Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

DLL1 promoter deletion variant identified here has been observed at a low frequency in the gnomAD structural variant database. This case study furthers our knowledge of the phenotypic spectrum of *DLL1*-related disease and suggests that the dosage of DLL1 and variant location may be important for determining clinical presentation.

https://doi.org/10.1016/j.gim.2022.01.359

eP325

Medically actionable DNA variation from the GENCOV COVID-19 Genome Sequencing Study

Erika Frangione[1], Monica Chung[1], Chloe Mighton[2], Selina Casalino[1], Sunakshi Chowdhary[1], Harpreet Kaur Satnam Singh[3], Linda Xu[3], David Di Iorio[3], Anjali Jain[3], Ayesha Kidwai[3], Queenie Wong[3], Navneet Aujla[3], Janice Min Li[3], Manal Quraishi[3], Greg Morgan[3], Marc Clausen[4], Chun Yiu Jordan Fung[1], Georgia MacDonald[1], Elisa Lapadula[1], Saranya Arnoldo[5], Erin Bearss[1], Alexandra Binnie[5], Bjug Borgundvaag[3], Howard Chertkow[6], Luke Devine[3], Steven Marc Friedmen[7], Anne-Claude Gingras[3], Zeeshan Khan[8], Tony Mazzulli[3], Allison McGeer[3], Shelley McLeod[3], Trevor Pugh[9], David Richardson[10], Jared Simpson[9], Seth Stern[8], Lisa Strug[11], Ahmed Taher[12], Iris Wong[8], Natasha Zarei[8], Deepanjali Kaushik[10], Lee Goneau[13], Marc Dagher[14], Elena Greenfeld[3], Hanna Faghfoury[15], Yvonne Bombard[16], Abdul Noor[3], Jennifer Taher[3], Jordan Lerner-Ellis[3]

[1]Mount Sinai Hospital, Sinai Health; [2]Mount Sinai Hospital, Sinai Health; St. Michael's Hospital, Unity Health Toronto; [3]Mount Sinai Hospital, Sinai Health; University of Toronto; [4]St. Michael's Hospital, Unity Health Toronto; [5]University of Toronto; William Osler Health System; [6]Baycrest Health Sciences; [7]Mount Sinai Hospital, Sinai Health; University Health Network; [8]Mackenzie Health; [9]University Health Network; Ontario Institute for Cancer Research; [10]William Osler Health System; [11]University of Toronto; The Hospital for Sick Children; [12]University of Toronto; University Health Network; Mackenzie Health; [13]Dynacare Molecular Laboratories; [14]Women's College Hospital; [15]University Health Network; [16]University of Toronto; St. Michael's Hospital, Unity Health Toronto

Introduction: DNA biobanks developed for COVID-19 research have the potential to discover medically actionable findings that may be relevant not only for identifying individuals at high risk for COVID-19 related disease, but that also predict genetic conditions for which prevention, treatment or management strategies may be available.

The GENCOV study was designed as a prospective, observational cohort study conducted among adult COVID-19 patients in Toronto and aims to identify the relationship between host genetic differences, immune response and severity of disease. Genome sequencing results are returned to ostensibly healthy participants and health outcomes are being evaluated. Participants have the opportunity to choose which information they would like returned by way of genetic counselling and a decision aid, including information on genetic conditions from the following categories: clinically actionable, carrier screening, rare genetic and untreatable disease, common disease risk and drug response.

Advances in genomic research have created an opportunity for scientific researchers to study genetic contributions to disease and has afforded the right of participants to freely share in the potential benefits of these scientific advancements. In keeping with the moral and material interests of participants and the 'duty to contact', the GENCOV study returns information that may impact health. Here we report on medically actionable information identified from participants of the GENCOV study.

Methods: Of 1195 participants enrolled into GENCOV to date, 860 genomes have been sequenced and 136 genomes analyzed for return of genomic results. Pathogenic or likely pathogenic variants as classified by one or more reputable laboratories from ClinVar and assessed using the ACMG criteria for the interpretation of sequence variation were identified from whole genome data. Here we present data from variants that were identified in two gene panels, one comprised of 73 genes from the ACMG secondary findings v.3.0 panel "clinically actionable" list and the other a custom 920 carrier screening gene panel designed for reproductive planning, developed using several databases and resources (Clinical Genomic Database (CGD), ClinGen, OMIM, CSER. The total number of pathogenic and likely pathogenic variants were tabulated for each panel and per individual. In addition, the total copy number variants (CNVs) were tabulated and evaluated for pathogenic variants in either the 73 ACMG genes or for a deleted region anywhere in the genome encompassing genes with a known disease-gene relationship. The CNVs were detected using a combination of CNVnator, ERDS, and Manta for structural variant calls. Deletions were reported if they were greater than 10kb, occurred within exonic regions from OMIM morbid genes, CNVs were removed if greater than 1% frequency in DGV or MSSNG databases.

Results: In total, 1334 variants were identified with a likely pathogenic or pathogenic classification in 136 genomes (CNVs excluded); 700 were observed once and 634 had two or more observations. 379 were confirmed as pathogenic; the remaining 955 (71.6%) variants were false positives. One-hundred and sixty-seven variants (120 unique) were identified in the carrier screening panel in 76 genes, all were heterozygous. Twenty-eight variants (19 unique) were in the ACMG panel in 8 genes, all in the heterozygote state, 22 in genes with autosomal recessive inheritance (AR), 4 in 3 genes with autosomal dominant inheritance (AD) and 3 in 2 genes were associated with both AR and or AD inheritance (one variant overlaps). Nineteen variants overlapped with both panels. Two-hundred and three variants fell into rare genetic disease panels other than ACMG or carrier screening.

A total of 125 of 136 (91.9%) individuals had a pathogenic variant (excluding CNVs). There were 11 individuals in the cohort who had no variants identified, 25 individuals who had 1 likely pathogenic or pathogenic variant, 37 individuals with 2 variants, 23 individuals with 3 variants, 19 individuals with 4 variants, 6 individuals with 5 variants, 9 individuals with 6 variants, 2 individuals with 7 variants, 1 individual with 8 variants, 2 individuals with 9 variants and 1 individual with 11 variants.

There were no clinically significant CNV calls that were identified in the ACMG genes in this cohort. There were 36 putative pathogenic CNVs greater than 10kb identified in autosomal recessive genes. Twenty-five out of 136 (18.4%) individuals had one or more deletions. One pathogenic deletion was identified in the Duchenne muscular dystrophy gene in a carrier female and associated with X-linked recessive inheritance and having implications for reproductive planning.

Four individuals (2.9%) had a clinically actionable pathogenic variant in an AD inherited ACMG panel gene. One was identified in a hereditary cancer gene for Lynch Syndrome with clinical management and at-risk testing recommendations for other family members. One was identified in the *ENG* gene responsible for AD hereditary hemorrhagic telangiectasia, a vascular dysplasia leading to telangiectases and arteriovenous malformations for which there are treatments available. Two individuals had a reduced-penetrance *APC* variant (p.Ile1307Lys) associated familial adenomatous polyposis. Exclusion of these variants results in a clinically actionable dominant disease frequency of 1.5%. The most common known pathogenic ACMG panel variant was c.1270G>C (p.Asp424His) in

the *BTD* gene associated with AR biotinidase deficiency, identified in 9 heterozygotes. The most common known pathogenic variant in our carrier screening panel was the AR variant c.-21G>A in the *RBM8A* gene in 9 heterozygotes and associated with TAR syndrome. Ten variants were also observed in *CYP21A2*, nine had the c.754G>T variant in the heterozygous state; this variant is associated with adrenal hyperplasia.
Conclusion: This study reports the number and frequency of pathogenic variants identified in clinically actionable or carrier status genes from an ostensibly healthy population of 136 individuals receiving results back as part of the GENCOV study. Future analysis of data from 1195 individuals will estimate the frequency of pathogenic variation in various gene panels. As genome sequencing becomes common place for population-based screening or diagnostic programs, this work will provide valuable insight into what types of medically actionable genetic results may be identified and what implications they may have for individuals and families. Knowing whether or not this information will lead to clinical benefit will help inform health programs on the utility of genome technology for personalized medicine.

https://doi.org/10.1016/j.gim.2022.01.360

eP326

Genome sequencing reveals *BHLHA9* gene duplication as cause of multi-generational split-hand/foot malformation with long bone deficiency

Raymond Caylor[1], Timothy Fee[1], Andrew Lay[1], Cindy Skinner[1], David Everman[1], Elizabeth Blue[2], Michael Bamshad[2], Charles Schwartz[1], Michael Friez[1], Roger Stevenson[1]

[1]*Greenwood Genetic Center, Greenwood, SC;* [2]*University of Washington, Seattle, WA*

Introduction: Split-hand/foot malformation (SHFM) is a form of distal limb deficiency that affects the central rays of the hands and/or feet. The phenotypic variability exhibited in SHFM is considerable and occurs between families, within families, and even between the limbs of a single individual. The hand and/or foot findings in affected individuals may occur in isolation or with other anomalies. Split-hand/foot malformation with long bone deficiency (SHFLD) is a rare autosomal dominant form of SHFM associated with deficiency of the tibia or other long bones and characterized by variable expressivity and incomplete penetrance. One cause of SHFLD is a duplication on 17p13.3 in which the minimally duplicated region needs to include the *BHLHA9* gene. The *BHLHA9* gene encodes a basic helix-loop-helix family member a9, and it is expressed in the limb bud mesenchyme, which underlies the apical ectodermal ridge in mouse and zebrafish embryos.
Methods: Genome sequencing of a proband with an extensive family history of SHFLD was performed to identify the molecular cause of the family's long sought genetic diagnosis.
Results: We identified a ~40kb duplication on 17p13.3 that included the critical *BHLHA9* gene. This duplication had been missed by multiple microarray platforms performed throughout the years since this individual had been originally seen at our Center. Subsequent targeted qPCR testing of family members (n=52) revealed ~55% penetrance of the duplication in the extended family with a gender bias (ie, males are more frequently affected than females and females more likely to be unaffected).
Conclusion: We identified a familial case of SHFLD that was caused by a *BHLHA9* gene duplication that is small enough to evade detection by multiple microarray platforms. While targeted gene XON array and/or qPCR testing for microduplication/deletion syndromes involving a single critical gene can be performed in otherwise negative cases with strong clinical suspicion, genome sequencing provides an unbiased analysis for other disorders with genetic heterogeneity that also do not exhibit robust, classic features. Additionally, due to its ability to analyze non-coding regions, genome sequencing may also prove to be beneficial by detecting genetic modifiers in multi-generational families with disorders characterized by reduced penetrance and/or variable severity. Ongoing studies for this family include genome sequencing on select family members (both affected and unaffected individuals with the gene duplication) in an attempt to determine if a primary modifier can be identified.

https://doi.org/10.1016/j.gim.2022.01.361

eP327

A quantitative trait GWAS on lens thickness identifies risk loci on *PTPRM* in the narrow-angle individuals anatomically susceptible to PACG

Sudipta Chakraborty[1], Samsiddhi Bhattacharjee[1], Moulinath Acharya[1]

[1]*National Institute of Biomedical Genomics*

Introduction: Quantitative traits (QTs) are highly heritable. Estimation of QT is important for the risk factor characterization that would help in localising the genetic susceptibility factors. Primary angle closure glaucoma (PACG) is one of the leading causes of blindness worldwide, especially in the east and southeast Asia. A couple of risk factors including narrow-angle between iridotrabecular contacts and increased lens thickness leading to shallow anterior chambers are present in the anatomically predisposed eyes, which could raise intraocular pressure followed by optic neuropathy and subsequent blindness. There are several QTs studied on PACG as endophenotypes. Nevertheless, to date, none of the studies has been conducted on lens thickness. Thicker and more anterior orientation of the crystalline lens contributes to the shallow anterior chamber depth. The shallow anterior chamber depth is often the first clinical sign of a person who is at risk of PACG. Therefore, we conducted a genome-wide search (GWS) on lens thickness as the quantitative trait reflective of PACG in Indian populations. Our findings reveal genetic risk factors associated with LT, which may shed light on PACG disease pathophysiology. This would facilitate an understanding of the molecular mechanisms leading to PACG from a holistic perspective and would aid in early intervention for a better prognosis.
Methods: A total of 240 narrow angle individuals were recruited after clinical evaluation from Rajendra Prasad Centre for Ophthalmic Sciences in AIIMS, New Delhi and 5 ml of peripheral venous blood was collected with written informed consents in accordance with approval from Institutional Ethics Committees of AIIMS, New Delhi and NIBMG, Kalyani, India. The gonioscopic examination was carried out and quantitative parameters like lens thickness and narrow angle (ASOCT) were recorded. Correlation tests were performed between LT and ASOCT to find the correlation of these clinical parameters. Thereafter, two hundred and forty narrow iridocorneal angles (<15 degrees) individuals were genotyped followed by quality check and population stratification. Subsequently, genome-