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Common genetic variants improve risk stratification after the atrial switch operation for transposition of the great arteries

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A B S T R A C T

Background: Clinical factors are used to estimate late complication risk in adults after atrial switch operation (AtrSO) for transposition of the great arteries (TGA), but heterogeneity in clinical course remains. We studied whether common genetic variants are associated with outcome and add value to a clinical risk score in TGA-AtrSO patients.

Methods and results: This multicenter study followed 133 TGA-AtrSO patients (aged 28 [IQR 24–35] years) for 13 (IQR 9–16) years and examined the association of genome-wide single-nucleotide polymorphisms (SNPs) with a composite endpoint of symptomatic ventricular arrhythmia, heart failure hospitalization, ventricular assist device implantation, heart transplantation, or mortality. Thirty-two patients (24%) reached the endpoint.

The genome-wide association study yielded one genome-wide significant (p = 1 × 10−8) locus and 18 suggestive loci (p < 1 × 10−5). A genetic risk score constructed on the basis of independent SNPs with p < 1 × 10−5 was associated with outcome after correction for the clinical risk score (HR = 1.26/point increase [95%CI 1.17–1.35]). Risk stratification improved with a combined risk score (clinical score + genetic score) compared to the clinical score alone (p = 2 × 10−10, C-statistic 0.95 vs 0.85). In 51 patients with a clinical intermediate (5–20%) 5-year risk of events, the combined score reclassified 32 patients to low (<5%) and 5 to high (>20%) risk. Stratified by the combined score, observed 5-year event-free survival was 100%, 79% and 31% for low, intermediate, and high-risk patients, respectively.

Abbreviations: ACHD, adult congenital heart disease; AtrSO, atrial switch operation; AUC, area under the curve; eQTL, expression quantitative trait locus; IQR, interquartile range; LV, left ventricle; QC, quality control; ROC, receiver operating characteristic; RV, right ventricle; SNP, single-nucleotide polymorphism.; TGA, transposition of the great arteries; VAD, ventricular assist device.

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1. Introduction

Transposition of the great arteries (TGA), affects approximately 3 per 10,000 live births [1,2]. The first surgery to facilitate survival into adulthood with this severe defect was the atrial switch operation (AtrSO); a technique of rerouting the systemic and pulmonary venous returns via surgically created venous tunnels, leaving patients with a systemic right ventricle (RV). This has increased survival to 65% at age 40 [3] and TGA patients now comprise about 5% of ACHD population [4]. Currently, the AtrSO has largely been replaced by the arterial switch operation. Most TGA-AtrSO patients have now reached adulthood and are at high risk of late complications including heart failure, arrhythmias, and premature death [5]. Yearly follow-up is therefore advised in the adult congenital heart disease (ACHD) clinic [6,7].

Recently, we published a clinical risk score for risk prediction in TGA-AtrSO including six easily available clinical markers [5]. This model could stratify patients into low (<5%), intermediate (5–20%) and high (>20%) 5-year risk of major clinical events. The predicted absolute risk was very divergent, but it remains unknown why the clinical course is so heterogeneous.

Genetic predisposition may play a role in RV deterioration and subsequent clinical events, just as genetic variants have recently been associated with LV wall thickness and adverse clinical events in patients with hypertrophic cardiomyopathy [8,9]. In some other common heart diseases, the use of genetic risk scores including multiple common single-nucleotide polymorphisms (SNPs) could improve risk prediction over the use of clinical factors alone [10–12]. The few prior studies on the prognostic role of genetics in CHD focused on known defects or syndromes, the use of genetic risk scores including multiple common SNPs could improve risk prediction in ACHD, specifically TGA, has not been studied to date.

We here aimed to study the genome-wide association of common SNPs with event-free survival in TGA patients after the AtrSO and examine whether genetic predictors have added value to a clinical risk model.

2. Methods

2.1. Study population

This study consisted of unrelated patients included in the CONCOR registry and biobank [15] via five tertiary medical centers, with simple or complex TGA (defined as TGA with concomitant ventricular septal defect, left ventricular outflow tract obstruction, or coarctation of the aorta) after AtrSO. Exclusion criteria were reported extra-cardiac congenital abnormalities or known genetic syndromes. Patients were followed from the first hospital visit after written informed consent for inclusion in the CONCOR registry (earliest inclusion in 2001) until 2019. Data were collected from electronic hospital records and a clinical risk score was computed in previously described [5]. The clinical risk score ranges between 0 and 7.5 points and includes the following factors: age >30 years: 1 point; age at repair >1 year: 1.5 point; prior symptomatic ventricular arrhythmia: 1 point; moderate or greater RV dysfunction: 1 point; severe tricuspid regurgitation: 1.5 point; mild or greater LV dysfunction: 1.5 point (Supplementary table 1). CONCOR conforms to the Declaration of Helsinki and was approved by the ethics boards of the participating centers [15].

2.2. Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our study.

2.3. Outcome definitions

The primary endpoint was time to the first event out of a composite of hospitalizations for heart failure, heart transplantation, ventricular assist device (VAD) implantation, symptomatic non-sustained ventricular arrhythmia, sustained ventricular arrhythmia, and all-cause mortality [5]. The rationale for combining these events is the hypothesis that these events largely stem from underlying deterioration of RV function.

2.4. Genetic analysis

Genotypic data were generated using the Illumina HumanOmniExpress beadchip (genotyping at ~700,000 SNPs) and quality control was performed as described previously [16] (Supplementary methods).

2.5. Existing polygenic risk scores

To test whether existing genetic risk scores were associated with event-free survival in TGA-AtrSO, we extracted genetic scores from the Polygenic Score (PGS) catalog [17]. We hypothesized that our composite endpoint would largely reflect events related to deteriorating ventricular function. Therefore, we extracted the 3 genetic risk scores present in the PGS catalog on April 23rd, 2021 on heart failure [18] (multi-PGS including 183,287 SNPs), ventricular function [19] (28 genome-wide significant SNPs), and cardiomyopathy [9] (27 genome-wide significant SNPs). One additional genetic risk score on cardiomyopathy [8] was tested, which was to be submitted to the PGS catalog.

2.6. Statistical analysis

Data are expressed as numbers (%), mean ± SD, or median (inter-quartile range [IQR]), as appropriate. Statistical analyses were performed in RStudio V.1.2.1335 (RStudio Team, Boston) using R-version 3.6.1 (R Core Team, Vienna, Austria).

2.6.1. Genome-wide association study (GWAS)

The association of allele dosage with the primary endpoint was tested using Cox proportional hazards regression assuming an additive genetic model, adjusting for age at inclusion and the top two PCs using the gwasurvivr package (version 1.2.0) in R [20]. P-values were corrected for the genomic inflation factor (λ). SNPs associated with a p < 5 × 10^{-8} were considered genome-wide significant, the suggestive threshold was p < 1 × 10^{-5}. A sensitivity analysis excluding patients with a history of heart failure hospitalization or symptomatic ventricular arrhythmia was performed, as these patients may have an altered risk profile compared to event-naïve patients.

For annotation purposes, summary statistics of the GWAS were uploaded to the Functional Mapping and Annotation (FUMA) platform [21]. Additionally, genes were assigned to genomic risk loci by expression quantitative trait locus (eQTL) mapping as implemented in FUMA, restricting to cis-eQTL effects from cardiac and muscle tissues (Supplementary methods).

SNP based heritability of event-free survival was estimated by LD Score regression [22].

Conclusions: Common genetic variants may explain some variation in the clinical course in TGA-AtrSO and improve risk stratification over clinical factors alone, especially in patients at intermediate clinical risk. These findings support the hypothesis that including genetic variants in risk assessment may be beneficial.
2.6.2. Genetic risk score

We constructed a weighted genetic risk score of all lead SNPs with a
$p < 1 \times 10^{-5}$ in the primary analysis, calculated as sum of risk allele
counts weighted with $\beta$ coefficients. Similarly, a genetic risk score
including the SNPs from loci that reached the suggestive threshold in
both the primary and the sensitivity analysis was constructed. Correlation
between the genetic risk score and the clinical risk score and its
factors was tested using Spearman’s rank test. Cox proportional hazards
regression was used to test whether any of the genetic risk scores were
associated with event-free survival, adjusted for the clinical risk score.
The added value of the genetic risk score to the clinical risk score was
test by likelihood ratio
regression was used to test whether any of the genetic risk scores were
associated with event-free survival, adjusted for the clinical risk score.

3. Results

3.1. Study population

Of the 167 patients included in the clinical follow-up study, genome-
wide genotypic data was available in 139 patients (Supplementary fig.
1). During QC steps, 6 samples were excluded (1 due to low call rate, 5
outliers in PCA analysis (Supplementary fig. 2)). Characteristics of the
remaining 133 patients (median age at inclusion 28 [IQR 24–35], 59%
males) are presented in Supplementary table 2. Patients were followed
for a median of 13 (IQR 9–16) years, up to a median age of 42 (IQR
37–47) years. Thirty-two (24%) patients reached the combined
endpoint. Of these patients, 11 had ventricular arrhythmias, 22 were
hospitalized for heart failure, 2 had a VAD implanted, 2 had a heart
transplantation, and 13 patients died. Twelve patients had events before
inclusion (6 had been hospitalized for heart failure, 5 had had ventricu-
lar arrhythmias, and 1 had experienced both events).

3.2. Genome-wide association analysis

Of the 670,773 SNPs that were genotyped, 94,007 SNPs were
excluded in the QC. After genetic imputation, 5,275,874 SNPs were
analyzed. The genomic inflation factor suggested some statistic inflation
($\lambda = 1.17$, Q-Q plot in Supplementary fig. 3), which was corrected for in
the analysis. Fig. 1 shows the Manhattan plot, with the $p$-values of the
association of each SNP with the combined endpoint. One locus on
chromosome 10 exceeded the genome-wide significance threshold (lead
SNP rs79407850; HR = 10.4 [95% CI 4.51–24.1], $p = 5 \times 10^{-8}$, Sup-
plementary fig. 4). The lead SNP had no known eQTL in heart and
muscle tissue, nor did it have overlap with SNPs of the GWAS Catalog. Its
nearest gene is a non-coding RNA (LINC001163, see Supplementary fig.
5), about which not much is known. Its nearest coding gene is MKI67, a
marker of cell proliferation, which is expressed in myocardium during
pressure-induced cardiac hypertrophy [23]. Further investigation of the
locus using epigenetic datasets and EMERGE [24], an in silico prediction
tool that can identify sequences with gene regulatory sequences poten-
tial, demonstrated that the lead SNP is in a topologically associated
domain with 7 genes, and does not overlap with any predicted heart
enhancers, nor is it located in a conserved region. Of the 7 genes in the
domain, DOCK1 is of interest, as it is involved in cardiovascular devel-
opment [25] and DOCK1 KO mice display heart defects including
persistent truncus arteriosus and double outlet RV [26].

An additional 18 loci on 12 different chromosomes reached the
suggestive threshold (Supplementary table 3, Supplementary fig. 6). Six
loci, including the genome-wide locus, maintained a $p < 1 \times 10^{-5}$ in the
sensitivity analysis which excluded patients with prior events (Supple-
mental fig. 7). Three loci included coding SNPs (locus 3 in GLRX2,
locus 9 in FAM185A, and locus 11 in AKRI1C1, Supplementary table 4).
At 3 loci, lead SNPs were in moderate to high linkage disequilibrium (R$^2$
$> 0.6$) with SNPs identified in prior GWAS (Supplementary table 5). In
total, 13 genes with eQTL in heart or muscle tissue were assigned to 9 of
the loci that passed the suggestive threshold in the primary analysis
(Supplementary table 6). These included genes that have been linked to
cardiovascular disease, like SHROOM3 and GLRX2. SHROOM3 has been
linked to LV wall thinning and cardiac defects [27,28]. Low levels of
GLRX2 have been associated with myocardial fibrosis, hypertrophy, and
infarction in mice and human hearts [29–31]. Consistent with these
findings [29–31], the risk allele of locus 3 decreased expression of
GLRX2. The locus also included a coding SNP for GLRX2 (R$^2 = 0.70$
with lead SNP) and a SNP associated with cardiovascular diseases in a prior
GWAS (R$^2 = 0.79$ with lead SNP [32]).

Fig. 1. Manhattan plot of the genome-wide association results. $p$-
values of all tested SNPs on a $-\log_{10}$ scale from the main cox
regression analysis, corrected for genomic inflation. The red
line represents the genome-wide significance $p$-value threshold
of $5 \times 10^{-8}$, the blue line represents the suggestive threshold of
$1 \times 10^{-5}$. Genes associated with cardiovascular disease at loci
reaching the suggestive threshold or the genome-wide threshold are depicted in grey and black, respectively.
To assess the overall contribution of common variants on the primary endpoint we calculated the SNP heritability, which was estimated to be 0.12 (SE 0.045).

3.3. Addition of genetic risk score to clinical risk score

The existing genetic risk scores on heart failure, LV end-systolic volume, and hypertrophic cardiomyopathy were not associated with event-free survival in TGA-AtrSO (Supplementary table 7). The genetic score derived from the 19 independent suggestive SNPs in our GWAS (median score of 8 points, IQR 5–13, range 0–32) was associated with two factors in the clinical score: ≥ moderate RV dysfunction and severe tricuspid regurgitation (p = 0.001 and p = 0.004, respectively, Supplementary fig. 8) and had a moderate linear association with the clinical score (r = 0.38, p < 0.001, Fig. 2A). After correction for the clinical score, the genetic score remained an independent predictor for the primary outcome (HR = 1.26/point increase [95% CI 1.17–1.35], p = 4 × 10^{-10}). We constructed a combined risk score of the clinical score + 0.2 score point per point increase in genetic score. This combined score satisfied the proportional hazard assumption, discriminated very well between patients who did and did not reach the primary endpoint, and performed better than the clinical score alone (p = 2 × 10^{-16}, optimism corrected C-statistic 0.95 [95% CI 0.93–0.97] vs 0.85 [95% CI 0.80–0.90]). The calibration slope was 0.80 (95% CI 0.63–0.98), Fig. 2.
indicating that the model underestimated the absolute risk of events (Supplementary fig. 9). We stratified patients into low (< 5%), intermediate (5–20%), and high (> 20%) 5-year predicted risk of events based on the combined score (score: < 5 for low [n = 104], 5–6.8 for intermediate [n = 16], and > 6.8 for high risk [n = 13]). Forty patients (30%) were classified differently by the combined score compared to the clinical score alone (Fig. 2B-C). These were mostly patients with intermediate clinical risk (32 out of 51 patients were reclassified to low risk, 5 were reclassified to high risk). Observed 5- and 10-year event-free survival was excellent in low-risk patients (100% and 98%), but poor in intermediate (79% and 36%) and high-risk patients (31% and 15%) (Fig. 3). Combined models that only included the genome-wide significant SNP or the 6 SNPs that remained in the sensitivity analysis also improved prediction over the clinical score alone, but less than the genetic score including all 19 lead SNPs (Fig. 4).

4. Discussion

This is the first study that investigates the genome-wide association of SNPs with late complications in TGA after AtrSO. One genome-wide significant locus on chromosome 10, and 18 suggestive loci were identified for association with the combined endpoint of heart failure, ventricular arrhythmia, and mortality. Moreover, the addition of genetic information significantly improved risk prediction compared to the use of clinical risk factors alone. This integrated approach of clinical and genetic data illustrates the next step in risk assessment of these patients.

4.1. Value of a genome wide study for outcomes

Although increasingly more clinical markers are available for risk prediction in ACHD, it is likely that other, genetic, factors play a substantial role in the clinical course [33]. In our study, common variants explained part of the variation in outcome, mainly driven by heart failure. The genetic risk score comprising lead SNPs was associated with RV dysfunction and severe tricuspid regurgitation, which suggests that the underlying genetic factors decrease the ability to cope with RV pressure overload. Published genetic risk scores on heart failure [8,9,18] and LV volume [19] were not associated with outcome in this study, suggesting that the underlying pathway of disease in this population with right ventricular heart failure may differ from left-sided heart failure.

The study yielded 1 genome-wide significant locus on chromosome 10 associated with adverse clinical outcome in TGA-AtrSO and 18 suggestive loci. Some of these loci were linked to genes that have been associated with cardiovascular disease. Testing these promising variants in an independent set of patients is needed to confirm their role in modulating the clinical course after AtrSO.

This is a step toward elucidating the genetic underpinnings and pathophysiology of pressure overloaded RV failure. This is also of interest to other ACHD patients, such as patients with tetralogy of Fallot, congenitally corrected TGA, or a functional univentricular RV. Global collaborative efforts of cardiologists and geneticists are required to further address the paucity in data. Therefore, it is important for cardiologists and their patients to get involved in genetic research collaborations.

4.2. Clinical implications

This is the first use of a polygenic risk score in TGA after atrial switch. Although the study is small and the findings await replication, the results show that clinical implementation of a genetic risk score in prediction models for ACHD is promising, as the addition of the genetic risk score improved prediction significantly. The combined model primarily altered risk estimates among patients at intermediate clinical risk, as also seen in atrial fibrillation and coronary artery disease [11,34]. In our study, many patients were at intermediate (5–20%) clinical risk, suggesting that an intensive follow-up strategy for early detection and treatment of complications, e.g. with heart failure medication or implantable cardioverter-defibrillator, could be contemplated. With addition of the genetic score, many patients were stratified to low risk (<
5%), suggesting that a less intensive strategy, e.g. postponing the initiation of medication, may be considered.

Eventually, when a given genetic risk score is replicated and robustly linked with outcomes, it should be contemplated to include the genetic score in clinical care, as it may add predictive power [35]. Genetic scores could help determine whether patients reach a threshold of risk that may justify preventive treatment [36]. In practice, clinicians could calculate clinical risk with a risk tool such as we provide in Supplementary file 2, table 1. Subsequently, a panel of genetic risk SNPs may be tested via a clinical geneticist to calculate the genetic and combined risk as in Supplementary file 2, table 2 and 3.

4.3. Limitations

The main limitation of this study is the small population size, which limited the statistical power and increased the chance of false positive associations. Furthermore, the genetic score was tested for association with outcome in the same population in which it was derived, which leads to overfitting. Its relevance therefore awaits confirmation in an independent set of patients. Associations of the specific loci and the combined risk score with outcome in TGA should therefore be interpreted with caution. As the disease is relatively rare, with variable phenotypes, no additional cohort of TGA patients with both long-term follow-up and genetic data was presently available to perform external validation or increase sample size. No indels or triallelic SNPs were available in our dataset. This limited the value of some of the existing genetic risk scores of the PGS catalog that were tested, which included indels and triallelic SNPs.

To address the limitations and increase statistical power, we used a combined endpoint, included both event-naïve patients and patients with events prior to inclusion, and performed a time-to-event analysis instead of a case-control setup. Furthermore, we studied a homogeneous cohort of non-syndromic TGA patients from European, mainly Dutch, descent.

5. Conclusion

This work provides the first evidence that common SNPs may be implicated in the heterogeneous clinical course of TGA after AtrSO. Moreover, we show that the addition of genetic information can improve risk prediction over the use of a clinical risk model alone, especially in patients at intermediate clinical risk. This calls for further research into the impact of genetic variants on outcome in ACHD, including replication in an independent cohort. Implementation of genetic testing in practice may eventually improve management in the ACHD clinic.

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CRediT authorship contribution statement

Odilia I. Woudstra: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. Doris Skoric-Milosavljevic: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing. Barbara J.M. Mulder: Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition. Folkert J. Meijboom: Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition. Marco C. Post: Resources, Writing – review & editing, Supervision, Funding acquisition. Monique R.M. Jongbloed: Resources, Writing – review & editing. Arie P.J. van Dijk: Resources, Writing – review & editing. Joost P. van Melle: Resources, Writing – review & editing. Thelma C. Konings: Resources, Writing – review & editing. Alex V. Postma: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Funding acquisition. Connie R. Bezzina: Conceptualization, Methodology, Resources, Writing – review & editing. Berto J. Bouma: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.
Supervision, Funding acquisition. Michael W.T. Tanck: Conceptualization, Methodology, Software, Formal analysis, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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