HEART CENTRE BIOBANK REGISTRY

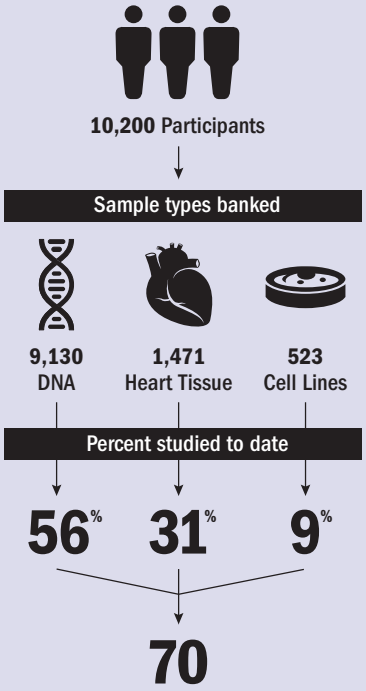
Participant Newsletter

ISSUE 08 · DECEMBER 2021

Your samples put to work

Your donated samples are helping researchers at SickKids, in Canada and across the world to work together to understand what causes heart disease and how to better manage it.

We highlight below some of the biobank supported studies that are helping understand the genetic basis of congenital heart disease.



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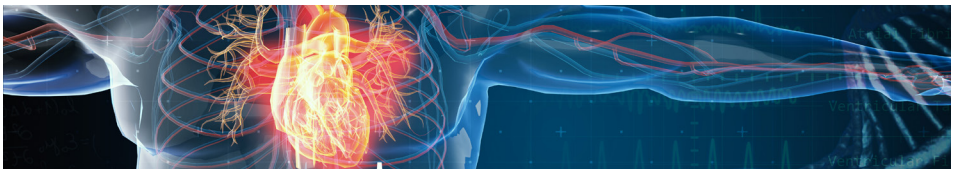
Novel insights into the genetics and developmental basis of left-sided congenital heart disease



Left-sided obstructive heart disease accounts for over a quarter of all congenital heart defects and includes a spectrum of conditions including hypoplastic left heart syndrome (HLHS), aortic stenosis, bicuspid aortic valve, coarctation of the aorta, and interrupted aortic arch. However, the genetic cause is known in only 10% of patients. Researchers working together using DNA samples from the Heart Centre Biobank have begun to unravel the genetic basis of these lesions. An international consortium funded by the Leducq Foundation found that rare mutations in the SMAD6 and ROBO4 genes can cause bicuspid aortic valve and aortopathy[1,2]. More recently, we showed that it is not just rare mutations but multiple common defects in the PCDHA gene can also cause left-sided heart lesions[3]. Through the study of heart tissue and stem cells from patients with HLHS, we found that cells that are critical to the development of valves and blood vessels are defective during development and likely cause HLHS[4]. The defect in the blood vessels is not just limited to the heart but can also affect other organs like the brain[5] which may contribute to some of the neurodevelopmental challenges in HLHS. By working together and leveraging our biobank, we are thus making important advances in understanding the complex genetics of HLHS and left-sided heart lesions.

This knowledge is also critical for developing therapies that can correct defects that interfere with the development of heart muscle, valves and blood vessels. A team from SickKids is studying molecules naturally secreted by the heart to see if they can help in repairing the heart. These molecules were discovered from left-over ventricular tissue samples from cardiac surgery from biobank participants. These studies provide hope for therapies that can help heart regeneration in the coming years[6].

1 Gillis E, et al. Candidate Gene Resequencing in a Large Bicuspid Aortic Valve-Associated Thoracic Aortic Aneurysm Cohort: SMAD6 as an Important Contributor. Front Physiol. 2017 Jun 13;8:400.

2 Gould RA, et al. ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. Nat Genet. 2019 Jan;51(1):42-50.

3 Teekakirikul P, et al. Common deletion variants causing protocadherin-α deficiency contribute to the complex genetics of BAV and left-sided congenital heart disease. HGG Adv. 2021 Jul 8;2(3):100037

4 Miao Y, et al. Intrinsic Endocardial Defects Contribute to Hypoplastic Left Heart Syndrome. Cell Stem Cell. 2020 Oct 1, 27(4):574-589

5 Kinnear C, et al. Abnormal fetal cerebral and vascular development in hypoplastic left heart syndrome. Prenat Diagn. 2019 Jan;39(1):38-44

6 Traister A, et al. Cardiac regeneration capacity is age- and disease-dependent in childhood heart disease. PLoS One. 2018: 13(7)

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Heart Centre Biobank

Thank you for participating and for your continued support!

For the most up-to-date news, check us out at www.theheartcentrebiobank.com

Phone: at 416-813-8428 Email: heartcentre.biobank@sickkids.ca

TED ROGERS CENTRE FOR HEART RESEARCH

If you are a parent that isn't already participating or you have parents that would like to, please call or email the Biobank team for information.

Attend the patient/parent symposium to hear more!

A virtual physician, researcher and patient forum is being planned for June 2022. Discussions will relate to the current and future landscape of personalized medicine for congenital heart disease, with a special fous on TOF and TGA.

For more information, ensure you are on the mailing list by contacting heartcentre.biobank@sickkids.ca and visit heartcentrebiobank.com for updates.

What are you curious about? Ask us!

We would like our next participant newsletter, issued annually, to focus on you, our audience! Ask us anything you would like to know about the Heart Centre Biobank or research being conducted through the registry and we will select some of your questions to focus on in our next issue. If we select your question, you will be gifted a certificate valued at $100! Email us your question/topic here: heartcentre.biobank@sickkids.ca. We will treat your questions confidentially and respond to them anonymously.

Risk calculator available for use online!

In previous newsletters, we shared our work on developing a tool to predict the risk of sudden cardiac death in children with hypertrophic cardiomyopathy. This tool is now available online as a web calculator for use by physicians anywhere in the world taking care of patients with hypertrophic cardiomyopathy at www.primacycalculator.com.

Understanding what causes Tetralogy of Fallot and Transposition of the Great Arteries

Tetralogy of Fallot (TOF) and Transposition of the great arteries (TGA) are the leading causes of cyanotic congenital heart disease i.e. "blue" babies. Through an international collaboration funded by the ERAPerMed and using genetic data from over 1500 TOF patients, our team found that rare mutations in the gene, KDR, are an important cause of TOF and suggest that this gene should be evaluated for mutations in TOF patients[7]. Another study by the same consortium in patients with TGA found that several common variants near the gene, WNT5A, may explain the risk of inheriting this heart condition[8]. This work suggests that TGA can be the result of several gene variants rather than a single gene variant.

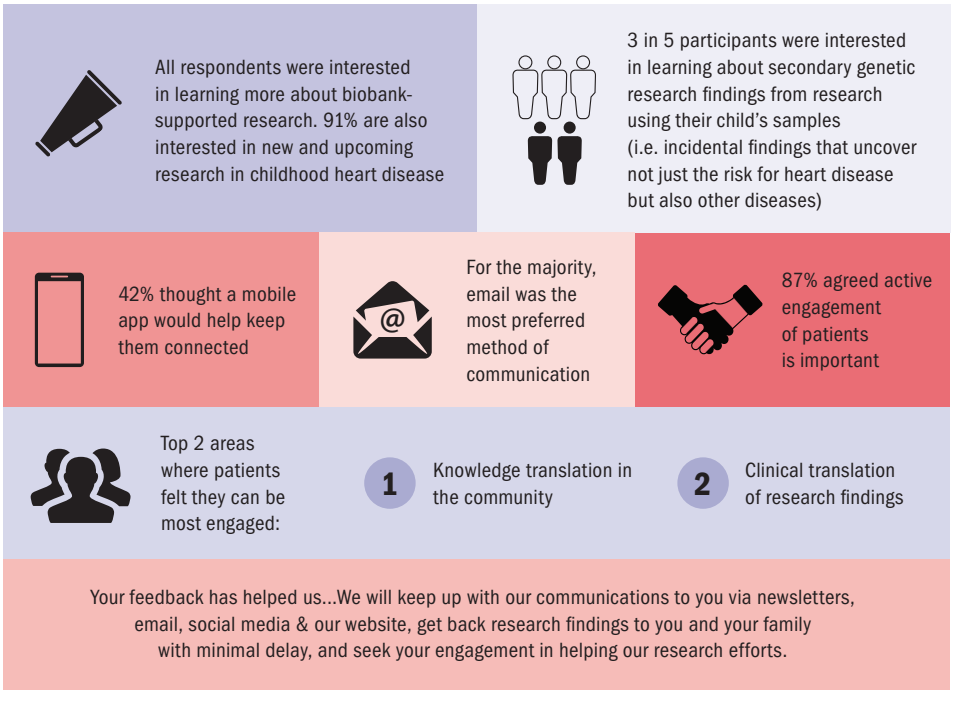
At SickKids, we are expanding this research by using whole genome sequencing to find defects not only within genes but in other parts of the genome that are not routinely captured in clinical genetic testing to identify the genetic basis of TOF and TGA. In the coming years, we expect that yield on genetic testing will be greatly increased for patients and families with these heart conditions.

[7] Skoric-Milosavljevic D, et al. Common Genetic Variants Contribute to Risk of Transposition of the Great Arteries. Circ Res. 2021 Dec 10

[8] Skoric-Milosavljevic D, et al. Rare variants in KDR, encoding VEGF Receptor 2, are associated with tetralogy of Fallot. Genet Med. 2021; 23(10):1952-1960

Participant survey

In 2019 we surveyed you, our participants, for your preferences on research communications and engagement. This is what we learnt:



A Message from the Heart Centre Biobank

The discoveries made through the research highlighted in this newsletter would not have been possible without your participation in the Heart Centre Biobank Registry. Your contribution is a gift that keeps on giving as your samples and data are used to support research in all types of childhood onset heart disease. The Heart Centre Biobank is thankful to you for your contribution to these discoveries.

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