

# CardioGeneScan

## Familial Arrhythmia – an Overview

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### Overview Summary

Cardiac arrhythmias are generally characterized by abnormal electrical activity in the heart, putting patients at high risk of embolic stroke and/or sudden cardiac death (SCD; reviewed in<sup>1-3</sup>). Arrhythmias are classified by site of origin and are thus typically described as atrial, ventricular, atrio-ventricular, or junctional arrhythmias.<sup>2</sup> The five most common arrhythmic disorders are Atrial Fibrillation (AF), Long QT Syndrome (LQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C), and Brugada Syndrome (BrS) (Table 1).<sup>2-4</sup> While each of these disorders has a different etiology and a different prognosis, the clinical presentation is generally similar, including syncope, palpitations, dizziness, dyspnea, stroke, and/or SCD.<sup>1-4</sup> Prevention of stroke and SCD may be achieved through treatments including administration of anti-arrhythmic and/or anti-coagulation drugs, implantable cardioverter defibrillator (ICD) therapy, and certain lifestyle changes (Table 1); however, identification of at-risk individuals who may benefit from these treatments can be difficult since abnormal electrocardiogram profiles may not always be clear

and since stroke or SCD may be the presenting clinical manifestation.<sup>2-4</sup> Genetic testing for presence of a germline mutation in the genes known to be associated with LQTS, CPVT, ARVD/C, AF, and BrS can confirm a diagnosis and help differentiate between different forms of disease, clarifying the prognosis and alerting patients and physicians to the most common arrhythmia triggers, which may be specific to the underlying genetic cause.<sup>2,4</sup> Once a familial mutation has been identified, genetic testing can greatly facilitate detection of at-risk family members in familial forms of disease, which account for 30-60% of all cases.<sup>5-9</sup> Family members carrying familial mutations detected in the index patient for the family are at highly increased risk of arrhythmias, while family members not carrying these mutations are at lesser risk.<sup>2,4</sup> Familial arrhythmias are most commonly transmitted in an autosomal dominant manner and less commonly transmitted in an autosomal recessive manner.<sup>2,4</sup> Genetic causes of arrhythmias tested for in the ARRHYTHMIA DNA sequencing evaluation account for up to 75% of familial arrhythmia cases (see Table 2).

**Table 1: Disease Facts** <sup>1-4,6,8,10-14</sup>

| Disease Name                                | Long QT Syndrome (LQTS)  | Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)   | Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD/C)  | Atrial Fibrillation (AF)  | Brugada Syndrome (BS)   |
|---|--|--|--|---|---|
| <b>MIM Number</b>                           | 192500   | 604772   | 107970   | 608583  | 601144  |
| <b>Characteristic EKG patterns</b>          | Prolonged repolarization phase (QT interval; >390 msec in males and >400 msec in females) and broadened T wave   | Ventricular tachycardia seen as an alternating 180 degree-QRS axis on a beat-to-beat basis (bi-directional VT) typically when a heart rate of 100-120 bpm is reached | Incomplete or complete right bundle branch block; inverted T waves in the anterior precordial leads; localized prolongation of the QRS complex in leads V1 and V2; epsilon waves | Absence of P waves, with unorganized electrical activity in their place due to chaotic atrial depolarization; irregular R-R intervals due to irregular conduction of impulses to the ventricles | Incomplete right bundle branch block and ST elevations in the anterior precordial leads |
| <b>Characteristic morphological changes</b> | none   | none   | Replacement of normal myocardial tissue with fibrotic adipose tissue; right ventricular thickening   | none  | none  |
| <b>Arrhythmia type</b>                      | Ventricular  | Ventricular  | Ventricular  | Atrial  | Ventricular   |
| <b>Common triggers</b>                      | Exercise; emotional stress   | Exercise; emotional stress   |  | Extreme fatigue, emotional stress, severe infections, severe pain, heavy drinking or illegal drug use   |   |
| <b>Estimated Prevalence</b>                 | 1:3000   | 1:10000  | 1:1000   | 1:100   | 1:2000 (Southeast Asians); much lower in Caucasians                                     |
| <b>Penetrance</b>                           | 45-100%  | 75-100%  | 20-100%  | 90-100%   | 30-100%   |
| <b>Average Age of Onset (years)</b>         | 12   | 8  | 30   | 40  | 40  |
| <b>Selected Symptoms</b>                    | Syncope, seizures, palpitations, dizziness, dyspnea, stroke, sudden cardiac death (SCD)  |  |  |   |   |
| <b>Additional SCD information</b>           |  | Accounts for roughly 10% of all SCD cases <sup>15</sup>  | Common cause of SCD in juveniles and athletes <sup>16,17</sup>   |   | Accounts for roughly 20% of all SCD cases <sup>14</sup>                                 |
| <b>Selected Therapies</b>                   | Anti-arrhythmic drugs, anti-coagulation drugs, potassium supplements, implantable cardioverter defibrillator or pacemaker, avoidance of stressful/emotional situations, avoidance of competitive sports or other strenuous physical activities |  |  |   |   |

| Table 2: Molecular Genetics |  |                        |  |    |                   |  |
|-----------------------------|--|------------------------|--|----|-------------------|--|
| Gene (Protein)              | Proportion (%) of Disease Attributable to Gene (reference)<br>-transmission is autosomal dominant unless otherwise stated- |                        |  |    |                   | Comments   |
|                             | LQTS   | CPVT                   | ARVD/C   | AF | BrS               |  |
| AKAP9                       | <1% <sup>18</sup>  |                        |  |    |                   | The AKAP9 variant, S1570L (Exon 18), was identified in a patient with a severe LQTS phenotype. <sup>18</sup>   |
| ANK2                        | <1% <sup>19</sup>  |                        |  |    |                   | Type IV LQTS; complex cardiac defects; high risk of sudden cardiac death; prolonged QT intervals not always present <sup>19, 20</sup>  |
| ATP1B1                      | unknown  |                        |  |    |                   | Genome-wide association study revealed an association of an ATP1B1 variant in patients with prolonged QT intervals. <sup>21</sup>  |
| CACNA1C                     | 100% for Timothy syndrome <sup>22, 23</sup>  |                        |  |    |                   | Timothy syndrome is syndromic LQT with several manifestations, which may include syndactyly, autism, and a high risk of SCD; average age of onset is 3 years; disease is caused by one of two mutations in the CACNA1C gene, which determine a milder (type 1) vs. a more severe phenotype (type 2; reviewed in <sup>23</sup> ). |
| CACNB2                      |  |                        |  |    | <1% <sup>25</sup> | A CACNB2 mutation was reported in one family with BrS. <sup>25</sup>   |
| CASQ2                       |  | 1-2% <sup>26, 27</sup> |  |    |                   |  |
| CAV3                        | <1% <sup>28</sup>  |                        |  |    |                   | CAV3 mutations have also been seen in patients with Sudden Infant Death Syndrome (SIDS). <sup>30</sup>   |
| DSC2                        |  |                        | 1-5% <sup>30, 31</sup>   |    |                   |  |
| DSG2                        |  |                        | 10% <sup>32-34</sup>   |    |                   |  |
| DSP                         |  |                        | 6-16% <sup>35, 36</sup><br><br>100% for Carvajal syndrome (AR) <sup>37</sup> |    |                   | Carvajal syndrome is syndromic ARVD/C with hair and skin abnormalities. <sup>37</sup>  |
| GINS3                       | unknown  |                        |  |    |                   | Genome-wide association studies revealed a strong association of a locus containing the GINS3 gene in patients with prolonged QT intervals. <sup>38</sup>  |
| GPD1L                       |  |                        |  |    | <1% <sup>39</sup> | GPD1L mutations have been reported in a large family with BrS <sup>39</sup> and in cases of sudden infant death syndrome (SIDS). <sup>40</sup>   |

| Table 2: Molecular Genetics (Continued 2) |  |                        |   |                   |     |   |
|---|--|------------------------|---|-------------------|-----|---|
| Gene (Protein)                            | Proportion (%) of Disease Attributable to Gene<br>(reference)<br>-transmission is autosomal dominant unless otherwise<br>stated- |                        |   |                   |     | Comments  |
|   | LQTS   | CPVT                   | ARVD/C  | AF                | BrS |   |
| JUP                                       |  |                        | <1% <sup>41</sup><br><br>100% for<br>Naxos<br>disease<br>(AR) <sup>42</sup> |                   |     | Naxos disease is syndromic ARVD/C with hair and skin abnormalities. <sup>42</sup>   |
| KCNA5                                     |  |                        |   | 3% <sup>43</sup>  |     |   |
| KCNE1                                     | LQTS: 1% <sup>9, 44</sup><br><br>JLNS: 9.5%<br>(AR) <sup>45, 46</sup>  |                        |   |                   |     | Patients with JLNS have congenital deafness with LQTS and a high risk of SCD. <sup>45, 46</sup>   |
| KCNE2                                     | 1-3% <sup>9, 44, 47</sup>  |                        |   | 7% <sup>48</sup>  |     |   |
| KCNH2                                     | 16-58% <sup>49, 50</sup>   |                        |   |                   |     |   |
| KCNJ2                                     | 70% for<br>Andersen-<br>Tawil<br>syndrome<br><sup>51</sup>   | 2-25% <sup>51-53</sup> |   |                   |     | Andersen-Tawil syndrome is syndromic LQT with episodic flaccid muscle weakness; patients may present with tachycardias that look similar to those seen in Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). <sup>51</sup> |
| KCNQ1                                     | LQTS: 26-<br>42 % <sup>44, 46</sup><br><br>JLNS: 90%<br>(AR) <sup>45, 46, 55</sup>   |                        |   | <1% <sup>56</sup> |     | Patients with JLNS have congenital deafness with LQTS and a high risk of SCD. <sup>45, 46</sup>   |
| LIG3                                      | unknown  |                        |   |                   |     | Genome-wide association studies revealed an association of a <i>LIG3</i> variant in patients with prolonged QT intervals. <sup>21, 38</sup>   |
| NOS1AP                                    | unknown  |                        |   |                   |     | Genome-wide association studies revealed an association of a <i>NOS1AP</i> variant in patients with prolonged QT intervals. <sup>21, 38</sup>   |
| NPPA                                      |  |                        |   | <1% <sup>57</sup> |     |   |
| NUP155                                    |  |                        |   | <1% <sup>58</sup> |     | Reported in one family with a history of early sudden cardiac death <sup>58</sup>   |

| Table 2: Molecular Genetics (Continued 3) |  |                         |                          |    |                   |  |
|---|--|-------------------------|--------------------------|----|-------------------|--|
| Gene (Protein)                            | Proportion (%) of Disease Attributable to Gene<br>(reference)<br>-transmission is autosomal dominant unless otherwise<br>stated- |                         |                          |    |                   | Comments   |
|   | LQTS   | CPVT                    | ARVD/C                   | AF | BrS               |  |
| <i>PKP2</i>                               |  |                         | 10-43% <sup>59, 60</sup> |    |                   | ARVD/C patients with <i>PKP2</i> mutations tend to have a significantly earlier (by ~8 years) age of onset. <sup>59</sup>  |
| <i>PLN</i>                                | unknown  |                         |                          |    |                   | Genome-wide association studies revealed an association of a <i>PLN</i> variant in patients with long QT intervals. <sup>38</sup>  |
| <i>RYR2</i>                               |  | 50-58% <sup>61-63</sup> | <1% <sup>64</sup>        |    |                   | <i>RYR2</i> mutations were reported in four Italian ARVD families with a history of effort-induced ventricular arrhythmias. <sup>64</sup><br><br>CPVT patients with <i>RYR2</i> mutations tend to have an earlier age of onset than those without; males are at higher risk of syncope than females. <sup>63</sup> |
| <i>SCN1B</i>                              |  |                         |                          |    | <1% <sup>65</sup> | Certain <i>SCN1B</i> mutations have been associated with cardiac conduction disease in patients with BrS. <sup>65</sup>  |
| <i>SCN4B</i>                              | <1% <sup>66</sup>  |                         |                          |    |                   | A <i>SCN4B</i> mutation was reported in a large Mexican family with a history of sudden cardiac death and LQTS. <sup>66</sup>  |
| <i>SCN5A</i>                              | 2-11% <sup>47, 67, 68</sup>  |                         |                          |    | 20% <sup>14</sup> | Cardiac event trigger is typically sleep-related in patients with LQTS-associated <i>SCN5A</i> mutations. Some families with <i>SCN5A</i> mutations have been described to have both LQTS and BrS. <sup>69</sup>   |
| <i>SNTA1</i>                              | unknown  |                         |                          |    |                   | Severe LQTS <sup>70</sup>  |
| <i>TGFB3</i>                              |  |                         | <1% <sup>71</sup>        |    |                   |  |
| <i>TMEM43</i>                             |  |                         | <1% <sup>72, 73</sup>    |    |                   | Mutations in <i>TMEM43</i> are associated with severe ARVD/C with high penetrance; age of onset earlier for men than women (by 12 years); high incidence of SCD. <sup>72, 73</sup>   |

Key: AR (Autosomal Recessive)

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