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# Noncompaction cardiomyopathy and heterotaxy syndrome☆

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ABSTRACT

Left ventricular noncompaction cardiomyopathy (LVNC) is characterized by compact and trabecular layers of the left ventricular myocardium. This cardiomyopathy may occur with congenital heart disease (CHD). Single cases document co-occurrence of LVNC and heterotaxy, but no data exist regarding the prevalence of this association. This study sought to determine whether a non-random association of LVNC and heterotaxy exists by evaluating the prevalence of LVNC in patients with heterotaxy.

In a retrospective review of the Indiana Network for Patient Care, we identified 172 patients with heterotaxy (69 male, 103 female). Echocardiography and cardiac magnetic resonance imaging results were independently reviewed by two cardiologists to ensure reproducibility of LVNC. A total of 13/172 (7.5%) patients met imaging criteria for LVNC. The CHD identified in this subgroup included atrioventricular septal defects [11], dextrocardia [10], systemic and pulmonary venous return abnormalities [7], and transposition of the great arteries [5]. From this subgroup, 61% ($n$ = 8) of the patients developed arrhythmias; and 61% ($n$ = 8) required medical management for chronic heart failure.

This study indicates that LVNC has increased prevalence among patients with heterotaxy when compared to the general population (0.014–1.3%) suggesting possible common genetic mechanisms. Interestingly, mice with a loss of function of *Scrib* or *Vangl2* genes showed abnormal compaction of the ventricles, anomalies in cardiac looping, and septation defects in previous studies. Recognition of the association between LVNC and heterotaxy is important for various reasons. First, the increased risk of arrhythmias demonstrated in our population. Secondly, theoretical risk of thromboembolic events remains in any LVNC population. Finally, many patients with heterotaxy undergo cardiac surgery (corrective and palliative) and when this is associated with LVNC, patients should be presumed to incur a higher peri-operative morbidity based on previous studies. Further research will continue to determine long-term and to corroborate genetic pathways.

## 1. Introduction

Left ventricular noncompaction (LVNC) is a clinically heterogeneous 1 currently classified as a primary genetic cardiomyopathy by the American Heart Association [1]. It is characterized by a two-layered structure consisting of prominent trabeculations and inter-trabecular recesses [2–4]. The mechanistic basis for this cardiomyopathy remains controversial but it is thought to be secondary to an early fetal arrest of myocardial development with lack of compaction of the myocardial meshwork [2,3,5–7]. Based on the morphologic appearance of the myocardium, diagnostic criteria have been generated from different imaging modalities [8–12]. The prevalence of LVNC is rather difficult to accurately obtain however some studies estimate it at about 0.014–1.3% in the general population [3,7,8,13–15]; however, this is probably an underestimate, since improved echocardiographic image quality and increasing awareness of LVNC has led to enhanced recognition. LVNC has been associated with different modes of inheritance including: X-linked, autosomal recessive, autosomal dominant, mitochondrial [12,16]. This cardiomyopathy has also been associated with several genetic syndromes, inborn errors of metabolism, and mitochondrial disorders [1]. In addition, single genetic causes of LVNC have been associated to genes encoding sarcomeric and cytoskeletal proteins, and genes implicated in cardiac morphogenesis, such as *DTNA, LDB3, MYH7, MYBPC3, ACTC1, NNT,* among others [2,16–19]. Corroboration of LVNC in association with various forms of congenital heart disease (CHD) has been documented; some of these

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**Table 1**
Summary of cardiovascular phenotype of the heterotaxy/LVNC group.

| Subjects | CHD diagnosis | Initial surgical procedure | Genetics analysis | Current CV medical therapy | EP disturbances |
|---|---|---|---|---|---|
| Subject 1 | Dex, AVSD, DORV, L-TGA, PS | Modified BTS and PDA ligation. | n/a | Captopril, Atenolol, Digoxin, Sildenafil, Aspirin | Postoperative junctional ectopic tachycardia |
| Subject 2 | Dex, AVSD, PAPVR, iIVC with Azy cont, LSVC | AV canal repair | 1.17-megabase duplication at 13q31.1 identified by CGH. | None | Atrial ectopic tachycardia, complete AV block |
| Subject 3 | Dex, uAVSD, AS, PAPVR, LSVC | DKS + modified BTS | n/a | Aspirin | Complete AV block |
| Subject 4 | Levocardia, uAVSD, TAPVR, iIVC with Azy cont | AV canal repair | n/a | None | Atrial ectopic tachycardia |
| Subject 5 | Levocardia, AVSD, CoA, iIVC with Azy cont | CoA repair | 1.19-megabase deletion at 1q21.1 identified by CGH. | None | Postoperative junctional ectopic tachycardia |
| Subject 6 | Levocardia, uAVSD, iIVC with Azy cont, LSVC, PAPVR | uAVSD | 596.05-kb deletion at 3q25 identified by CGH. | Losartan | None |
| Subject 7 | Dex, L-TGA, VSD, PS | None | n/a | None | None |
| Subject 8 | Dex, L-TGA, ASD, VSD, PS, PAPVR | Double switch, PAPVR repair | n/a | Digoxin, Metoprolol | Atrial flutter |
| Subject 9 | Dex, uAVSD | Glenn procedure | n/a | Carvedilol | Atrial ectopic tachycardia |
| Subject 10 | Dex, uAVSD, iIVC with Azy cont | AV canal repair | n/a | Carvedilol | None |
| Subject 11 | Dex, AVSD, DORV, LSVC, TAPVR | Pacemaker implantation | Normal CMA, 4 VUS from the heterotaxy gene panel by GeneDx® | Milrinone | Congenital compete AV block |
| Subject 12 | Dex, L-TGA, PS, uAVC, Ebstein's anomaly | Modified BTS | Normal 22q FISH analysis | Aspirin, Captopril, Coumadin, Furosemide | None |
| Subject 13 | Dex, D-TGA, PS, uAVSD | DKS + modified BTS | n/a | Digoxin, Lisinopril | None |

This table is assorted by subject number and it describes the cardiac phenotype in these patients, their initial surgical procedure, the post-operative medical regimen, and their genetic analysis when available.
(AS) aortic valve stenosis; (ASD) atrial septal defect; (AV) atrioventricular; (AVSD) atrioventricular septal defect; (Azy cont) azygous vein continuation to the superior vena cava; (BTS) Blalock-Taussig shunt; (CGH) comparative genomic hybridization; (CMA) chromosomal microarray; (CoA) coarctation of the aorta; (CTJ) cervicothoracic junction; (CV) cardiovascular; (DD) developmental delay; (Dex) dextrocardia; (DKS) Damus-Kaye-Stansel procedure; (DORV) double outlet right ventricle; (D-TGA) D-transposition of the great arteries; (EP) electrophysiological; (FISH) fluorescent *in situ* hybridization; (iIVC) interrupted inferior vena cava; (LSVC) left superior vena cava; (L-TGA) L-transposition of the great arteries; (PAPVR) partial anomalous pulmonary venous return; (PDA) patent ductus arteriosus; (PS) pulmonary valve stenosis; (TAPVR) total anomalous pulmonary venous return; (uAVSD) unbalanced atrioventricular septal defect; (VSD) ventricular septal defect; (VUS) variant of unknown significance.