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Research Interests

Our laboratory is dedicated to understanding the genetic basis of neurodevelopmental and neuropsychiatric disorders. Our research focuses on translating the understanding of the underlying cause into novel therapeutic strategies for some of these devastating conditions.

The alpha7 nicotinic receptor and neuropsychiatric disease: The *CHRNA7* gene, which encodes the alpha7 nicotinic acetylcholine receptor, plays a prominent role in the etiology of neuropsychiatric disease (intellectual disability, epilepsy, autism, bipolar disorder, and others). We have collected a large cohort of families with *CHRNA7* mutations (deletions, duplications, triplications, point mutations), and study their clinical, behavioral, and electrophysiological phenotypes.

In the laboratory, we study the genetics of *CHRNA7* and its chimeric fusion gene *CHRFAM7A*, which is a human-specific paralog that has arisen by segmental duplication during human evolution. Using molecular, biochemical, mouse genetic, and behavioral analyses, as well as induced pluripotent stem cell technology, we investigate the role of *CHRFAM7A*, and its physical and functional interaction with *CHRNA7*.

Schaaf-Yang syndrome: *MAGEL2* is a maternally imprinted, paternally expressed gene on chromosome 15q11 in the region critical for Prader-Willi syndrome. The protein encoded by *MAGEL2* facilitates ubiquitination of the WASH complex, and endosomal protein recycling. Our group recently described that individuals with truncating mutations in *MAGEL2* manifest a condition that has significant overlap with Prader-Willi syndrome, yet is distinct due to the presence of joint contractures and a high prevalence of autism spectrum disorder (Schaaf-Yang syndrome, OMIM #615547).

In the laboratory, we investigate the unique therapeutic potential of *MAGEL2* in the context of Prader-Willi syndrome and Schaaf-Yang syndrome, aiming to identify molecules that unsilence its "dormant" maternal allele. In addition, we explore MAGE-L2 and its key protein interactors in the context of endosomal protein recycling, a molecular pathway poised to play an important role in intellectual disability, autism, and associated disorders.

Bosch-Boonstra-Schaaf Optic Atrophy syndrome (BBSOAS): Mutations in *NR2F1* are the cause of BBSOAS (OMIM #615722), a neurodevelopmental disorder characterized by optic nerve atrophy with vision loss, intellectual disability, hypotonia, and other neurological and behavioral features. The protein encoded by *NR2F1*, and orphan nuclear receptor and transcription factor, plays a critical role in the establishment of fiber tracts and projections in the developing brain. Our lab investigates the critical molecular pathways involved, and we use translational approaches to better understand the role of this gene in neurodevelopment.

The genetics of developmental regression – Among all individuals with intellectual disability, those who develop normally for several years, and then manifest profound developmental regression, are the most devastating and intriguing. We have recently identified a novel gene that may account for a rare form of autism with severe regression. Using traditional molecular biology, large-scale proteomics, mouse genetics, and behavioral analyses, we investigate the function of the respective protein, and the pathophysiologic consequences of its loss of function.

We are interested in both bedside-to-bench and bench-to-bedside investigations. The former make use of the wealth of intriguing patients presenting to our medical genetics clinic, and the abundance of fascinating cases sent to the Molecular Genetics Laboratory. The latter is our attempt to translate molecular genetics and our growing understanding of the pathophysiology of disease back into the clinic, to ultimately benefit the affected patients and their families.

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Selected Publications

Gillentine MA, **Schaaf CP** (2015). The human clinical phenotypes of altered CHRNA7 copy number. **Biochem. Pharmacol.** 97: 352-62.

Fountain MD Jr, **Schaaf CP** (2015). MAGEL2 and Oxytocin-Implications in Prader-Willi Syndrome and Beyond. **Biol. Psychiatry** 78: 78-80.

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Schaaf CP, Zoghbi HY (2011). Solving the autism puzzle a few pieces at a time. **Neuron** 70: 806-8.

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