The clinical and electrophysiological spectrum of cardiac sodium channel mutations
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CHAPTER 2.1

MECHANISMS OF INHERITED CARDIAC CONDUCTION DISEASE

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1.0 INTRODUCTION

Cardiac conduction disease (CCD) is a serious, and a potentially life threatening disorder of the heart.\(^1\) In CCD, the integrity of the conduction system is impaired, such that impulse conduction will be slowed or even blocked and life-threatening rhythm disturbances may ensue. The pathophysiological mechanisms underlying CCD are diverse, but irrespective of its cause, the ultimate treatment may be pacemaker implantation.\(^1,2\) Notwithstanding that, it is worthwhile to consider the pathophysiological basis of CCD in more detail, since it may have implications for diagnostics, development of new treatment strategies, and prognosis. Also, if an inherited form of CCD is suspected, this knowledge may have consequences for family members of the affected individual.

Historically, CCD was viewed purely as a structural disease of the heart in which macro- or microscopical structural abnormalities in the conduction system underlie disruption of normal impulse propagation. In a substantial number of cases, however, conduction disturbances are found to occur in the absence of anatomical abnormalities. In these cases, functional rather than structural alterations appear to underlie conduction disturbances (figure 1). Frequently functional CCD is found to be a so-called ‘primary electrical disease’ of the heart, a group of inherited diseases that result from functionally abnormal, or absent, proteins encoded by mutated genes.\(^3,5\) The affected proteins are often cardiac ion channel proteins involved in cardiac impulse formation.

It can thus be hypothesised that patients with inherited structural or functional CCD suffer from fundamentally different diseases, although overlap between the two pathophysiological mechanisms may still exist.

In this review we aim to categorise and discuss reports on congenital and inherited CCD to find supportive evidence for these ideas. The questions we have attempted to answer while reviewing these reports were: 1) is the reported disease congenital and if so, inherited or acquired? 2) what is known about the pathophysiological mechanism of the reported disease? 3) can we relate reported clinical parameters to a particular pathophysiological mechanism? and finally, 4) are structural and functional CCD indeed different diseases?
2.0 THE CARDIAC CONDUCTION SYSTEM

2.1 Structural components
Before we continue our considerations about fundamental differences between structural and functional CCD, we should consider the structures involved in conduction in the heart. The cardiac conduction system enables fast and co-ordinated contraction of the heart. It is composed of specialized cardiac structures that are responsible for impulse formation and propagation. The cardiac impulse is generated by the sinus node in the right atrium, and is conducted to the left atrium via the Bachmann bundle. From the atria, electrical activity is transmitted to the ventricular myocardium through the atroioventricular node, the bundle of His, the right and left bundle branches, and the Purkinje fibre network successively, to ensure synchronized contraction of the heart.

Macro- or microscopical structural abnormalities in CCD may occur at any level in the conduction system and disrupt normal impulse propagation. These structural abnormalities may range from partial or total absence of structures, to gradual replacement of the normal tissues by fatty and/or fibrous tissue and calcification.

2.2 Functional components
The cardiac impulse, or action potential, is generated in the sinoatrial node through the combined action of several different types of ion conducting proteins. Shortly, the main
Mechanisms of inherited cardiac conduction disease

Players in the upstroke and repolarization of the SA node action potential are the depolarizing L- and T-type calcium currents and the repolarizing delayed rectifier potassium currents respectively. The repolarization of the action potential is followed by the diastolic depolarization, a slow spontaneous depolarization towards the threshold for generating another action potential. For fast propagation of the action potential through the atria, His-Purkinje system and the ventricles, the voltage gated sodium channel and gap junctions are of major importance. The speed of depolarization of the cells in these tissues, which is represented by the upstroke velocity of the action potential, is dependent on the magnitude of the sodium current and thus on sodium channel function and availability. The depolarizing current is transmitted from cell to cell through intercellular channels, the gap junction channels. These channels are constructed of two hemi-channels, each composed of 6 protein subunits, the connexins. Developments in molecular biology and genetics have increased our understanding of the molecular mechanisms of inherited cardiac conduction abnormalities and arrhythmia syndromes in general. We now know that these familial primary electrical diseases of the heart, that occur in the absence of structural heart disease or systemic disease, result from mutations in cardiac ion channel genes and associated or modifying proteins, such as cytoskeletal proteins.

3.0 METHODS

The Medline/OVID literature database was searched for original reports using the search terms: cardiac, conduction, congenital, genetics, heart, inherited, Lenegre, Lev, SCN5A and sodium channel. In addition, relevant references in this set of papers which were not identified by the Medline/Ovid literature database, were also retrieved. To further complete our database we checked for follow up reports on the original publications. We have limited our search to original reports on cardiac phenotypes. Reviewing and comparing data from original reports (Tables 1-3) that span more than 50 years of scientific progress, comes with some problems. Firstly, the earlier reports are mainly case reports of small groups of patients, or individual patients. For the study of the inherited nature of diseases and genetic screening, large patient-groups are needed. Such screening could not be performed in earlier times, since the techniques for genetic analysis have come available only very recently. Only in the more recent studies, the presence of mutations in the SCN5A, PRAKG2, NKX2-5 and LMNA genes was investigated. These genes were recently
found to be linked to cardiomyopathies, (isolated) conduction disease and (isolated) arrhythmias (Tables 1, 2 and 3). Secondly, in most reports the presence of discrete structural, histological abnormalities of the heart and the specialized conduction system cannot always be excluded because of the limited diagnostic possibilities in those days or because they were not looked for. Also, some individuals reported with CCD may have been suffering from other cardiac diseases associated with fainting spells and arrhythmias that have only recently been recognized, such as the Brugada syndrome.
### Table 1. Patients with inherited cardiac conduction disease related to anatomical abnormalities of the heart and/or the specialized conduction system

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of cases</th>
<th>sex</th>
<th>age of onset</th>
<th>ECG</th>
<th>abnormal anatomy heart</th>
<th>abnormal anatomy conduction system</th>
<th>histology myocard</th>
<th>histology conduction system</th>
<th>inheritance</th>
<th>proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wendkos 1947</td>
<td>6/3</td>
<td>?</td>
<td>B</td>
<td>complete AV block WPW</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
<td>AD</td>
<td>structural? possibly no His bundle</td>
</tr>
<tr>
<td>Griffith 1965</td>
<td>8.5</td>
<td>?</td>
<td>C</td>
<td>1,2* complete AV block SCD</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>AD (?)</td>
<td>cardiomypathy (?)</td>
<td></td>
</tr>
<tr>
<td>Lev 1967</td>
<td>2 cases</td>
<td>?/?</td>
<td>IU/C</td>
<td>complete AV block</td>
<td>ASD</td>
<td>Y/Y</td>
<td>I-F</td>
<td>I-F</td>
<td>?</td>
<td>secondary to ASD absent AV node</td>
</tr>
<tr>
<td>Lev 1971</td>
<td>1 case</td>
<td>-</td>
<td>C</td>
<td>CHB VT V F complete AV block</td>
<td>H</td>
<td>Y</td>
<td>FE+ C</td>
<td>FE+ C</td>
<td>?</td>
<td>disruption penetrating portion of the AV bundle: F+ FE+ C</td>
</tr>
<tr>
<td>Lev 1971</td>
<td>1 case</td>
<td>-</td>
<td>B</td>
<td>complete AV block</td>
<td>ASD</td>
<td>Y</td>
<td>FE+ C</td>
<td>FE+ C</td>
<td>?</td>
<td>disruption penetrating portion of the AV bundle: F+ FE+ C</td>
</tr>
<tr>
<td>Waxman 1975</td>
<td>28/6</td>
<td>?</td>
<td>A (&gt;40y)</td>
<td>pr. AV block &quot;abnormal QRS&quot; AF/VT SCD</td>
<td>+</td>
<td>SA node: F AV node: F His bundle: F</td>
<td>-</td>
<td>NA</td>
<td>AD</td>
<td>progressive F</td>
</tr>
<tr>
<td>Anderson 1977</td>
<td>1 case</td>
<td>-</td>
<td>B</td>
<td>CCHB</td>
<td>-</td>
<td>abnormal connection A and AV node / no RBB</td>
<td>NA</td>
<td>NA</td>
<td>case</td>
<td>abnormal anatomical development</td>
</tr>
<tr>
<td>Anderson 1977</td>
<td>1 case</td>
<td>?</td>
<td>IU</td>
<td>bradycardia IU CCHB small QRS frequent PVC's</td>
<td>ASD / F</td>
<td>abnormal connection A and AV node / no RBB</td>
<td>NA</td>
<td>NA</td>
<td>C</td>
<td>abnormal anatomical development</td>
</tr>
<tr>
<td>Reference</td>
<td>No of cases</td>
<td>sex</td>
<td>age of onset</td>
<td>ECG</td>
<td>abnormal anatomy heart</td>
<td>abnormal anatomy conduction system</td>
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<td>histology conduction system</td>
<td>inheritance</td>
<td>proposed mechanism</td>
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</tr>
<tr>
<td>Anderson 1973</td>
<td>1 case</td>
<td>☐</td>
<td>IU</td>
<td>bradycardia IU/ CCHB/ small QRS</td>
<td>Y</td>
<td>discontinuity AV junction and Ventricle</td>
<td>NA</td>
<td>NA</td>
<td>C</td>
<td>abnormal anatomical development</td>
</tr>
<tr>
<td>Stephan 1985</td>
<td>19/5</td>
<td>☐&gt;☐</td>
<td>A</td>
<td>RBBB+LA D/CHB/ progressive</td>
<td>none</td>
<td>none</td>
<td>F</td>
<td>Fibrosis</td>
<td>AD</td>
<td>Lev disease, progressive</td>
</tr>
<tr>
<td>Bezzina 2003</td>
<td>5/2</td>
<td>☐&gt;☐</td>
<td>B</td>
<td>broad complex tachycardia / atrial and ventricular conduction delay/SCD</td>
<td>VH+D</td>
<td>Y</td>
<td>FE+ C+ N+1</td>
<td>F</td>
<td>CH</td>
<td>W156X/ R225W SCN5A mutation/sec . to prog. degenerative process</td>
</tr>
<tr>
<td>Miller 1972</td>
<td>1 case</td>
<td>☐</td>
<td>IU/ B</td>
<td>complete AV block RBBB+LA HB RBBB+LP HB</td>
<td>Y</td>
<td>Y</td>
<td>FE</td>
<td>F+C</td>
<td>?</td>
<td>absent AV node/ no communicatio n atria-AV node</td>
</tr>
<tr>
<td>Schott 1998</td>
<td>4 families</td>
<td>☐&gt;☐</td>
<td>?</td>
<td>progressive AV block/16% AV block absent no structural heart defects/SD</td>
<td>cardiac septation defects</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
<td>mutation in homeobox transcription factor gene NKX2-5 (T178M, Q170ter)</td>
</tr>
<tr>
<td>Benson 1999</td>
<td>4 families</td>
<td>☐&gt;☐</td>
<td>?</td>
<td>1-3(\text{rd}) degree AV block, AV block principle finding in 23% of cases</td>
<td>cardiac septation defects</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
<td>mutation in homeobox transcription factor gene NKX2-5 (Q149ter, R186G, Y259ter and N188K)</td>
</tr>
<tr>
<td>Hosoda 1999</td>
<td>1 family</td>
<td>☐</td>
<td>AA</td>
<td>AV block/ AF with slow AV conduction</td>
<td>ASD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD ?</td>
<td>mutation in homeobox transcription factor gene NKX2-5 (Q198ter)</td>
</tr>
</tbody>
</table>
## Mechanisms of inherited cardiac conduction disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of cases</th>
<th>sex</th>
<th>age of onset</th>
<th>ECG</th>
<th>abnormal anatomy heart</th>
<th>abnormal conduction system</th>
<th>histology myocard</th>
<th>histology conduction system</th>
<th>inheritance</th>
<th>proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wanatabe* 2002</td>
<td>2 families (n=15 and 9)</td>
<td>?/?</td>
<td>?/A</td>
<td>1-3&lt;sup&gt;th&lt;/sup&gt; degree AV block/AF</td>
<td>cardiac septation defects</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>AD</td>
<td>mutation in homeobox transcription factor gene NKX2-5 (deletion)</td>
</tr>
<tr>
<td>Gollob 2001</td>
<td>1 family (n=10)</td>
<td>?</td>
<td>AA</td>
<td>AF and atrial flutter, high progressive high grade conduction disease</td>
<td>N</td>
<td>accessor bundle</td>
<td>?</td>
<td>?</td>
<td>AD</td>
<td>mutation in PRKAG2 gene encoding a protein kinase regulatory subunit (R531G)</td>
</tr>
<tr>
<td>Gollob 2001</td>
<td>2 families (n=69 and 23)</td>
<td>?</td>
<td>A</td>
<td>Brady-arrhythmia/SA, AV block progressive/affected individuals &gt;30yrs 76% need pacing</td>
<td>N</td>
<td>accessor bundle, hypertrophy (n=3)</td>
<td>?</td>
<td>?</td>
<td>AD</td>
<td>mutation in PRKAG2 gene encoding a protein kinase regulatory subunit (R302Q)</td>
</tr>
<tr>
<td>Fatkin 1999</td>
<td>5 families (n=11, 12, 7, 10 and 11)</td>
<td>?=?</td>
<td>A</td>
<td>SB, 1-3&lt;sup&gt;th&lt;/sup&gt; degree AV block/AF, PM</td>
<td>DCM</td>
<td>?</td>
<td>F/H</td>
<td>1 case F, fatty infiltration SA, AV node and AV bundle</td>
<td>AD</td>
<td>mutation in LMNA gene encoding lamin A/C (R60G, L85R, N195K, E203G and R571S)</td>
</tr>
<tr>
<td>Arbusini* 2002</td>
<td>5 families (n=25)</td>
<td>?=?</td>
<td>C/A</td>
<td>SB, 1-3&lt;sup&gt;th&lt;/sup&gt; degree AV block, PM</td>
<td>DCM</td>
<td>?</td>
<td>DCM</td>
<td>?</td>
<td>AD</td>
<td>mutation in LMNA gene encoding lamin A/C (K97E, E111X, R190W and 317K)</td>
</tr>
<tr>
<td>Reference</td>
<td>No of cases</td>
<td>sex</td>
<td>age of onset</td>
<td>ECG</td>
<td>abnormal anatomy heart</td>
<td>abnormal anatomy conduction system</td>
<td>histology myocard</td>
<td>histology conduction system</td>
<td>inheritance</td>
<td>proposed mechanism</td>
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</tr>
<tr>
<td>Sebillon* 2003 &quot;n</td>
<td>1 family (n=5)</td>
<td>A</td>
<td>1-3&lt;sup&gt;rd&lt;/sup&gt; degree AV block, AF, PM, SD</td>
<td>DCM</td>
<td>?</td>
<td>DCM</td>
<td>?</td>
<td>AD(?)</td>
<td></td>
<td>mutation in LMNA gene encoding lamin A/C (E161K and R377H)</td>
</tr>
<tr>
<td>Charniot*2003 &quot;n</td>
<td>1 family (n=12)</td>
<td>A</td>
<td>1-3&lt;sup&gt;rd&lt;/sup&gt; degree AV block, LBBB, (i)RBBB, PM, AF, SD</td>
<td>DCM</td>
<td>?</td>
<td>DCM/F/ H</td>
<td>?</td>
<td>AD</td>
<td></td>
<td>mutation in LMNA gene encoding lamin A/C (R377H)</td>
</tr>
<tr>
<td>Taylor* 2003 &quot;n</td>
<td>2 families (n=5)</td>
<td>A</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; degree AV block, AF, AES, VES, VT, SD</td>
<td>DCM</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>AD</td>
<td></td>
<td>mutation in LMNA gene encoding lamin A/C (G266T and C1718T)</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS** (Table 1,2 and 3)

**Column age of onset:** AA= all ages, A= adulthood, B= birth, C= congenital, IU=in utero. **Column ECG characteristics:** AF= atrial fibrillation, AF1= atrial flutter, AV= atrio-ventricular, CCHB= congenital complete heart block, CHB= complete heart block, IVF= idiopathic ventricular fibrillation, LAD= left axis deviation, LAF= left anterior fascicle, LAHB= left anterior hemiblock, LPF= left posterior fascicle, LPHB= left posterior hemiblock, PB=parietal block, PM=artificial pacemaker, PVC= premature ventricular complex, RBBB= right bundle branch block, SB= sinus bradycardia, SD= sudden death, TdP= Torsade des Pointes, VT= ventricular tachycardia, VF= ventricular fibrillation, WPW= Wolf-Parkinson-White syndrome. **Columns abnormal anatomy and histology heart, conduction system:** A= atrium, ASD= atrial septum defect, C= calcification, CTD= connective tissue disease, DCM= dilated cardiomyopathy F= fibrosis, FE= fibroelastosis, H= hypertrophy, I= inflammation, V= ventricle. **Column inheritance:** AD= autosomal dominant, C= case, CH= compound heterozygosity "additional 1 patient group with idiopathic 2<sup>nd</sup> or 3<sup>th</sup> degree AV block was studied for NKX2-5 mutations and a second group with Tetralogy of Fallot.**additional 16 individuals with a familial history of cardiomyopathies and 34 isolated cases were studied.** cases of CD (AV) occur without structural disease.
### Table 2. Patients with inherited cardiac conduction disease related to an SCN5A mutation

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of cases</th>
<th>sex</th>
<th>age of onset</th>
<th>ECG</th>
<th>abnormal anatomy heart</th>
<th>abnormal anatomy conduction system</th>
<th>histology myocardium</th>
<th>histology conduction system</th>
<th>inheritance</th>
<th>proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probst et al 2003</td>
<td>65/25</td>
<td>1&lt;2</td>
<td>=</td>
<td>RBBB, LPHB, LBBB, HBB/LAHB/LPB, HBB/PB, degree AV block, CHB</td>
<td>none</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
<td>SCN5A mutation: exon 22-deletion non-functional sodium channel</td>
</tr>
<tr>
<td>Tan et al 2001</td>
<td>10/5</td>
<td>1&lt;2</td>
<td>C</td>
<td>bradycardia AV-nodal escape, broad P, long PR, wide QRS</td>
<td>none</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
<td>SCN5A mutation G514C febrile illness induced</td>
</tr>
<tr>
<td>Shirai et al 2001</td>
<td>25 IVF cases; 1 patient</td>
<td>?</td>
<td>?</td>
<td>1st degree AV-block, Rate dependent RBBB, IVF</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>?</td>
<td>SCN5A mutation S1710L</td>
</tr>
<tr>
<td>Schott et al 1999</td>
<td>family 1: &gt;150, family 2: 6/3</td>
<td>?</td>
<td>1A, 2B</td>
<td>RBBB, LBBB, left anterior hemiblock, PR&gt;210</td>
<td>none</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
<td>SCN5A missence mutation/progressive</td>
</tr>
<tr>
<td>Schott et al 1999, Herfst et al 2003</td>
<td>9/5</td>
<td>1&lt;2</td>
<td>B</td>
<td>broad p-wave, 1st degree AV block, BBB</td>
<td>none</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
<td>missence SCN5A mutation 5280delG/trafficking defect no channels on the cell membrane</td>
</tr>
<tr>
<td>Valdivia et al 2002</td>
<td>1 case</td>
<td>?</td>
<td>B</td>
<td>2:1 AV block, QTc prolonged, TdP/SCD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>de novo mutation</td>
<td>M1766L SCN5A mutation reduced channel expression persistent Na</td>
</tr>
<tr>
<td>Bezzina et al 2003</td>
<td>5/2</td>
<td>1&lt;2</td>
<td>B</td>
<td>b</td>
<td>broad complex tachycardia atrial and ventricular conduction delay, SCD</td>
<td>VH+D</td>
<td>Y</td>
<td>FE+C N+1</td>
<td>F</td>
<td>CH</td>
</tr>
<tr>
<td>Reference</td>
<td>No of cases</td>
<td>sex</td>
<td>age of onset</td>
<td>ECG</td>
<td>abnormal anatomy heart</td>
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<td>proposed mechanism</td>
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<tr>
<td>Wang et al. 2002</td>
<td>6/3</td>
<td>both</td>
<td>C</td>
<td>1(^{st}) degree incomplete AV block/ RBBB</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>?</td>
<td>SCN5A mutation D1595N/ I(_{Na}) reduced</td>
</tr>
<tr>
<td>Wang et al. 2002</td>
<td>1 case</td>
<td>?</td>
<td>C</td>
<td>2(^{nd}) 3(^{rd}) degree A-V block</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD(?)</td>
<td>SCN5A mutation G298S/ I(_{Na}) reduced</td>
</tr>
<tr>
<td>Viswanathan 2003</td>
<td>5/2</td>
<td>(\approx)</td>
<td>C</td>
<td>2(^{nd}) degree AV-block</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD(?)</td>
<td>SCN5A mutation T512I/ I(_{Na}) modification by SCN5A polymorphism mH558R</td>
</tr>
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<td>Groenewegen 2003</td>
<td>44/10</td>
<td>?</td>
<td>A</td>
<td>AS/ AV-block</td>
<td>none</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
<td>SCN5A mutation, D1275N isolated or combined with a connexin 40 polymorphism</td>
</tr>
</tbody>
</table>
### Table 3. Patients of inherited cardiac conduction disease of unknown origin

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of cases</th>
<th>sex</th>
<th>age of onset</th>
<th>ECG</th>
<th>abnormal anatomy heart</th>
<th>abnormal anatomy conduction system</th>
<th>histology myocard</th>
<th>histology conduction system</th>
<th>inheritance</th>
<th>proposed mechanism</th>
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<tr>
<td>Brink 1977, 1995; van der Merwe 1986</td>
<td>1 family 55/31 investigated</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>none</td>
<td>none</td>
<td>AD</td>
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<td></td>
<td></td>
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<td>Sarachck 1972</td>
<td>43/15</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<td>NA</td>
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<td>AD</td>
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<td>Gazex 1965</td>
<td>35/11 (8 documented with ECG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>AD</td>
<td>unknown</td>
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- RBBB: Right Bundle Branch Block
- LAD: Left Anterior Descending
- RAD: Right Anterior Descending
- CHB: Complete Heart Block
- SCD: Sudden Cardiac Death
- NA: Not applicable
- AD: Autosomal Dominant
- IH: Inheritance
- IU: Individual
- "": undefined
<table>
<thead>
<tr>
<th>Reference</th>
<th>No of cases</th>
<th>Sex</th>
<th>Age of onset</th>
<th>ECG</th>
<th>Abnormal anatomy heart</th>
<th>Abnormal anatomy conduction system</th>
<th>Histology myocard</th>
<th>Histology conduction system</th>
<th>Inheritance</th>
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<tr>
<td>Simonsen <strong>1970</strong></td>
<td>30/5</td>
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<td>SR, bradycardia 1-2-3th degree AV-block LBBB/ RBBB</td>
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<td>ab</td>
<td></td>
<td>C</td>
<td>CCHD</td>
<td>1 case Y</td>
<td>1 case Y</td>
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<td>ab</td>
<td></td>
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<td>AV-disassociation CHB/ RBBB/ SCD</td>
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<td>-</td>
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<td>-</td>
<td>AD</td>
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<tr>
<td>McCue <strong>1977</strong></td>
<td>22 (4*)</td>
<td>ab</td>
<td></td>
<td>C</td>
<td>CCHB</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>?</td>
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<td>Winkler <strong>1977</strong></td>
<td>11/4</td>
<td>ab</td>
<td></td>
<td>A/C</td>
<td>bradycardia AV block, CHB, RBBB, LBBB</td>
<td>+ CTD associated cases</td>
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<td>I/C CTD associated cases</td>
<td>NA</td>
<td>?</td>
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<td>Veracochca <strong>1967</strong></td>
<td>8/3 (3+ cases)</td>
<td>ab</td>
<td></td>
<td>B</td>
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<tr>
<td>Esscher <strong>1975</strong></td>
<td>9/20</td>
<td>ab</td>
<td></td>
<td>B</td>
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<td>none</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
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<tr>
<td>Balderston <strong>1989</strong></td>
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<td></td>
<td>C</td>
<td>AV block/ CHB/LBBB pattern</td>
<td>none</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>AD</td>
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</table>

Note: Abnormal anatomy heart includes: SR, bradycardia 1-2-3th degree AV-block LBBB/ RBBB. ECG refers to specific cardiac conduction system abnormalities. Histology refers to myocardial and conduction system characteristics. Inheritance categories include AD (autosomal dominant), AR (autosomal recessive), and X-linked. Proposed mechanisms include genetic, structural, non-structural, and progressive.
4.0 HISTORY

4.1 Historical description of cardiac conduction disease
Without actual electrical recordings we are left guessing at the mechanisms of what are the first descriptions of ‘fainting spells’. It was not until the beginning of the 20th century that the development of the electrocardiogram by Willem Einthoven (1860-1927) made electrical recordings of impulse conduction through the heart possible. Giovanni Battista Morgagni (1682-1771), however, was probably the first to link recurring fainting episodes in a man to a simultaneously observed slow pulse rate. In the 19th century first Robert Adams (1827) and later William Stokes (1854) made similar observations. The first known report of an Adams-Stokes attack combined with ECG recordings came from van den Heuvel who described a case of congenital heart block. Lenegre and Lev combined clinical observations, ECG recordings and detailed post mortem studies of the heart, whereby they proved their direct relationship in the 1960’s. The names Lenegre and Lev have since thenceforth become synonymous with (progressive) cardiac conduction disease. Electrocardiographically, both Lenegre and Lev disease are characterized by chronic conduction delay through the His-Purkinje system, resulting in partial or complete AV-block and right or left bundle branch block. In both diseases a sclerodegenerative process causes fibrosis of the His-Purkinje fibers. The severity and extent of the fibrosis in either disease, however, is different. In Lenegre disease, a diffuse fibrotic degeneration is limited to the conduction fibers, while in Lev disease the sclerodegenerative abnormalities affect both the specialized conduction system and the fibrous skeleton of the heart. An inherited component may be involved in both diseases. However, particularly Lev disease may be a variation of the normal aging process.

4.2 Congenital or inherited abnormalities in cardiac conduction
The recognition that CCD can be as well inherited as acquired, dates from the beginning of last century. In 1901 Morquio described, what was probably congenital complete atrioventricular block in a family. The disease was evidenced by syncopal periods with slow pulse rates. Congenital heart block was at that time already reported in new-borns from mothers suffering from connective tissue diseases. Other, early recognized causes for congenital CCD are infectious diseases such as diphtheria, rheumatic fever and congenital syphilis. Due to the absence of electrocardiographical, or histological analysis, exact diagnosis is difficult in these early cases of congenital CCD.
The discovery of gene mutations that are causally involved in inherited CCD are relatively recent. Nowadays for example, mutations have been found in genes encoding (transcription) factors that regulate cardiac morphogenesis. Such mutations cause inherited CCD due to, or in combination with, cardiac malformations. Similarly, mutations have been found in inherited non-structural CCD, often encoding cardiac ion channel proteins. Some genes involved in nonstructural inherited CCD, however, remain to be identified. A good example are two reports from 1977 on two types of progressive congenital or familial heart block (PFHB), type I and II, among families in South Africa. In 1995, PFHB type I was linked to a gene located on chromosome 19q13.2-q13.3. This discovery proved the inherited nature of the disease but the pathophysiological mechanism, the affected protein and the genetic defect have not been identified yet.

5.0 STRUCTURAL CCD

In case of structural CCD, anatomical abnormalities underly the impairment of normal impulse propagation. This concerns macro- or microscopical structural abnormalities that may occur at any level in the conduction system. The structural abnormalities, as mentioned, may range from partial or total absence of structures to gradual replacement by fatty and/or fibrous infiltration and calcification. In many reports, the term structural heart disease is reserved for overt anatomical abnormalities of the heart and does often not include the specialized conduction system, which is often not studied (Tables 1-3). Therefore, hearts that are considered to be structurally normal may still have histological abnormalities, such as focal myocarditis or segmental cardiomyopathy. Structural CCD may be either congenital or inherited (Figure 2).

5.1 Structural CCD of congenital nature

The causes of congenital structural CCD are many, they can be part of a syndrome and be associated with abnormalities in other organ systems. For example, anatomical heart defects may occur in chromosomal disorders like Down, Edward’s, Pateau or Turner syndrome. Although congenital anatomical heart defects frequently occur in these and other chromosomal disorders, still in the majority of cases no chromosomal abnormalities can be found. Other causes for structural heart disease may be the intra-uterine exposure to infectious agents or toxic agents (e.g. nicotine, drugs). As mentioned before, infectious diseases like diphtheria, syphilis and rheumatic fever had a significant role in congenital CCD
Mechanisms of inherited cardiac conduction disease

in the past. Although nowadays relatively less frequent, viral and bacterial infectious diseases still have a role in congenital CCD. Finally, another important cause of congenital structural CCD, is intra-uterine exposure to maternal auto-antibodies. Because the structural abnormalities in these cases may be very subtle or even absent, the underlying mechanism will be considered separately below (5.1.1).

5.1.1 Autoimmune mechanisms

Autoimmune diseases can affect the whole cardiovascular system including the cardiac conduction system. CCD in autoimmune disease may be secondary to myocarditis
because of inflammation and infiltration, as in Systemic Lupus Erythematosus (SLE), scleroderma and polymyositis. Vasculitis and oblitative endarteritis are examples of autoimmune diseases that indirectly affect the myocardium by causing ischaemia. Cardiac conduction may be affected to a variable degree in the various autoimmune diseases. In HLA-B27 associated diseases for instance, such as the seronegative spondylarthropathies, CCD is of frequent occurrence although structural abnormalities may be absent (see also paragraph 6.2.2) In this latter group the conduction abnormalities usually consist of A-V block, sinus node disease and bradycardia. These abnormalities can be irreversible or intermittent. The latter argues for a reversible, functional, inflammatory process rather than permanent fibrosis. (see 6.2.2)

5.2 Structural CCD of inherited nature

5.2.1 Septation defects

Mutations have been identified in familial forms of cardiac malformations. These mutations have been found in genes encoding proteins that regulate septation of the heart, resulting in atrial septum defects (ASD) or ventricular septum defects (VSD). Mutations in TBX5, a T-box transcription factor, have been identified in patients suffering from Holt-Oram syndrome. This autosomal inherited syndrome is characterized by cardiac septation defects and extra-cardiac abnormalities. Sometimes, mutation carriers have CCD and atrial fibrillation in the absence of septation defects. Mutations in NKX2.5, encoding a homeobox transcription factor, have been found in cases of familial ASD without extracardiac abnormalities (Table 1). Although the initial description was in individuals with autosomal inherited ASD and progressive AV block, it now seems that the clinical spectrum may be more diverse, including also VSD and tetralogy of Fallot. Finally, a number of familial cases of cardiac septation defects with progressive AV block have been diagnosed in which the involved proteins and genes still await identification.

5.2.2 The cytoskeleton

Mutations in genes encoding cytoskeletal proteins and nuclear membrane proteins have been found to be causally involved in inherited cardiomyopathies and muscular dystrophies (Table 1). An intact cytoskeleton is required for proper myocyte structure and is additionally involved in cell signalling processes.

Cardiac arrhythmias and conduction disease are common in patients suffering from muscular dystrophies and dilated cardiomyopathies (DCM). Mutations in the LMNA gene, encoding laminin, have been described to be causally involved in autosomal dominant Emery-Dreifuss
muscular dystrophy, as well as in families with DCM and severe cardiac conduction defects without skeletal muscle involvement. In these latter families, however, some individuals had severe conduction abnormalities in the absence of DCM or other clinically identified structural heart disease. In these patients CCD probably precedes the development of DCM.

5.2.3 Protein kinase disorders

Recently a mutation (R302Q) in the PRKAG2 gene, which encodes for a regulatory subunit (γ-2) of adenosine monophosphate-activated protein kinase (AMPK), has been described (Table 1). This mutation was found in patients with the Wolff-Parkinson-White (WPW) syndrome, a disease characterized by ventricular preexcitation, atrial fibrillation and conduction defects. In 76% of the carriers of the R302Q mutation, in addition to preexitation, conduction disease was found, such as SA- and AV-block. Hypertrophy was found in 26 percent of the mutation carriers. Mutations in the PRKAG2 gene thus cause structural heart disease, such as accessory conduction pathways between the atrial and ventricular myocardium, and cardiac hypertrophy.

6.0 FUNCTIONAL CCD

Functional CCD we defined as CCD without any structural, anatomical or histological abnormalities of the myocardium and its conduction system. In these circumstances the detrimental effects on cardiac conduction are usually due to altered function of cardiac ion channels or associated proteins, similar to the primary electrical diseases of the heart among which inherited CCD. Like in structural CCD, we can distinguish acquired, congenital and inherited forms. Isolated CCD may precede other disease symptoms and in some cases functional CCD may be the first symptom of a disease that eventually will result in structural damage to the heart.

6.1 Acquired forms of functional CCD

Acquired functional CCD may be induced by several drugs, especially antiarrhythmic and anaesthetic drugs, and their effects are reversible. Additionally, there are several naturally occurring toxins, which may affect conduction. The working mechanism of these toxins on conduction is often through a direct effect on ion channel function. Disturbances of ion concentrations in intra- or extracellular fluids may additionally be a cause of CCD.
6.2 Functional CCD of congenital nature

6.2.1 Autoimmune mechanisms

Next to the inflammatory mechanism giving rise to structural forms of CCD in autoimmune diseases, there may also be a functional component in neonates born from mothers suffering from SLE or other connective tissue diseases.\textsuperscript{56-59} Namely, in a number of cases, the congenital heart block may be transient and regress when the maternal IgG antibodies are washed out.\textsuperscript{56-59} Usually these individuals have a 1\textsuperscript{st} degree A-V block combined with sinus bradycardia. Maternal SSA/Ro and/or SSB/La (IgG) antibodies that cross the transplacental membrane and enter the foetal circulation underly this CCD.\textsuperscript{56-59} In order to elucidate the mechanism, Boutjdir et al. retrogradely perfused a human fetal heart on a Langendorff perfusion system with purified IgG antibodies from a mother who gave birth to a child with CCD and who was diagnosed with SLE. In this system they were able to induce a partially reversible but total A-V block.\textsuperscript{57} Similar results are obtained in different animal experimental models.\textsuperscript{56} It is postulated that the block is due to modification of the L-type calcium channels in foetal A-V node myocytes by maternal IgG antibodies.\textsuperscript{59} Although the number of cases where functional CCD in these children is involved is limited, it is worthwhile to consider its role because it may present a pharmacological treatable form of CCD.

6.3 Functional CCD of inherited nature

6.3.1 Protein kinase disorders

Recently a missense mutation (R531G) and another constitutively active mutation (T172D) in the PRKAG2 gene have been described in patients with WPW syndrome.\textsuperscript{70} In contrast to the R302Q mutation in the PRKAG2 gene (paragraph 5.2.2.),\textsuperscript{59} carriers of these two mutations did not have cardiac hypertrophy but did have sinoatrial or atrioventricular block.\textsuperscript{70} Because these mutations occur in the gene encoding the γ2 regulatory subunit of AMP-activated protein kinase, they may have an effect on cardiac conduction by affecting the phosphorylation state of several cardiac ion channels,\textsuperscript{71} as has been shown for the T172D mutation. This mutation affected the inactivation properties of the human cardiac sodium channel in a cell expression model. In addition, AMPK has been shown to be a modifier of other human ion channels besides the cardiac sodium channel.\textsuperscript{71}

6.3.2 Fatty acid oxidation disorders

Fatty acid oxidation disorders are inborn errors of metabolism that affect normal transport and metabolism of fatty acids due to enzymatic defects.\textsuperscript{72} The heart is one of the organs that may be affected and cardiomyopathy with conduction and rhythm abnormalities may be one of the
Mechanisms of inherited cardiac conduction disease

presenting symptoms. Fatty acid oxidation disorders can also present as conduction disease and atrial arrhythmias, without structural heart disease. Usually these patients have defects in enzymes that regulate mitochondrial transport of long-chain fatty acids (carnitine palmitoyl transferase type II, carnitine-acylcarnitine translocase). The pathophysiology of conduction disease and other clinical features in fatty acid oxidation disorders, results from accumulation of fatty acid metabolites downstream from the enzyme defect. The long chain fatty acid metabolites accumulating in these enzyme defects may be toxic to myocytes, but additionally they may affect ion channel proteins. They have been shown to reduce the inward rectifying K⁺ and depolarizing Na⁺ current, to activate Ca²⁺ channels, and to impair gap-junction hemi-channel interaction. With the exception of the effects on Ca²⁺ channels, these alterations negatively affect conduction in the heart. Since multiple types of ion currents are simultaneously affected, they may deliver a substrate for cardiac arrhythmias. These disorders are rare, and probably underestimated, but present a potentially treatable cause of childhood arrhythmias and conduction disease.

6.3.3 The cytoskeleton

Sometimes the first and most prominent symptom of inherited cardiomyopathy or muscular dystrophy is isolated CCD, without or before the development of detectable structural cardiac abnormalities. It may be speculated that in these cases, mutations in cytoskeletal proteins directly or indirectly, alter ion channel function. Some recent studies that show the association of ion channel and cytoskeletal proteins, support this view. That is, the intracellular located protein γ-syntrophin, associates and interacts with the pore forming α-subunit of the cardiac sodium channel, thereby regulating its membrane expression and gating behaviour. As mentioned previously, this ion channel is vital for normal cardiac conduction. Syntrophin additionally associates with the cell-membrane associated proteins dystrophin and ankyrin, the latter are known to interact with the modulatory β-subunits of rat brain voltage gated sodium channels. β-Subunits are small transmembrane proteins that have extracellular regions which interact with extracellular matrix proteins. Disruption of cytoskeletal organization may therefore be involved in abnormalities of cardiac conduction, as well arising from structural as from functional malfunctioning. Inversely, these interactions may additionally explain why in some cases of sodium channel mutations, exaggerated fibrosis is found, probably resulting from abnormal function or expression of sodium channels. The role of the cytoskeleton in electrical diseases of the heart was
additionally convincingly proven by the identification of a loss-of-function mutation in ankyrin in the long QT syndrome type 4.\textsuperscript{10}

6.3.4 Mutations in the SCN5A gene

The first and as yet only gene that has been found to play a role in functional familial CCD is SCN5A, encoding the α-subunit of the cardiac sodium channel (hH1).\textsuperscript{32-44} In 1999 in one family with progressive CCD and in another with non-progressive CCD, a causal relationship was found with two different mutations in the SCN5A gene.\textsuperscript{32} Both these mutations resulted in non-functional human cardiac sodium channels. Carriers of these mutations are thus expected to have only 50\% of the normally available sodium channels, namely those encoded by their normal allele. Consequently, a considerable reduction in depolarizing sodium current is to be anticipated, which will give rise to a slowing of conduction. Other mutations in the SCN5A gene involved in CCD alter the function of sodium channels. These mutations usually reduce the cardiac sodium current by reduction of their membrane expression, probably through actions of the quality control system in the endoplasmatic reticulum of the cell, or by a changing the gating properties of the channel.\textsuperscript{3}

Presently 11 SCN5A mutations have been published that are causally related to inherited cardiac conduction disease.\textsuperscript{32-44} Combinations of SCN5A mutations and degenerative abnormalities have however also been reported and it is likely that such combinations will be present in ageing SCN5A mutation carriers as well (6.3.3).\textsuperscript{36}

6.3.5 Polymorphisms in the connexin gene

Connexins are the building blocks of gap junction channels that functionally and electrically connect cardiac myocytes.\textsuperscript{7,9} They are responsible for coupling and current conduction between neighbour myocytes.\textsuperscript{7,9} Presently only one polymorphism in the atrial connexin40 gene has been identified in familial atrial standstill and CCD. These patients additionally carried an SCN5A mutation (D1275N) that reduced Na-current.\textsuperscript{38}

7.0 RELATIONSHIP BETWEEN PATHOPHYSIOLOGICAL MECHANISM UNDERLYING CCD AND CLINICAL PHENOTYPE

Comparison of the clinical symptoms that accompany structural or functional CCD respectively, reveal some (small) differences that relate to the age of clinical manifestation, the extent of the disease, and the incidence of arrhythmias.
7.1 Age of clinical manifestation

Symptoms of structural congenital CCD due to anatomical defects of the heart and the conduction system, such as those found in chromosomal disorders and septation defects due to mutations in transcription factor genes, may already be present in utero or at birth. However, in the great majority of the reports where these defects were found to be causally related to mutations in *PRKAG2*, *NKX2-5*, or *LMNA*, the disease is recognized at an adult age (Table 1). Presenting symptoms may therefore be due to the structural cardiac abnormalities (e.g., shunting) or due to conduction abnormalities. Symptoms of congenital CCD caused by sclerodegenerative abnormalities, e.g., due to the autoimmune mechanism, are often already present at an early age. Functional congenital CCD, on the other hand, may be incompatible with life or becomes evident early in life (Table 2). However, in one report on CCD associated with a reduction in $I_{Na}$ due to a mutation in *SCN5A*, symptoms of CCD appeared only later in life. On the basis of this report we may speculate that a reduction in available functional sodium channels, and the consequent reduction in $I_{Na}$, can probably be tolerated to some extent. The effects of a reduction in $I_{Na}$ may therefore sometimes not become evident until a later age, when conduction in the heart becomes impaired because of the naturally occurring aging process. Interestingly the normal ageing process usually involves sclerosis, although evidence is emerging that sclerosis is enhanced in carriers of loss-of-function *SCN5A* mutations.

7.2 Extent of the disease

In structural CCD, the conduction abnormalities are often localized to a specific part of the specialized conduction system. Obviously, in CCD associated with chromosomal disorders or mutations in transcription factor genes, conduction problems are limited to the part of the specialized conduction system involved in the septation defect. Symptoms of congenital CCD caused by sclerodegenerative abnormalities, e.g., due to the autoimmune mechanism, are mostly restricted to the AV-nodal region. The only exception upon this, forms the group of DCM due to *LMNA* mutations, in which the atria, the bundle of His, the bundle branches and the working myocardium are affected.

If we consider the group of purely functional CCD, without structural abnormalities, than this group is mainly represented by cases of CCD due to *SCN5A* mutations. Cardiac conduction seems to be more generally impaired in reports where an *SCN5A* mutation is involved. This is to be expected in view of the fact that the cardiac sodium channel is present and functional
throughout all regions of the heart. A mouse model with a loss-of-function SCN5A mutation, nicely supports this view. Mice homozygous for the mutation display in vivo impaired atrioventricular conduction and preparations of the isolated hearts show impaired atrioventricular, delayed intramyocardial conduction and increased ventricular refractoriness. Besides these abnormalities, ventricular tachycardia due to reentry occurred in the isolated hearts.

7.3 Cardiac arrhythmias
Because of the limited information and the low number of patients in many of the clinical reports, a statement about the incidence of arrhythmias with relation to structural or functional CCD, is precarious. The occurrence of tachy-arrhythmias and sudden cardiac death (SCD), may be expected to be more frequent in patients with CCD that carry loss of function SCN5A mutations, comparable to patients with SCN5A-associated idiopathic VF and Brugada syndrome. Evaluation of tables 1 to 3 shows that this difference is not as clear as expected. In the 26 reports on structural CCD (Table 1) SCD is reported 8 times and in 6 cases (dilating) cardiomyopathy is involved. Atrial arrhythmias are reported 10, and ventricular arrhythmias 3 times (Table 1). In the 11 reports on CCD in the presence of an SCN5A mutation (Table 2) SCD is reported 2 times and ventricular arrhythmias 3 times. Among the 16 reports of congenital CDD of unknown cause (Table 3), SCD is reported 6 times, of which 5 times due to complete heart block. In this group atrial or ventricular arrhythmia (broad complex tachycardia of unknown origine) is reported once. Thus, from these numbers cardiac arrhythmias do not seem to be more frequent among patients with functional CCD due to SCN5A mutations.

8.0 CONCLUSION
In congenital CCD there are two pathophysiological pathways, a structural and a functional. Each pathway can be further divided in inherited, congenital or acquired pathophysiological mechanisms (Figure 2). Structural and functional CCD are two mechanistically different diseases which may however have some overlap. Reduced sodium current due to mutations in the SCN5A gene, encoding the cardiac sodium channel, is the most important mechanism in congenital CCD without structural abnormalities and may already be symptomatic at an early age. Additionally, this mechanism may be involved in congenital CCD associated with abnormalities of the cytoskeleton of the heart.
Mechanisms of inherited cardiac conduction disease

More detailed knowledge of the function of the cardiac sodium channel, by studying inherited electrical disorders like congenital CCD, may enable us to develop a pharmacological treatment for this form of congenital CCD. Additionally it may enable us to develop drugs to treat other cardiac diseases that are caused by loss-of-function \( SCN5A \) mutations. Until than the treatment for \( SCN5A \) related CCD is pacemaker implantation, as in other forms of CCD. Due to the fact that the whole myocardium may be affected in \( SCN5A \) related CCD pacemaker treatment may, however, be less successful in these circumstances.\(^{33}\)

Hence for both treatment and scientific purposes, an accurate, genetic diagnosis in inherited CCD is important.

ACKNOWLEDGEMENTS

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