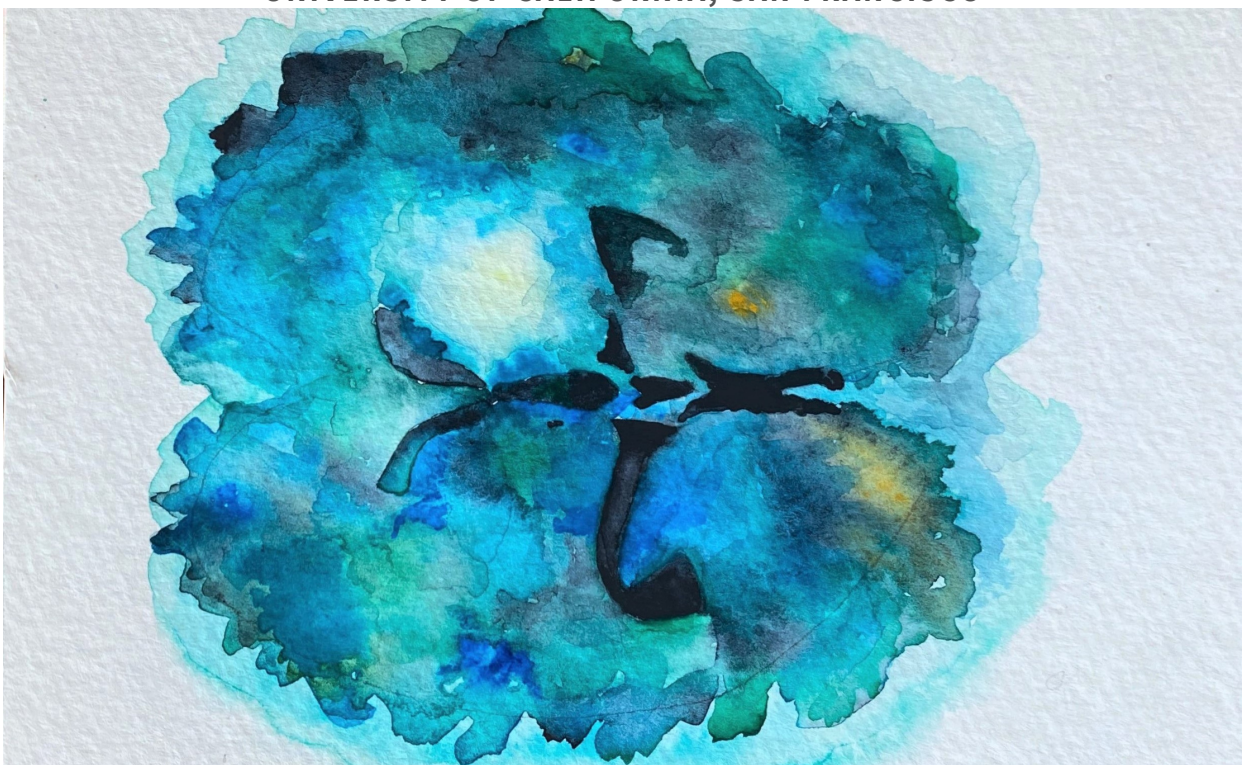
BRAIN DEVELOPMENT RESEARCH PROGRAM

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO



Welcome! - Dr. Elliott Sherr

Welcome to the Brain Development Research Program here at UCSF (brain.ucsf.edu). We are overdue for our regular update on progress from the lab, in part due to the Covid-19 crisis, but also due to work that we have been putting in to discover the genetic causes of callosal dysgenesis. Please read the first section below this introduction where we have outlined our progress and how you might benefit from that information. Including these genetic advances, our lab hopes that overall you find this update interesting and pertinent. We are sending this to all of our research participants and to all of the "friends of the Sherr lab" (collaborators and clinicians) who have helped us make progress in advancing our science. None of this progress would have been possible without all of you, for which we are immensely grateful. We realize that many of you have been adversely affected in a significant way by Covid-19. We wish that all of you make it through this storm. If you have specific questions, please don't hesitate to reach out to us directly. The easiest point of contact would be our clinical research coordinator Kendall Parks: kendall.parks@ucsf.edu or via phone: (415)-502-8039.

All the best for the future,

Elliott

Sherr Lab BDRP Brain Development Research Program

IN THIS NEWSLETTER...

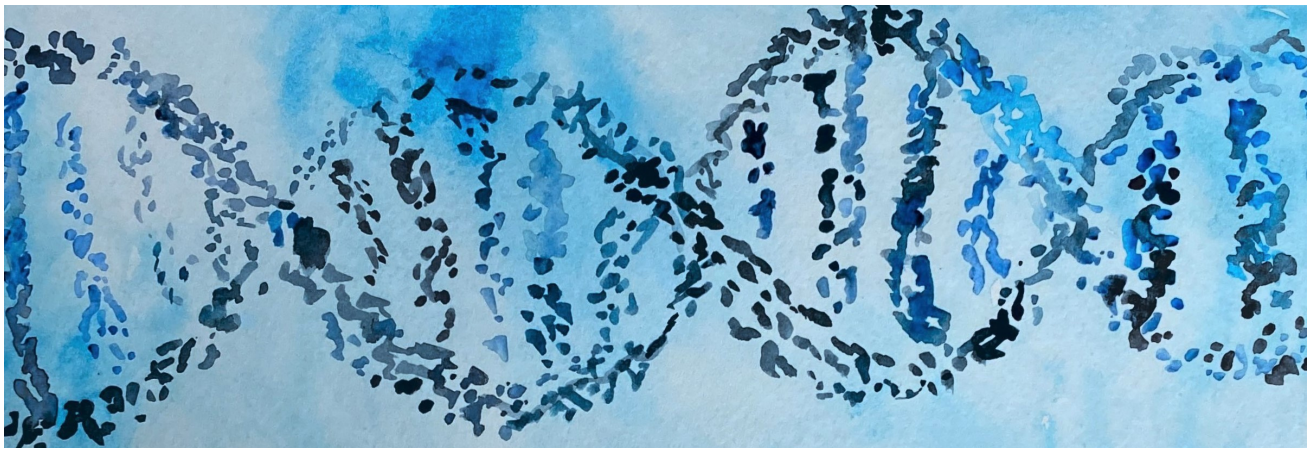
Genetics of Callosal Dysgenesis - Dr. Emanuella Argilli

This project is led by Dr. Emanuela Argilli, and a team including Dr. Jiang Li, Gilberto da Gente, Kendall Parks, our many undergraduate research assistants (Carolyn, Mandy, Gabe, Fiona) and our collaborators in the Dobyns Lab at the University of Minnesota and the Richards Lab at the Queensland Brain Institute in Brisbane, Australia. Many of you have contributed blood or saliva for DNA extraction, with the goal of DNA sequencing and uncovering the causes of callosal agenesis. We have completed sequencing for approximately 500 families in which we have received data from the participant with ACC and both parents along with another 200 individuals with ACC for whom we do not have DNA from both parents (a full trio). Our preliminary data suggest we have identified the genetic cause of callosal agenesis in more than 40% of these cases. Because this may have important implications for your families, we have sent many families a letter with guidelines about how to follow up on these observations with their geneticist or physician. If you have any questions, please reach out to Kendall Parks (contact information above). With a candidate mutation, we will work with families to reach out to their local genetic counselor or geneticist to arrange for confirmation testing. This can allow families to arrive at confirmed diagnoses from which they can obtain informed guidance about recurrence, both within the immediate family and possibly to the extended family.

In addition to the clinical implications of this work, we are discovering new genes and new mechanisms of brain development. This is an ongoing project and we hope to have more to say about this in our next update.

C12ORF57 Update - Dr. Malek Chouchane and Ruiji Jiang

This year, we further developed our understanding of *C12orf57* role in neurons. Dr. Malek Chouchane joined our lab as a postdoctoral fellow and has made great strides into unlocking the underlying physiology of neurons from mice lacking the *C12orf57* gene (knock out, KO). We found that mice deficient in *C12orf57* are more susceptible to develop pharmacologically-induced seizures. We also showed that in vitro KO neurons have higher excitation levels due to an increased AMPA receptor expression. This inherent high neuronal excitability and its connection to our previous work on *C12orf57* function and role in *CaMKIV* signaling may be the key to understanding why patients develop intractable epilepsy and intellectual disability. In the coming year, we will continue looking further into the mechanism behind *C12orf57* loss of function and increased neuronal excitability.



DDX3X Project - Dr. Bethany Johnson-Kerner, Ruiji Jiang, and Lindsey Suit

Dr. Bethany Johnson-Kerner, Ruiji Jiang, and Lindsey Suit led this project along with our collaborators in the Floor Lab at UCSF and the Silver Lab at Duke University.

Since Spring 2015, we have studied how this novel *DDX3X* gene affects brain development. At a cellular level, *DDX3X* regulates protein translation during key phases of brain development. We have also found many patients with mutations in *DDX3X* also have dysgenesis of the corpus callosum. A subset of these patients will also have the brain malformation polymicrogyria (PMG) which was associated with more clinical impairment, such as spasticity (increased tone in the limbs), epilepsy, and microcephaly (small heads). Our initial observations were published in the scientific journal ***Neuron*** entitled: **Pathogenic DDX3X Mutations Impair RNA Metabolism and Neurogenesis During Fetal Cortical Development** (link).

This project is moving forward robustly. We are continuing to recruit individuals and perform studies on the long-term clinical development of individuals with specific mutations. In collaboration with Drs. Snidjers-Blok and Kleefstra, we have published a scientific article in ***Gene Reviews*** (link). This work will serve as a summary of the clinical features seen in patients (both girls and boys) with *DDX3X* mutations—something that parents can read and a useful document to be given to clinicians caring for these patients.

Our lab is also studying how *DDX3X* functions in human neurons in more detail. To gain access to human neurons, we made induced pluripotent stem cells (iPSCs) from the blood of individuals with *DDX3X*. We are currently working on understanding what could make these neurons different from the neurons of typically-developing children. We hope that these efforts will create tools that will help us understand the *DDX3X* gene much better and guide us toward novel therapies.

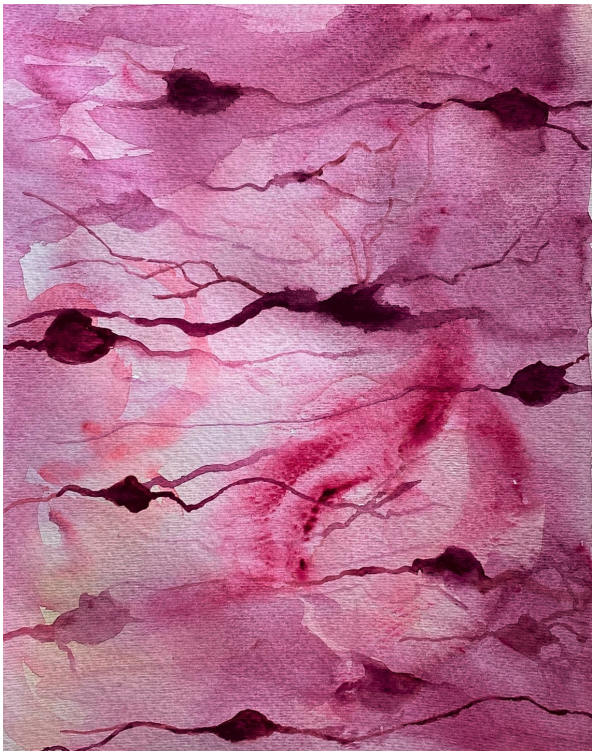
In closing, we want to say what a wonderful time we had at the 5th annual DDX3X conference in San Antonio, Texas in November 2019. We are excited to see that the DDX3X foundation has received the prestigious award from the Chan Zuckerberg Initiative and will be moving forward to improve the lives of these patients (https://chanzuckerberg.com/grants-ventures/grants/).

Deletion of Tmtc4 activates the unfolded protein response causing postnatal hearing loss – Dr. Jiang Li

Hearing loss is a significant public health concern affecting over 250 million people worldwide. Both genetic and environmental etiologies are linked to hearing loss, but in many cases the underlying cellular pathophysiology is not well understood, highlighting the importance for further discovery. We found that inactivation of the gene, *Tmtc4* (transmembrane and tetratricopeptide repeat 4), which was broadly expressed in the mouse cochlea, caused acquired hearing loss in mice by day of life 24. Our data showed *Tmtc4* is enriched in the endoplasmic reticulum, and that it functioned by regulating Ca2+ dynamics and the unfolded protein response (UPR). Given this genetic linkage of the UPR to hearing loss, we demonstrated a direct link between the more common noise-induced hearing loss (NIHL) and the UPR—this same essential function in all cells. These experiments suggested a novel approach to treatment. We demonstrated that the small-molecule UPR and stress response modulator ISRIB (Integrated Stress Response Inhibitor which activates eIF2B) prevented NIHL in a mouse model. Moreover, in an inverse genetic complementation approach, we demonstrated that mice with homozygous inactivation of both *Tmtc4* and *Chop* had less hearing loss than knockout of the *Tmtc4* gene alone. This study implicated a novel mechanism for hearing impairment, highlighting a potential treatment approach for a broad range of human hearing-loss disorders.

ACC Infant Study with CalTech

Our collaborator, Dr. Lynn Paul at the California Institute of Technology, is actively enrolling families in a research study for infants (less than 15 months old) who have agenesis/dysgenesis of the corpus callosum. If you or your family are interested in participating, you may find more information on their website https://accinfantstudy.com or email their research team at admin@accinfantstudy.com.



VAMP2 and its role in cognition and behavior

Dr. Sherr in collaboration with Dr. Roxanne Simmons and Dr. Susan Voglmaier here at UCSF and Dr. Ege Cavalali at Vanderbilt University, have just recently published a manuscript on the gene *VAMP2* and its role in cognition and behavior. VAMP2 is one of the central proteins critical for release of neurotransmitters from synaptic vesicles, thus how neurons "talk" to one another. The manuscript was just published in the scientific journal called ***Human Mutation*** in September of 2020 — **Overcoming Presynaptic Effects of VAMP2 Mutations with 4-Aminopyridine Treatment** (link). The work not only represents an important scientific advance, but also is an excellent example of "precision medicine." Of the individuals identified in the paper, one of the patients was treated with the medication Ampyra, which prolongs the opening of potassium channels which enhances the release of neurotransmitter and can lead to a marked improvement in the patient's cognition and behavior. This type of advance may be possible for other patients with similar impairments in neurotransmission and point to an optimistic future for a large class of genetic disorders of the brain.