University of Washington

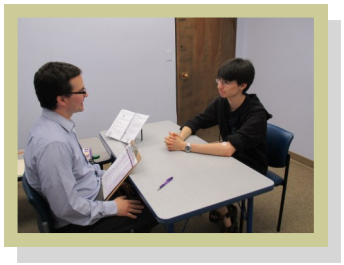
Summer 2015

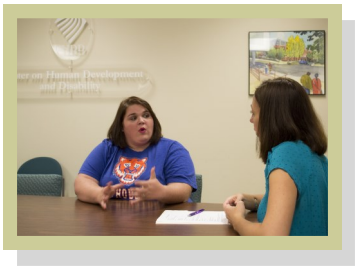
RABLAB NEWSLETTER

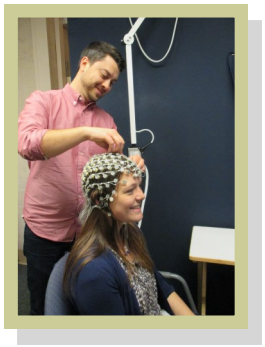
WELCOME TO RABLAB!

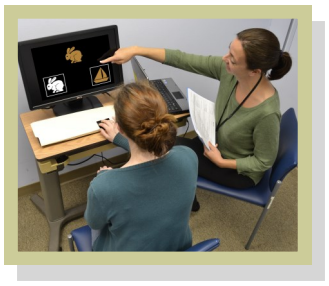
HTTP://DEPTS.WASHINGTON.EDU/RABLAB/

RABLAB is named after our principal investigator, Dr. Raphael A. Bernier. The Bernier Lab is committed to understanding the biological underpinnings of autism spectrum disorders (ASD) and other related developmental disabilities. We use a "genetics-first approach" by identifying rare genetic variants that are likely contributing to ASD and following up with an in-depth and multi-faceted evaluation to understand the individual and the family on many levels. Following this methodology, we seek to identify meaningful subtypes of ASD that have distinct etiologies and phenotypic presentations in order to lead to more individualized treatments and knowledge about outcomes for people and families with ASD.









Current RABLAB Studies

ZEBRA

We have seen 20 families so far! We are still looking for families with children ages 8-17 for an EEG study of brain mechanisms and behavior in ASD.

TIGER

We have seen 35 families so far! We are still looking for individuals ages 4 and up for a comprehensive study of particular genetic events associated with ASD.

TWIN

We are looking for identical twin pairs ages 4 and up in which at least one twin has ASD to participate in a genetic study.

GABA

We are looking for adults with ASD and without ages 18-30 to participate in a study of how the brain processes sensory information.

UPCOMING STUDY!

We will also have another study for children ages 4-12 beginning later this summer!

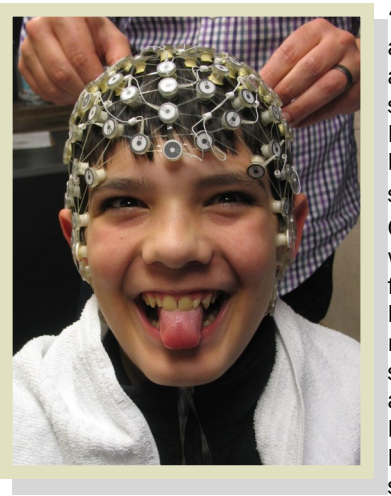
If you are interested in participating in any of our studies, please contact us at (206) 616-2889 or rablab@uw.edu.

Be sure to check out our new lab website at http://depts.washington.edu/rablab/

RABLAB Research at IMFAR

This May, members of the Bernier lab team went to the International Meeting for Autism Research (IMFAR) in Salt Lake City, Utah, to present some of the research we have been working on! IMFAR meets every spring to discuss new research in the field of autism. Dr. Bernier is currently the Treasurer of the International Society for Autism Research, which organizes IMFAR every y ear. Check out some of the research we presented at the conference!

Social Perception EEG Study: Dr. Caitlin Hudac, a postdoctoral fellow who joined the lab this year, presented one of our electroencephalography (EEG) studies during a symposium focused on describing biomarkers (biological indicators of autism). As part of the TIGER and ZEBRA studies, we were interested in social perception biomarkers related to having a *de novo* or "new" genetic mutation that is associated with ASD. In this EEG study, ~40 children viewed silent movies of social motion (hands clapping, dancing) and nonsocial motion (tubes swinging, ball bouncing). For each child, we computed a brain biomarker called mu attenuation, which is known to be greater when children observe social motion. We found that in general children with ASD have equal levels of mu attenuation for social and nonsocial motion. However, in the ASD group, children with a gene mutation exhibited a typical biomarker compared to children with idiopathic ASD (i.e., not caused by a gene mutation). Looking more closely, we found that only children with a gene mutation that is not targeted by the gene *CHD8* (i.e., "upstream" from *CHD8*) had this typical biomarker. Children with a *CHD8* gene mutation or *CHD8*-targeted gene mutation (i.e., "downstream" from *CHD8*) exhibited an atypical biomarker (reduced mu attenuation, no differences between social and nonsocial perception). Lastly, we found that having typical biomarker was related to better social skills and adaptive functioning.



Overall, we are excited about this work because it shows that brain function may be distinct for certain kinds of genetic mutations, which may help us better identify unique subgroups of autism. This study was also a great success because the biomarker robustly described social brain function, regardless of IQ or ASD symptoms that sometimes impede our ability to test lower-functioning children. Currently we are looking into other brain biomarkers that may be associated with these different genetic mutations with the hope of deepening our understanding of these different ASD subtypes.

Sleep difficulties across ASD-related gene mutations: Sleep difficulties, such as difficulty falling asleep, frequent waking, and restless sleep, are common in ASD. Recent studies report profound sleep problems in children with ASD-associated gene disruptions, CHD8 and ADNP. Further exploration of sleep problems in individuals with disruptive, ASD-associated gene mutations can inform common etiological contributions to ASD and sleep by expanding symptom profiles associated with gene disruptions. As part of the TIGER and ZEBRA studies, we collect information on incidence and type of sleep issues experienced by our participants via parent report. We were interested in clarifying the kinds of sleep issues that accompany de novo or "new" likely gene disrupting (LGD) mutations. We looked at sleep issue endorsement by parents of children with four recurrent gene disrupting mutations: CHD8, ADNP, DYRK1A, and TBR1. Inspection of sleep issues in individuals with these four LGD mutations suggests the emergence of unique sleep issue profiles. Parents reported frequent difficulty falling asleep for children with DYRK1A and CHD8 gene mutations. Children with ADNP and TBR1 mutations are reported to have frequent and prolonged nighttime awakenings. Findings suggest a potentially disruptive impact of these LGD mutations on biological mechanisms responsible for sleep maintenance. We look forward to further analysis of sleep issues in other gene mutations. With a greater understanding of the specific kinds of sleep issues facing families of children with certain LGD mutations, it is our hope that more targeted treatment and support for children and their families will become available.

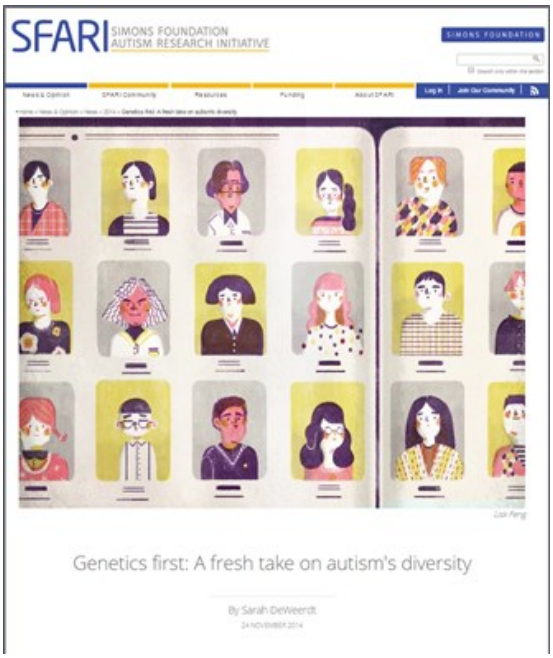
	CHD8		ADNP		DYRK1A		TBR1	
Sleep Problem	Count (n=12)	%	Count (n=4)	%	Count (n=3)	%	Count (n=3)	%
Difficulty going to bed (SBP)	3	25%	1	25%	1	33%	0	0%
Difficulty falling asleep (SBS)	9	75%	2	50%	3	100%	1	33%
Parent lays down (SBD)	6	50%	3	75%	1	33%	1	33%
Difficulty breathing at night (BPM)	1	8%	2	50%	0	0%	0	0%
Sleep apnea dx (BAP)	0	0%	1	25%	0	0%	0	0%
Frequent night awakenings (NAF)	6	50%	3	75%	1	33%	2	67%
Sleepwalking (NAS)	3	25%	0	0%	0	0%	0	0%
Difficulty waking in morning (DDW)	2	17%	0	0%	0	0%	0	0%
Daytime tiredness (DDS)	4	33%	1	25%	0	0%	0	0%
Long/Frequent napping (DDN)	2	17%	2	50%	0	0%	1	33%

Study on CHD8 Mutations Receives Media Atention

Last summer, Dr. Bernier and colleagues around the world published a widely publicized study of people with a mutation to the gene CHD8. The study found that people with a CHD8 mutation not only have ASD, but they also have larger head size, different facial features, sleep challenges, and gastrointestinal issues suggesting that CHD8 mutations may lead to a subtype of autism. The study highlights the growing importance of a "genetics-first" approach to understanding the complex nature of autism. By studying people with ASD who also have a common genetic mutation we hope to identify unique subtypes of autism, which could lead to earlier detection of autism risk and more specific treatments and interventions. Since the study on CHD8 was published, more research on CHD8 and associated genes has provided additional evidence for the link between CHD8 mutations and risk for developing ASD. There is a lot more research to be done, however, and our lab is continuing to explore CHD8 and other genes that may lead to subtypes of ASD. For more information on the CHD8 study check out a great article published by Scientific American.

Recent Lab Publications

- Van Bon et. al, "Disruptive de novo mutations of DYRK1A lead to a syndromic form of autism and ID," *Molecular Psychiatry*, February 2014.
- Higdon et. al, "The promise of multi-omics and clinical data integration to identify and target personalized healthcare approaches in autism spectrum disorders," *OMICS,* April 2015.
- Deritziotis et. al, "De novo TBR1 mutations in sporadic autism disrupt protein functions," *Nature Communications*, September 2014.
- Vandeweyer et. al, "The transcriptional regulator ADNP links the BAF (SWI/SNF) complexes with autism," *American Journal of Medical Genetics*, September 2014.
- Bernier et. al, "Disruptive CHD8 mutations define a subtype of autism early in development," *Cell,* July 2014.
- Stessman et. al, "A genotype-first approach to defining the subtypes of a complex disease," *Cell*, February 2014.



Genetics first: a Fresh Take on Autism's Diversity

Two families who participated in our autism genetics studies were featured in a news article published online in November, 2014 highlighting the diversity of autism spectrum disorder. Journalist Sarah DeWeerdt met with both families and observed portions of their assessment during their research study visits with our team at the University of Washington. The article tells the story of the differences (and some similarities) between these individuals with two different genetic events, both of which have been associated with autism spectrum disorder. The article was published at SFARI.org and Wired online. http://sfari.org/news-and-opinion/news/2014/genetics-first-a-fresh-take-on-autisms-diversity