

Hidden Genetic Disease in Coarctation of the Aorta: Insights from Whole-Genome Sequencing in a Swedish Cohort

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Research Article

Keywords: Whole-genome sequencing, Genetic diagnostics, Pediatric Cardiology, Variant interpretation

Posted Date: October 12th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11192080/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background: Congenital heart defects (CHDs) are the most common birth anomalies worldwide, with a substantial but incompletely characterized genetic contribution. Coarctation of the aorta (CoA) is a common CHD for which the diagnostic yield of comprehensive genomic testing remains insufficiently defined.

Methods: In a single-center Swedish cohort, 19 pediatric patients with CoA with or without associated aortic arch hypoplasia, bicuspid aortic valve, or additional simple CHDs, and no prior genetic diagnosis were prospectively enrolled at the time of surgical repair and underwent whole-genome sequencing (WGS).

Results: WGS identified pathogenic or likely pathogenic variants in 3/19 patients (16%), and genetic variants of uncertain significance were identified in 3/19 patients (16%). Thus, genomic findings were reported in 6 patients (32%) overall, although only the pathogenic or likely pathogenic variants were considered diagnostic. Several identified diagnoses had not been suspected based on clinical assessment alone, highlighting the limited sensitivity of phenotypic evaluation during early infancy.

Conclusions: The proportion of genetically explained CoA in this surgically treated cohort supports the consideration of genetic testing, particularly in individuals with CoA accompanied by other congenital cardiac defects or extracardiac manifestations. Importantly, an underlying genetic disorder may be present despite the absence of overt clinical signs during infancy. Recognition of this possibility should encourage thorough phenotypic assessment and expanded clinical evaluation to identify potential genetic syndromes. Early genetic diagnosis may improve clinical management, surveillance, and genetic counseling for affected families.

Introduction

Congenital heart defects (CHDs) represent the most prevalent birth defects globally, affecting approximately 10–12 per 1,000 live births [1,2]. These anomalies encompass a spectrum from simple lesions to severe, complex malformations. The etiology of CHD is multifactorial, involving both environmental and genetic components. In cohorts comprising individuals with diverse types of CHD, genetic etiologies are identified in approximately 20–25% of cases [3–5]. However, the genetic basis of many CHDs remains incompletely characterized, contributing to diagnostic uncertainty and potentially missed opportunities for personalized clinical care.

Coarctation of the aorta (CoA) is a common form of CHD, characterized by an abnormal narrowing of the aortic isthmus at the site of insertion of the ductus arteriosus, frequently accompanied by aortic arch hypoplasia [6], bicuspid aortic valve (BAV), variable degrees of hypoplasia of left sided structures or other types of CHD such as ventricular septal defects (VSD) [7]. With an incidence of approximately 1 in 2,500 live births, CoA accounts for 6–8% of all CHDs and exhibits a male predominance [8,9]. Untreated neonatal critical CoA carries a particularly high risk of mortality [10]. Neonatal presentations of CoA comprise 60% of cases, while the remainder are often diagnosed later due to unspecific symptoms [11]. According to recent Swedish data spanning 2020–2024 CoA was operated in the neonatal period (first month of life) in 62% due to severe presentation (<https://www.swedcon.ucr.se/>). CoA can be categorized as either syndromic or non-syndromic. Syndromic cases are associated with an underlying genetic syndrome and often additional extracardiac features, whereas non-syndromic cases occur in the absence of a recognized syndromic diagnosis.

Genetic analysis strategies for CHD are heterogeneous, both across and within healthcare institutions. Currently, a minority of patients with CoA in Sweden are referred for genetic counseling and genetic testing is typically performed only if there is a clinical suspicion of a co-existing genetic syndrome. Genetic testing has become an increasingly important component of the evaluation of CHD, with a higher rate of identifying a causative genetic background in syndromic than in isolated CHD [12,13].

Recent advancements in genetic testing have demonstrably impacted patient care and outcomes in CHD. Recommendations from the American Heart Association (AHA), endorsed by the American Academy of Pediatrics, highlight the necessity of establishing a precise genetic diagnosis to identify pathology in other organ systems, information of prognosis, determine the risk of recurrence, and provide guidance for screening family members at elevated risk [2,18]. Several recent studies in patients with CHD have demonstrated that abnormal genetic test results are correlated with worse surgical outcomes [19-21].

Subsequent investigations have confirmed that use of broad genetic testing methodologies enhances the identification of genetic disease, thereby deepening clinical understanding of the patient's condition and prognosis [22]. Rapid whole genome sequencing leads to changes in clinical management as confirmed genetic diagnosis frequently provides actionable information that directly influences treatment decisions. This includes clarifying disease prognosis, identifying syndromic conditions requiring additional organ-specific surveillance, guiding or modifying surgical and intensive care strategies, and in some cases avoiding invasive or non-beneficial interventions when the underlying condition is known to have a poor prognosis or limited therapeutic options. In other cases, it enables targeted monitoring for known complications associated with the genetic disorder, thereby refining and personalizing patient care¹⁹. However, Diab et al. estimated that a specific molecular diagnosis remains elusive in up to 55% of affected individuals of CHD. This observation supports a multifactorial model in which chromosomal abnormalities, copy number variants, *de novo* mutations, inherited variants, and gene–environment interactions collectively contribute to disease pathogenesis [23].

The objective of this study was to examine the prevalence and spectrum of genetic etiologies in children with CoA and to evaluate the diagnostic utility of WGS in a well-characterized Swedish cohort. The aim was to better understand the prevalence of genetic etiologies in children affected by CoA, to further improve clinical management, surveillance, and genetic counseling for affected families.

Material and methods

The study was approved by Swedish Ethical Review Authority (Dnr 2015/883–31/4; Dnr 2016/389–31; Dnr 2025/03605-01). Material was obtained through the Swedish National Biobank for Congenital Heart Disease Consortium (SNAB-CHD). The legal guardians of the children included in this study signed an informed consent for the donation of the removed tissue and blood for research purposes and for storage in the national biobank of congenital heart disease in Sweden (www.snab-chd.se).

Patients

The patients were recruited between April 2016 - May 2021 at Skane University Hospital Lund, one of the two tertiary centers for pediatric heart surgery in Sweden. In the present study 21 pediatric patients scheduled for

surgery at Pediatric Heart Center Lund of CoA donated blood samples for research.

Inclusion criteria comprised isolated CoA, with or without associated aortic arch hypoplasia, BAV, VSD, mild aortic stenosis (AS), atrial septal defect, or patent ductus arteriosus. Patients with CoA associated with critical AS, aortic atresia, Shone complex, borderline left heart structures, hypoplastic left heart syndrome or other complex congenital heart defects were excluded. Of the 21 enrolled patients, two were excluded from the final analysis. One patient had severe cardiac anomalies requiring Rastelli procedure, and one patient emigrated and lacked sufficient clinical follow-up data. The final study cohort therefore consisted of 19 patients. Clinical follow-up spanned 4.6-7.9 years (mean 5.9 years $\pm$ 1.14SD). This cohort has previously been included in studies investigating gene expression in aortic tissue obtained during surgical repair [14].

Genetic analysis

Whole genome short read sequencing was performed on DNA extracted from buffy coats obtained from the SNAB-CHD biobank. Sequencing was performed at NGI (National Genomics Infrastructure, Sweden) using SMARTer Thruplex DNA library preparations sequenced on Illumina NovaSeq S4-300. Bioinformatic analysis was performed using DRAGEN v4.0 and variant filtering and ranking were performed using Emedgene v.35 (Illumina), where the software's AI was supplied with the HPO term HP:0001680 "Coarctation of aorta". Variant interpretation was performed according to ACMG criteria by clinical laboratory personnel with expertise in cardiogenetic analysis[15].

Clinical data

To describe the clinical phenotype, data was extracted from the medical record of the patient from the referring hospital during 2025 (Table 1). Clinical data was structured into categories containing cardiac diagnosis, complications, onset of disease and extracardiac morbidity. There was a variety in the age of presentation. Three patients were diagnosed prenatally with coarctation of the aorta by ultrasound. Nine patients were neonates (<28 days of age), four were infants (28 days to 1 year), and three were older than one year at the time of surgery. Birth weights did not differ significantly from the Swedish median birth weight. The median birth weight in the cohort was 3,350 g, and gestational age ranged from 36+5 weeks to 42 weeks. Patient 16 showed significant growth restriction, with a height of -2 standard deviations. No cases of microcephaly were observed in the cohort.

According to information obtained from the medical records, none of the patients had a documented family history of a genetic syndrome or congenital heart disease.

Results

Among the 19 included patients, pathogenic or likely pathogenic findings were identified in three patients (16%): one with 16p11.2 duplication syndrome and two with Kabuki syndrome associated with variants in *KDM6A* or *KMT2D*. Three additional patients carried variants of uncertain significance (VUS) in *MAF*, *KMT2D*, and *SMAD6*. Thus, genomic findings were reported in 6 patients (32%) overall, although only the pathogenic or likely pathogenic variants were considered diagnostic.

Pathogenic/Likely Pathogenic variants

Two patients (Patients 16 and 18) were found to harbor pathogenic variants consistent with a molecular genetic diagnosis of Kabuki syndrome. Kabuki syndrome is primarily caused by pathogenic variants in *KMT2D* (Kabuki syndrome type 1) or *KDM6A* (Kabuki syndrome type 2), both of which encode epigenetic regulators involved in histone modification and transcriptional control during embryogenesis, including cardiac development.

Patient 16 carried a pathogenic *KDM6A* canonical splice site variant, predicted to lead to exon skipping of exon 26 and frameshift, consistent with Kabuki syndrome type 2 (OMIM #300867). This patient exhibited a complex phenotype including CoA, AS, BAV, VSD, hypotonia, immune deficiency, skeletal abnormalities, and chronic bronchitis.

Patient 17 harbored a likely pathogenic truncating variant in *KMT2D* variant, consistent with Kabuki syndrome type 1 (OMIM #147920), and presented with multiple cardiac anomalies, psychomotor developmental delay, and syndromic features.

Patient 8 was diagnosed with a 16p11.2 microduplication syndrome (OMIM #614671), a recurrent copy number variant associated with neurodevelopmental disorders, developmental delay, and variable congenital anomalies. In this case, the duplication was identified prenatally in the context of polyhydramnios rather than suspected CHD. The patient presented CoA and BAV, along with recurrent coarctation.

Variants of Uncertain Significance (VUS)

Three patients (Patients 10, 14, and 18) carried variants classified as VUS, including changes in *MAF*, *KMT2D*, and *SMAD6*:

Patient 10 had a missense variant in *MAF* (c.137G>T, (p. Cys46Phe)). The variant is not present in the healthy population and *in silico* algorithms predict a deleterious effect on gene function (REVEL 0.864, AlphaMissense 0.9951). Several other missense variants in the vicinity have been reported in association with Ayme-Gripp syndrome [OMIM #601088], which is not classically associated with CoA or CHD. The variant was linked to CoA through the analysis software's AI phenotype prediction.

Patient 14: had an in-frame variant in *KMT2D* (c.11151_11153dup,(p.Glu3718dup)). *KMT2D* is associated with Kabuki syndrome type 1 (OMIM #147920) which can present with CoA. In addition, this gene has been implicated in isolated CoA[16]. The variant is predicted to lead to the duplication of one amino acid and is present in one individual in the healthy population (gnomADv4.2). While pathogenic variants in this gene have been established to be associated with Kabuki, there is evidence that some variants may be associated with CHD – in the Human Gene Mutation Database (HGMD database), over 600 variants, the majority missense, have been reported as possibly disease causing for CHD.

Patient 18 was found to have a missense variant in *SMAD6* (c.548T>C (p.Leu183Pro)). *SMAD6* is associated with Aortic valve disease 2 [OMIM # 614823] and is strongly linked to CHDs including BAV and CoA. This variant is present in 7 healthy individuals in gnomAD v4.2, all from the non-Finnish European population. *In silico* algorithms suggest deleterious effect on gene function (REVEL 0.925, AlphaMissense 0.9966). While mainly truncating variants in this gene have been established as disease causing, some missense variants,

including variants in the same exon as the variant identified in this patient, have been reported as disease-causing for CHD[17].

Table 1. Patient characteristics and genetic findings. ADHD – Attention Deficit Hyperactivity Disorder, AS – aortic stenosis, ASD – atrial septal defect, AVSD – atrioventricular septal defect, BAV – bicuspid aortic valve, CoA – coarctation of the aorta, MV – mitral valve, PgE – Prostaglandin E2, Re-CoA – recurrent coarctation of the aorta, URI – upper respiratory tract infection, VSD – ventricular septal defect, VUS – variant of unknown significance. Variant nomenclature using MANE transcripts.

Patient	Cardiac diagnosis	Complications	Time of diagnosis, medication	Co-Morbidity	Genetic findings	Interpretation
Pat 1	CoA, BAV	None	Neonatal, PgE	None	None	-
Pat 2	CoA, BAV, AS	Re-CoA	Neonatal, PgE	ADHD	None	-
Pat 3	CoA, muscular VSD	None	Infant, None	Asthma	None	-
Pat 4	CoA, VSD	Re-CoA	Neonatal, None	None	None	-
Pat 5	CoA	None	Neonatal, PgE	Celiac disease	None	-
Pat 6	CoA, BAV	None	Infant, None	None	None	-
Pat 7	CoA, BAV	None	Neonatal, PgE	None	None	-
Pat 8	CoA, BAV	Re-CoA	Neonatal, PgE	Asthma, Recurrent URI	16p11.2 micro-duplication Prenatal diagnosis	Pathogenic Chromosome 16p11.2 duplication syndrome (OMIM #614671)
Pat 9	CoA, Subvalv. AS	Re-CoA	Neonatal, PgE	Esofageal, Atresia, anal atresia, (VACTERL), Asthma, GERD	None	-
Pat 10	CoA, BAV	None	Neonatal, PgE	Asthma	MAF c.137G>T p.Cys46Phe	VUS
Pat 11	CoA, PDA	None	Infant, None	Mild sensori-neural hearing defect	None	-
Pat 12	CoA, intermediary AVSD, spontaneous VSD closure, double orifice MV	None	Infant, None	None	None	-
Pat 13	CoA, BAV, Hypoplastic aortic arch, ASD	None	Neonatal, PgE	Asthma	None	-

Pat 14	CoA	Re-CoA	Neonatal, PgE	None	KMT2D c.11151_11153dup p.Glu3718dup	VUS
Pat 15	CoA	None	Neonatal, PgE	None	None	-
Pat 16	CoA, BAV, AS, muscular VSD	Re-CoA	Neonatal, PgE,	Hypotonia, immune deficiency, skeletal abnormality, chronic bronchitis	KDM6A c.3892+1G>T p.?	Pathogenic Kabuki syndrome 2 (OMIM #300867)
Pat 17	CoA, BAV, aortic arch hypoplasia, VSD, double orifice MV	None	Neonatal, PgE	Psychomotor development delay, syndromic features	KMT2D c.213C>A p.Cys71Ter	Likely pathogenic Kabuki syndrome 1 (OMIM #147920)
Pat 18	CoA, muscular VSD	None	Infant, PgE, Milrinone post op	Hemangioma, asthma, hearing loss	SMAD6 c.548T>C p.Leu183Pro	VUS
Pat 19	CoA, BAV	None	Neonatal, PgE	None	None	-

Discussion

In this cohort, 19 patients with CoA were genetically evaluated, all of whom had undergone surgical repair, and only the patient with 16p11.2 duplication syndrome had a genetic diagnosis or suspicion of a genetic variant at the time of surgery. Of note, this patient was diagnosed due to prenatal polyhydramnios and not because of suspicion of CHD. Potentially clinically relevant genetic findings were identified: three patients had established genetic diagnoses, with pathogenic or likely pathogenic variants consistent with a syndromic disorder. An additional three patients harbored VUS.

Two individuals received a molecular genetic diagnosis of Kabuki syndrome, and an additional patient harbored a VUS in a Kabuki syndrome-associated gene. Kabuki syndrome is a heterogeneous genetic disorder characterized by multiple congenital anomalies, including distinctive facial dysmorphism, postnatal growth deficiency, and mild-to-moderate intellectual disability[24]. Kabuki syndrome is a rare genetic condition with an estimated prevalence of approximately 1 in 32,000 live births[24]. Clinical suspicion is typically raised by a combination of five cardinal features, including the characteristic ocular phenotype with long palpebral fissures and broad, arched eyebrows with lateral sparseness[25,26]. However, establishing a clinical diagnosis in infants under 1 year of age is often challenging, as the phenotype may still be subtle or incompletely developed [25]. Kabuki is prone to both missed diagnosis and misdiagnosis. Today, patients typically receive a clinical diagnosis at age 3-5 years of age and often a molecular/genetic confirmation even later[27,28].

Kabuki syndrome is strongly associated with CHD, reported in up to 60% of affected individuals, with left-sided obstructive lesions such as CoA and septal defects being among the most frequent cardiac manifestations[26,29]. This finding supports the notion that CoA is not solely an isolated structural anomaly but may represent part of a broader genetically mediated developmental phenotype. The enrichment of left-sided defects in individuals with pathogenic or likely pathogenic variants reinforces the importance of incorporating genetic evaluation into the clinical assessment of patients with CoA.

One of the included patients was diagnosed with a 16p11.2 microduplication syndrome; a recurrent copy number variant associated with neurodevelopmental disorders, developmental delay, and variable congenital anomalies[30]. In this case, the duplication was identified prenatally in the context of polyhydramnios rather than suspected CHD. There are only a few reports linking 16p11.2 duplication to CHD, and the proportion of individuals with both the 16p11.2 duplication syndrome and CHD is relatively low. However, isolated cases have been described, predominantly involving VSD and transposition of the great arteries[31-33]. This case illustrates that clinically relevant genomic abnormalities may be detected incidentally and may not initially be suspected based on cardiac phenotype alone. It also supports the concept that broader genetic screening in CHD populations may uncover syndromic diagnoses that would otherwise remain unrecognized.

In our cohort, three patients carried variants classified as VUS, including changes in *MAF*, *KMT2D*, and *SMAD6*. VUS findings represent a major interpretative challenge in clinical genomics[15], particularly in CHD, where gene–disease associations are still evolving. Although these variants cannot currently be classified as pathogenic, they may still be biologically relevant and warrant careful clinical and genetic re-evaluation. Of particular interest is *SMAD6*, a gene involved in BMP/TGF- β signaling pathways that are critical for left ventricular outflow tract development. Previous studies have implicated *SMAD6* variants in left-sided obstructive lesions, including CoA, suggesting that even VUS in this gene should be interpreted in the context of the clinical phenotype and may require re-evaluation as new evidence emerges[17,34].

Similarly, *KMT2D* variants located outside well-established functional domains can be difficult to interpret, particularly in the absence of a full syndromic phenotype. Collectively, these findings underscore the importance of periodic reanalysis of genomic data as variant classification systems and gene–disease associations continue to evolve [35].

One of the three VUS was identified in *MAF*, a gene with uncertain and limited evidence for association with CHD. *MAF* encodes a BZIP transcription factor primarily implicated in ocular development, with its strongest established phenotype being congenital cataracts[36]. While *MAF* has been included in some CHD gene panels, robust gene–disease association with cardiac defects has not yet been established, and current resources classify it as having limited or no definitive evidence for CHD causality. Consequently, a VUS in *MAF* should be interpreted with caution and requires careful clinical correlation, including evaluation for ocular anomalies and other features of the *MAF*-associated phenotype. As with other genes with emerging or uncertain CHD associations, periodic re-evaluation of this variant is warranted as gene–disease evidence accumulates, and classification criteria evolve.

Given the difficulties in prenatal detection of CoA and the limited use of prenatal WES/WGS in routine clinical practice, some underlying monogenic or syndromic disorders may escape prenatal diagnosis. These considerations provide rationale for postnatal genetic assessment of patients with CoA, especially in cases

diagnosed postnatally or when the phenotypic presentation evolves during infancy and childhood[39,40]. Against this background, and in line with emerging evidence on the heterogeneous genetic architecture of CoA and other congenital heart defects[19,37,38], the systematic use of comprehensive genomic testing, such as WGS, may be justified in children undergoing surgery for CHD, including CoA.

However, implementing routine broad genomic testing such as WGS in pediatric cardiology also presents important challenges. These include the interpretation of VUS, the need for continuous reclassification of genetic findings, and the psychological and ethical implications of incidental findings. Furthermore, effective integration of genomic testing requires multidisciplinary collaboration, including pediatric cardiologists, clinical geneticists, molecular geneticists, and genetic counselors. Such collaboration is essential to ensure appropriate pre-test counseling, informed consent, and accurate post-test interpretation for patients and their families.

Notably, neither patient with Kabuki syndrome was clinically suspected to have the disorder before genetic testing. This likely reflects the well-recognized difficulty of establishing a clinical diagnosis during early infancy, when the characteristic craniofacial features are incompletely developed and neurodevelopmental manifestations have not yet emerged. As CoA repair is frequently performed in the neonatal period, reliance on clinical examination alone may fail to identify syndromic disease. These findings illustrate the complementary value of genomic testing in uncovering clinically occult genetic disorders.

An interesting observation in the present study is that two of the three pathogenic genetic findings were Kabuki syndrome. Although the sample size is small and no prevalence estimate can be made, this suggests that clinicians should maintain a particularly high index of suspicion for Kabuki syndrome in infants presenting with CoA, especially when additional left-sided obstructive lesions or extracardiac findings are present.

Study Strengths and Limitations

One of the limitations of this study was a small sized patient cohort compared to the prevalence of CoA, and this was due to the available material. The follow-up time for outpatients was variable and thus it is possible that some patients may develop a phenotype during future development. Further studies in larger CoA cohorts are required to replicate and validate the findings of this study.

Strengths in this study were comprehensive genetic analysis investigating a well characterized clinical patient cohort enabling genotype-phenotype correlation.

Conclusion

In this cohort of children undergoing surgical repair for coarctation of the aorta, WGS identified a molecular genetic diagnosis in 16% of patients, including syndromic conditions that had not been suspected clinically. These findings support the use of genetic testing in patients with CoA, particularly when accompanied by additional cardiac defects or extracardiac features, and highlight the limitations of relying solely on phenotypic assessment during infancy

Abbreviations

AS - aortic stenosis

BAV – Bicuspid Aortic Valve

CHD – congenital heart disease

CoA – Coarctation of the Aorta

VSD – Ventricular Septal Defect

VUS – Variant of Uncertain Significance

WES-Whole Exome Sequencing

WGS – Whole Genome Sequencing

Declarations

We declare that there are no conflicts of interest. This manuscript has not been published and is not under consideration for publication elsewhere. All authors have contributed to the work and have approved the final version for publication. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rada Ellegård, Erik Green, Cecilia Gunnarsson, Antheia Kissopoulou, Eva Fernlund, Constance Weismann, Ida von Konow, Kalliopi Kazamia, Torsten Malm, Anneli Norden Björnlert and Hanna Klang Årstrand. The first draft of the manuscript was written by Erik Green and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This research was funded by ALF Grants, Region Östergötland, grant number RÖ-974174, RÖ-966451, RÖ-417841, RÖ-392391. Medical research council of Southeast Sweden, grant numbers FORSS-937721, FORSS-982242, FORSS-941313, FORSS-909301. The Swedish Heart Lung Foundation, grant number 20220418.

Author Contribution

CG, EF, TM and RE conceptualized the study. TM and IK aided in material acquisition. RE, HKÅ, and ANB performed data analysis and interpretation. EG, EF and CW compiled clinical data. CG and RE coordinated the project. RE, CG and EG wrote the original manuscript draft. All authors participated in manuscript editing and reviewed the manuscript.

Acknowledgement

The authors want to thank the patients and their legal guardians. Special thanks to research nurse Elin Friberg, Pediatric Heart Center Lund for assistance. The authors appreciated all support from the steering group of the national biobank of congenital heart disease in Sweden (www.snab-chd.se). Members of the SNAB-CHD consortium not named in author list: Gunnar Bergman, gunnar.e.bergman@regionstockholm.se, Department of Women's and Children's Health, Karolinska Institutet; Britt-Marie Ekman Joelsson, britt-mari.ekman-joelsson@vgregion.se, Department of Pediatrics, The Institute of Clinical Sciences, Sahlgrenska University Hospital; Stefan Hallhagen, stefan.hallhagen@vgregion.se, Department of Pediatric Cardiac Surgery, Sahlgrenska University Hospital; Joanna Hlebowicz Frisén, joanna.hlebowicz@med.lu.se, Department of Clinical Sciences, Lund University; Annika Rydberg, annika.rydberg@umu.se, Department of Clinical Sciences, Umeå University; Camilla Segerström, camilla.segerstrom@skane.se, Children Heart Center, Skåne University Hospital; Amanda Skog-Andreasson, amanda.skog@ki.se, Department of Medicine, Karolinska Institutet; Kiet Tran, phan.kiet.Tran@skane.se, Children Heart Center, Skåne University Hospital; Christina Christersson, christina.christeresson@akademiska.se, Department of Medical Sciences, Cardiology, Uppsala University; Marie Wahren-Herlenius, marie.wahren@ki.se, Department of Medicine, Karolinska Institutet.

Data Availability

Raw sequencing data and patient details not included in manuscript are not publicly available due to Swedish GDPR law.

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