DOCTORAT BIOLOGIE BRETAGNE SANTE LOIRE

Year 2022/2023

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** **Requested** ☒ **Acquired** ☐	**Funding origin:**
Thesis title: **C-UN-identification and characterization of the genetic factors underlying the phenotypic variability in the arrhythmogenic right ventricular cardiomyopathy**		3 keywords: genetics, epigenetics, cardiomyocytes derived iPSC
Unit / team: **Inserm UMR 1087/CNRS UMR 6291 TEAM I : Human genetics- JJ Schott – R Redon**		
Supervisor's name: **Jean-Jacques Schott**		Phone number: 0228080151 Email address: Jean-Jacques.Schott@univ-nantes.fr

Socio-economic and scientific context (approximately 10 lines):
The arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare disease, characterized by a progressive replacement of cardiomyocytes by fibrosis and adipose tissues. Ventricular arrhythmic events or even sudden death can be the first symptom, especially in young (sportive) adults. The early diagnosis of this disease is mandatory in order to provide appropriate clinical management with the reduction of mortality and prevention of disease progression. Diagnostic criteria are standardized in a Task Force, requiring a combination of structural, electrocardiographic, rhythmic, histological and genetic factors. About 50% of affected patients carry a variant in genes encoding desmosomal proteins (PKP2 (Plakophilin-2), DSC2 (Desmocollin-2), DSG2 (Desmoglein-2), DSP (Desmoplakin) and JUP (Junction Plakoglobin). Despite an autosomal dominant model described initially, the low penetrance and the large variability of expressivity observed among mutations carriers, even within a family 1) avoid to use the molecular diagnostic to apply risk stratification and preventive strategies, 2) suggest that modulators may play a major role in the phenotype variability observed.

Working hypothesis and aims (approximately 8 lines):
In another rare cardiac disorder at risk of sudden cardiac death (the Brugada syndrome), we demonstrated through a genome wide association study (GWAS) the major role of common variants in the disease susceptibility, new genes and pathways implied in the pathophysiology of the Brugada syndrome. Furthermore, we successfully applied the genetics markers identified on other and more common cardiac disease, confirming the relevance of these rare disease as a model for more common and complex cardiovascular disorders. (Barc et al. *Nature Genetics*, 2022)

The aim of our study is to uncover by a GWAS genetic loci that modulate susceptibility to ARVC, to characterize further the ARVC genetic architecture and to uncover new molecular mechanisms underlying the disease. The ultimate aim of this thesis is to propose a (more) personalized medicine to stratify the risk of arrhythmic event inpatients and the adapt the clinical management.

Main milestones of the thesis (approximately 12 lines):
Based on a large cohort of >850 unrelated ARVC cases and > 5600 controls individuals, we have performed a pilot GWAS analysis and uncover 3 susceptibility variants that passed the genome-wide statistical significance threshold (P< 5.10-8) and 2 additional with a suggestive P-value (<1. 10-6). Among those 2 are in the vicinity of desmosal gene loci (PKP2 and DSC2) and 4 point to new genes, of which KLF12 already reported to play a role in cardiac conduction. All signals are located in non-coding regions, functional annotation with epigenetic and chromatin conformation data suggest the implication of enhancer regions and gene distance regulation mechanisms. Functional studies, using genome editing on human iPSC derived cardiomyocytes are required to disclose the role of the genes/regulatory region identified. This approach run in routine in the group will allow to perform 1) functional annotation of the genome to locate and characterize the role of the non-coding region associated with the phenotype, 2) identify the molecular mechanisms associating these non-coding/regulatory regions to target genes and 3) conduct functional analysis to characterize the role of these genes in the pathophysiology of the ARVC. Furthermore, a collaboration with Dr Moore-Morris at the Institute of Functional Genomics of Montpellier with be established to characterize the role of the new genes in cardiac (patho)physiology.

This project owns an international component through the International Research Project (IRP-Gaines) that will allow short stays of the PhD student at our long-lasting collaborators lab (the group of Prof. Bezzina; Amsterdam university) where a similar effort is ongoing. This collaboration in the context of such large genome wide studies has been recently successful and led recently to the publication of an article in Nature Genetics (DOI: 10.1038/s41588-021-01007-6). The merge of the two patient populations will allow to the PhD student to reach a critical size to develop a polygenic risk score and then propose a personalized risk stratification.

Scientific and technical skills required by the candidate (2 lines):
Genetics, epigenetics, iPSC cell culture, IPSC differentiation into cardiomyocytes, genome editing, molecular biology, cardiac physiology, knowledge in new generation sequencing data interpretation.

3 publications from the team related to the topic (last 5 years):

1. Genome-wide association analyses identify new Brugada syndrome risk loci and highlight a new mechanism of sodium channel regulation in disease susceptibility.
Barc J, Tadros R, Glinge C, Chiang DY, Jouni M, Simonet F, Jurgens SJ, Baudic M, Nicastro M, Potet F, Offerhaus JA, Walsh R, Choi SH, Verkerk AO, Mizusawa Y, Anys S, Minois D, Arnaud M, Duchateau J, Wijeyeratne YD, Muir A, Papadakis M, Castelletti S, Torchio M, Ortuño CG, Lacunza J, Giachino DF, Cerrato N, Martins RP, Campuzano O, Van Dooren S, Thollet A, Kyndt F, Mazzanti A, Clémenty N, Bisson A,

Corveleyn A, Stallmeyer B, Dittmann S, Saenen J, Noël A, Honarbakhsh S, Rudic B, Marzak H, Rowe MK, Federspiel C, Le Page S, Placide L, Milhem A, Barajas-Martinez H, Beckmann BM, Krapels IP, Steinfurt J, Winkel BG, Jabbari R, Shoemaker MB, Boukens BJ, Škorić-Milosavljević D, Bikker H, Manevy FC, Lichtner P, Ribasés M, Meitinger T, Müller-Nurasyid M; KORA-Study Group, Veldink JH, van den Berg LH, Van Damme P, Cusi D, Lanzani C, Rigade S, Charpentier E, Baron E, Bonnaud S, Lecointe S, Donnart A, Le Marec H, Chatel S, Karakachoff M, Bézieau S, London B, Tfelt-Hansen J, Roden D, Odening KE, Cerrone M, Chinitz LA, Volders PG, van de Berg MP, Laurent G, Faivre L, Antzelevitch C, Kääb S, Arnaout AA, Dupuis JM, Pasquie JL, Billon O, Roberts JD, Jesel L, Borggrefe M, Lambiase PD, Mansourati J, Loeys B, Leenhardt A, Guicheney P, Maury P, Schulze-Bahr E, Robyns T, Breckpot J, Babuty D, Priori SG, Napolitano C; Nantes Referral Center for inherited cardiac arrhythmia, de Asmundis C, Brugada P, Brugada R, Arbelo E, Brugada J, Mabo P, Behar N, Giustetto C, Molina MS, Gimeno JR, Hasdemir C, Schwartz PJ, Crotti L, McKeown PP, Sharma S, Behr ER, Haissaguerre M, Sacher F, Rooryck C, Tan HL, Remme CA, Postema PG, Delmar M, Ellinor PT, Lubitz SA, Gourraud JB, Tanck MW, George AL Jr, MacRae CA, Burridge PW, Dina C, Probst V, Wilde AA, **Schott JJ, Redon R**, Bezzina CR.
Nat Genet. 2022 Feb 24. doi: 10.1038/s41588-021-01007-6.

2. RRAD mutation causes electrical and cytoskeletal defects in cardiomyocytes derived from a familial case of Brugada syndrome.
Belbachir N, Portero V, Al Sayed ZR, Gourraud JB, Dilasser F, Jesel L, Guo H, Wu H, Gaborit N, Guilluy C, Girardeau A, Bonnaud S, Simonet F, Karakachoff M, Pattier S, Scott C, Burel S, Marionneau C, Chariau C, Gaignerie A, David L, Genin E, Deleuze JF, Dina C, Sauzeau V, Loirand G, Baró I, **Schott JJ**, Probst V, Wu JC, Redon R, Charpentier F, Le Scouarnec S. *Eur Heart J. 2019 Oct*

3. Progressive Atrial Conduction Defects Associated With Bone Malformation Caused by a Connexin-45 Mutation.
Seki A, Ishikawa T, Daumy X, Mishima H, **Barc J**, Sasaki R, Nishii K, Saito K, Urano M, Ohno S, Otsuki S, Kimoto H, Baruteau AE, Thollet A, Fouchard S, Bonnaud S, Parent P, Shibata Y, Perrin JP, Le Marec H, Hagiwara N, Mercier S, Horie M, Probst V, Yoshiura KI, Redon R, **Schott JJ**, Makita N. *J Am Coll Cardiol. 2017 Jul*

National and international collaborations:

Extensive collaboration in the setting of the IRP GAINES:

- Prof. Connie Bezzina; University of Amsterdam's Faculty of Medicine, Amsterdam, The Netherlands

- Prof. Makita Naomasa; National Cerebral and Cardiovascular Center Osaka, Japan

- Prof. Mundlos Stephan at the Max Planck institute for Molecular genetics in Berlin, Germany

Extensive collaboration in the setting of the ARVC network:

- Prof. E. Gandjbakhch, Institut de Cardiologie CHU Pitie Salpêtrière, Inserm 1166, Paris, FR

- Prof. P. Chevalier, Hospices Civils de Lyon, Institut Neuromyogène, CNRS UMR 5310/INSERM U1217, Lyon, FR

- Drs N. Roux-Buisson, J. Thevenon et G. Billy, CHU Grenoble-Alpes, FR

- Prof Lia Crotti, Istituto Auxologico Italiano IRCCS, Milan, IT