eXtraOrdinarY Kids Program

Children's Hospital Colorado, University of Colorado Anschutz Medical Campus

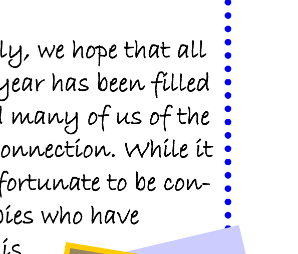
Research Newsletter

Volume 2, September 2020

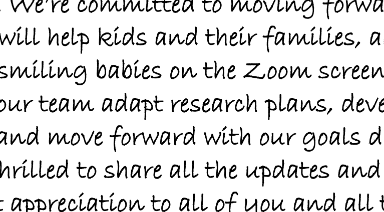
From the Desk of Dr. T.

Dear families,

Wow, a lot has happened since our last newsletter. Most importantly, we hope that all our research participants and their families have been healthy. This year has been filled with a lot of unexpected and emotional events, but has also reminded many of us of the importance of shifting our priorities to health, family, and human connection. While it seems like the unprecedented events of 2020 keep coming, we've felt fortunate to be connected to so many parents, kids, teens, young adults, and little babies who have kept in touch, reached out for support, and participated in research this year. We're committed to moving forward with productive research that will help kids and their families, and all those friendly faces and smiling babies on the Zoom screens were great motivators to help our team adapt research plans, develop safety protocols, write papers and move forward with our goals during this challenging time. I'm thrilled to share all the updates and progress below, and extend great appreciation to all of you and all the truly amazing research team members who have worked so hard to bring these results to our eXtraordinarY families. —Sincerely, Dr. T



eXtraordinarY Babies Study



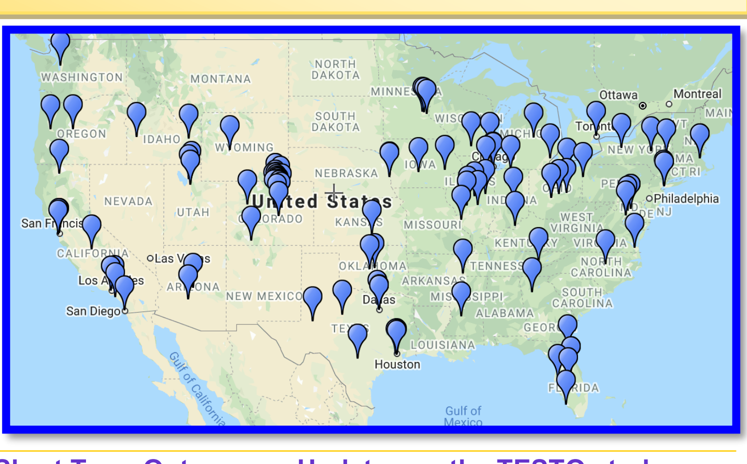
	Enrolled in eXtraordinarY Babies Study	Study Visits (including remote research visits)
XXY	137	315
XYY	20	40
XXX	34	67
XXYY	6	11
TOTAL	197	433

The eXtraordinarY Babies study is still going strong!

This natural history study aims to document the early neurodevelopmental and medical features in children with prenatally diagnosed sex chromosome trisomies. Study visits include physical exam, comprehensive neurodevelopmental testing, and a battery of parent questionnaires. To date, the study sites in Colorado and Delaware/Philadelphia (led by Dr. Judith Ross) have enrolled **197 participants** and conducted over **430 research visits**!

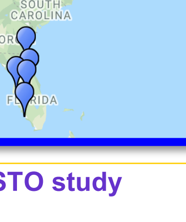
With research restrictions related to the COVID-19 pandemic, we have shifted some visits to telehealth appointments. As of August 2020, we have conducted over **50 remote research visits**! We are thankful to all the families who take the time to complete the online questionnaires, "Zoom" with us for remote visits, and come to the hospital for direct assessments when possible. Both sites are seeing patients in-person again (see updates below). We are still recruiting prenatally diagnosed infants, 12-months and under, so please share our contact information with families you think might be interested!

Participant Hometowns
Families travel from all over to participate in TESTO and the eXtraordinarY Babies Study!



Testosterone Effects on Short Term Outcomes: Updates on the TESTO study

The TESTO study, led by **Dr. Shanlee Davis,** has officially completed enrollment of 70 participants! The last boys will finish the study in six months and we hope to have results on the effects of testosterone on early health and development for infants with Klinefelter syndrome/ 47,XXY by the end of 2021. A big thank you to all of the TESTO families!


Shanlee Davis, MD

INSIGHTS Registry: Inspiring New Science in Guiding Healthcare in Turner Syndrome

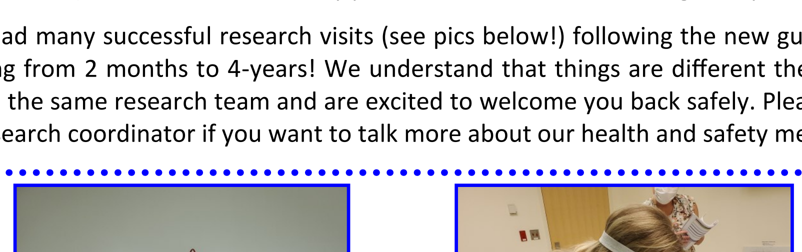
The eXtraOrdinary Kids Turner Syndrome Clinic, led by **Dr. Shanlee Davis,** in partnership with the Turner Syndrome Global Alliance, has started the INSIGHTS Registry for girls with Turner syndrome! We are now collecting patient data from clinics around the country and will track important outcomes from hundreds of patients over time allowing us to answer questions we have not had the numbers for before. A similar registry for other SCA conditions is now in progress!

Changes in our research protocols due to COVID-19

Children's Hospital Colorado and the eXtraordinarY Kids research team have implemented new procedures to assure the **safety of our participants and staff** as we have resumed our in-person research visits. Here are a few of the important ways we are working to keep everyone safe:

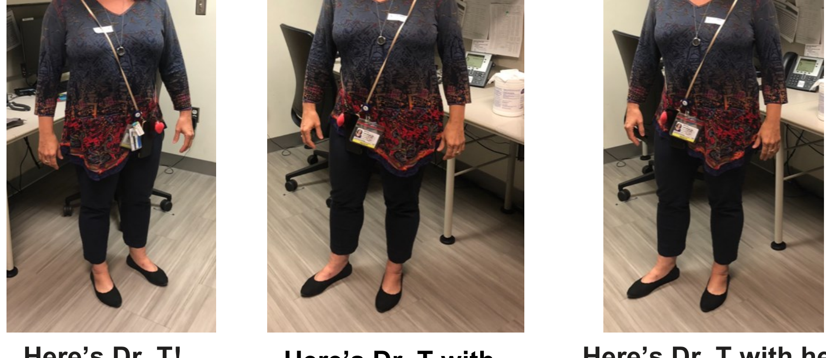
- ◊ **Remote research visits** for some or all of the visit (parent interviews, signing consent). How much we can do remotely depends on the age of the child, and we prefer in-person visits especially for our 3-year old patients.
- ◊ All staff and participants take **daily health screenings** prior to entering the hospital
- ◊ Staff wear **face masks and shields** for all patient contact (see photos below!)
- ◊ All research participants and family members (over the age of two) wear **face coverings** until they enter the study room. (We understand this is challenging for young children and we will work with all children individually).
- ◊ **Increased cleaning** of all testing materials and room surfaces. But, no more shared toys to play with (although you are welcome to bring your own!)
- ◊ **Physical distancing** between families in public areas of the hospital (waiting areas, cafeteria). No more than 1 family per research room and waiting area per day.

We have had many successful research visits (see pics below!) following the new guidelines with kids ranging from 2 months to 4-years! We understand that things are different these days, but we are still the same research team and are excited to welcome you back safely. Please reach out to your research coordinator if you want to talk more about our health and safety measures.



2-month eXtraordinarY Babies and TESTO visit:
Developmental assessment and physical exam with new health and safety measures

Preparing for a visit!



Here's Dr. T! She is going to get ready to see you!

Here's Dr. T with her mask on.....

Here's Dr. T with her mask and shield on. She is ready for the visit!

She may look different, but she is the same person under the mask and shield!

eXtraOrdinarY Kids Training Program

COVID-19 hiring restrictions and limited hospital access meant we had to scale down our 2020 summer student training program. However, we were still fortunate to have some fantastic summer research interns join our team! Find out more about two of these up-and-coming scholars and their summer projects on X & Y variations in the interviews below:

Can you tell us a little bit about yourself?

Brisa: My name is Brisa Avila, and I am a Sophomore at the University of Colorado Denver. I am in the BA/BS-MD program at UCD!

Isani: My full name is Isani Singh, and I am a rising junior at Harvard University. I am working with Dr. Davis and the eXtraOrdinarY kids research team through the Summer Research Fellowship with the Endocrine Society.

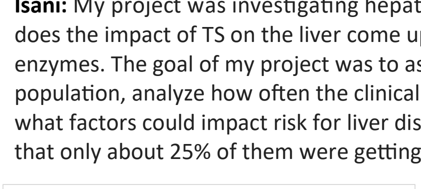
Can you please describe your summer research project?

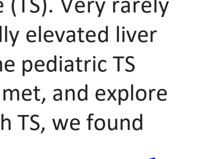
Brisa: This summer, I conducted a systematic review analyzing all the studies done in X&Y variations research, and looked at the level of diversity of the subject population (racially, ethnically, and socioeconomically). We found that much of the research lacks diversity in participants. Increasing diversity would ensure study populations represent the whole population and allow experts to understand how ancestry, financial, cultural, and environmental differences affect these conditions.

The current lack of diversity exemplifies the disparities and inequality minorities and those less advantaged already suffer from. Research allows participants to have access to developmental assessments, treatment, experts, and other resources. Our review will alert the field to this lack of diversity, and hopefully future studies will apply methods to increase diversity. As a community, we can talk to those around us about research, how it benefits, and why it is important to participate. We can be the bridge that unites diverse groups of people and research to continue to make advancements in medicine!


Brisa Avila

Isani: My project was investigating hepatic abnormalities in girls with Turner syndrome (TS). Very rarely does the impact of TS on the liver come up, but a lot of girls and women report chronically elevated liver enzymes. The goal of my project was to assess the prevalence of liver abnormalities in the pediatric TS population, analyze how often the clinical guidelines for liver screening in TS were being met, and explore what factors could impact risk for liver disease in TS. By analyzing over 2000 patients with TS, we found that only about 25% of them were getting consistent yearly liver screening, as recommended per the guidelines, even though almost 58% of them recorded some enzyme abnormality. The prevalence of these abnormalities was fairly consistent across all ages and was especially high in girls with diabetes or cardiac conditions. Generally, girls with elevated liver enzymes remained in the elevated range during the time of the study but did not worsen. The prevalence of various diagnosed liver conditions including fatty liver, hepatitis, and cirrhosis/fibrosis was also higher in the TS population. Given these results, it is important for girls with TS to monitor liver enzymes yearly, potentially starting even earlier than the clinical guideline recommendation of age 10. While enzyme elevation is common in this group, the prevalence of diagnosed liver conditions is higher and thus additional screening upon abnormal results is warranted.




Isani Singh

What did you learn through your internship experience with the eXtraOrdinarY Kids research team that will help you in your future careers?

Brisa: Currently, I am pursuing a career in the medical field. As a daughter of first-generation immigrants, I see firsthand the lack of resources that minorities have when it comes to the medical field. The project I worked on this summer helped me realize the inequalities that minorities and those of lower social standing experience in other aspects of the world. This project will allow me to advocate for these individuals by helping them get more resources available to them when it comes to research and treatment options for them and their families.

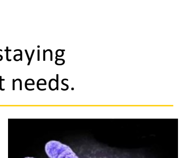
Isani: I learned the importance of thinking critically about every decision made in the research planning and analysis process. Working with Dr. Davis to carefully planning out the analyses we were interested in showed me how important a roadmap and organized thinking is to yield high quality work that can be really impactful!

Where do you see yourself in terms of your career five years from now?

Brisa: In five years, I see myself in a pediatric residency program. I am hoping to become a pediatrician in the future to help children and their families. During my high school years, I volunteered with the special education program and absolutely loved aiding the students. By being the first in my family to attend college and become a professional, I am hoping that in five years I can become a role model for those younger in my family and minorities that want to go into a professional field. I hope to continue volunteering in places that aid minorities, like Casa de Paz. Lastly, I want to be an advocate for those that are less advantaged by taking advantage of my professional degree!

Isani: Five years from now I see myself in medical school and still continuing research and staying curious about science! I also hope to be involved in health policy to best advocate for patient needs.

New Publication on Trisomy X !



It has been known for some time that there is an increased risk for premature ovarian failure (POF) (early menopause and fertility problems) in women with Trisomy X, however very little research on how frequently this occurs and when it may begin. There is a hormone made by eggs in the ovaries called AMH (anti-mullerian hormone) that can be measured to determine the overall health of the ovaries. In this study, we compared AMH levels in 15 girls with Trisomy X (average age 13) to 26 girls without Trisomy X of the same age. Overall, we found that the Trisomy X group had much lower AMH levels, and that 2 in 3 girls with Trisomy X already had an AMH level below the normal range. This suggests that the ovaries in girls with Trisomy X are aging too fast. We have more research to do about how AMH changes over time and whether it predicts fertility in Trisomy X specifically. We are working with reproductive medicine specialists to better understand this in Trisomy X and offer options for fertility preservation (harvesting / freezing their eggs). As we work on additional research to better understand this, our clinic recommends checking AMH levels yearly starting around 13 years of age or when girls start to have periods. If AMH levels are already low or decreasing over the years, then we refer them to our fertility specialists to discuss egg preservation if they are interested in this. In the near future, fertility preservation options may be available for younger girls who have not yet started puberty as well.

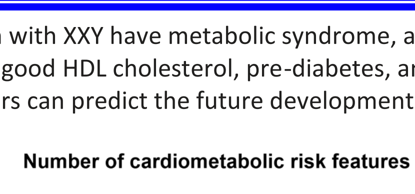
Diminished Ovarian Reserve in Girls and Adolescents with Trisomy X Syndrome. Davis SM, Soares K, Howell S, Cree-Green M, Buyers E, Johnson J, Tartaglia N. [published online ahead of print, 2020 Jun 23]. Reprod Sci. 2020;10.1007/s43032-020-00216-4. doi:10.1007/s43032-020-00216-4

Special Issue of American Journal of Medical Genetics: Seminars in Medical Genetics

Dr. Tartaglia served as an invited guest editor for a special issue of the American Journal of Medical Genetics on sex chromosome aneuploidies. The issue was published on June 25, 2020 and included 28 articles from an international group of esteemed researchers covering a range of topics including genetics, medical findings, neurodevelopment, and more. Ten included authors from our Denver eXtraordinarY Kids research team! See highlights from some of the papers below. AXYS (www.genetic.org) will be highlighting different articles and inviting authors for webinars. You can download the entire issue here (fees apply for some articles): https://onlinelibrary.wiley.com/toc/15524876/2020/184/2

Check out some of the studies from our team below:

Cardiometabolic risk factors in XXY: Up to 1 in 2 men with XXY have metabolic syndrome, a state of increased abdominal fat, high LDL cholesterol, low good HDL cholesterol, pre-diabetes, and high blood pressure. These cardiometabolic risk factors can predict the future development of diabetes and heart disease. In this study, 50 adolescent boys with XXY were compared to 50 adolescent boys without XXY but of the same age and body mass index (BMI). Almost all adolescent boys with XXY had at least one cardiometabolic risk factor and they were 2.5 times more likely to have 3 or more cardiometabolic risk factors than controls (see figure). Boys with XXY had higher abdominal fat, higher triglycerides, and lower HDL compared to boys without XXY. Therefore, even though boys with XXY were NOT obese, they were more likely to have a high risk cardiometabolic profile. The next step is to try to find lasting interventions that can improve this profile at an early age. Until we know more, eating a healthy diet and getting daily physical activity are the most important steps you can take to help improve your own profile.

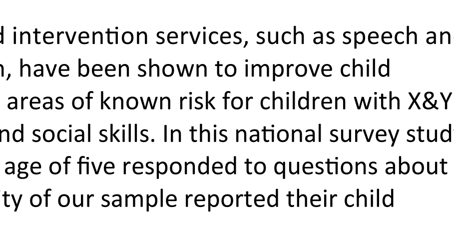


High prevalence of cardiometabolic risk features in adolescents with 47,XXY/Klinefelter syndrome. Davis SM, DeKlotz S, Nadeau KJ, Kelsey MM, Zeitler PS, Tartaglia NR. Am J Med Genet C Semin Med Genet. 2020 Jun 16. doi: 10.1002/ajmg.c.31784. PMID: 32542985

Executive Function in XXY: Executive functions (EF) are skills responsible for purposeful, goal-directed behavior, such as judgment, planning, organization, and decision-making. Attention is also closely related to EF. This study sought to explore EF skills in boys with XXY using both performance-based tests of the boys themselves and parent-report questionnaire measures. Seventy-seven boys and adolescents with XXY (average age= 12.5 years) participated in the study. As a group, the boys with XXY showed a distinct EF profile, with the greatest deficit in attention and more moderate deficits in aspects of EF including working memory, switching, and planning/problem solving. Parents also reported these to be areas of difficulty, and further endorsed problems with inhibiting behavior. There were no differences between boys diagnosed or not diagnosed with ADHD on performance-based tests, although parents of boys diagnosed with ADHD reported more difficulties. There was variability within the group, however overall boys diagnosed pre- and post-natally did not perform differently on neuropsychological tests, although parents of postnatally diagnosed boys reported more EF problems. This study highlights the importance of evaluating EF through both traditional neuropsychological tests as well as parent report. Given deficits seen in many EF in boys with XXY, this is an important area of consideration when developing school plans and thinking about their skills and behaviors.

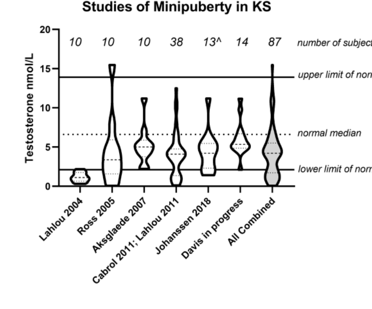
Executive Function in XXY: Comparison of Performance-Based Measures and Rating Scales Janusz J, Harrison C, Boada C, Cordeiro L, Howell S, Tartaglia N, Boada R. N. Am J Med Genet C Semin Med Genet. 2020 Jun. doi: 10.1002/ajmg.c.31804. PMID: 32519473.

Early interventions in X&Y variations: Early childhood intervention services, such as speech and motor therapies and early childhood special education, have been shown to improve child outcomes across all developmental domains including areas of known risk for children with X&Y variations such as early academics, problem solving, and social skills. In this national survey study, 105 parents of children with X&Y variations under the age of five responded to questions about early therapies and preschool supports. A large majority of our sample reported their child received some kind of early intervention service (public/private/both) prior to entering kindergarten. Speech therapy was the most common intervention for all ages (~45%) and approximately one-quarter reported receiving some type of motor therapy. Parents of preschoolers also described supports for academics (~40%) and social skills (~20%). Despite relatively high rates of intervention in our sample, parents also reported services were challenging to obtain due a lack of knowledge about X&Y variations amongst early intervention therapists, challenges navigating the early intervention system, and a tendency for children to slip through the cracks, just barely missing qualification criteria for services. Our results support the need for enhanced provider training in X&Y variations, policy change for early childhood intervention qualification criteria, and increased collaboration between medical and early childhood settings.



A Current Survey of Early Childhood Interventions in infants and young children with Sex Chromosome Aneuploidies
Thompson T, Howell S, Davis SM, Wilson R, Janusz J, Boada R, Pyle L, Tartaglia N. Am J Med Genet C Semin Med Genet. 2020 Jun. doi: 10.1002/ajmg.c.31785. PMID: 32449585

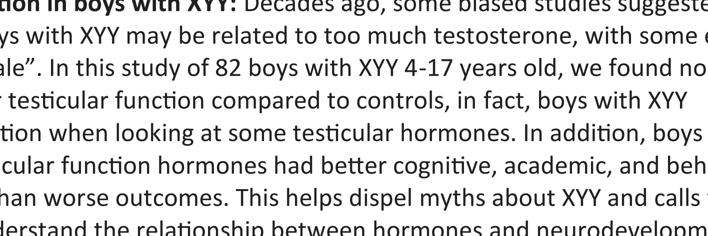
Mini-Puberty paper: Dr. Davis collaborated with other researchers to put together a review on what is known about the mini-puberty period in infant boys with XXY. Hormone levels from 87 boys with XXY have been published to date (see figure). Almost all boys in these studies had a testosterone level below the normal median and over a quarter had a testosterone level below the lower limit of normal. Studies with larger numbers and control groups are needed, as well as intervention studies, to interpret what these results mean for boys with XXY. The TESTO and eXtraordinarY Babies Studies will greatly add to this literature.



Minipuberty in Klinefelter syndrome: Current status and future directions.
Aksglaede L, Davis SM, Ross JL, Juul A. Am J Med Genet C Semin Med Genet. 2020 Jun 1. doi: 10.1002/ajmg.c.31794. PMID: 32476267

Testicular function in boys with XYY: Decades ago, some biased studies suggested behavior problems in boys with XYY may be related to too much testosterone, with some even dubbing the term "super male". In this study of 82 boys with XYY 4-17 years old, we found no evidence to suggest greater testicular function compared to controls, in fact, boys with XYY had *worse* function when looking at some testicular hormones. In addition, boys with XYY who had better testicular function hormones had better cognitive, academic, and behavioral outcomes overall rather than worse outcomes. This helps dispel myths about XYY and calls for more research to understand the relationship between hormones and neurodevelopmental phenotype.

Testicular function in boys with 47,XYY and relationship to phenotype.
Davis SM, Bloy L, Roberts TPL, Kowal K, Alston A, Tahsin A, Truxon A, Ross JL. Am J Med Genet C Semin Med Genet. 2020 Jun 16. doi: 10.1002/ajmg.c.31790. PMID: 32544298



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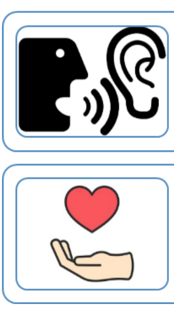
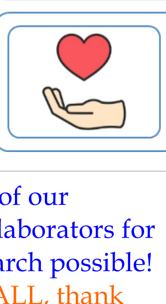


Participate
- Go to our website to see if you are eligble for any current research studies
- www.extraordinarykidsclinic.org

Spread the word
- Share this newsletter or our contact information with your social networks!



Donate
- Tax deductible!
- Go to: childrenscoloradofoundation.org/extraordinarykidsclinic

Thank you to all of our sponsors and collaborators for making this research possible! And, MOST OF ALL, thank you to the eXtraOrdinarY Kids and Families who participated!