P212

Modifiers of arterial stenosis in Williams syndrome: Using genomics to discover drivers of vessel-specific outcomes

Ashley Golbus[1], Delong Liu[1], Mark Levin[1], Neelam Raja[1], Elisa Biamino[2], Maria Bedeschi[3], Maria Digilio[4], Gabriella Squeo[5], Roberta Villa[3], Joy Lynne Freeman[1], Sharon Osgood[1], Giuseppe Merla[5], Barbara Pober[6], Carolyn Mervis[7], Amy Roberts[8], Colleen Morris[9], Lucy Osborne[10], Beth Kozel[1]

[1]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; [2]Department of Pediatrics, University of Turin, Italy; [3]Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico Medical Genetic Unit, Milan, Italy; [4]Medical Genetics Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [5]Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (Foggia), Italy; [6]Section of Genetics, Department of Pediatrics, Massachusetts General Hospital, Boston, MA; [7]Department of Psychological and Brain Sciences, University of Louisville, Louisville, KY; [8]Department of Cardiology and Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA; [9]Department of Pediatrics, Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV; [10]Departments of Medicine and Molecular Genetics, University of Toronto

Introduction: Williams syndrome (WS) is caused by a hemizygous deletion of 1.5-1.8 Mb of chromosome 7q11.23. People with this condition exhibit great vessel discrete and long segment stenosis in the setting of a variety of other developmental and medical features. In WS, deletion of the elastin gene (*ELN*) results in the associated vascular phenotypes including, but not limited to, supravalvar aortic stenosis (SVAS), supravalvar pulmonic stenosis (SVPS), and branch pulmonary artery (PA) stenosis. While genetic modifiers of SVAS severity have been described, it is unclear whether pulmonary vascular outcomes are modified by the same gene variants.

Methods: As part of a collaborative phenotyping study, we collected records on 455 individuals with WS. From those, 328 participants with records documenting both their vascular disease in infancy (<2 years of age) and older age (>3 years) were retained for further analysis. Discrete vascular stenosis was scored on the aorta (SVAS) and pulmonary vessels (main PA stenosis and/or branch PA stenosis) as surgical, mild/moderate, or none, based on review of medical records and imaging reports. Extreme phenotype modifier analysis was also performed utilizing a previously described small cohort size pipeline that included non-synonymous variant prioritization, gene set enrichment and pathway level association tests. Comparisons were made between the modifier pathways identified through this analysis and our earlier SVAS study (https://doi.org/10.1101/2023.09.25.23296124).

Results: Overall, surgery was performed for branch PA stenosis and/or SVPS in 14.6% of those with WS (n=48), while 23.7% (n=78) had surgery for SVAS. PA stenosis and SVAS were significantly associated ($p=2.2x10^{-16}$, chi-square test), but some differences in outcome remain. Thirty-four of 48 (71%) of those needing surgery for branch PA stenosis and/or SVPS also required SVAS repair, while only 34/78 (44%) of those in whom SVAS surgery was performed required surgery on their PAs. On the other hand, 6 children with no evidence of SVAS had surgery on their PAs and 9 children with no history of PA disease had SVAS repair.

Previous modifier studies assessing common variant contribution to discrete SVAS showed statistically significant association of surgical SVAS with variants in genes in 39 overlapping genetic pathways (88= surgical and 137= no focal SVAS). When the same pipeline was applied to participants with surgical vs no discrete pulmonary vascular disease (45=x surgical and 133= no focal SVPS/branch PS), 43 statistically significant modifier pathways were identified. Twenty-seven of the pathways were shared with those in the SVAS analysis and included those in extracellular matrix, adaptive (but not innate) immune, development, ciliary function, and g-protein signaling/sensory. SVAS-associated pathways involved with lipid metabolism and KRAS signaling were not identified in the pulmonary analysis, while new pathways impacting rho-gtpase signaling and ion channels were now associated.

Conclusion: Taken together, our analysis shows a high percentage of surgical SVAS in those requiring surgical intervention on pulmonary vessels, but a lower percentage of those with clinically significant pulmonary stenosis in those with surgical SVAS. Genetically derived determinants of these phenotypes can be identified using bioinformatic tools and include variants in extracellular matrix and immune pathways for individuals with either stenosis type, while other pathways like lipid metabolism and rho-gtpase signaling may be tissue-specific. Although ~30% of children with surgical PA stenosis didn't have surgery for SVAS, it is possible that the similarity in the pathways discovered is at least partially driven by shared cohort membership. Future work will be directed at distinguishing the unique variants present only in people with surgical SVAS or surgical SVPS/branch PA stenosis. Knowledge of these pathways can aid investigators in prioritizing therapeutic targets for generalized vs site-specific stenosis.

https://doi.org/10.1016/j.gimo.2024.101109

P213

Exploring heterogeneity among gene lists proposed for newborn sequencing

Thomas Minten[1], Sophia Adelson[2], Laura Amendola[3], David Bick[4], François Boemer[5], Alison Coffey[3], Nicolas Encina[6], Bianca Russell[7], Laurent Servais[8], Kristen Sund[9], Ryan Taft[3], Robert Green[10], Nina Gold[11]

[1]KU Leuven; [2]Brigham and Women's Hospital, Stanford School of Medicine; [3]Illumina Inc; [4]Genomics England; [5]CHU Liège, University of Liège; [6]ICoNS, Ariadne Labs, Harvard T.H. Chan School of Public Health; [7]University of California, Los Angeles; [8]University of Oxford, University of Liège; [9]Nurture Genomics; [10]Mass General Brigham, Broad Institute, Ariadne Labs and Harvard Medical School; [11]Massachusetts General Hospital, Harvard Medical School

Introduction: At least 22 international research studies and commercial initiatives are exploring the use of genomic sequencing to screen newborns and children (NBSeq) to detect risk for treatable genetic disorders. These groups share a goal of providing medically important information as well as investigating the clinical utility and cost-effectiveness of NBSeq. Despite common goals, however, the lists of genes selected by each group vary considerably. We are exploring the concordance across groups, as well as statistically analyzing all of the lists to empirically detect qualities guiding the patterns of inclusion of genes on each list.

Methods: To date, we have compared the content of 12 publicly available lists of genes, 9 from research trials of newborn sequencing and 3 from commercial newborn screening gene panels. The research trials were BabyDetect (Belgium), BabyScreen+ (Australia), BabySeq (US), BeginNGS (US), EarlyCheck (US),

Generation (UK), Guardian (US), and pilot studies from China and South Korea. The commercial panels were from Fulgent, Nurture Genomics, and PerkinElmer. Comparison of gene lists was conducted on the basis of unique gene names. We used linear regressions to identify factors associated with gene-disease pairs that were most often included in the gene lists.

Results: The number of genes included in each list ranged from 142 to 954 (median = 308). In total, 1403 unique genes were included in at least one of the screens, with 626 (45%) out of 1403 genes represented on only one gene list. Genes associated with metabolic (34%), immunologic (12%) and endocrinologic (11%) disorders were most highly represented.

Twenty-five genes associated with core and secondary conditions on the US Recommended Uniform Screening Panel (RUSP) appeared on all 12 lists, as did 4 genes (*ALPL*, *G6PC1*, *OTC*, *SLC37A4*) that were not on the RUSP. A total of 22 other genes associated with disorders that are primarily metabolic (11 genes; *AGL*, *ALDOB*, *ARSB*, *G6PC1*, *GALNS*, *NAGS*, *OTC*, *PNPO*, *SLC25A15*, *SLC2A1*, *SLC37A4*), immunologic (5 genes; *ADA*, *DCLRE1C*, *IL2RG*, *RAG1*, *RAG2*), endocrinologic (3 genes; *ALPL*, *DUOX2*, *TSHR*), hematologic (1 gene; *G6PD*), neurologic (1 gene; *TH*), or renal (1 gene; *CTNS*) appeared on at least 10 of 12 of the gene lists.

Using a linear regression model, characteristics of gene-disease pairs most strongly associated with inclusion on multiple gene lists were: the knowledge base for the gene-disease pair, with diseases previously defined as having the highest knowledge base score being 23.6% (se=2.5%) more likely to be included in gene lists; disease severity (19.9%, se=2.9%); high penetrance (17.8%, se=1.4%) and a neonatal or infant onset (12.4%, se=2.2%) of disease. Finally, for each additional 10% of rare disease experts recommending screening for a gene, an increase in gene list inclusion of 10.5% (se=0.47%) was observed.

Conclusion: Although there is significant heterogeneity across NBSeq gene panels, there is high concordance for 72 genes, 22 of which are not currently on the RUSP. Discrepancies between the gene lists likely reflect the use of different sources and thresholds for inclusion, as well as imperfect knowledge about characteristics such as penetrance, severity and treatability for many of the considered gene-disease pairs. Using a linear regression model, we illustrate gene characteristics associated with a higher rate of inclusion on the gene lists, which could be used to proactively identify future candidate genes for population-based newborn screening. As more gene lists are made available from research and commercial groups around the world, this analysis will be updated.

https://doi.org/10.1016/j.gimo.2024.101110

P214

SeqFirst DDi: Early whole genome sequencing improves access to early precise genetic diagnosis for children with developmental differences

Katrina Dipple[1], Daniel Doherty[2], Kailyn Anderson[2], Olivia Sommers[2], Tara Wenger[2], Kate MacDuffie[2], Alexandra Keefe[2], Abbey Scott[3], Lukas Kruidenier[3], Jamie Love-Nichols[3], Heidi Gildersleeve[2], Chayna Davis[2], Kati Buckingham[2], Jessica Chong[2], David Veenstra[2], Danny Miller[2], Deborah Copenheaver[4], Jane Juusola[4], Kyle Retterer[4], Kirsty McWalter[4], Paul Kruszka[4], Joon-Ho Yu[2], Michael Bamshad[2]

[1]*Seattle Children's Hospital;* [2]*University of Washington;* [3]*Seattle Children's Hospital;* [4]*GeneDx*

Introduction: The Seq First Developmental Differences (DDi) project aims to improve early and equitable access to a precise genetic diagnosis (PrGD) in children with atypical development by offering whole genome sequencing (WGS) upon presentation rather than after a conventional staged evaluation and testing. We hypothesized that a simplified clinical workflow and early access to WGS would lead to increased access to a PrGD, for more participants than those who received conventional care.

Methods: Families were referred from one of two Early Intervention Centers (EICs) or from an academic neurodevelopmental clinic (NDV) from 4/2021 to 11/2023. Eligibility criteria included age less than 3 years and moderate or severe delay, or mild developmental delay plus abnormalities in growth, physical features, or organ systems. Exclusion criteria included prior evaluation or genetic testing for atypical developmental or a non-genetic explanation of findings. To date, 228 participants have been referred; 31 were ineligible, 87 declined or withdrew, and 110 were enrolled. Each enrolled participant was randomized to either an immediate WGS (ie, test; n=57) or control (ie, conventional care for two years followed by WGS; n=53) group. Results from WGS were returned to families in the test group by a clinical geneticist and genetic counselor.

Results: Of the 228 participants that were referred 18 were from EIC and 210 were from NDV clinic. Of the 53 participants who received immediate WGS, 26 (49%) had a PrGD that explained, or partially explained, their atypical development. Of the 41 participants in the control group, who were enrolled for at least 6 months 31 (76%) had access to genetic testing (eg, SNP microarray, fragile X and whole exome sequencing). Yet a PrGD that explained or partially explained their atypical development was identified in only 7/41 (17%). Two of the control group have genetic testing pending.

Conclusion: Compared to the control group, a simplified clinical workflow in the test group including broad inclusion criteria markedly increased access to a PrGD. Moreover, despite a more inclusive approach to offering testing, the overall diagnostic rate remained high. These observations suggest that children who might not otherwise be offered testing, or offered testing later in childhood, could benefit substantially (earlier access to precise interventions, reduced morbidity, etc) from a simplified clinical workflow including WGS upon identification of abnormal development and that this strategy could reduce healthcare costs (fewer non-specific evaluations, tests, etc). Whether these benefits will be realized is under evaluation. Surprisingly, recruitment from EICs (n= 18) proved challenging and nearly 40% of families eligible declined to participate. Identifying barriers to referral from EICs and enrollment and developing alternative strategies (eg, community or primary-care provider-based) will be critical to ensuring we build equitable capacity for a PrGD.

https://doi.org/10.1016/j.gimo.2024.101111