Clinical and genetic spectrum of hereditary cardiac arrhythmia syndromes

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During the last decade, we have seen a growing list of genes and mutations linked to the pathophysiology of arrhythmias of genetic origin. But, we still lack genetic pathobiological evidences for a large number of patients with inherited arrhythmias or sporadic arrhythmias with a suspected genetic origin. Presently, speeded efforts are ongoing to identify new genes, germline mutations and linking the mutations to the pathology of various congenital arrhythmias. Somatic mutations, common in various oncological disorders, were also recently reported in cardiac gap-junction protein connexin 40 (GJA5) in AF patients.1 Somatic mutations are present only in the affected tissues or organs and are not transmitted to the offspring unlike the germline mutations. Perhaps, due to limitations in access, somatic mutations have not been seriously looked for in most cardiac ion channel or desmosomal genes, which might add to the list of genes and mutations. We and others could see that the yield in RYR2 mutations in familial CPVT cases is >80%, but this rate drops to ~50% (average 30%) in sporadic cases, although their CPVT diagnosis were clinically confirmed by experienced cardiologists in this field.2-4 RYR2 mutations confined to the diseased tissues (somatic mutations) might be looked for in mutation negative CPVT cases. A similar strategy could also be taken in screening the desmosomal genes in ARVD/C (or ARVD/C like) patients. A pilot screening could be initiated with the archived cardiac tissues. Presently, the precise mechanistic basis of RyR2 dysregulation into the pathogenesis of CPVT is a debated issue. Attenuation in binding affinity of the FKBP12.6 protein for RyR2, although proposed as the main pathology in altered Ca2+ handling in CPVT-1, is not supported unanimously.5-7 It was further proposed that this interaction between FKBP12.6 and RyR2 is conformation dependent.8 All the functional studies were done in the context of a single missense mutation in RYR2. In our study (Bhuiyan et al. 2007), our patients lack the N-terminal 35 amino-acids p.Asn57_Gly91 in RyR2.9 We could speculate that, this conformation is surely more distorted with a large deletion in RYR2, as found in our study. This could be a good model in solving the ongoing puzzle about the role of FKBP12.6 in CPVT-1 pathogenesis and will lead us one step ahead in understanding the pathology of CPVT. Like the novel CPVT-3 locus in our study (Bhuiyan et al. 2007), there are convincing studies where the locus has been identified, but the candidate gene/s are yet to be found.10 Gene copy-number variations (CNV) were reported in various familial diseases and also were shown to influence disease penetrance.11 Role of CNVs, big deletions/insertions, mutations in the regulatory regions would shed new light in cardiac arrhythmia pathology. We see an intriguing observation regarding HERG autoantibody mediated LQT2.12 Studies are also awaited about the role of autoantibody mediated various cardiac channelopathies. Studies also lack about the modulators (some say modifier) which perhaps play a pivotal
role in disease pathogenesis, manifestation and progression. Disease penetration among mutation carriers varies, sometimes even within the family members. What makes them susceptible despite having both the same mutation? Why one develops fibrillation earlier, or not at all, than other? Complex interaction of various factors (SNPs, environment), perhaps plays a role in the interindividual variation of disease expression. As we have previously mentioned, we see only few studies elucidating the modifier effect of an otherwise silent/innocuous SNPs (within the causative gene and or in the genes in the functional network) in exaggerating/ameliorating the clinical presentation of arrhythmias.\textsuperscript{13-15} β-adrenergic blockade is the first line of treatment in patients with arrhythmias. Modifier/modulatory effects of common SNPs of the adrenergic signalling pathway genes on the clinical severity, therapy outcome, both in cardiac channelopathies and desmopathies remain to be extensively studied. We also miss twin studies conducted in this field, which would have shed more light into this topic of gene environment interaction in familial arrhythmia cases due to a known mutation.

Extensive studies are required not only characterizing each ion channel function, elucidating the signalling pathways with identification of important signalling molecules are also crucial. This would lead to the identification of novel surrogate clinical/bio markers in disease diagnosis and progression and novel therapeutic intervention. Very few studies are focusing on the gene and mutation specific clinical management. Current treatments for arrhythmias are also limited mainly to β-blockers and in therapy resistant cases by expensive devices such as implantable defibrillators and pacemakers. Novel therapeutic approaches including biological interference treatment modalities may be developed.

**Functional role of Nonsense Mediated Decay (NMD) in Arrhythmogenesis:**

We have shown for the first time the role of nonsense-mediated decay (NMD) into the pathogenesis of LQT2 arrhythmias.\textsuperscript{16-17} NMD removes aberrant mRNAs with premature termination codons from eukaryotic cells.\textsuperscript{18} In our study, we have found that heterozygous Q1070X HERG mutation carriers have virtually no LQT2 phenotypes. On the other hand homozygous carriers suffered from intrauterine fatal arrhythmias, where the severest phenotype is observed in homozygous \textit{KCNH2} mutation carriers.\textsuperscript{17} In vitro functional assays with the Q1070X mutant showed normal cellular localisation and electrical properties. We have eventually discovered that mutant Q1070X mRNAs are susceptible to NMD degradation, which leaves nearly negligible amount of mRNA to make any functional HERG protein. This finding also explains why heterozygous carriers have no phenotype as the mutant allele is unable to translate to protein and confer its dominant negative effect on WT HERG for functional aberration. Haploinsufficiency of HERG did not cause LQT2 phenotypes in our studied patients.\textsuperscript{17} From the published report, we see that not all non-sense or frameshift
KCNH2 mutation carriers are without any phenotype.\textsuperscript{16,19} This could possibly be caused by the fact that, not all non-sense or frameshift KCNH2 mutations are equally susceptible to NMD degradation, which needs to be investigated. Interindividual variation in NMD might also be evident in some cases which remain to be investigated.\textsuperscript{20}

**Emerging role of microRNA in Arrhythmia pathogenicity:**

We have mentioned in the beginning of this chapter that an extensive crosstalk between mechanical and electrical junctions is required for proper, coordinated heart function. Several recent reports add a new component, microRNA (miRNA) to this orchestrated function that is essential to prevent the heart from generating arrhythmias. miRNAs are endogenous \~22-nucleotide non-coding RNAs that regulate gene expression at the post-transcriptional level by annealing to inexact complementary sequences in the 3’-untranslated regions of target mRNAs of protein-coding genes.\textsuperscript{21} MiRNAs negatively regulate gene expression by promoting mRNA degradation and inhibiting mRNA translation. MiR-133 was found to repress KCNH2 expression and prolonged the QT interval in diabetic hearts of experimental animals.\textsuperscript{21} An elevated level of miR-1 was observed in patients with coronary artery disease, which has been reproduced in the mouse heart model of myocardial infarction.\textsuperscript{22} This increased miR-1 reduced the expression of Cx43 and Kir2.1, which in return caused slowed electrical conduction and prolongation of repolarization potential and predisposed the heart to arrhythmias.

Given the emerging role of miRNAs in arrhythmogenesis, more research is needed especially in the context of their role into the pathogenetic mechanism of arrhythmias. Modulation of expression of cardiac miRNAs might be a future therapeutic strategy, but more studies are required before bringing it to the clinic. Their route of delivery should also be studied. Do all the ion channel genes, genes in the pathway, all express in a similar intensity day and night, perhaps not. Do their expression change/modify due to various stimuli or disease triggering agents? They also don’t express in all heart compartments in a similar fashion.\textsuperscript{23} This rhythm of expression of various ion-channel genes, miRNAs and also their signalling genes need to be investigated.

An understanding from various viewpoints is required to understand the pathobiology of arrhythmias, leading to a gene and individual specific, effective clinical management.

**References:**


