The clinical and electrophysiological spectrum of cardiac sodium channel mutations
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CHAPTER 3.2

GENOTYPE-PHENOTYPE RELATIONSHIP IN BRUGADA SYNDROME

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INTRODUCTION

In their initial report in 1992, on the disease that is now known as the Brugada syndrome, Pedro and Joseph Brugada mentioned concerning its etiology that “a hereditary factor could be suspected from the occurrence of the syndrome in two siblings and the family history of unexplained sudden death in two other patients”.

Since then, the inherited nature of the Brugada syndrome has been convincingly established and was proven in 1998 by linking the syndrome to mutations in the $SCN5A$ gene on chromosome 3p21 (table 1). However, in only 15-30% of Brugada syndrome cases and families a mutation in the $SCN5A$ gene has been found. In one family, the syndrome has been linked to a locus on chromosome 3, 3p22-25, however, the affected gene awaits identification (table 3). In the remaining cases of Brugada syndrome, although many of them familial, no responsible gene or chromosome has been identified yet.

Because the $SCN5A$ gene encodes the pore forming α-subunit of the cardiac sodium channel (h11), and the fact that the resulting reduction in depolarising sodium current theoretically explains the Brugada syndrome phenotype, the syndrome is considered an ion channel disease. Whether this is true for all Brugada syndrome cases, remains to be established, but it is our current working hypothesis.

Knowing that other genes have to be involved, we may wonder if a genotype-phenotype relationship in Brugada syndrome exists, as in the inherited Long QT syndrome. If such a relationship exists, knowledge of it may speed up a clinical and genetic diagnosis. Additionally, it may have consequences for mutation specific prognosis, treatment and possibly of identification of pro-arrhythmic effects of drugs and/or environmental triggers.

However, before such possibilities might become available, we will first have to identify those other genes. Isolation of those genes may be possible if we carefully look at Brugada syndrome patients and families and search for what may be minute phenotypical differences between them. What these phenotypical differences may be, considering the theoretical basis for the Brugada syndrome, the involved genes and proteins, will be discussed in the following sections.
FACTORS THAT ARE THEORETICALLY INVOLVED IN THE BRUGADA SYNDROME

**Ion currents**

The cardiac action potential is shaped by balanced and strictly regulated depolarising and repolarizing ion currents traversing through and controlled by ion selective transmembrane channels. In general, ion channels consist of a transmembrane, pore forming, α-subunit which may co-express with one or more modulator β-subunit(s) 8.

The action potential (AP) shape in different regions of the heart and myocardium depends on the ion currents that are present and reflects differences in functional requirements 8. Changes in ion currents and AP shape may underlie changes of the ECG and abnormalities in cardiac conduction and rhythm. The proposed pathophysiological basis for the Brugada syndrome is a rebalancing of the currents that contribute to phase 1, leading to an accentuation of the action potential notch in right ventricular epicardium 5. The presence of a prominent $I_{TO}$ in this tissue makes it more sensitive to a reduction in depolarising currents, such as $I_{Na}$ during phase 0 (the rapid upstroke) or $I_{Ca-L}$ during phase 2 (the plateau phase). Thus, reduction of depolarising ion currents, $I_{Na}$ and $I_{Ca-L}$, or increase in early repolarising ion current, $I_{TO}$, during the early phase of the cardiac action potential due to abnormal expression or function, may give rise to the Brugada syndrome phenotype. In table 1, the genes and the chromosomal locations of the α- and β-subunits of depolarising and repolarising ion currents involved in rapid depolarisation, early repolarisation and the plateau phase of the cardiac action potential, are summarized.

Presently, all $SCN5A$ mutations in Brugada syndrome have been found to encode non-expressing or totally or partially dysfunctional sodium channels, resulting in a reduction in $I_{Na}$.

**Modulatory subunits**

Modulatory subunits of cardiac ion channels may importantly affect the function of the pore forming subunit of the ion channel (table 1). The presence of modulatory subunits may be needed for channel assembly, trafficking and membrane expression 8. Finally, β-subunits may associate with the pore forming α-subunit in the cell membrane and modulate its function. In the Brugada syndrome, no mutations have been found in genes that encode β-subunits.

A potential role for the Na$^+$ channel β-subunit is, however, evidenced by the fact that the β1-subunit of the cardiac sodium channel modifies the effects of mutations in the α-subunit, and it possibly has a role as a chaperone protein for the Na$^+$ channel α-subunit 9,10.
Table 1. Ion currents, their subunits, encoding genes and chromosome location

<table>
<thead>
<tr>
<th>Current</th>
<th>Gene</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na}$</td>
<td>$SCN5A$</td>
<td>3p21</td>
</tr>
<tr>
<td>$I_{Na}$</td>
<td>$β_i$ ($SCN1B$)</td>
<td>19q13.1-q13.2</td>
</tr>
<tr>
<td>$I_{Na}$</td>
<td>$β_o$ ($SCN2B$)</td>
<td>11q23</td>
</tr>
<tr>
<td>$I_{cav}$</td>
<td>$α_i$ ($CACNL1A1$)</td>
<td>12pter-p13.2</td>
</tr>
<tr>
<td>$I_{cav}$</td>
<td>$β_i$ ($CACNB1$)</td>
<td>17q21-q22</td>
</tr>
<tr>
<td>$I_{cav}$</td>
<td>$β_o$ ($CACNB2$)</td>
<td>10q12</td>
</tr>
<tr>
<td>$I_{cav}$</td>
<td>$α_oβ$ ($CACNA2D1$)</td>
<td>7q21-22</td>
</tr>
<tr>
<td>$I_{to}$</td>
<td>$Kv4.3$ ($KCND3$)</td>
<td>1p13.2</td>
</tr>
<tr>
<td>$I_{to}$</td>
<td>kChip2 ($KCNIP2$)</td>
<td>10q24</td>
</tr>
</tbody>
</table>

**Ion channel expression**

Expression of hH1 in the surface membrane of the myocyte is not a random process, but is guided by intracellular proteins. The C-terminus of Na⁺ channels from several different tissues interacts with the PDZ domain of syntrophin, a protein in the dystrophin-associated protein complex, directing Na⁺ channels to specific sites on the membrane. Mutations in PDZ domains may therefore be expected to disrupt this interaction and proper channel expression. The recently resolved mechanism of the long QT syndrome type 4 illustrates the role of the cytoskeleton in ion channel expression. In a family suffering from LQT4, a loss of function mutation in the gene encoding ankyrin B was found. Through ankyrin, the spectrin-actin cytoskeleton of cells connects with ion channels, and other ion transporting proteins, anchoring it to the cell membrane.

In a heterozygous mouse model of this mutation, several cardiac ion pumps were affected, due to abnormal protein localization and reduced expression levels. Mutations in proteins regulating ion channel expression, which may be a role for β-subunits, would therefore be a
possible cause for reduced expression of \( \text{Na}^+ \) channels, and other ion channels in Brugada syndrome.

**Ion channel modification**

While in the ER, and when expressed in the cell membrane, ion channel function will be affected by processes such as (de)glycolysation\(^{14} \), (de)phosphorylation\(^{14,15} \). These processes may affect sodium channel expression, and also channel gating properties\(^{16} \).

Direct modification of ion channel function by protein-protein interaction has recently been shown for hH1, by binding of calmodulin (CaM)\(^{16} \) to it in a \( \text{Ca}^{2+} \) dependent manner\(^{17} \). Due to the binding of CaM, gating properties of hH1 changed, enhancing slow inactivation. Because CaM is an intracellular \( \text{Ca}^{2+} \)-sensing protein, the intracellular \( \text{Ca}^{2+} \) concentration therefore affects sodium channel function\(^{17} \). This and similar mechanisms may be very well involved in Brugada syndrome.

**Potential parameters that may reflect a genotype-phenotype relationship in Brugada syndrome**

Parameters that may reflect a genotype-phenotype relationship may be similar to those in the long QT syndrome. In the long QT syndrome, these parameters are: the presenting symptoms, the age at which the first symptoms occur, the triggering event, and the ECG morphology\(^{6,7} \). All these parameters are easily available.

Presently, the only known parameters, discriminating two genotypically different groups in Brugada syndrome, are those related to cardiac conduction\(^{18} \).

**Demographic characteristics**

Although Brugada syndrome is an autosomal inherited disease, it affects males 8-10 times more than females\(^{3} \). The male predominance probably reflects the gender differences in expression of I\(_{\text{TO}}\) and I\(_{\text{Ca-L}}\)\(^{19,20} \). An increase in I\(_{\text{TO}}\) or a reduction in I\(_{\text{Ca-L}}\) may theoretically alter the normal AP, similarly to a reduction in I\(_{\text{Na}}\). When such alterations occur, for example due to mutations in the genes encoding I\(_{\text{TO}}\) and I\(_{\text{Ca-L}}\), this must have a different effect on male or female carriers. The observation that surgical castration in males alleviates ST-segment elevation suggests that male hormones also play a role\(^{21} \).

In the long QT syndrome age-related, genotypical differences have been well established\(^{6,7} \). The mean age for a first arrhythmic event to occur in the Brugada syndrome is approximately 40 years (range: 1 to 77 years)\(^{3} \). Presently, neither gender nor age at the moment of the first arrhythmic event has been found to distinguish a specific group of Brugada syndrome patients from each other.
Clinical characteristics

Triggering events

Similarly to the congenital long QT syndrome, differences in the genes underlying the disease may theoretically result in different arrhythmia triggers. Presently, two triggers are known to unmask the typical ECG and induce arrhythmias: these are sleep and fever. Whether the rise in body temperature, the changes in the (humoral) immune system, or both, trigger symptoms, is not known. Until now, no remarkable differences in triggers between Brugada syndrome patients or families have been established.

ECG characteristics

In the inherited long QT syndrome, the morphology of the T-wave and QTc-duration are genotype-specific\(^6\). A similar relationship for the Brugada syndrome is possible, because the shape of the ST-segment is critically dependent on the magnitude and timing of the balance of ion currents\(^8\). Two different shapes of the ST-segment are recognised, the coved and the saddle back type. The magnitude and shape of the ST-segment shows considerable intra- and inter-individual variation. Patients may show spontaneous ST-segment changes in time, the abnormalities may become aggravated or may normalize. Inter-individual variation in the ST-segment abnormalities can frequently be observed between family members who carry the same SCN5A mutation. Both the intra- and inter-individual ST-segment variation may reflect normal and abnormal modification of ion channels. These spontaneous variations will make the establishment of a genotype-specific ST-segment unlikely. In a recent report, the magnitude of the spontaneous ST-segment elevation was not found to be different between carriers of SCN5A mutations as compared to non-mutation carriers\(^18\).

Abnormalities in ion channel function or expression will not only affect the morphology of the ST-segment, but also other electrical properties of the heart, for example conduction. Loss of function mutations in the SCN5A gene, as in the Brugada syndrome (table 2)\(^23\)-\(^34\), have been identified in patients suffering from inherited cardiac conduction disease (ICCD) (table 4)\(^25\),\(^29\),\(^30\),\(^35\)-\(^39\). SCN5A mutations in ICCD reduce the sodium current due to trafficking or gating defects of the channel. The functional differences between sodium channel dysfunction in Brugada syndrome and ICCD is often not easy to understand. Two SCN5A mutations, G1406R\(^25\) and S1710L\(^29\),\(^30\), have been reported to result in both an ICCD and a Brugada syndrome phenotype. The phenotype of carriers of the G1406R mutation was gender-dependent. All Brugada syndrome patients were male, and all but one (6 out of 7) ICCD patients were female\(^25\). In addition to these two mutations, conduction abnormalities are often reported in Brugada syndrome patients.
The first report on a phenotype-genotype relationship in the Brugada syndrome stems from this observation. In this report, 23 Brugada syndrome patients, with 19 different SCN5A mutations, were compared to 54 Brugada syndrome patients in whom an SCN5A mutation had been excluded. The SCN5A mutation carriers were found to have significantly longer PQ-intervals on their 12-lead ECG and longer His-to-Ventricle (HV) intervals during EPS (Figure 1). Therefore, it was concluded that the presence of impaired conduction in a Brugada syndrome patient points to an underlying SCN5A mutation and is genotype-specific. Other ECG parameters, such as the QRS interval, the QTc interval and the magnitude of ST-segment elevations were not found to be different.

**Flecainide challenge**

An important test in the diagnosis of the Brugada syndrome is a pharmacologic challenge with class I antiarrhythmic drugs, preferably flecainide or ajmaline. Class I sodium channel blocking drugs will reduce the sodium current during phase 0 of the cardiac action potential, thereby, theoretically, disturbing the balance between depolarising ion currents and repolarizing I_{TO}. If this balance is already disturbed, because of a loss of function SCN5A mutation, the ST-segment may become elevated or its shape may change. Hence the effect of flecainide challenge might be expected to be ion channel-specific and probably mutation-specific. However, the change in ST-segment shape or elevation, due to flecainide challenge, was not found to be different between carriers of an SCN5A mutation and Brugada syndrome patients without a mutation. Ion channel, or I_{Na}, specific effects have been shown in the longer QRS-prolongation in carriers of an SCN5A mutation as compared to non-carriers (Figure 1). Another interesting finding is that flecainide testing preferentially puts Brugada syndrome patients, who carry an SCN5A mutation, at risk to develop ventricular tachyarrhythmias.

Mechanistic proof for this ion channel specific effect, and for the effects on the ST-segment in Brugada syndrome, comes from a study of the effects of flecainide on the 1795InsD. The 1795InsD mutant channels were found to be more sensitive to the blocking effects of flecainide compared to wild-type channels. Thus, when cardiac conduction is already compromised by a reduction in I_{Na} due to an SCN5A mutation, flecainide may be expected to further aggravate this. Mutation specific effects of the flecainide challenge may result from the fact that, depending on the amino-acid substitution in the cardiac sodium channel, the effect of flecainide may be different.

**Synopsis**

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Genotype-phenotype relationship in Brugada syndrome

Brugada syndrome is a genetically heterogeneous inherited disease. Therefore genotype-specific differences may be present in Brugada syndrome patients and families. The variable penetrance of the disease complicates the establishment of a phenotype-genotype relationship. Without knowledge of possibly the majority of involved genes and proteins, and without full understanding of its pathophysiology, this search is even more complicated. A first step has been made by recognizing that there is one patient group carrying an SCN5A mutation, and another very large one that does not, and that these groups are indeed phenotypically different.

Additionally, we know that there is one family with a non-malignant disease course, in which the disease has been linked to an as yet unidentified gene on chromosome 3p22-23 (table 3.).

Brugada syndrome SCN5A mutations, identified and investigated in cellular expression models, have consistently shown that $I_{Na}$ is reduced. This finding is consistent with the proposed pathophysiological mechanism for the disease. Between the Brugada syndrome and two other sodium channel associated arrhythmia syndromes, the long QT syndrome type 3 and cardiac conduction disease, phenotypical overlap exists. There are several reports of loss of function SCN5A mutations, that are causally related to both Brugada syndrome and cardiac conduction disease. In Brugada syndrome patients with an SCN5A mutation, compromised conduction is therefore not surprising. Indeed, these differences in cardiac conduction are presently the only known differences that can discern between the group of SCN5A-related, and non-related Brugada syndrome patients. Matters, however, are complicated already by the fact that the Brugada syndrome patients, in whom the disease was linked to a site on chromosome 3 (3p22-25), also have conduction abnormalities. A possible explanation in this case, and others, may be that mutations in other proteins, also affecting the sodium current, may be involved.
Table 2. Clinical data from Brugada syndrome mutations that have been studied in heterologous expression systems predicting a reduction in sodium current.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Index event</th>
<th>Family</th>
<th>ECG conduction disease</th>
<th>flecaïnide challenge</th>
<th>EPS arrhythmia inducible?</th>
<th>HV (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L567Q</td>
<td>SCD</td>
<td>+</td>
<td>ST↑</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>(ref. 22, 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G752R</td>
<td>none</td>
<td>+</td>
<td>ST↑</td>
<td>PR↑</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>(ref. 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1406R</td>
<td>palp.</td>
<td>+</td>
<td>&quot;typical&quot; PR↑</td>
<td>RBBB, LAHB</td>
<td>PR ↑↑</td>
<td>PVT↑</td>
</tr>
<tr>
<td>(ICCD+Brugada)</td>
<td>dizziness</td>
<td>(ref. 25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1432G</td>
<td>syncope</td>
<td>?</td>
<td>RBBB pattern</td>
<td>PR 240ms</td>
<td>ST↑</td>
<td>nd</td>
</tr>
<tr>
<td>(ref. 26, 27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1512W</td>
<td>syncope</td>
<td>-</td>
<td>RBBB pattern</td>
<td>PR 220ms</td>
<td>no</td>
<td>55</td>
</tr>
<tr>
<td>(ref. 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1710L</td>
<td>syncope</td>
<td>VF</td>
<td>1st degree AV block</td>
<td>1st degree VF</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>(ICCD/IVF/BS)</td>
<td>VF</td>
<td>(Ref. 29, 30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L795InsD</td>
<td>SCD</td>
<td>+</td>
<td>RBBB</td>
<td>PR ↑↑</td>
<td>ST↑</td>
<td>no</td>
</tr>
<tr>
<td>(LQT3+Brugada)</td>
<td>QT↑</td>
<td>(ref. 31, 32, 33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y1795I</td>
<td>none</td>
<td>-</td>
<td>(i)RBBB pattern</td>
<td>RBBB</td>
<td>ST↑</td>
<td>non</td>
</tr>
<tr>
<td>(ref. 34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1924T</td>
<td>none</td>
<td>-</td>
<td>&quot;typical&quot; no</td>
<td>no</td>
<td>nd</td>
<td>?</td>
</tr>
<tr>
<td>(ref. 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SCD sudden cardiac death, palp. palpitations, ICCD inherited cardiac conduction disease, (c)RBBB (complete) right bundle branch block, LAHB left anterior hemi block, c covered. VT ventricular tachycardia, PVT polymorph ventricular tachycardia.
Table 3. The only non SCN5A related Brugada syndrome mutation. Clinical characteristics.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Index event proband</th>
<th>Family history</th>
<th>ECG conduction disease</th>
<th>INa challenge</th>
<th>EPS arrhythmias inducible</th>
<th>HV (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3p22–25 (ref. 4)</td>
<td>syncope</td>
<td>+</td>
<td>1st degree AV block RBBB, left axis</td>
<td>ST↑↑</td>
<td>VF</td>
<td>60</td>
</tr>
<tr>
<td>7p22-25</td>
<td>RBBB right bundle branch block, coved. VF ventricular fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Cardiac conduction disease mutations that have been studied in heterologous expression systems predicting a reduction in sodium current INa. Clinical characteristics.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Index event proband</th>
<th>Family history</th>
<th>ECG conduction disease</th>
<th>INa challenge</th>
<th>EPS arrhythmias inducible</th>
<th>HV (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W156X+R225W† (ref. 35)</td>
<td>broad complex tachycardia</td>
<td>+</td>
<td>progressive conduction disease in both atrium and ventricle</td>
<td>nd.</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>G298S (ref. 36)</td>
<td>2nd degree AV block At age 6 yrs</td>
<td>?</td>
<td>2nd degree AV block progressive to 3rd degree</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>T512I+H558R‖ (ref. 37)</td>
<td>ir. heart beat</td>
<td>-</td>
<td>2nd degree AV-block</td>
<td>nd.</td>
<td>nd.</td>
<td></td>
</tr>
<tr>
<td>G514C (Ref. 38)</td>
<td>bradycardia</td>
<td>+</td>
<td>broad P wave PR↑, QRS↑</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>IVS22+2 (ref. 29)</td>
<td>syncope</td>
<td>+</td>
<td>RBBB complete AV block LBBB, LAHB, LPHB</td>
<td>nd.</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>G1406R (ICCD+Brugada) (ref. 25)</td>
<td>palp dizziness</td>
<td>+</td>
<td>&quot;typical&quot; PR↑ RBBB,LAHB</td>
<td>PR↑↑ QRS↑↑ PVT</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>D1595N (ref. 36)</td>
<td>2nd degree AV block</td>
<td>+</td>
<td>PR↑ RBBB</td>
<td>PR↑ 70ms</td>
<td>AH</td>
<td>210</td>
</tr>
<tr>
<td>S1710L (ICCD/IVF/BS) (ref. 29,30)</td>
<td>syncope VF</td>
<td>+</td>
<td>1st degree AV block QRS↑ at increased HR</td>
<td>1st degree AV block QRS↑ at increased HR</td>
<td>VF</td>
<td>↑</td>
</tr>
<tr>
<td>S1710+75X (ref. 39)</td>
<td>1st degree AV-block</td>
<td>+</td>
<td>1st degree AV-block RBBB, coved. VF ventricular tachycardia</td>
<td>nd.</td>
<td>nd.</td>
<td></td>
</tr>
</tbody>
</table>

†compound heterozygosity; ‡T512I mutation, H558R polymorphism, SCD sudden cardiac death, palp palpitations, ICCD inherited cardiac conduction disease, ic IRBBB (complete) right bundle branch block, LAHB left anterior hemi block, LPHB left posterior hemi block, c coved, VT ventricular tachycardia, PVT polymorphic ventricular tachycardia
CONCLUSION

Establishment of a phenotype-genotype relationship in the Brugada syndrome is important for understanding of the pathophysiology of the disease. When we understand the basis of the disease, we may be able to develop an ion channel-, or protein mechanism-specific pharmacologic treatment. When indeed Brugada syndrome is caused by mutations in different genes, this could mean that in the future we can divide Brugada syndrome into different types. Like in the long QT syndrome, this may lead to finding Brugada syndrome types. These different types may each have a different epidemiology, different clinical characteristics and requiring different, preferably pharmacologic, treatment\textsuperscript{6,7}.

At present, only conduction parameters seem to discriminate between Brugada syndrome patients with and without a mutation in the SCN5A gene\textsuperscript{18}.

Further phenotype-genotype relations may be established, if we are able to identify Brugada syndrome patients, or preferably families, who are phenotypically different from other
Brugada syndrome patients. In such patients, an educated guess, for example based on some remarkable ECG recording, might lead to the identification of the causally involved gene.
REFERENCES


