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sister underwent cardiac arrest as well. Family workup revealed asymptomatic parents and siblings, of which one had a positive stress test with multifocal premature ventricular contractions (PVCs). Gly3118Arg missense mutation was found in RYR2 with typical recessive segregation: The affected members are homozygous for the mutation whereas the non-affected parents and siblings are heterozygous (figure). This variant was only once described, and classified as variant of uncertain significance. It was not found in 60,000 sequenced genomes from unrelated individuals' database and is located in an area which is conserved in evolution. In the RYR2 protein the mutation is located in the cytosolic component of the RYR2 outside the areas with frequent cluster mutations.

The three affected members underwent ICD implantation and have been receiving metoprolol therapy. During nine years of follow up the female had an episode of multiple ventricular fibrillation episodes and shocks (figure). The Metoprolol dose was increased and no further episodes occurred.

Conclusion: This is a first report of an RYR2 variant and autosomal recessive CPVT1. It suggests different or a less severe mechanism for the disruption of RYR2 function.

P1581

Genetic polymorphism of Ryanodine receptor 2 and left atrial voltage in patients with atrial fibrillation

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Background: Abnormal calcium release from sarcoplasmic reticulum (SR) is considered an important mechanism of atrial fibrillation (AF). Dysfunction of type-2 ryanodine receptor channels (RyR2) promote ectopic activity, conduction abnormalities, and AF-related remodeling.

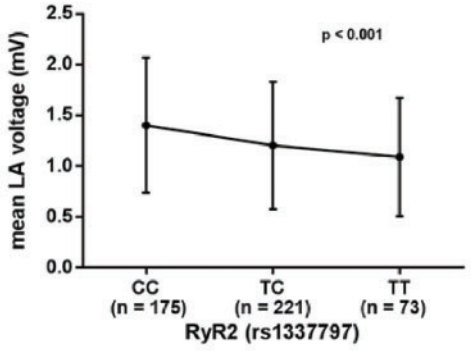
Purpose: We investigated the association between genetic polymorphisms of RyR2 and left atrial (LA) voltage among AF patients.

Methods: Mean LA voltage was obtained from individual LA voltage mapping in 469 patients who underwent AF ablation. Total 292 single nucleotide polymorphisms (SNPs) in RyR2 were analyzed.

Results: In multivariate linear regression analysis adjusted by age, sex, and AF type, two SNPs (rs1337797, rs2490372) in RyR2 were independently associated with mean LA voltage after Bonferroni adjustment (rs1337797: beta -0.182, 95% confidence interval [CI] -0.261 to -0.102, $p = 9.6x10\text{-}6$, $p = 0.004$ with Bonferroni adjustment; rs2490372: beta -0.164, 95% CI -0.243 to -0.083, $p = 7.1x10\text{-}5$, $p = 0.028$ with Bonferroni adjustment). In rs1337797, the heterozygous haplotype ($n = 221$) demonstrated a 14% lower mean LA voltage (1.20 mV) and the homozygous risk allele carriers ($n = 73$) demonstrated a 22% lower mean LA voltage (1.09 mV) compared with wild type ($n = 175$, 1.40 mV) ($p < 0.001$).

Conclusions: Two risk alleles in RyR2, rs1337797 and rs2490372, are independently associated with decreased mean LA voltage in AF patients. Our findings suggest that common genetic variations in RyR2 also related to atrial structural remodeling.

Figure. Mean left atrial voltage according to genotype of rs1337797.



Abstract P1581 Figure.

P1582

Molecular basis of cardiac pacemaker ageing in mouse

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Background: With ageing it has been shown that there is a decline in the pacemaker function within the heart. There is a reduced maximal and intrinsic heart rate, an increase in the prevalence of sinus node disease such as sick sinus syndrome, as well as a reduction in heart rate variability, which is associated with increased mortality and morbidity.

Purpose: The aim of this study was to examine how the mRNA expression of key transcripts relating to pacemaking function in the sinus node changes with age.

Methods: Sinus node tissue was collected from 3 month old adult (n=10) and 18 month old aged (n=7) C57/Bl6J mice. No difference in heart weight/body weight ratio was observed. The tissue was characterised by confirming high expression of HCN4 and low expression of GJA1 (Cx43) mRNA expected within sinus node tissue. 90 genes were investigated by qPCR using TaqMan Array cards. A moderated t-test was used for statistics. $P<0.05$ was taken to be significant.

Results: We found no significant difference in the expression of the hyperpolarization-activated cyclic nucleotide–gated channel (HCN) genes, HCN1, HCN2 and HCN4, responsible for funny current (If), or CACNA1C (Cav1.2) and CACNA1D (Cav1.3) responsible for the L-type Ca2+ current (ICaL). CACNA1H (Cav3.2, ICaT) expression was significantly increased in the aged sinus node as was the expression of Na+ channel β subunits SCN1B, SCN2B and SCN4B. No change was seen in KCNQ1 (KvLQT1, IKs), KCNH2 (ERG, IKr) and KCNA5 (Kv1.5, IKur) expression, which contribute to the delayed outward rectifier currents. GJC1 which encodes the small conductance gap junctional protein Cx45 was significantly increased with age, and there was a significant reduction in the mRNA expression of Col3a1. The mRNA expression of transcription factor Nkx2.5 was significantly increased with age, and TBX5 and GATA4 both showed a tendency towards a weak up regulation. These transcription factors are involved in the establishment and maintenance of the pacemaking phenotype in the sinus node.

Conclusion: Our data shows no significant changes in the mRNA expression for ion channels responsible for the major pacemaking currents in the sinus node, If, and ICaL. The change in expression of Na+ channel β subunits may alter the kinetics and trafficking of the Na+ channels contributing to delayed repolarization and action potential prolongation in the aged sinus node. The altered sinus node function seen with ageing may be due to altered protein expression rather than a major remodelling of the ion channel mRNA expression.

P1583

Targeted sequencing identified de novo RYR2 mutation cause catecholaminergic polymorphic ventricular tachycardia

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Background: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an exercise-induced hereditary arrhythmia syndrome often manifesting as ventricular arrhythmias, syncope or sudden death. CPVT is characterized by the occurrence of adrenergic mediated polymorphic ventricular tachyarrhythmias.

Purpose: To study a young patient with multiple syncope and a complicated arrhythmias, try to find out the genetic basis and possible pharmacotherapy.

Methods: We performed next-generation targeted semiconductor sequencing of the proband using a custom designed "arrhythmia" panel. The "arrhythmia" panel included all five CPVT pathogenic genes, RYR2, CASQ2, KCNJ2, CALM1 and TRDN. The filtered mutation was bi-directional Sanger sequencing validated in the patient with all healthy relatives as well as 500 unrelated age and geographic matched healthy controls.

Results: An otherwise healthy boy born in 2010 and suffered from CPVT. He had recurrent syncope since age 3. Episodes occurred multiple times per year, typically, the episodes appeared to be triggered by sudden stressful events such as noises, fever, physical movement, or fear. ECG revealed atrial flutter and Holter monitoring showed polymorphic ventricular tachycardia. After genetic testing, we identified a de novo heterozygous likely pathogenic missense mutation c.12534C>G (p.Asn4178Lys) in RYR2 gene of the patient. Except for this mutation, we detected no other likely pathogenic mutation in all 74 hereditary arrhythmia related genes. This mutation was not exist in all healthy relatives of the patient or in the in the 500 unrelated ethnically matched healthy controls by Sanger sequencing. It was not in the commonly used databases either. A combination of drug therapy of beta-blocker and verapamil was used and no more syncope and VT events in the patient.

Conclusions: We identified a novel de novo heterozygous pathogenic missense mutation c.12534C>G (p.Asn4178Lys) in RYR2 gene in a Han Chinese CPVT pedigree using targeted next-generation sequencing and Sanger sequencing. This mutation was co-segregated in the pedigree and not identified in an extra 500 unrelated matched healthy controls. Our study enriches the mutation spectrum of CPVT and will facilitate the genetic diagnosis of this disease.

P1584

A HCN4 previously undescribed variant in a large kindred with familial atrial fibrillation

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On behalf of: ITACA proyect investigators

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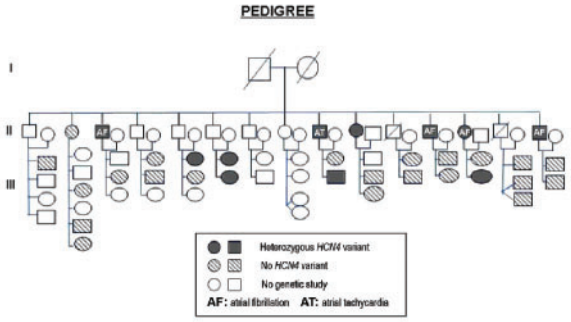
BACKGROUND: Genetic background can be difficult to relate to accepted mechanisms of atrial fibrillation (AF). Mutation of genes encoding ionic channels can result in early onset, familial AF while other variants can be associated to AF risk without clear definition of mechanisms. Mutations in hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4 - 15q24.1) belong to the second category.
OBJECTIVE: Genetic and clinical study of three generations (G) of a large kindred with high incidence of AF (Figure). First G (G-I), both parents dead, no clinical information. Second G (G-II) made of 15 siblings, 4 with clinical AF. Third generation (G-III) made of 43 subjects.
METHODS: Long-term ECG monitoring (average 12 days / 282 ±55 h / 22 ±1.5 h per day) in subjects without clinical AF by means of full time recording of 1 ECG lead supported by a new type of textile electrodes mounted on a wearable band, with good tolerance. Full visual review of continuous recordings by 2 cardiologists, supported by analysis software, blinded to genetic testing. Doubtful findings resolved by wider consensus.
Genetic study: The 4 affected siblings were genotyped by next generation sequencing by means of a Haloplex Custom panel including coding regions and untranslated (UTR) boundaries of 82 genes encoding cardiac ion channels, proteins of cardiac channelosomes, and other proteins that modulate ion channel activity. Variants found were confirmed by the Sanger method.
RESULTS: Fifty % of subjects were women (33% in G-II, 53% in G-III, P =0.65). Average age 38±14 y/o G-II subjects were older (63±7 y/o vs 32±8, P<0.001), had more hypertension (50% vs 0%, P=0.004), dislipidemia in (50% vs 24%, P=0.3), smoking habit (50% vs 7.7%, P=1), overweight (80% vs 38%, P=1) and sleep apnea (50% vs 24%,P=0.034). Genetic testing and Holter were performed in 7 of 13 living G-II and 26 of 43 G-III subjects (Figure). All 4 G-II subjects with clinical AF shared a heterozygous variant (NM_005477.2:c.3488C>A) at the HCN4 gene, leading to substitution of Pro1163 residue, located at the end of the C-terminus of the channel, to His (p.P1163H hcn4). This variant was also indentified by Sanger in 2 other G-II subjects, of whom 1 had frequent atrial extrasystoles and a 6 min run of atrial tachycardia in Holter. Five G-III subjects had the same heterozygous HCN4 mutation but no AF clinically or in Holter. Sinus node dysfunction was not evident in any of the subjects clinically or by Holter.
CONCLUSION: This large family with a new HCN4 variant and a high clinical incidence of AF shows a complex genotype/phenotype relationship. The incidence of AF was not related to sinus node dysfunction. The relationship of the HCN4 variant with the incidence of AF remains obscure, suggesting a multi-factorial mechanism, including age, and the possible effect on ionic currents other than If. Follow-up of relatives without AF should help clarify the issue.



Abstract P1584 Figure. Pedigree.

P1585

Spectrum of manifestations of a rare Channelopathy

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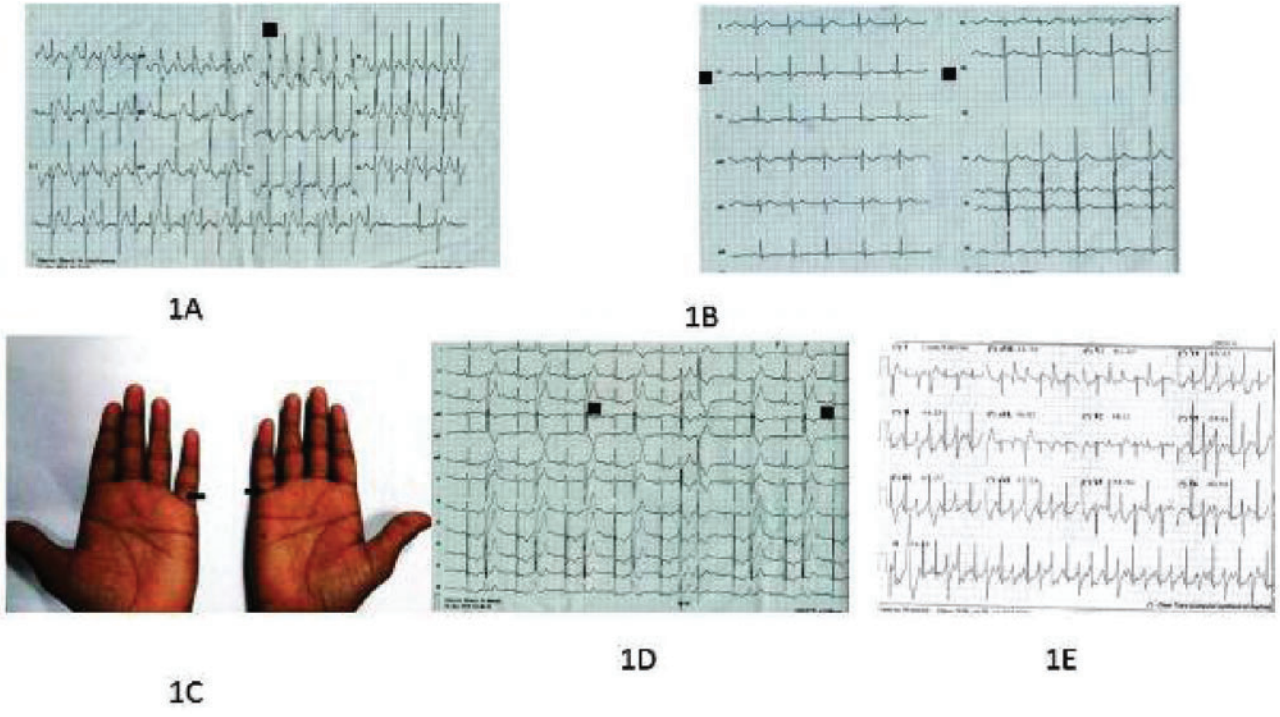
Background: Andersen Tawil Syndrome is a rare Channelopathy characterized by triad of dysmorphic features, neuro muscular abnormalities and arrhythmias. We describe two cases with different clinical presentations.
Material and methods: NA
Results:
Case 1: 10 years aged male child presented with history of exertional palpitations without any history of syncope or family history of similar disorder. His electrocardiogram (ECG) showed bidirectional ventricular tachycardia (figure 1A). It was reverted to sinus rhythm by combination of beta-blocker and flecainide. ECG in sinus rhythm showed U wave in mid precordial lead with prolong QU interval(Figure 1B).General physical examination documented fifth finger clinodactyly(Figure 1C). Although he had no history of muscle weakness, neuro electrophysiological examination after short and prolong exercise showed initial increase in compound muscle action potential amplitude(CAMP) with a progressive drop over 20-40 minutes with slow recovery over one hour. Genetic analysis showed heterozygous variant in the KCNJ2 gene.



Abstract P1585 Figure.