2 (CBX2.2) were identified. Functional studies showed that the variant CBX2.2s failed to regulated genes known to be important for sex determination, implicating CBX2.2 in the early development of the gonad.
In the course of my doctoral work, I also contributed in the identification of a novel DAX1/NR0B1 variant in a boy with X-linked adrenal hypoplasia congenital. Analysis of the functional consequences on the protein level using in silico bioinformatics approaches (molecular dynamics) showed that the variant leads to a truncation of the protein. Finally, we discovered for the first time a variant in the estrogen receptor beta (ESR2) leading to an early onset ovarian failure and complete lack of estrogen action (absent breast development, primary amenorrhea and osteoporosis) in a 46,XX patient. Molecular studies showed that the functional problem might lie on the impaired interaction between ESR2 and its co-activator NCOA1.

The findings of this work help to gain further knowledge about the influence of CBX2 in human sex development and sex development pathways in general. Furthermore, the combination of clinical oriented observation with next generation sequencing, molecular bench-work and bioinformatics allows us to advance our understanding of the links between phenotype and genotype.

Jury:
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