Public Abstract

The role of Asxls in Bohring-Opitz Syndrome

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Up until 2013, only mutations in the *Asxl1* gene have been linked to Bohring-Opitz Syndrome (BOS). These mutations code for dysfunctional ASXL1 proteins (1, 2). Recently, mutations in an additional member of the *Asxl* gene family, *Asxl3*, has been associated with cases of BOS-like syndrome (3). Since BOS is a congenital disease that exhibits a broad spectrum of defects, we hypothesized that the ASXL proteins, probably together with other factors, play a crucial role in the very first stages of life. Therefore, to shed light on BOS, we work on discovering the functions of ASXLs in normal human development and in models of BOS. It occurred to us that the ideal model for BOS would be one that is based on human pluripotent stem cells that are generated by reprogramming of patient skin cells. The reprogramming process produces human embryonic-like cells, known as induced pluripotent stem cells (iPS cells), which can be differentiated in tissue culture for imitating human embryonic and fetal development. Such iPS cells and differentiation protocols can be used as a system to study the mechanisms of BOS.

To achieve these goals we make use of state-of-the-art molecular biology techniques for reprogramming. We begin with very small skin biopsies from BOS patients, producing patient specific iPS cell lines within several weeks. Then we analyze molecular pathways that are perturbed by the mutations in *Asxl1* during differentiation of patient iPS cells. We investigate genetic and epigenetic pathways; this means that we analyze how *Asxls* control gene expression of embryonic genes, and how mutations in *Asxls* disrupt control of gene expression and protein function. Our prospect for this project is that it will shed light into what is “going wrong” in the developmental progress of BOS patients, and we hope that this knowledgebase in turn will allow us to develop therapies for BOS. Since so little is known about the mechanisms that underlie BOS, we feel that basic studies of BOS on the cellular level are necessary for therapeutic breakthroughs.

Our research group is located in the Helmholtz Center Munich, and we are deeply interested in broadening our patient sample panel, and in information about patients that can assist us in understudying BOS. Therefore we would be thankful for communications with families as well as physicians and geneticists.
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(1) Hoischen A et al. (2011) De novo nonsense mutations in **ASXL1** cause **Bohring-Opitz** syndrome. Nat Genet. 43(8):729-31.
(2) Magini P et al. (2012) Two novel patients with **Bohring-Opitz** syndrome caused by de novo **ASXL1** mutations. Am J Med Genet A. 158A(4):917-21.
(3) Bainbridge MN et al. (2013) De novo truncating mutations in ASXL3 are associated with a novel clinical phenotype with similarities to **Bohring-Opitz** syndrome. Genome Med. 5(2):11.