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Publication date
2011

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Citation for published version (APA):
Scicluna, B. P. (2011). *Systems-based approach for the identification of novel genes influencing cardiac electrical traits*.

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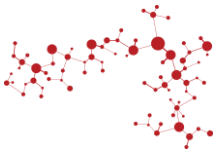

Chapter 2

The primary arrhythmia syndromes: same mutation, different manifestations.
Are we starting to understand why?

Scicluna BP, Wilde AAM, Bezzina CR.

Journal of Cardiovascular Electrophysiology 2008;19: 445-522.

"What matters, therefore, is not the meaning of life in general but rather the specific meaning of a person's life at a given moment"

Viktor E. Frankl

Abstract

The discovery of pathogenic mutations primarily in genes encoding cardiac ion-channel proteins underlying the primary cardiac arrhythmia syndromes has had a remarkable impact on the management of these disorders, especially in patients with the Long QT syndrome. The availability of a genetic diagnostic test has added an important diagnostic tool, providing new opportunities for patient management such as early (presymptomatic) identification and treatment of patients at risk of developing fatal arrhythmias, risk stratification, and installation of gene-specific therapy. However, the fact that the identification of the causal mutation within a family allows diagnosis in other family members independently from the ECG features and the arrhythmic manifestations quickly led to the recognition that extensive variability in clinical manifestations (e.g. extent of ECG abnormality and/or symptomatology) may be observed among family members carrying an identical mutation in a single ion channel gene. It is commonly held that this clinical variability stems from interactions between environmental and genetic modifiers with the particular pathogenic mutation. This “Molecular Perspectives” article reviews current knowledge on these modifiers of disease expression in the cardiac arrhythmia syndromes with particular reference to genetic modifiers.

Introduction

The discovery of pathogenic mutations primarily in genes encoding cardiac ion-channel proteins[1] underlying the primary cardiac arrhythmia syndromes has had a remarkable impact on the management of these disorders, especially in patients with the Long QT syndrome. Importantly, the availability of a genetic diagnostic test has added an important diagnostic tool, providing new opportunities for patient management such as early (presymptomatic) identification and treatment of patients at risk of developing fatal arrhythmias, risk stratification,[2,3] and installation of gene-specific therapy.[4,5] Furthermore, the fact that the identification of the causal mutation within a family allows diagnosis in other family members independently from the ECG features and the arrhythmic manifestations has demonstrated that the primary cardiac arrhythmias are not spared from the genetic phenomena of *reduced penetrance* and *variable expression* typical of monogenic disorders and the related consequences for clinical management.

The penetrance of a disease is defined as the percentage of individuals possessing the same primary genetic defect that develop the associated clinical manifestations - the mutation carrier either expresses the disease phenotype or not. Variable expression is defined as the variation in clinical features (type and severity) among carriers of the same primary genetic defect that can range from mildly affected to severely affected individuals even within the same family. Ever since their inception in genetic research these phenomena have been tightly linked to interactions between environmental and genetic modifiers with the particular pathogenic mutation. We shall here review current knowledge on these modifiers of disease expression in the cardiac arrhythmia syndromes with particular reference to genetic modifiers.

Variability in ECG manifestations and symptomatology in the primary cardiac arrhythmia syndromes

Thus, in the primary cardiac arrhythmia syndromes extensive variability in clinical manifestations (phenotypic variability) may be observed among family members carrying an identical mutation in a single ion channel gene, where some individuals carrying the mutation may exhibit overt ECG abnormalities or suffer fatal arrhythmias, while others carrying the same primary genetic mutation might not have the ECG changes or may never develop any arrhythmias. The first notation of reduced penetrance was done for the Long QT syndrome by Vincent and co-workers back in 1992 in a large family displaying linkage to the *KCNQ1* gene (encoding the repolarizing K^+ current, I_{ks}) locus on chromosome 11, even before the gene itself was identified as the culprit gene.[6] In this study, not all 83 carriers of the chromosome 11 DNA markers associated with the disorder exhibited QT-interval prolongation. Examples were subsequently presented by Priori and co-workers who reported penetrances as low as 25% and 12.5% in small families with the Long QT syndrome[7] and Brugada syndrome,[8] respectively. More recently in an extended multiplex South African kindred segregating the *KCNQ1* gene founder mutation A341V, Brink et al. demonstrated large variability in QTc interval as well as symptomatology among 86 mutation carriers.[9] Furthermore, a significant number of mutation carriers (12%) exhibited QTc-intervals within the normal range. Our group has made similar observations of variable expressivity among 43 carriers of the *SCN5A* gene (encoding the cardiac Na^+ current, I_{Na}) mutation 1795insD segregating in a large Dutch kindred.[10,11] Moreover, in the latter family besides variability in clinical severity, multiple primary electrical disease phenotypes, previously only recognized as distinct clinical entities, were observed including bradycardia-related QT-interval prolongation (typical of *SCN5A*-related Long QT syndrome), right precordial ST-elevation (the hallmark ECG feature of Brugada Syndrome), sinus bradycardia, and conduction defects,[12] occurring in isolation or in combinations thereof. It was

subsequently recognized that combinations of multiple ECG manifestations, a phenomenon that has become known as “overlap syndrome” of cardiac sodium channel disease, is not uncommon in the cardiac sodium channelopathies.[13-15] Electrophysiological studies *in vitro* as well as in a transgenic mouse model[16,17] have demonstrated that one specific mutation can indeed lead to multiple biophysical defects of the Na^+ channel that explain the co-occurrence of the multiple phenotypes. However, the fact that not all phenotypic manifestations occur in all mutation carriers argues in favor for a role of environmental and genetic modifiers in the determination of the actual phenotypic manifestation of the mutation.

Identification of modifiers

The identification of modifiers of the ECG or arrhythmia phenotype is regarded as the next major goal in our understanding of the primary arrhythmia syndromes[18]. Some important modifiers are already recognized. Gender is a well known modifier of the ECG phenotype and arrhythmia manifestations in both the Long QT syndrome[2] and Brugada syndrome.[14,19] Another modulator of phenotype in these disorders is age.[20-22] In some cases of Long QT syndrome latent (sub-clinical) disease can be unmasked by QT-prolonging drugs[23-25] or metabolic derangements such as hypokalemia.[26] The signature ST elevations of Brugada syndrome can increase during vagal stimulation,[27] hyperthermia[28] and pharmacological Na^+ channel blockade.

Genetic modulation of the phenotypic consequences of ion channel gene mutation has increasingly drawn the attention of several investigators in the last years and is expected to remain a major focus of arrhythmia genetics research in the years to come. In some instances co-inheritance of a second mutation (compound mutations) as occurs in approximately 5% of probands with the Long QT syndrome helps explain exaggerated disease severity compared to other family members carrying single disease alleles.[29,30] Although their exact prevalence is unknown, compound

mutations in *SCN5A* may also account for more severe phenotypic manifestations in conduction disease[31] and Brugada syndrome.[32]

In the absence of compound mutations, another genetic mechanism for variable clinical presentation of the disease is the coexistence of modifier alleles carrying genetic variation that is frequent in the population. To investigate this hypothesis, we have recently compared the phenotypic effects of the *Scn5a* 1798insD mutation[17] (homolog of the human *SCN5A* 1795insD mutation mentioned above) in 2 different mouse genetic backgrounds, namely 129P2 and FVB/N.[33] In this study we demonstrated that severity of conduction disease associated with this mutation depends on genetic background, providing the first conclusive evidence that intrinsic genetic modifiers influence disease severity in cardiac ion channelopathies.

Genetic variation between individuals takes various forms with the largest part being due to single nucleotide polymorphisms (SNPs, “snips”) which make up about 90% of all human genetic variation (**Figure 1**). SNPs occur when a single nucleotide (A,T,C, or G) in the genome sequence is altered. They occur every 100 to 300 bases along the 3-billion-base human genome and are found both in coding and noncoding regions (the latter regions may have regulatory functions). For a variation to be considered a SNP, it must occur in at least 1% of the population. Genetic modification by polymorphisms may occur in two forms; interaction of genetic variation within the same (disease) gene locus, or, interaction of genetic variation at one or more genetic loci distinct from the disease gene locus itself. In both instances the interaction may exacerbate or alleviate the severity of the disease.

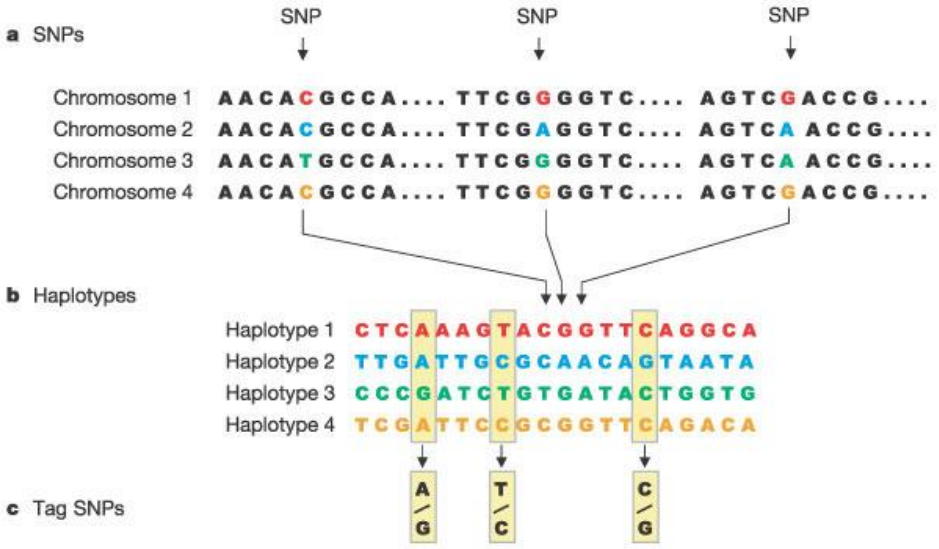

Figure 1. (a) SNPs. Shown is a short stretch of DNA from four versions of the same chromosome region in different people. Most of the DNA sequence is identical in these chromosomes, but three bases are shown where variation occurs. Each SNP has two possible alleles; the first SNP in panel a has the alleles C and T. (b) Haplotypes. A haplotype is made up of a particular combination of alleles at nearby SNPs. Shown here are the observed genotypes for 20 SNPs that extend across 6,000 bases of DNA. Only the variable bases are shown, including the three SNPs that are shown in panel a. For this region, most of the chromosomes in a population survey turn out to have haplotypes 1–4. (c) Tag SNPs. Genotyping just the three tag SNPs out of the 20 SNPs is sufficient to identify these four haplotypes uniquely. For instance, if a particular chromosome has the pattern A–T–C at these three tag SNPs, this pattern matches the pattern determined for haplotype 1. Note that many chromosomes carry the common haplotypes in the population. Reprinted by permission from Macmillan Publishers Ltd: Nature 2003;426:789-796, copyright (2003).

Modulation of mutation effect by polymorphisms residing within the same gene

Fascinating examples of modulation by genetic variation residing within the same gene as the primary genetic defect were first described in the cardiac Na^+ channelopathies and are based primarily on *in vitro* electrophysiological studies. Initial heterologous expression studies into the biophysical defects caused by a given mutation considered the effect of the mutation in isolation i.e. they did not take into account any polymorphic variation residing in the same allele (in *cis*) or in the other allele (in *trans*). Such considerations were however made by Viswanathan and co-workers[34] who introduced the concept that the interaction of polymorphisms and mutations may exert relevant effects on the functional consequences of the mutation. These investigators studied the biophysical properties of the *SCN5A* T512I mutation found in a proband with conduction disease that was also homozygous for the H558R polymorphism (present with an allelic frequency of 18% and 28% in Whites and Blacks, respectively) in the same gene (**Figure 2**). The fact that the proband was homozygous for H558R immediately implied that the T512I mutation occurred on an allele that also encoded the R558 variant. Through careful comparison of the biophysical properties of wild-type Na^+ channels, Na^+ channels carrying the T512I mutation alone, and Na^+ channels carrying both the T512I mutation and the R558 variant, they demonstrated that the biophysical defect associated with the mutation was mitigated by the presence of the polymorphism in the same channel molecule. Similar observations of "intramolecular complementation" by the *SCN5A* H558R polymorphism were made at around the same time by Ye and co-workers[35] who through *in vitro* studies demonstrated that the plasma membrane-targeting defect associated with the *SCN5A* M1766L mutation was rescued when it was expressed on a Na^+ channel also carrying R558.

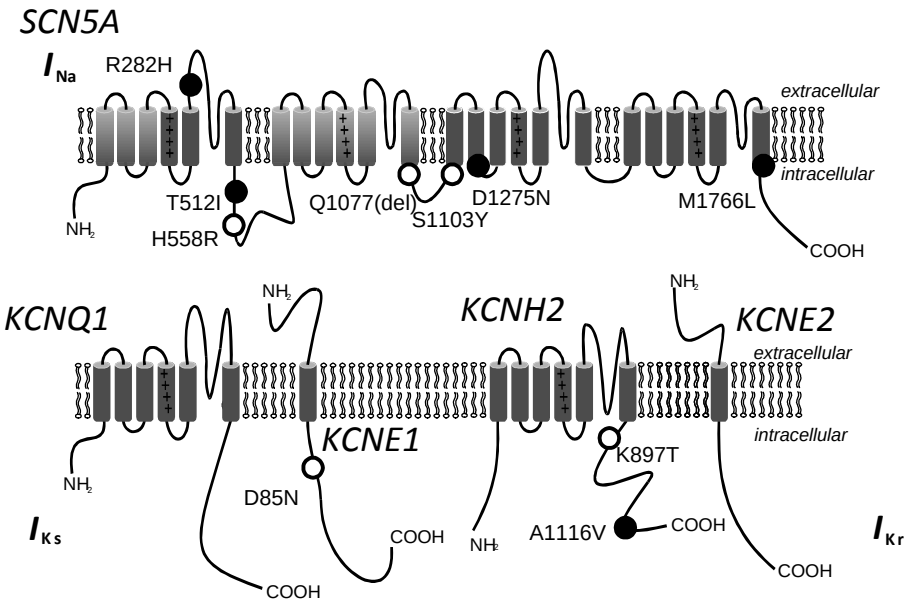

Figure 2: Diagrammatic representation of mutations and modulating polymorphisms in their respective ion-channel domain.

Mutation ● Polymorphism ○

More recently, Poelzing and co-workers[36] also provided evidence for a trans-complementation effect of the R558 variant. In this study, they demonstrated that in heterologous cells, expression of R282H (mutation segregating in a Brugada syndrome family) mutant Na^+ channels alone did not produce any Na^+ current. However, co-expression of R282H mutant channels together with channels carrying the R558 variant produced significantly greater current than co-expression of the mutant with channels carrying the H558 variant, demonstrating that the polymorphism rescues the cell surface expression of the mutation. The molecular mechanism underlying this rescue however remains to be elucidated.

It has been proposed that such cis/trans-complementation effects in the *SCN5A* gene itself could underlie at least in part the low penetrance in Brugada syndrome[36] and the wide variability in phenotype of cardiac Na^+ channel defects such as why loss-of-function mutations lead to different types of conduction disease,[34] and why certain mutations can present with different phenotypes (e.g. QT interval prolongation versus ST-segment elevation) in different persons.[35] However one must sound a word of caution in attempting to extrapolate these findings directly to the clinical situation. The question of whether the expression levels and the kinetic behavior of channels expressed in heterologous cell systems faithfully recapitulate their function in the intact heart remains a common limitation. Furthermore, statistical support for the effects of these polymorphisms in large multiplex pedigrees is missing. Nevertheless these studies underscore the need to start considering the context of polymorphisms on which mutations occur.

Alternative splicing of a single amino acid of *SCN5A* at the beginning of exon 18 causes insertion of glutamine at position 1077 (Q1077), resulting in two splice variants, one that forms a 2,016-amino acid protein designated Q1077 and a 2,015-amino acid protein designated Q1077del.[37] Both splice variants exist in heart, with a 65% predominance of the shorter 2,015-amino acid variant Q1077del.[37] The trafficking defect associated with the Brugada Syndrome mutation G1406R was shown to depend on the background splice variant in which it was expressed, being worse in the Q1077 variant. Although no evidence exists, one could speculate that conditions that upset the normal 2:1 ratio of the Q1077del and Q1077 variants could also modulate the phenotype associated with specific *SCN5A* mutations.

Co-inheritance of the K897T polymorphism (allelic frequency ~24% in Caucasians) on the opposite allele has been proposed to expose latent Long QT syndrome in a patient with the mild A1116V mutation in *KCNH2* (encoding the repolarizing current, I_{kr}).[38] In this study, coexpression of *KCNH2*-A1116V and *KCNH2*-K897T channels together resulted in significantly reduced current amplitude as compared with coexpression of

either channel with the wild-type. Thus, the presence of *KCNH2*-K897T is predicted to exaggerate the reduction in repolarizing K^+ current caused by the A1116V mutation. However, for the latter as for the *SCN5A*-related examples described above, evidence is only based on *in vitro* electrophysiological studies. The K897T polymorphism has also received much attention as a locus controlling QT-interval in the general population, as discussed in a later section of this review, where we also caution against over-interpretation of electrophysiological data obtained in *in vitro* heterologous expression studies.

Modulation of mutation effect by polymorphisms residing within a different gene

Searching for polymorphic variation that may determine the impact of the primary mutation *outside* the gene carrying the primary genetic defect opens a plethora of possibilities. Starting most proximal to the ion channel gene or protein itself there are various points at which modulation of expression level or structure of an ion channel protein is possible. Such modification could act for example via transcriptional regulation, (alternative) splicing or post-translational modification. A case in point is a study performed on two mouse strains that in spite of carrying the same splice site mutation in the *Scn8a* gene exhibited markedly different expressivity of the hereditary neurodegenerative disease "motor-endplate disease" (med).[39] In this study phenotypic variability and expressivity were correlated to splicing patterns of the *Scn8a* gene; in the mildly affected mice 10% of the transcripts were correctly spliced while in the severely affected mice 5% of the transcripts were correctly spliced. Positional cloning in these mice identified the *Scnm1* gene, a putative RNA splicing factor as a modifier gene.

Another consideration is that ion channels do not function in isolation but form part of large dynamic multi-protein complexes comprising not only the pore-forming component and auxiliary β-subunits but also regulatory kinases and phosphatases, trafficking proteins, components of the

cytoskeleton and extracellular matrix proteins.[40,41] It can very well be envisaged that polymorphic variation in any of these interacting components may affect ion channel expression and function and consequently modulate the effect of a given mutation.

To our knowledge, in the cardiac ion channel literature, there are as yet only 2 examples of modulation by polymorphisms residing in a gene different from that carrying the causal mutation. One involves the D85N polymorphism (allele frequency ~1% in Caucasians[42]) in the *KCNE1* gene which encodes the modulatory β-subunit for the *KCNQ1*-encoded I_{ks} current. Here it has been suggested that the D85N polymorphism in *KCNE1* aggravates the Long QT syndrome phenotype in some families with mutation in *KCNQ1.*[29]

A second example comes from our group and deals with modulation of the effect of the *SCN5A* mutation D1275N segregating in a family with atrial standstill.[43] Besides carrying the *SCN5A* mutation, the 3 individuals affected by atrial standstill in this family were also homozygous for 2 linked polymorphisms forming a *haplotype* (**Figure 1**) in the regulatory (promoter) region of the *GJA5* gene encoding the gap junction protein connexin 40. Reporter gene studies on the *GJA5* promoter polymorphisms showed a reduction in reporter gene expression compared with the wild-type promoter sequence. This finding, together with the fact that individuals who inherited the D1275N change but were not homozygous for the *GJA5* promoter polymorphisms exhibited mild PR interval prolongation but not atrial standstill, led us to suggest that the combined effect of the *SCN5A* mutation and the *GJA5* promoter polymorphisms conspired to produce the atrial standstill in the affected individuals of this family. A similar observation was subsequently made in a Japanese boy with atrial standstill who carried the L212P mutation in *SCN5A* and who was heterozygous for the *GJA5* promoter polymorphisms.[44]

Genetic variation controlling ECG parameters

Attempting to link genetic variants to the extent of ECG abnormality (e.g. QT interval prolongation or QRS-widening) or arrhythmia risk in patients with primary arrhythmia syndromes carries certain practical implications. The genetic component modulating the expression of the ECG trait or occurrence of arrhythmias is expected to be polygenic i.e. multiple genetic variants are expected to be operative, each providing a small contribution to risk. This implies that for adequately-powered genetic association or linkage studies for identification of such genetic variants, large numbers of individuals need to be considered. Moreover, in order to increase the power of such a search one must be careful in considering as much as possible a single mechanism with respect to the primary genetic defect, necessitating that the individuals under study must preferably possess the same mutation (a scenario that is not easy to achieve since mutations are mostly family-specific and very few founder mutations segregating in multiplex kindreds are known)[9,10,41] or at least carry mutations in the same gene.

Instead of attempting to build direct bridges between genetic variation to ECG manifestations or occurrence of arrhythmias in the primary cardiac arrhythmias some researchers are focusing on linking genetic variation to specific cardiac electrical phenotypes which could represent endophenotypes (intermediate phenotypes) in these disorders. These studies have till now primarily addressed the QT-interval, known to be influenced by genetic variation[45] and have been carried out in (large) healthy population cohorts with available ECGs.

Polymorphisms modulating the QT-interval

Some studies have looked for association of specific nonsynonymous polymorphisms (i.e. leading to amino acid change) within candidate genes[42,46,47] (**Table**). The first polymorphism to be linked to the QT-interval and that has attracted the interest of several researchers is the K897T polymorphism in *KCNH2*. Discordant findings have however been

reported for this polymorphism. While studies in Finnish women appear to link the allele encoding T897 to *longer* QT intervals,[48-50] studies in Western European populations (German and French), that have investigated larger sample sizes, on the other hand appear to consistently link this allele to *shorter* QT-intervals,[46,47,51] as did a study in the Framingham Heart Study population.[52] The disparity between these studies could reflect population differences such as population-specific differences in the occurrence of other (functional) polymorphisms, possibly in regulatory regions of the gene, which are in linkage disequilibrium (correlated) to this polymorphism. *In vitro* electrophysiological studies on the polymorphism have also led to conflicting findings.[46,49,53] Any biophysical differences between *KCNH2* channel proteins carrying either K897 or T897 are likely to be very mild, reflecting the very small effects of these alleles on the QTc-interval which could be as small as -2 ms per T897 allele.[51] Thus, conflicting data from *in vitro* electrophysiological studies may very well stem from differences in conditions under which these variants were studied.

Gene	Nucleotide change	ref SNP ID	Minor allele frequency (MAF) *	Amino acid change (when applicable)	Effect	Reference
KCNH2	A/C	rs1805123	0.155[1]; 0.24[2]; 0.017[3]	K897T	↑ QT interval	48-50
					↓ QT interval	46,47,51,52
KCNH2	A/G	rs3807375	0.383[2]; 0.242[3]; 0,3[5]; 0.182[6]		↑ QT interval	52
KCNH2	A/G	rs3815459	0.2[2]; 0.202[4]; 0.278[5]; 0.193[6]		↑ QT interval	51
KCNE1	G/T	rs727957	0.152[2]; 0.022[4]; 0[5]; 0[6]		↑ QT interval	51
KCNQ1	A/G	rs757092	0.358[2]; 0.167[3]; 0.398[5]; 0.367[6]		↑ QT interval	51,55
SCN5A	A/G	rs1805124	0.183[2]; 0.277[4]; 0.078[5]; 0.133[6]	H558R	↑ QT interval	42,55
NOS1AP	A/T	rs4657139	0.29[2]; 0.033[3]; 0.311[5]; 0.25[6]		↑ QT interval	54, 56

Table: Polymorphisms modulating QT-interval in control subjects. Only those polymorphisms for which the effect has been confirmed in an independent sample/study are included. *MAF representative of HapMap data. [1]Scandinavian Finn, [2]Central European, [3]sub-saharan African, [4]African American, [5]Han Chinese (Beijing), [6]Japanese (Tokyo).

Gouas et al.[47] compared the frequency of candidate polymorphisms within ion-channel encoding genes in 200 subjects with the longest QTc-interval versus 200 subjects with the shortest QTc-interval, sampled from the extremes of the QTc distribution of a community-based sample in France. In accordance with the more-severe QT-intervals and higher incidence of arrhythmias in *KCNQ1* mutation carriers who also carried the N85 variant of the *KCNE1* D85N polymorphism,[29] these investigators found an enrichment of the N85 variant in the high-QTc group. In the same study these investigators demonstrated an enrichment of the polymorphism encoding the R558 variant of the *SCN5A* H558R polymorphism in the group with the longest QT-interval, confirming the suggestion of such an association previously made by Aydin et al. in a German population.[42]

While these studies investigated single or small numbers of candidate polymorphisms, the efforts of the genetic community in identifying and cataloging common genetic variation in the genome through the HapMap project (www.hapmap.org) as well as the availability of high-throughput technologies for genotyping, has recently enabled a more-comprehensive analyses of candidate genes[51,52], as well as a genome-wide approach,[54] leading to the identification of novel variants controlling QTc (**Table**). At the basis of these studies is the *tagSNP* approach. TagSNPs are SNPs that can serve as proxies for the correlated SNPs in a given haplotype allowing for the selection of a few SNPs for genotyping that capture most of the common genetic variation (**Figure 1**). In this approach, association of a trait with a genetic variant can be detected if the causal genetic variant is genotyped directly or more commonly if it is correlated with a genotyped SNP or combination of SNPs (haplotype).

In their analysis of 174 SNPs spread throughout the K^+ channel genes *KCNQ1*, *KCNH2*, *KCNE1* and *KCNE2* in a large community-based sample of Germans from the KORA project, Pfeufer and co-workers identified 3 novel variants controlling the QT-interval, rs757092 in *KCNQ1*, rs727957 in *KCNE1* and rs3815459 in *KCNH2*.[51] Besides confirmation of

these associations in an independent sample of the KORA population within the same study, the effects of rs757092 and rs3815459 were also subsequently confirmed by Gouas et al in their French sample.[55] In a study concentrating on *KCNH2* polymorphic variation carried out in the Framingham Heart Study population, Newton-Cheh et al. have recently linked another *KCNH2* variant (rs3807375) with QT interval.[52] Also here, the effect of the polymorphism was demonstrated in two independent samples of the study population. Since the minor allele of rs3807375 is correlated with the minor allele of rs3815459 from the study of Pfeufer et al.,[51] it is likely that these two observations relate to the effect of the same functional polymorphism.

The genome-wide association approach of Arking and co-workers[54] was the first one to be carried out for a cardiac electrophysiological phenotype. The fact that the strongest association for QTc in this study was found for a SNP in a gene previously unlinked to cardiac electrophysiology underscores the power of this approach in identifying novel molecular players for the phenotype of interest. This was a SNP (rs4657139) located 5' of exon 1 of the *NOS1AP* gene (also known as CAPON), encoding a regulator of nitric oxide synthase. The association of variation in the *NOS1AP* gene with QTc interval has recently been replicated in an independent population.[56]

NOS1AP is the C-terminal PDZ domain ligand to neuronal nitric oxide synthase (nNOS, encoded by the *NOS1* gene) and affects NMDA receptor-gated Ca^{2+} influx.[57] *NOS1AP* is expressed in human left ventricle.[54] Further knowledge on the effect of the *NOS1AP* gene product on cardiac electrophysiology presently relates to preliminary work in guinea pig ventricular myocytes.[58,59] These studies demonstrated interaction of the *NOS1AP* gene product with nNOS in heart, and that over-expression of *NOS1AP* accelerates cardiac repolarization via a reduction of L-type Ca^{2+} current (and to a lesser extent reduction of delayed rectifier K^+ current). Overexpression of *NOS1AP* is thought to lead to a reduction of L-type Ca^{2+} current by an upregulation of the nNOS-NO pathway. A common finding in

all of these studies is the fact that individual variants explain only a very small percentage of QT interval variation in the population (typically <1.5%) emphasizing the need for large sample sizes in searching for the underlying variants. Furthermore, effects could be gender dependent[46,51] and it is therefore vital to consider gender as a confounder variable during design of such association studies.

Polymorphisms modulating ECG conduction parameters

We have recently explored the concept that variability in regulation of cardiac Na^+ channel expression contributes to interindividual variability in cardiac conduction.[60] In this study we demonstrated that a haplotype within the promoter region of *SCN5A* (HapB) which is common in Asians (allele frequency 22%) and absent in Whites and Blacks, reduced reporter gene activity *in vitro* and was associated with longer PR and QRS intervals both in control subjects as well as in Brugada syndrome patients. The presence of HapB also influenced the extent of QRS-widening during challenge with Na^+ channel blockers in Brugada syndrome patients, identifying variability in expression of the drug target (the Na^+ channel) as a key mediator of variable response to Na^+ channel blockade. The fact that HapB is common in Asians (in whom Brugada syndrome is common) while absent in whites and has a large negative impact on cardiac conduction, a long-recognized feature of Brugada syndrome, prompted us to suggest that it could contribute to differences in Brugada syndrome as a function of ethnicity.

Polymorphisms modulating arrhythmia risk in common cardiac pathologies

Myocardial infarction, cardiac ischemia and cardiomyopathy are common risk factors for life-threatening cardiac arrhythmias in the general population. However not all individuals with these pathologies suffer arrhythmias and it is commonly held that also here, genetic variation, perhaps even at the same genetic loci as those modulating arrhythmia risk in

the primary rhythm diseases, could modulate risk. In support for a role of genetic modifiers of arrhythmia risk during myocardial infarction, we have recently demonstrated that a family history of sudden death constitutes a strong independent risk factor for ventricular fibrillation during a first acute myocardial infarction.[61] The nature of this genetic variation is however largely unknown. A polymorphism suspected to modulate arrhythmia risk in the general population is the S1103Y (referred to as S1102Y in some publications) polymorphism in *SCN5A.*[62,63] This variant is thought to promote arrhythmia susceptibility during exposure to extrinsic factors such as QT-prolonging medication, in line with a multi-hit pathogenesis for acquired cardiac arrhythmia.[64] This polymorphism occurs with a frequency of 8-13 % in Blacks and is absent in Caucasians, again pointing to a possible role of ethnic-specific polymorphisms in different incidence of arrhythmias across ethnicities.[62,65]

Concluding Remarks

The identification of genetic variation modulating risk in the primary arrhythmia syndromes would improve personalized risk assessment enabling assignment of optimal therapy through the development of risk prediction algorithms incorporating genetic factors in addition to clinical parameters. Genetic variants that to date have been identified for ECG intermediate phenotypes have till now only been associated with small effects, raising concerns that genetic modulation of cardiac electrophysiological phenotypes in general may be too modest and may consequently lack clinical discrimination. One could still argue that the additive effect of co-inheritance of groups or combinations of such polymorphisms could on the other hand prove useful. Nevertheless, as exemplified by the identification of *NOS1AP*, previously unlinked to cardiac electrophysiology, as a modulator of QT-interval, our efforts in identification of such modifiers can still point the way to a better understanding of

processes such as cardiac repolarization and conduction with the potential of identifying new therapeutic targets.

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