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Modeling disease of the peripheral nervous system using human pluripotent stem cells

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Functional and molecular aspects of the human genetic disease can be recapitulated *in vitro* using patient-specific pluripotent stem cells (PSCs). Familial Dysautonomia (FD) is a debilitating developmental and degenerative disorder that primarily affects derivatives of the neural crest (NC), such as the peripheral nervous system (PNS). For unknown reasons, FD patients present with mild or severe disease despite carrying the identical, homozygous point mutation in *IKBKAP*. We present *in vitro* phenotypes at various stages of development that capture severe and mild FD in human PSC-derived cellular lineages. Patient-specific cells only from severe but not mild FD display an impaired capacity of developing into NC derivatives, such as autonomic and sensory neurons, thus they have neurodevelopmental defects. Interestingly, however, both severe and mild FD cells show defects in peripheral neuron survival, indicating neurodegeneration as the primary culprit in mild FD. Importantly, we found that neuronal degeneration in mild FD can be halted by treatment with candidate therapeutic compounds. Genetic rescue of the FD mutation in severe FD iPSCs reversed NC, but not sensory neuron lineage phenotypes, implicating that the known FD mutation does not account for all symptoms. Employing whole-exome sequencing, we identified candidate mutations that were only found in severe but not mild FD patients, providing evidence that FD may constitute two genetic sub-diseases. Our study demonstrates that human iPSC-based disease modeling is sensitive in recapitulating disease severity. This paves the road for applications in personalized medicine and raises the prospect that individual patient's disease could be studied *in vitro*.

Biography

Nadja Zeltner completed her Master's degree in Zoology at the University of Zurich, in her native Switzerland. She then earned her PhD in gene therapy and virology at the Icahn School of Medicine at Mount Sinai, followed by a postdoc in stem cell biology and neurodevelopment at the Sloan Kettering Institute in New York. She established her research group as a junior faculty member at the Center for Molecular Medicine at the Universtiy of Georgia in the spring of 2018, where she is also affiliated with the Cellular Biology Department and the Department of Biochemistry and Molecular Biology. She has published several high-impact papers describing the *in vitro* modeling of various diseases as well as pioneered the establishment of *in vitro* differentiation protocols for a variety of neural cell types.

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