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Atrial fibrillation: from Mechanisms to Population Science

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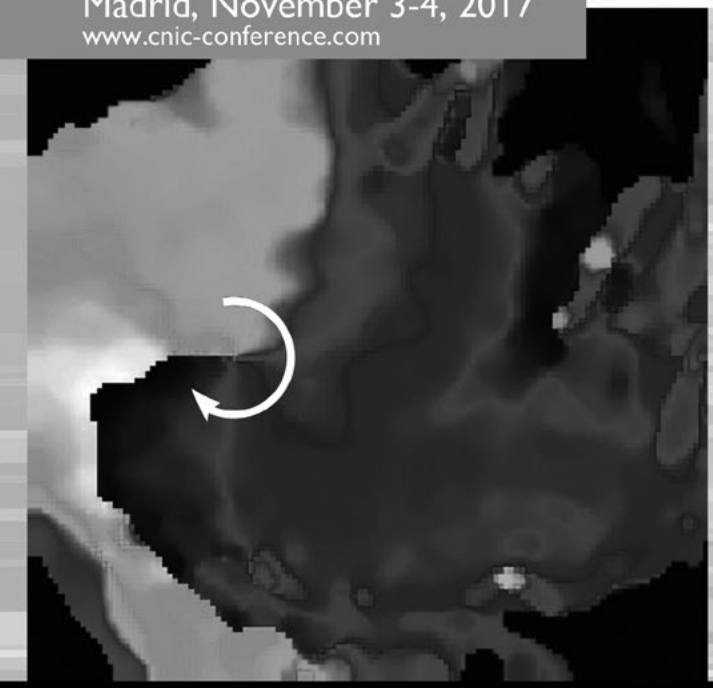

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PROGRAMME

Friday, November 3, 2017

08:00-08:30 Registration

08:30 Welcome

08:30-09:00 Opening talk: **Borja Ibáñez**. CNIC Clinical Research Director

Session I - AF in populations, genomics and epigenetics

Discussion leaders: Guadalupe Sabio, Miguel Manzanares

09:00-09:30 **Emelia Benjamin.** Boston University School of Medicine, USA
"Can we prevent atrial fibrillation?"

09:30-10:00 **Patrick Ellinor.** Harvard University, Boston, USA
"Emerging directions in the genetics of atrial fibrillation"

10:00-11:00 **Coffee break & poster session**

11:00-11:30 **Vincent Christoffels.** University of Amsterdam, Holland
"Transcriptional control of cardiac electrical patterning"

Selected short talks

11:30-11:45 **Rosa Doñate.** INMG, University of Lyon, France
"Atrial structural remodeling gene variants in patients with atrial fibrillation"

11:45-12:00 **Raquel Rouco.** Center for Arrhythmia Research, USA, and CNIC, Spain
"Genomic expression during atrial fibrillation progression in a sheep model of persistent AF"

12:00-13:30 **Poster session & Lunch**

Session II - Pathogenesis of AF

Discussion leaders: Juan Bernal, Juan Tamargo

13:30-14:00 **Ulrich Schotten.** University of Maastricht, Holland
"The multifactorial pathogenesis of atrial remodelling and atrial fibrillation"

14:00-14:30 **Barbara Casadei.** Oxford University, UK
"Atrial fibrillation and cardiomyopathy: the chicken or the egg?"

PROGRAMME

	Selected short talks
14:30-14:45	**Sandra Hoffmann.** Institute of Human Genetics, Heidelberg, Germany *"SHOX2 – A promising candidate gene for atrial fibrillation"*
14:45-15:00	**Diego Franco.** University of Jaen, Spain *"Hyperthyroidism, but not hypertension, impairs PITX2 expression leading to Wnt-microRNA-ion channel remodeling"*

Session III - Altered metabolism and atrial adiposis

Discussion leaders: Julian Pérez-Villacastín, Javier Saiz

15:00-15:30	**Sander Verheule.** University of Maastricht, Holland *"Metabolic impact of AF"*
15:30-16:00	**Stephane Hatem.** Sorbonne Université, Paris, France *"Cardiac adipose tissue and atrial fibrillation"*
	Selected short talks
16:00-16:15	**Alexey Kulikov.** Cardiology Research And Production Complex, Moscow, Russia *"Electrophysiologic study of atrioventricular conduction and electrophysiological parameters of atria in patients with long-standing persistent atrial fibrillation undergoing surgical correction of mitral valve pathology combined with 'maze IIIB' procedure"*
16:15-16:30	**Miguel Rodrigo.** Universitat Politecnica de Valencia, Spain. Stanford Hospital and Clinics, USA *"Driver location by body surface and endocardial basket mapping of human atrial fibrillation"*
16:30-17:30	**Coffee break & poster session**

Session IV - Genes, ion channels and gene therapy in AF

Discussion leaders: Felipe Atienza, David Filgueiras

17:30-18:00	**Eva Delpón.** Complutense University, Madrid, Spain *"Novel ion channel modifying genes in atrial fibrillation"*

PROGRAMME

18:00-18:30	**Dobrimir Dobrev.** University of Duisburg-Essen, Germany *"Molecular basis and role of dysregulated Ca2+-dependent K+channels in AF patients"*
18:30-19:00	**Rishi Arora.** Northwestern University, Chicago, USA *"Novel gene therapy approaches to target electrical and structural remodeling in atrial fibrillation"*

Saturday, November 4, 2017

Session V - The rotor substrate in silico, ex vivo and in humans

Discussion leaders: Francisco García-Cosío, David Calvo

08:30-09:00	**Natalia Trayanova.** Johns Hopkins University, Baltimore, USA *"AF rotors in the fibrotic substrate"*
09:00-09:30	**Omer Berenfeld.** University of Michigan, USA *"Spatio-temporal AF excitation patterns in the frequency and phase domains"*
09:30-10:00	**Sanjiv Narayan.** Stanford University, USA *"Rotational drivers in clinical atrial fibrillation"*
10:00-10:30	**Stefan Luther.** Max Planck Institute, Göttingen, Germany *"Electromechanical vortex filaments during cardiac fibrillation"*
10:30-11:00	**Coffee break**

Session VI - The real world in today´s AF therapy

Discussion leaders: Jesús Almendral, José Luis Merino

11:00-11:30	**John Camm.** St George's University of London, UK *"The classification of atrial fibrillation: research, guidelines, clinical practice and back again"*
11:30-12:00	**Meleze Hocini.** University of Bordeaux, France *"AF ablation guided by noninvasive mapping: from stepwise to rotor ablation"*
12:00-12:30	**Karl Heinz Kuck.** University of Hamburg, Germany *"What have we learned of ablation procedures for atrial fibrillation?"*
12:30-13:00	**Round up, prizes and farewell**

POSTER 7. A DLG1 POLYMORPHISM SHORTENS THE ACTION POTENTIAL DURATION AND THE QT INTERVAL

D. Tinaquero; P. Nieto-Marín; RG. Utrilla; S. Alfayate; M. Matamoros; M. Pérez-Hernández; M. Tamargo; J. Toquero; FG. Cosío; R. Peinado; J. Pérez-Villacastín; JA. Bernal; J. Tamargo; R. Caballero; E. Delpón

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Introduction: SAP97 is an scaffolding protein encoded by the DLG1 gene that interacts with several cardiac ion channels including those underlying the fast Na (I_{Na}), the inward rectifier (I_{K1}) and the transient outward (I_{to}) currents, respectively. By next generation sequencing we identified a common [5.3% in the European (non Finnish) population] DLG1 polymorphism (rs34492126) in a man and two sisters diagnosed with Brugada Syndrome, two siblings with familial atrial fibrillation, a man with idiopathic ventricular fibrillation and another with early repolarization syndrome.

Purpose: This work aimed to determine the electrophysiological consequences of the SAP97 p.P888L polymorphism and whether they can contribute to the phenotype of the patients.

Methods: Native (WT) and p.P888L SAP97 tagged with ds-red were cotransfected or not together with the cDNA encoding the alpha and beta subunits underlying human I_{Na}, I_{Ca}, I_{to}, and I_{K1} currents, respectively, in Chinese hamster ovary (CHO) cells. Two cardiac–specific transgenic-like mouse models on the basis of adeno-associated virus gene transfer were created expressing WT and p.P888L SAP97, respectively. Currents and action potentials (APs) were recorded using patch-clamp.

Results: Co-expression of WT SAP97 significantly increased the I_{K1}, I_{Na}, and I_{to} in CHO cells (by 181%, 44%, and 77% respectively, $n \geq 20$, $P<0.05$). These results were confirmed in ventricular myocytes from SAP97 overexpressing mice. Conversely, overexpression of WT SAP97 halved the I_{CaL} densities recorded in both CHO cells and mouse ventricular myocytes. The effects produced by p.P888L SAP97 over the I_{Na} and the I_{CaL} were undistinguishable from those produced by the WT form, results that were confirmed in p.P888L cardiomyocytes. Conversely, in both CHO cells and mouse myocytes, overexpression of p.P888L SAP97 markedly reduced the I_{K1}, i.e, the opposite effect to that produced by SAP97 WT. Regarding the I_{to}, p.P888L also increased the I_{to} peak density, but, more importantly, it doubled the time constant of current inactivation. The slowing of the inactivation process increased the I_{to} charge density (133%) in both CHO cells and mouse myocytes. As a consequence, the AP duration (APD) measured at 20% and 50% of repolarization of the APs recorded in p.P888L SAP97 myocytes was significantly shortened. Electrocardiographic recordings in transgenic-like mice demonstrated that p.P888L overexpression shortened the QT interval compared with WT SAP97 overexpressing mice.

Conclusions: The SAP97 p.P888L polymorphism shortens the QT interval and the APD as a consequence of a marked increase of the Ito charge. Therefore, this polymorphism could exacerbate the phenotypic manifestations in patients affected by arrhythmogenic syndromes characterized by the repolarization acceleration.

POSTER 8. A MUTATION IN THE GENE ENCODING THE TBX5 TRANSCRIPTION FACTOR IS ASSOCIATED WITH THE BRUGADA SYNDROME

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Introduction: Loss-of-function mutations in SCN5A, the gene encoding cardiac Nav1.5 channels, are associated with primary arrhythmogenic syndromes such as the Brugada syndrome. Strikingly, many patients with Brugada Syndrome do not carry SCN5A mutations, pointing to the implication of mutations in other genes affecting expression and/or function of Nav1.5 channels. The transcription factor Tbx5, encoded by the TBX5 gene, plays a key role in cardiac development. Moreover, it has been described that it drives SCN5A expression in the adult mouse heart. In a proband diagnosed with Brugada syndrome, in whom screening for mutations in all described Brugada Syndrome genes was negative, next generation sequencing identified a missense mutation in TBX5 encoding for p.F206L Tbx5. This variation was confirmed by Sanger, predicted as pathogenic and was not previously annotated.

Purpose: We aimed to study the effects of p.F206L Tbx5 on the cardiac sodium current (I_{Na}) to unravel whether it can be associated to Brugada syndrome.

Methods: Human native (WT) and mutated Tbx5 tagged with GFP were transfected in HL-1 cells or included in lentiviral particles for infecting human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM). Peak and late I_{Na} (I_{NaL}) were recorded using the whole-cell patch-clamp at room temperature. Luciferase reporter assays were conducted to determine the effects of this mutation on Nav1.5 channel promoter activity.

Results: Transfection of HL-1 cells with WT Tbx5 significantly increased the peak I_{Na} density (from -37.5±5.1 to -62.6±8.2 pA/pF, n≥6, P<0.05), whereas it did not modify the kinetics or voltage-dependence of activation and inactivation of the I_{Na}. Conversely, p.F206L Tbx5 strongly reduced the peak I_{Na} density (-6.7±0.2 pA/pF; n=6; P<0.01) compared to cells transfected or not with Tbx5 WT. However, p.F206L Tbx5 did not modify time- and voltage-dependent properties of the current. Neither WT nor p.F206L Tbx5, modified the I_{NaL} density (-1.9±0.7 pA/pF at -20 mV; P>0.05). The effects produced by Tbx5 either WT or mutated on HL-1 cells were completely reproduced in hiPSC-CM. Indeed, in hiPSC-CM, WT Tbx5 increased (-27.6±1.9 pA/pF; n=7), while p.F206L Tbx5 decreased (-9.5±1.9 pA/pF) the peak I_{Na} compared to non-infected cells (-19.4±2.8 pA/pF; n=10; P<0.05), leaving the time- and voltage-dependent properties of the current unaffected. Luciferase reporter assays demonstrated that WT Tbx5 doubled the activity of the human SCN5A minimal promoter, whereas p.F206L completely suppressed Tbx5 pro-transcriptional activity over SCN5A.

Conclusions: The p.F206L mutation disables the remarkable Tbx5 pro-transcriptional activity over human SCN5A. Therefore, loss-of-function TBX5 mutations could be associated with the Brugada syndrome.

POSTER 22. HCN4 AND GATA5 PREVIOUSLY UNDESCRIBED VARIANTS IN LARGE KINDRED WITH FAMILIAL ATRIAL FIBRILLATION

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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 the HCN4 and GATA5 genes encoding the hyperpolarization-activated cyclic nucleotide-gated channel 4 (hcn4) and the GATA5 transcription factor, respectively belong to the second category.

OBJECTIVE

Genetic and clinical study of two generations (G) of a large kindred with somewhat high incidence of AF.

First G (G-I) made of 15 siblings, 4 with clinical AF. Second generation (G-II) made of 43 subjects.

METHODS

Long-term ECG monitoring: Full-time, continuous monitoring of 1 ECG lead (average 12 days / 282 ±55 h / 22 ±1.5 h per day) was performed in subjects without clinical AF supported by a new type of textile electrodes mounted on a wearable band, with good tolerance. Full visual review of continuous recordings, supported by analysis software, was done by 2 cardiologists, blinded to genetic testing. Doubtful findings were 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. The confirmation of the variants found and the genetic test were done with the Sanger method. The variants found in the 4 index cases were searched in the rest of the family using the Sanger method.

RESULTS

We studied a total of 42 subjects through genetic study of which 40 were studied through prolonged monitoring, 7 of 13 living G-I and 35 of 43 G-II subjects. Fifty percent of subjects were women (33% in G- I, 53% in G-II, P =0.65). Average age 38±14 y/o G-I subjects were older (63±7 y/o vs 32±8, P<0.001), had more hypertension (50% vs 0%, P=0.004), dyslipidemia 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). All 4 G-I 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) and a heterozygous variant (chr20:61040536 G,A) at an intronic region of the GATA5 gene (NM_080473.4). The HCN4 variant was also indentified by Sanger in 4 G-I subjects and 6 G-II subjects, of whom, 1 had frequent atrial extrasystoles and 2 had frequent atrial tachycardia. No AF clinically or in Holter was detected. However, no significant differences were found regarding the incidence of atrial arrhythmias or left atrial size in the carriers of the variant. Sinus node dysfunction was not evident in any of the subjects clinically or by Holter. The GATA variant was also identified by sanger in 5 other G-I subjects and 13 G-II subjects, of whom 2 had frequent atrial extrasystoles and 3 had frequent atrial tachycardia. The only subject with AF not previously known also carries the variant. Nevertheless no significant differences were found regarding the incidence of atrial arrhythmias or left atrial size between subjects carrying or not the variant.

CONCLUSION

This large family with a new HCN4 and GATA5 variants and a somewhat high clinical incidence of AF shows a complex genotype/phenotype relationship. The incidence of AF was not related to sinus node dysfunction. The relationship with AF and other clinically silent atrial arrhythmias was not clear in this large kindred. Follow-up of relatives without AF should help clarify the issue.