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ORIGINAL RESEARCH

# Diagnostic Yield of Genetic Testing in Young Patients With Atrioventricular Block of Unknown Cause

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**BACKGROUND:** The cause of atrioventricular block (AVB) remains unknown in approximately half of young patients with the diagnosis. Although variants in several genes associated with cardiac conduction diseases have been identified, the contribution of genetic variants in younger patients with AVB is unknown.

**METHODS AND RESULTS:** Using the Danish Pacemaker and Implantable Cardioverter Defibrillator (ICD) Registry, we identified all patients younger than 50 years receiving a pacemaker because of AVB in Denmark in the period from January 1, 1996 to December 31, 2015. From medical records, we identified patients with unknown cause of AVB at time of pacemaker implantation. These patients were invited to a genetic screening using a panel of 102 genes associated with inherited cardiac diseases. We identified 471 living patients with AVB of unknown cause, of whom 226 (48%) accepted participation. Median age at the time of pacemaker implantation was 39 years (interquartile range, 32–45 years), and 123 (54%) were men. We found pathogenic or likely pathogenic variants in genes associated with or possibly associated with AVB in 12 patients (5%). Most variants were found in the *LMNA* gene (n=5). *LMNA* variant carriers all had a family history of either AVB and/or sudden cardiac death.

**CONCLUSIONS:** In young patients with AVB of unknown cause, we found a possible genetic cause in 1 out of 20 participating patients. Variants in the *LMNA* gene were most common and associated with a family history of AVB and/or sudden cardiac death, suggesting that genetic testing should be a part of the diagnostic workup in these patients to stratify risk and screen family members.

**Key Words:** conduction ■ diagnostic testing ■ inherited heart diseases ■ *LMNA*

The cause of atrioventricular block (AVB) is unknown in approximately half of patients with AVB younger than 50 years of age at the time of first pacemaker implantation despite preimplantation diagnostic workup.[1] The risk of death, heart failure hospitalization, ventricular tachyarrhythmia, and cardiac arrest is significantly higher in these patients compared with the general population.[2] Whether the poor prognosis in young patients with AVB of unknown cause is because of undiagnosed pathogenic genetic variants is unknown.

Over the past decade, the use of genetic testing in cardiac diseases has increased.[3] Several genes

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## CLINICAL PERSPECTIVE

### What Is New?

- In young patients with atrioventricular block of unknown cause, we found a possible genetic cause in 1 of 20 patients who accepted participation in the study.
- Variants in the *LMNA* gene were most common.
- Patients with variants in the *LMNA* gene all had a family history of atrioventricular block and/or sudden cardiac death.

### What Are the Clinical Implications?

- Genetic testing should be considered in young patients with atrioventricular block of unknown cause, especially in patients with a family history of atrioventricular block or sudden cardiac death.
- When performing genetic testing, it is important to be aware of the risk of incidental findings.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AVB** | atrioventricular block |
| **DCM** | dilated cardiomyopathy |
| **HCM** | hypertrophic cardiomyopathy |
| **SCD** | sudden cardiac death |

associated with cardiac conduction abnormalities have been identified,[4–6] and familial clustering in AVB has been described.[7] However, the contribution of genetic variants in AVB in younger patients remains unknown. In this study we aimed to estimate the prevalence of AVB-associated genetic variants in a nationwide cohort of patients <50 years of age receiving a pacemaker for advanced AVB with no clinically identified cause at the time of pacemaker implantation.

## METHODS

### Study Population

The Danish Pacemaker and Implantable Cardioverter Defibrillator (ICD) Registry is a clinical database, founded in 1982, to which all pacemaker implantation procedures in Denmark are reported.[8] Using the Danish Pacemaker and ICD Registry, we identified all patients younger than 50 years of age receiving a pacemaker because of AVB in Denmark in the period from January 1, 1996 to December 31, 2015. To identify patients with AVB of unknown cause, we performed a review of the medical records including the results from the diagnostic workup. The cause was registered as borreliosis, congenital AVB, or side effect to medical treatment if this was reported in the medical records. In cases with Steno-Fallot tetralogy, congenital corrected transposition, ventricular septal defect, or univentricular heart anatomy, the cause was registered as congenital heart disease.[9,10] If a known pathogenic genetic mutation associated with AVB was identified, the cause was registered as hereditary. In cases with documentation of AVB during a tilt-table test, the cause was recorded as cardioinhibitory reflex. If there was documentation of His ablation in the medical records, this was registered as the cause. AVB was regarded as a complication to radiofrequency ablation, cardiac surgery, or alcohol septal ablation if the patient had sinus rhythm before the procedure and AVB within 2 weeks after, regardless of the indication for the procedure. In cases of endocarditis, this was registered as the cause in cases where the atrioventricular conduction was affected in any way before surgery. Patients who were known to have cardiac sarcoidosis,[11] cardiomyopathy,[12] or muscular dystrophy[13] were registered with those as the cause. For ischemic heart disease, this was considered the cause in cases where the patients developed AVB in relation to acute myocardial infarction. To ensure consistency, all medical records were reviewed by the same physician (J.R.D., overseen by H.K.J.). If the medical records were not available, patients were excluded. During the review process, we confirmed that the indication for pacemaker implantation followed the European Society of Cardiology indications for pacing guidelines.[14] Thus, the indication for implantation was either (1) symptomatic first-degree AVB or symptomatic Mobitz type I AVB, (2) Mobitz type II AVB 2:1 or more advanced second-degree AVB, or (3) third-degree AVB. For all patients we reviewed, the documentation for AVB, which consisted of Holter monitoring, ECG, telemetric recording, loop recording, or a description of the AVB based on one of the mentioned modalities reported in the medical records. We excluded patients without documentation for AVB. Except for patients who had died since the pacemaker implantation, all remaining patients were invited to have genetic testing performed. The invitation was sent by letter, and if no reply was received within 3 weeks, a reminder was sent. Patients who volunteered to participate received written and oral information about genetic testing before signing the informed consent form. After signing the informed consent form, the patients had a sample of whole blood taken for genetic analysis. When the patients came for blood sampling, we collected data on family history of AVB, sudden cardiac death (SCD), and cardiomyopathy.

The study complies with the Declaration of Helsinki and was approved by the Danish Patient Safety Authority (record number: 3-3013-1970/1/), the Danish Data Protection Agency (record number:

1-16-02-440-16), and the regional ethics committee (record number: 62825). Because of the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

## Genetic Analysis

DNA was extracted from whole blood collected in 4-mL EDTA tubes stored at –80 °C. The samples were shipped on dry ice to deCODE genetics, Reykjavík, Iceland for DNA extraction, sequencing, and variant calling. All samples were subjected to the same whole-genome sequencing procedures using paired end sequencing with an average depth of 30× on the Illumina NovaSeq 6000 sequencing platform. Reads were processed in a quality control pipeline as previously described.[15] Data were sent to the Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark, where they were analyzed with the gene panel MOMA Heart panel version 4 consisting of 102 genes relevant to heart diseases (Table S1). Variants within ±10 bp were assessed including splice variants and small deletions, duplications, and indels. Genetic variants were classified according to the Sherloc Classification Guidelines.[16] Based on an assessment of existing literature, variants were categorized into 3 categories; genes associated with AVB, genes possibly associated with AVB, and genes probably not associated with AVB. Relevant variants were verified using Sanger Sequencing, and biological family members were offered cascade screening. Screening of family members is currently an ongoing process.

## Statistical Analysis

Continuous variables are expressed as median (interquartile range) and dichotomous variables as number (proportion). Comparisons were done using the $\chi^2$ test or the Mann-Whitney *U* test as appropriate. A $P<0.05$ was considered statistically significant. Statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, TX).

# RESULTS

## Clinical Characteristics

We identified 1242 patients younger than 50 years of age with AVB in the study period, of whom 154 patients had a missing medical report (Figure). The remaining 1088 patients were screened for inclusion. We excluded 571 patients because of either missing civil registration numbers (n=10), missing documentation of AVB (n=51), or known cause of AVB (n=510). We also excluded 4 patients with an already established genetic cause of AVB; these 4 all had variants in the *LMNA* gene (p.Ala132Pro, p.Trp514*, p.Arg471Cys, p.Glu355*). Thus, we identified 517 patients with AVB of unknown cause at the time of pacemaker implantation. Forty-six patients died after pacemaker implantation but before study enrollment, leaving 471 patients who were invited to participate in the study. The cause of death on the death certificates was registered as cardiovascular in 18 of 46 (39%) patients: acute myocardial infarction (n=4), cardiomyopathy (n=3), heart failure (n=3), pulmonary embolism (n=2), arrhythmias (n=2), aortic stenosis (n=1), mitral valve stenosis (n=1), endocarditis (n=1), and congenital heart disease (n=1). The remaining patients died of noncardiac causes.

Of the remaining 471 eligible patients, 226 (48%) signed an informed consent form and were included. The median age at time of pacemaker implantation was 39 years (interquartile range, 32–45 years), and 54% were men (Table 1). The vast majority of participants had second-degree Mobitz type II or more advanced AVB (93%); however, the proportion was slightly higher in nonparticipants (99%, $P=0.03$). Among the participants, 2 patients had symptomatic first-degree AVB, and 17 patients had symptomatic second-degree Mobitz type I AVB.

Comorbidity was infrequent, with hypertension (5% of participants) and atrial fibrillation/flutter (4% of participants) being the most prevalent. Nonparticipants were more likely to have ischemic heart disease (3% versus 0.4%, $P=0.05$), but otherwise there were no differences in characteristics between participants and nonparticipants.

Among participants, 12 (5%) had a family history of AVB before 50 years of age in a first-degree relative; 6 (3%) had a family history of SCD before 50 years of age in a first-degree relative, and 14 (6%) had a family history of dilated cardiomyopathy (DCM) or hypertrophic cardiomyopathy (HCM) in a first-degree relative.

## Genetic Findings and Associated Clinical Characteristics

We found a pathogenic, likely pathogenic, or variant of unknown significance in 20 patients (9%) (Table 2). All 20 patients had second-degree Mobitz type II or more advanced AVB. Twelve patients had a variant in a gene associated with or possibly associated with AVB (5%). Five patients (2%) had variants in the *LMNA* gene; 3 patients had a pathogenic variant (p.Arg321*, p.Ser143Pro, p.Glu82Lys), whereas the 2 remaining patients had likely pathogenic variants (p.Ala129Serfs*26, p.Gln656Argfs*42). Data on left ventricular ejection fraction on echocardiography at implantation time were available for 4 of the 5 patients. All 4 patients had a left ventricular ejection fraction above 50%. One patient with a pathogenic variant (p.Arg321*) had a dilated left ventricle on echocardiography. The 2 other patients with

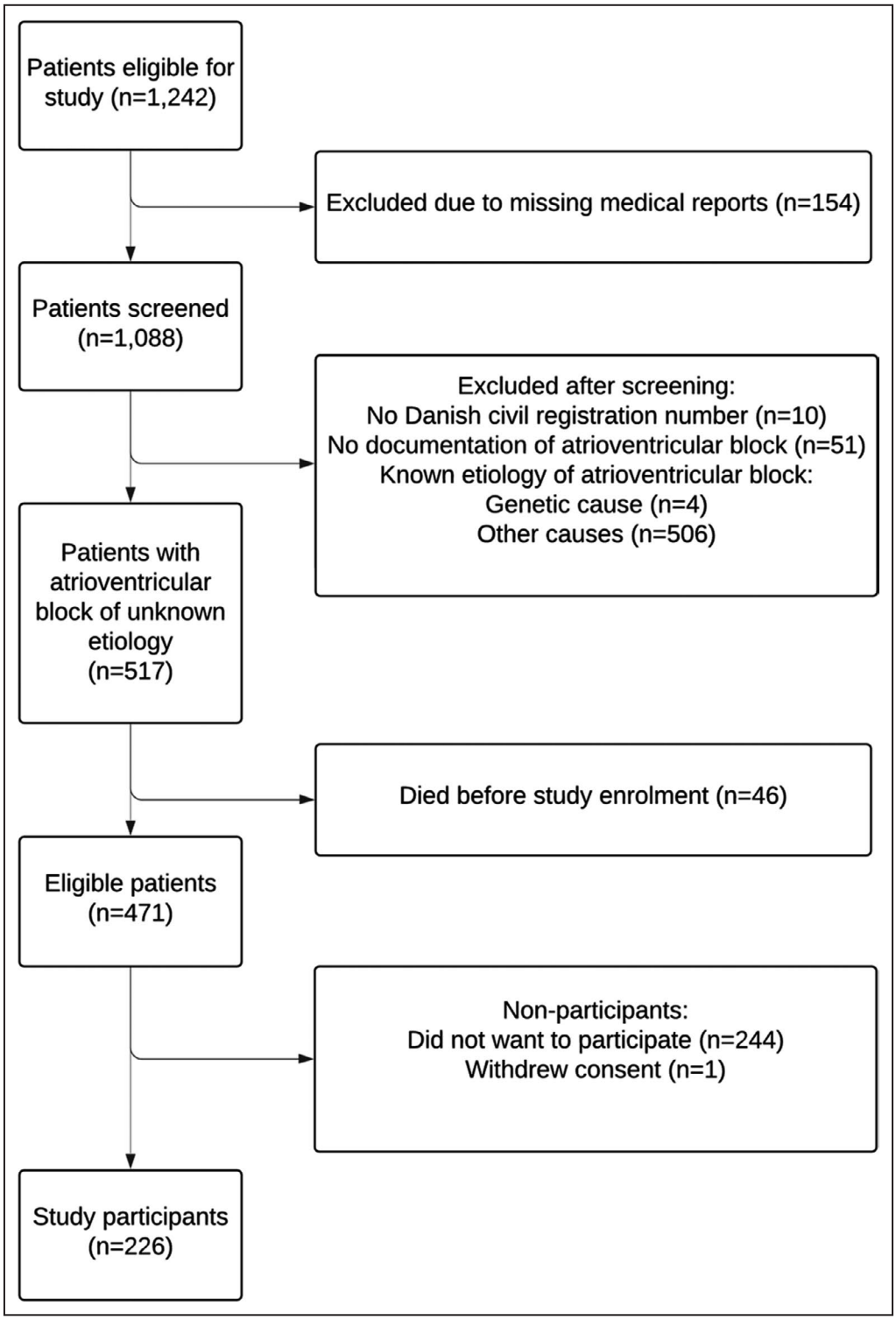


**Figure 1. Flowchart for inclusion of patients with atrioventricular block of unknown cause treated with pacemaker implantation before the age of 50 years.**

pathogenic variants in the *LMNA* gene (p.Ser143Pro and p.Glu82Lys) had a diagnosis of atrial fibrillation, whereas the remaining 2 did not have any comorbidities. Four of the 5 patients with variants in the *LMNA* gene had a family history of AVB, and 2 had a family history of SCD (Table 2). Thus, of the 12 patients with a family history of AVB before 50 years of age, 4 (33%) were carriers of variants in the *LMNA* gene, and of the 6 patients with

**Table 1. Characteristics of Young Patients With Atrioventricular Block of Unknown Cause at Time of First Pacemaker Implantation**

| | Participants, n=226 | Nonparticipants, n=245 | Total, n=471 | *P* value |
|---|---|---|---|---|
| Age at implant, y | 39 (32–45) | 41 (31–46) | 40 (31–45) | 0.70 |
| Male sex | 123 (54%) | 147 (60%) | 270 (57%) | 0.31 |
| Mobitz II/more advanced atrioventricular block | 211 (93%) | 242 (99%) | 453 (96%) | 0.03 |
| Family history in first-degree relative | | | | |
| Atrioventricular block before 50 y of age | 12 (5%) | … | … | … |
| Sudden cardiac death before 50 y of age | 6 (3%) | … | … | … |
| Dilated or hypertrophic cardiomyopathy | 14 (6%) | … | … | … |
| Symptoms at presentation | | | | |
| Dizziness | 122 (54%) | 118 (48%) | 240 (51%) | 0.18 |
| Syncope | 99 (44%) | 123 (50%) | 222 (47%) | 0.19 |
| Dyspnea | 51 (23%) | 50 (20%) | 101 (21%) | 0.50 |
| Malaise | 46 (20%) | 45 (18%) | 91 (19%) | 0.61 |
| Angina | 31 (14%) | 33 (13%) | 64 (14%) | 0.88 |
| Fatigue | 28 (12%) | 27 (11%) | 55 (12%) | 0.60 |
| Cardiac arrest | 2 (1%) | 1 (0.4%) | 3 (0.6%) | 0.51 |
| Asymptomatic | 16 (7%) | 22 (9%) | 38 (8%) | 0.48 |
| Comorbidity | | | | |
| Atrial fibrillation/flutter | 9 (4%) | 7 (3%) | 16 (3%) | 0.48 |
| Hypertension | 11 (5%) | 19 (8%) | 30 (6%) | 0.22 |
| Heart failure | 1 (0.4%) | 1 (0.4%) | 2 (0.4%) | 0.45 |
| Hypercholesterolemia | 6 (3%) | 11 (4%) | 17 (4%) | 0.30 |
| Diabetes | 2 (1%) | 6 (2%) | 8 (2%) | 0.20 |
| Ischemic heart disease | 1 (0.4%) | 7 (3%) | 8 (2%) | 0.05 |
| Connective tissue disease | 4 (2%) | 5 (2%) | 9 (2%) | 0.85 |

Data are presented as median (interquartile range) or number (percentage).

a family history of SCD before 50 years of age, 2 (33%) were *LMNA*-variant carriers. None of the patients had a family history of DCM or HCM.

We found variants in genes that are possibly associated with AVB in 7 patients (Table 2). None of the 7 patients had any comorbidities, and left ventricular ejection fraction was 60% in 4 patients, whereas data on left ventricular ejection fraction were missing in 3 patients. There was no family history of AVB, SCD, or cardiomyopathy in first-degree relatives of the 7 patients.

We found variants in genes probably not associated with AVB in 8 patients (Table 2). One patient with a variant in the *CACNA2D1* gene had a father with AVB before 50 years of age. Four patients had variants in genes associated with blood cholesterol regulation (*LDLR* and *PCSK9*). None of these patients had ischemic heart disease.

## DISCUSSION

The present study provides, to our knowledge, the first estimate of the yield of genetic testing in young patients with AVB of unknown cause in a population-based cohort. We found a possible genetic cause of AVB in ≈1 of 20 patients participating in the study. Five of the patients had a pathogenic or likely pathogenic variant in the *LMNA* gene, which is strongly associated with conduction abnormalities and DCM.[17] Three of the *LMNA* variants have been described as pathogenic in the literature (p.Arg321*,[18] p.Ser143Pro,[19] p.Glu82Lys[20,21]), whereas 2 likely pathogenic variants have not previously been described (p.Ala129Serfs*26 and p.Gln656Argfs*42). In addition, 4 of the excluded patients who had a known cause of AVB had variants in the *LMNA* gene. *LMNA* variants are usually inherited in an autosomal dominant manner,[22] and penetrance is high in *LMNA* genotype-positive family members,[23] emphasizing the importance of family history and screening. In this present study, all patients with a *LMNA* variant had a family history of AVB and/or SCD in a first-degree relative and comprised 33% of patients with a family history of AVB and SCD, respectively. The incidence of AVB in patients with DCM with *LMNA* variants has been estimated in previous studies to be ≈60%[23,24]; however, the true incidence of AVB in *LMNA* carriers is challenging to estimate because of the difficulties in identifying asymptomatic patients.

**Table 2. List of Genetic Variants in 20 Patients <50 Years of Age With AVB of Unknown Cause**

| Gene symbol | Reference sequence | Literature references* | Nucleotide | Protein change | Pathogenicity class† | Age at implantation, y | Sex | Family history in first degree family member | | | Comorbidity | LVEF | AVB type | Other information |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | AVB | SCD | CM | | | | |
| Genes associated with AVB | | | | | | | | | | | | | | |
| *LMNA* | NG_008692.2 | 12, 13, | c.961C>T | p.Arg321* | 5 | 46 | M | + | + | – | Dilated left ventricle | 60% | Intermittent 3 degree | Coronary angiography performed, normal |
| *LMNA* | NG_008692.2 | 12, 14 | c.427T>C | p.Ser143Pro | 5 | 39 | M | + | – | – | Atrial fibrillation | NA | Intermittent 3 degree | NA |
| *LMNA* | NG_008692.2 | 12, 15, 16 | c.244G>A | p.Glu82Lys | 5 | 45 | M‡ | + | – | – | Atrial fibrillation Stroke | 50% | Permanent 3 degree | NA |
| *LMNA* | NG_008692.2 | 12 | c.383dup | p.Ala129Serfs*26 | 4 | 36 | M | – | + | – | None | 60% | Intermittent 3 degree | NA |
| *LMNA* | NG_008692.2 | 12 | c.1967del | p.Gln656Argfs*42 | 4 | 48 | M | + | – | – | None | 60% | Intermittent 3 degree | NA |
| Genes possibly associated with atrioventricular block | | | | | | | | | | | | | | |
| *GAA* | NG_009822.1 | 27 | c.693-1G>A | Splicing error | 5 | 34 | F | – | – | – | None | 60% | Intermittent 3 degree | NA |
| *MYBPC3* | NG_007667.1 | 21, 22 | c.822-2A>T | Splicing error | 5 | 42 | F | – | – | – | None | 60% | Intermittent 3 degree | NA |
| *MYBPC3* | NG_007667.1 | 21, 22 | c.2827C>T | p.Arg943* | 5 | 44 | M | – | – | – | None | NA | Intermittent 3 degree | NA |
| *GAA* | NG_009822.1 | 27 | c.2238G>C | p.Trp746Cys | 5 | 35 | M | – | – | – | None | 60% | Intermittent 3 degree | NA |
| *KCNQ1* | NG_008935.1 | 28 | c.592A>G | p.Ile198Val | 4 | | | | | | | | | |
| *TTN* | NG_011618.3 | 24 | c.62002+2T>G | Splicing error | 4 | 38 | F | – | – | – | None | NA | Intermittent 3 degree | NA |
| *GLA* | NG_007119.1 | 25, 26 | c.427G>A | p.Ala143Thr | 4 | 24 | F | – | – | – | None | NA | Intermittent 3 degree | NA |
| *ACTN2* | NG_009081.2 | 23 | c.1840G>A | p.Val614Met | 3 | 22 | F | – | – | – | None | 60% | Intermittent 3 degree | NA |
| Genes probably not associated with AVB | | | | | | | | | | | | | | |
| *LDLR* | NG_009060.1 | NA | c.2475C>G | p.Asn825Lys | 5 | 25 | M | – | – | – | None | 60% | Intermittent Mobitz type II | NA |

*(continued)*

**Table 2. Contiuned**

| Gene symbol | Reference sequence | Literature references* | Nucleotide | Protein change | Pathogenicity class† | Age at implantation, y | Sex | Family history in first degree family member | | | Comorbidity | LVEF | AVB type | Other information |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | AVB | SCD | CM | | | | |
| *LDLR* | NG_009060.1 | NA | c.2475C>G | p.Asn825Lys | 5 | 45 | M | – | – | – | Surgery for coarctation of the aorta and bicuspid aortic valve at 13 years of age | 60% | Intermittent 3 degree | NA |
| *PCSK9* | NG_009061.1 | NA | c.1120G>A | p.Asp374Asn | 5 | 44 | M | – | – | – | None | 60% | Intermittent 3 degree | NA |
| *TNNI3* | NG_007866.2 | NA | c.497C>T | p.Ser166Phe | 4 | 49 | M | – | – | – | None | 60% | Permanent 3 degree | NA |
| *DSG2* | NG_007072.3 | NA | c.16G>T | p.Gly6* | 4 | 35 | M | – | – | – | None | NA | Intermittent 3 degree | NA |
| *LDLR*§ | NG_009060.1 | NA | c.2397_2405del | p.Val800_ Leu802del | 4 | 33 | M | – | – | + | None | 60% | Intermittent advanced 2 degree | Coronary angiography performed, normal; cardiac MRI performed, normal. |
| *LDLR*§ | NG_009060.1 | NA | c.1690A>C | p.Asn564His | 4 | | | | | | | | | |
| *CACNA2D1* | NG_009358.2 | NA | c.1648G>T | p.Asp550Tyr | 3 | 27 | F | + | – | – | None | 60% | Intermittent 3 degree | NA |
| *MYL3* | NG_007555.2 | NA | c.520dup | p.Ala174Glyfs*13 | 3 | 43 | F | – | – | – | Asthma | NA | Intermittent 3 degree | NA |

AVB indicates atrioventricular block; CM, cardiomyopathy (dilated/hypertrophic); F, female; LVEF, left ventricular ejection fraction; M, male; MRI, magnetic resonance imaging; NA, not applicable; and SCD, sudden cardiac death.

*Numbers refer to the references list.

†Pathogenicity class: 3=variant of unknown significance, 4=likely pathogenic, 5=pathogenic.

‡The patient also had a class 4 mutation in the *GLA* gene (c.427G>A, p.Ala143Thr).

§The patient had a double variant and was heterozygote for each of the 2 LDLR variants.

A Norwegian study found a high risk of ventricular arrhythmia in *LMNA* variant carriers, especially in patients with AVB.[23] Furthermore, mortality and risk of heart transplantation was high. Thus, early diagnosis and treatment is important in these patients to prevent malignant arrhythmia, heart failure, or SCD. Current guidelines recommend that an implantable cardioverter-defibrillator is considered in patients with DCM and a confirmed disease-causing variant in the *LMNA* gene.[25] A recent descriptive study from Finland with 60 patients with variants in the *LMNA* gene found that 61.7% (n=37) of *LMNA*-variant carriers underwent pacemaker implantation; however, 27% (n=10) of patients with a pacemaker needed an upgrade of their device to either implantable cardioverter-defibrillator and/or cardiac resynchronization therapy device.[26] In their study, the initial indication for device implantation typically was AVB. Because of the progressive nature of the phenotype, the authors recommend that the need for an implantable cardioverter-defibrillator is assessed early when planning device implantation. This highlights the importance of identification of *LMNA* variant carriers at time of implantation through genetic testing of young patients with AVB of unknown cause, in particular among patients with a positive family history of AVB, heart failure, and/or SCD.

In addition to *LMNA* variants, we found variants in genes that have previously been related to AVB, but with a less clear association. Several of these variants have also been identified in HCM. The *MYBPC3* gene is responsible for 40% to 50% of all cases of HCM, and complete AVB has been described in patients with *MYBPC3* variants both with and without HCM.[27,28] In addition, *ACTN2* variants are associated with HCM, and in a study of a family with HCM, complete AVB was frequent in patients with *ACTN2* variants.[29] Variants in the gene encoding titin, *TTN,* have been found in up to 25% of patients with DCM.[30] In a study of 133 DCM probands, AVB was found in 14% of patients with *TTN* variants; however, this was significantly less frequent than in probands with *LMNA* variants.[30] Besides AVB, the patients in our study with *TTN*, *MYBPC3*, and *ACTN2* variants did not show any signs of cardiomyopathy phenotypes, which could, however, be because of age-related penetrance. Furthermore, we found a variant in the *GLA* gene, which is associated with Fabry's disease, a rare X-linked lysosomal storage disorder characterized by an α-galactosidase A deficiency, which manifests in kidneys, skin, extremities, and the heart.[31] However, solitary cardiac involvement with no other organ manifestations has been described in a family with a *GLA* variant.[32] Another lysosomal storage disorder that can present with conduction abnormalities is Pompe disease.[33] One patient had a variant in the *GAA* gene, in which there is a defect in patients with Pompe disease. This was a male patient, 35 years of age at time of pacemaker implantation, and he had no comorbidities. This patient also had a variant in the *KCNQ1* gene, which has been described to be associated with AVB[34] but also to be associated with long-QT syndrome.[35] However, this patient had a normal QT interval. Although the association between these genetic variants and AVB is less clear than with *LMNA*, these findings might provide better insight into the genetic background for AVB. Furthermore, findings of genetic variants in these younger patients with AVB might facilitate further clinical examination and family screening to uncover possible undiagnosed cardiac and multiorgan diseases. However, it is important to be aware of the risk of incidental findings in genetic testing. In this study we identified 4 patients with variants in genes related to blood cholesterol regulation and other variants of unknown significance. Thus, it is important to inform patients that genetic testing might lead to findings that require further examination and family screening.

It is important to highlight that patients with known cause of AVB, such as congenital AVB and identified hereditary AVB, were excluded for this study. Thus, none of the patients in our study were children at the time of pacemaker implantation, which was presumably the reason we did not find genetic variants associated with congenital and hereditary AVB such as *SCN5A*.[36]

Our findings suggest genetic testing be considered in patients with AVB of unknown cause, especially in those with a family history of AVB or SCD.

## Limitations

Our study has some limitations. Importantly, only approximately half of the invited patients accepted participation in the study. Although clinical characteristics were comparable between participants and nonparticipants, there might be other factors that facilitated participation, which may have introduced selection bias. We have no information on family history in nonparticipants, including those who died before study enrollment. Thus, we cannot exclude that a positive family history might have encouraged patients to participate in the study. Nor can we exclude that there was a high prevalence of family history and genetic variants leading to a poor prognosis in the deceased patients, which might be underlined by the relatively high incidence of cardiovascular death in the 46 patients who died before study enrollment including death from cardiomyopathy, heart failure, and arrhythmias. This may have led to an underestimation of the proportion of patients with genetic variants.

Although the genetic variants we found to be possibly associated with AVB were previously described

in the literature, it is important to highlight that these variants might not be causal of AVB in our study. Furthermore, our genetic screening was limited to a panel of 102 genes associated with inherited heart disease. Thus, the patients might have variants in other genes associated with AVB that we did not screen for.

## CONCLUSIONS

In young patients with AVB of unknown cause, we found a possible genetic cause in 1 of 20 patients participating in the study. Variants were mostly found in the *LMNA* gene. Patients with *LMNA* variants all had a positive family history of AVB and/or SCD, suggesting that genetic testing should be a part of the diagnostic workup in these patients to stratify risk and screen family members.

## ARTICLE INFORMATION

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### Supplemental Material

Table S1

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# SUPPLEMENTAL MATERIAL

**Table S1**. **MOMA Heart Gene Panel version 4.**

| **Approved symbol** | **Approved name** | **HGNC ID** | **Location** |
|---|---|---|---|
| *ABCC9* | ATP binding cassette subfamily C member 9 | HGNC:60 | 12p12.1 |
| *ACTC1* | actin, alpha, cardiac muscle 1 | HGNC:143 | 15q14 |
| *ACTN2* | actinin alpha 2 | HGNC:164 | 1q43 |
| *AKAP9* | A-kinase anchoring protein 9 | HGNC:379 | 7q21.2 |
| *ANK2* | ankyrin 2 | HGNC:493 | 4q25-q26 |
| *ANKRD1* | ankyrin repeat domain 1 | HGNC:15819 | 10q23.31 |
| *ANO1* | anoctamin 1 | HGNC:21625 | 11q13.3 |
| *APOB* | apolipoprotein B | HGNC:603 | 2p24.1 |
| *BAG3* | BCL2 associated athanogene 3 | HGNC:939 | 10q26.11 |
| *BEST3* | bestrophin 3 | HGNC:17105 | 12q15 |
| *CACNA1C* | calcium voltage-gated channel subunit alpha1 C | HGNC:1390 | 12p13.33 |
| *CACNA2D1* | calcium voltage-gated channel auxiliary subunit alpha2delta 1 | HGNC:1399 | 7q21.11 |
| *CACNB2* | calcium voltage-gated channel auxiliary subunit beta 2 | HGNC:1402 | 10p12 |
| *CALM1* | calmodulin 1 | HGNC:1442 | 14q32.11 |
| *CALM2* | calmodulin 2 | HGNC:1445 | 2p21 |
| *CALM3* | calmodulin 3 | HGNC:1449 | 19q13.32 |
| *CASQ2* | calsequestrin 2 | HGNC:1513 | 1p13.1 |
| *CAV3* | caveolin 3 | HGNC:1529 | 3p25.3 |
| *CDH2* | cadherin 2 | HGNC:1759 | 18q12.1 |

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|---|---|---|---|
| *CRYAB* | crystallin alpha B | HGNC:2389 | 11q23.1 |
| *CSRP3* | cysteine and glycine rich protein 3 | HGNC:2472 | 11p15.1 |
| *CTNNA3* | catenin alpha 3 | HGNC:2511 | 10q21.3 |
| *DES* | desmin | HGNC:2770 | 2q35 |
| *DMD* | dystrophin | HGNC:2928 | Xp21.2-p21.1 |
| *DNAJC19* | DnaJ heat shock protein family (Hsp40) member C19 | HGNC:30528 | 3q26.33 |
| *DSC2* | desmocollin 2 | HGNC:3036 | 18q12.1 |
| *DSG2* | desmoglein 2 | HGNC:3049 | 18q12.1 |
| *DSP* | desmoplakin | HGNC:3052 | 6p24.3 |
| *DTNA* | dystrobrevin alpha | HGNC:3057 | 18q12.1 |
| *EMD* | emerin | HGNC:3331 | Xq28 |
| *EYA4* | EYA transcriptional coactivator and phosphatase 4 | HGNC:3522 | 6q23.2 |
| *FHL1* | four and a half LIM domains 1 | HGNC:3702 | Xq26.3 |
| *FHL2* | four and a half LIM domains 2 | HGNC:3703 | 2q12.2 |
| *FKTN* | fukutin | HGNC:3622 | 9q31.2 |
| *FLNC* | filamin C | HGNC:3756 | 7q32.1 |
| *FXN* | frataxin | HGNC:3951 | 9q21.11 |
| *GATA4* | GATA binding protein 4 | HGNC:4173 | 8p23.1 |
| *GLA* | galactosidase alpha | HGNC:4296 | Xq22.1 |
| *GPD1L* | glycerol-3-phosphate dehydrogenase 1 like | HGNC:28956 | 3p22.3 |
| *GAA* | glucosidase alpha, acid | HGNC:4065 | 17q25.3 |

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|---|---|---|---|
| *HCN4* | hyperpolarization activated cyclic nucleotide gated potassium channel 4 | HGNC:16882 | 15q24.1 |
| *JPH2* | junctophilin 2 | HGNC:14202 | 20q13.12 |
| *JUP* | junction plakoglobin | HGNC:6207 | 17q21.2 |
| *KCND3* | potassium voltage-gated channel subfamily D member 3 | HGNC:6239 | 1p13.2 |
| *KCNE1* | potassium voltage-gated channel subfamily E regulatory subunit 1 | HGNC:6240 | 21q22.12 |
| *KCNE2* | potassium voltage-gated channel subfamily E regulatory subunit 2 | HGNC:6242 | 21q22.11 |
| *KCNE3* | potassium voltage-gated channel subfamily E regulatory subunit 3 | HGNC:6243 | 11q13.4 |
| *KCNE5* | potassium voltage-gated channel subfamily E regulatory subunit 5 | HGNC:6241 | Xq23 |
| *KCNH2* | potassium voltage-gated channel subfamily H member 2 | HGNC:6251 | 7q36.1 |
| *KCNJ2* | potassium voltage-gated channel subfamily J member 2 | HGNC:6263 | 17q24.3 |
| *KCNJ5* | potassium voltage-gated channel subfamily J member 5 | HGNC:6266 | 11q24.3 |
| *KCNJ8* | potassium voltage-gated channel subfamily J member 8 | HGNC:6269 | 12p12.1 |

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|---|---|---|---|
| *KCNQ1* | potassium voltage-gated channel subfamily Q member 1 | HGNC:6294 | 11p15.5-p15.4 |
| *LAMA4* | laminin subunit alpha 4 | HGNC:6484 | 6q21 |
| *LAMP2* | lysosomal associated membrane protein 2 | HGNC:6501 | Xq24 |
| *LDB3* | LIM domain binding 3 | HGNC:15710 | 10q23.2 |
| *LDLR* | low density lipoprotein receptor | HGNC:6547 | 19p13.2 |
| *LMNA* | lamin A/C | HGNC:6636 | 1q22 |
| *MYBPC3* | myosin binding protein C, cardiac | HGNC:7551 | 11p11.2 |
| *MYH6* | myosin heavy chain 6 | HGNC:7576 | 14q11.2 |
| *MYH7* | myosin heavy chain 7 | HGNC:7577 | 14q11.2 |
| *MYL2* | myosin light chain 2 | HGNC:7583 | 12q24.11 |
| *MYL3* | myosin light chain 3 | HGNC:7584 | 3p21.31 |
| *MYOZ2* | myozenin 2 | HGNC:1330 | 4q26 |
| *MYPN* | myopalladin | HGNC:23246 | 10q21.3 |
| *NEBL* | nebulette | HGNC:16932 | 10p12.31 |
| *NEXN* | nexilin F-actin binding protein | HGNC:29557 | 1p31.1 |
| *PCSK9* | proprotein convertase subtilisin/kexin type 9 | HGNC:20001 | 1p32.3 |
| *PKP2* | plakophilin 2 | HGNC:9024 | 12p11.21 |
| *PLN* | phospholamban | HGNC:9080 | 6q22.31 |
| *PRDM16* | PR/SET domain 16 | HGNC:14000 | 1p36.32 |
| *PRKAG2* | protein kinase AMP-activated non-catalytic subunit gamma 2 | HGNC:9386 | 7q36.1 |
| *PSEN1* | presenilin 1 | HGNC:9508 | 14q24.2 |

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|---|---|---|---|
| *PSEN2* | presenilin 2 | HGNC:9509 | 1q42.13 |
| *PTPN11* | protein tyrosine phosphatase, non-receptor type 11 | HGNC:9644 | 12q24.13 |
| *RAF1* | Raf-1 proto-oncogene, serine/threonine kinase | HGNC:9829 | 3p25.2 |
| *RANGRF* | RAN guanine nucleotide release factor | HGNC:17679 | 17p13 |
| *RBM20* | RNA binding motif protein 20 | HGNC:27424 | 10q25.2 |
| *RYR2* | ryanodine receptor 2 | HGNC:10484 | 1q43 |
| *SCN10A* | sodium voltage-gated channel alpha subunit 10 | HGNC:10582 | 3p22.2 |
| *SCN1B* | sodium voltage-gated channel beta subunit 1 | HGNC:10586 | 19q13.11 |
| *SCN2B* | sodium voltage-gated channel beta subunit 2 | HGNC:10589 | 11q23.3 |
| *SCN3B* | sodium voltage-gated channel beta subunit 3 | HGNC:20665 | 11q24.1 |
| *SCN4B* | sodium voltage-gated channel beta subunit 4 | HGNC:10592 | 11q23.3 |
| *SCN5A* | sodium voltage-gated channel alpha subunit 5 | HGNC:10593 | 3p22.2 |
| *SGCD* | sarcoglycan delta | HGNC:10807 | 5q33.2-q33.3 |
| *SLC4A3* | solute carrier family 4 member 3 | HGNC:11029 | 2q35 |
| *SNTA1* | syntrophin alpha 1 | HGNC:11167 | 20q11.21 |
| *TAZ* | tafazzin | HGNC:11577 | Xq28 |
| *TCAP* | titin-cap | HGNC:11610 | 17q12 |
| *TMEM43* | transmembrane protein 43 | HGNC:28472 | 3p25.1 |
| *TMPO* | thymopoietin | HGNC:11875 | 12q23.1 |
| *TNNC1* | troponin C1, slow skeletal and cardiac type | HGNC:11943 | 3p21.1 |
| *TNNI3* | troponin I3, cardiac type | HGNC:11947 | 19q13.4 |
| *TNNT2* | troponin T2, cardiac type | HGNC:11949 | 1q32.1 |

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|---|---|---|---|
| *TPM1* | tropomyosin 1 | HGNC:12010 | 15q22.2 |
| *TRDN* | triadin | HGNC:12261 | 6q22.31 |
| *TRPM4* | transient receptor potential cation channel subfamily M member 4 | HGNC:17993 | 19q13.3 |
| *TTN* | titin | HGNC:12403 | 2q31.2 |
| *TTR* | transthyretin | HGNC:12405 | 18q12.1 |
| *VCL* | vinculin | HGNC:12665 | 10q22.2 |
| *ZBTB17* | zinc finger and BTB domain containing 17 | HGNC:12936 | 1p36.13 |

HGNC = HUGO Gene Nomenclature Committee; MOMA = Department of Molecular Medicine, Aarhus University Hospital, Denmark.