PhD position: Cardiac Regulome Impairment: New Mechanisms For Ventricular Arrhythmia Associated With Sudden Cardiac Death

Laboratory: l’institut du thorax, Inserm UMR 1087/CNRS UMR 6291, Nantes, France
Research team: Cardiovascular genetics team
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L’institut du thorax (ITX) is a structure at the forefront of translational research against cardiac arrhythmia at risk of sudden cardiac death (SCD). Our primary objective is to improve healthcare by combining basic research and clinical activity into translational research programs. Within the ITX, the team ‘Cardiovascular Genetics’ led by Jean-Jacques Schott, is developing state of the art projects in genomics and pathophysiology of cardiac arrhythmias. More specifically Schott’s team employs multi-omics screening strategies, on ‘sensitized’ models of SCD, such as the Brugada syndrome (BrS), taking advantage of large pedigrees and the largest worldwide cohorts of patients diagnosed with heart electrical disorders.

The lack of relevant markers for SCD led us to investigate the non-coding regions of the genome, seats of gene regulation. By extending our previous Brugada Syndrome (BrS) genome wide association study (Bezzina et al Nat Genetics 2013) with today’s, the largest worldwide BrS collection (>2800 BrS cases recruited over 40 international centres), we identified 21 variants (all located in non-coding regions) that increase dramatically the risk to develop the disease and are likely relevant to the broad problem of SCD. Among them, six are pointing to transcription factors (TF), suggesting a strong involvement of the transcriptional regulation in cardiac arrhythmia diseases.

Furthermore we initiated a large and comprehensive genetic exploration by applying whole genome sequencing (WGS) on a total set of 344 French & 500 Dutch/British BrS cases. This approach opens unique opportunities to interrogate the full spectrum genetic variations so far unexplored such as the low-frequency (MAF<5%) coding and non-coding genetic variants with BrS susceptibility.

However converting the genetic findings to molecular mechanisms is challenging since signals identified are located within non-coding regions. Hence, using human cardiomyocytes derived from induced pluripotent stem cells (iPSCs), the project aims to firstly characterize the human cardiac regulome by identifying the cardiac gene regulatory regions (GRRs) using ATAC-seq and ChIP-seq approaches and the nature and location of the major cardiac transcription factors (TF) implicated in gene regulation. We will then specifically investigate the 21 BrS loci by identifying the GRRs associated to the GWAS signals and the TF binding sites affected. We also aim to decipher the pathophysiological consequences on the phenotype by performing chromatin conformation experiments to identify the gene target(s) of the GRR and perform a transcriptomic study to appreciate the impact on the gene target expression. The next steps would consist into characterizing their impact on cardiac electrical activity in a pathophysiology context.

This PhD position takes place in a context of international collaborations allowing to the candidate to be trained for chromatin conformation approaches at Prof. Stephan Mundlos lab at the Max Planck institute for Molecular genetics in Berlin. The candidate will benefit support and training from an assistant engineer for the molecular biology assays, from Adrien Foucal and Pierre Lindenbaum for analysis and interpretation. The candidate will be co-supervised by Julien Barc, INSERM Research Associate. Furthermore the student will benefit from the last sequencing technology available on site at the GenoBIRD facilities.

**Key words:** functional genomics, epigenetics, cardiac arrhythmia, sudden cardiac death, iPSC

**Scientific and technical skills required by the candidate:** molecular biology, Next Generation Sequencing experience, cardiac physiopathology, epigenetics

5 Publications from the team related to the topic:

1. **RRAD mutation causes electrical and cytoskeletal defects in cardiomyocytes derived from a familial case of Brugada syndrome**

2. **Progressive Atrial Conduction Defects Associated With Bone Malformation Caused by a Connexin-45 Mutation**

3. **Familial Catecholamine-Induced QT Prolongation in Unexplained Sudden Cardiac Death**

4. **Role of common and rare variants in SCN10A: Results from the Brugada syndrome QRS locus gene discovery collaborative study**

5. **Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death**

To apply, please email application letter, CV, grade sheets and recommendations to: jjschott@univ-nantes.fr and Julien.Barc@univ-nantes.fr