The genetics of sudden cardiac death

Inherited cardiac arrhythmias are at the forefront of studies carried out by Drs Richard Redon and Jean-Jacques Schott, who provide an insight into Brugada syndrome, a heart condition with no external warning signs.

How did you both come to investigate the genetics of cardiac disorders?

JJS: Dr Richard Redon and I both trained in human genetics and molecular biology at the University Louis Pasteur in Strasbourg, France. I then specialised in the genetics of congenital heart defects in the Seidman laboratory at Harvard Medical School in Boston, USA, whereas Richard specialised in genome structural variation at the Wellcome Trust Sanger Institute in Cambridge, UK.

Research on the genetics of cardiac disorders began at Nantes University Hospital in the mid-1990s, when Chief Cardiologist Professor Hervé Le Marec and I identified a new susceptibility locus for the Long QT syndrome. In 1998, the French Institute of Health and Medical Research (Inserm) appointed me to join Professor Denis Escande’s laboratory in Nantes and further develop research on the genetics of cardiac arrhythmias with the notable support of the Alliance Against Sudden Cardiac Death (SDC), a former transatlantic Network of Excellence funded from 2006 to 2011 by the Leducq Foundation.

In 2009, my team (which had by now become part of l’institut du thorax) expanded, and Richard and Dr Christian Dina joined us to implement new approaches based on next-generation sequencing and high-throughput genotyping. We have since recruited two early-career investigators (Drs Julien Barc and Solena Le Scouarnec) and one computer biologist (Dr Pierre Lindenbaum) to further strengthen our team, which is fully dedicated to research on cardiovascular genetics.

For what reasons is a better understanding of the genetic factors that affect sudden cardiac death (SCD), and the arrhythmia disorders that precede these events, particularly relevant for better prevention and treatment strategies?

JJS: SCD is a major health burden in industrialised countries, which results, in most cases, from ventricular fibrillation – it typically occurs as the first clinical manifestation of a previously ignored cardiovascular disease (usually coronary artery disease). As a consequence, known risk factors for SCD overlap with those for coronary artery disease and thus cannot help in identifying individuals at higher risk of SCD in the population.

Evidence supporting the existence of a genetic ‘susceptibility factor’ predisposing to SCD has recently emerged from large-scale epidemiological studies. In particular, up to 10 per cent of SCD cases have been classified as direct phenotypic consequences of rare inherited arrhythmia syndromes, which are characterised by abnormal electrocardiogram (ECG) patterns.

Our group aims to explore these inherited arrhythmia disorders, identify new genetic factors modulating disease risk and address the relative involvement of all known susceptibility genes for inherited cardiac arrhythmias in the population burden of SCD.

Why have you decided to focus on determining rare genetic variants associated with Brugada syndrome?

RR: Brugada syndrome is an inherited cardiac arrhythmia disorder that provides us with a homogenous group of patients at high risk of SCD. This syndrome is highly amenable to genetic studies and thus can be exploited as a ‘sensitised model’ to identify both rare and common genetic variants predisposing to SCD.

Could you highlight how you will analyse the data from your whole-genome sequencing studies of Brugada syndrome?

RR: Our hypothesis is that predisposition to Brugada syndrome is increased by the presence of rare genetic variants, which may reside in genome sequences regulating the cardiac function. To test this hypothesis, we will systematically evaluate whether there is any genomic region carrying a significant enrichment in rare genetic variation among a population of cases with Brugada syndrome compared to an ancestry-matched reference population.

Any region harbouring such enrichment will be considered as associated to higher risk of Brugada syndrome. We will then further characterise its functional role in relation to the cardiac function.
How did you draw together your expert team of biologists, computer scientists and statisticians? Is such a broad range of skills essential for the problems your research tackles?

**RR:** Research in human genetics has been revolutionised by the emergence of massively parallel sequencing. The main challenge nowadays is not to produce DNA sequences, but to interpret genetic variation in the context of human disease. To address this challenge, we have progressively gathered cardiologists, geneticists, computer biologists and bio-statisticians around an integrative programme on SCD.

This organisation enables us to formulate important medical questions, design adequate experimental strategies and develop relevant methods facilitating the interpretation of our experimental results. In addition, we work in close partnership with cardiac physiologists at l’institut du thorax who can examine the cardiac function of any newly identified SCD susceptibility gene.

**What do you see as the next steps of this research?**

**JJS:** Prevention of SCD in the context of primary electrical disorders still relies on the use of implantable cardiac defibrillators (ICDs). We believe that genetics will help us in identifying new biological targets for earlier prevention of SCD in this context.

By implementing the latest concepts in genetic epidemiology and providing novel tools to unravel the genetic bases of these complex disorders, we should be able to identify the key molecular players involved in SCD risk and then to propose new strategies to interrogate them in the population.

Similar approaches will be applied to investigate predisposition to out-of-hospital sudden cardiac death in the young adult. Better understanding the genetic predisposition of such a health burden is the primary and obligatory step towards the development of efficient preventive strategies.

**How will your findings be translated into clinical benefits in the next five to 10 years?**

**JJS:** To facilitate the translation of our genetic discoveries for clinics, we work in close partnership with the National Reference Centre for Inherited Cardiac Arrhythmias, which was created in Nantes with the support of the French Ministry of Health. This Reference Centre coordinated by Professor Vincent Probst provides molecular diagnosis and integrated healthcare to patients with inherited cardiac arrhythmias and, in parallel, develops large DNA collections for research purposes. The Centre coordinates Rhythmogen, a large clinical network across France aiming to promote fundamental and clinical research against cardiac electrical disorders.

Scientists at l’institut du thorax in France have teamed up with a network of national and international collaborators to investigate the genetics of cardiac arrhythmias, with a view to improving sudden cardiac death prevention.

**SUDDEN CARDIAC DEATH** (SCD) affects roughly one in every 1,000 people. In some cases, SCD is caused by rare arrhythmia disorders such as Brugada syndrome. Although these conditions can be diagnosed using an electrocardiogram, patients are unfortunately often asymptomatic until the SCD event, making diagnosis unlikely. This means that many individuals at high risk of SCD are not fitted with the implantable cardiac defibrillators that could save their lives in the event of ventricular fibrillation.

New and improved strategies for the systematic identification of individuals with high risk of cardiac arrhythmia are therefore required. It is already established that conditions such as Brugada syndrome are inherited – mutations in 19 different genes have so far been associated with the condition, with the gene encoding the cardiac sodium channel (SCN5A) being by far the most commonly altered. However, recent studies led by researchers from l’institut du thorax indicate that these syndromes display complex genetic inheritance involving multiple genetic risk variants.
As such, any efforts that could further elucidate these genetic factors and so better enable identification of individuals with Brugada syndrome and other cardiac arrhythmia disorders would have widespread and significant implications for both patients and health systems.

**A GROUNDBREAKING GENETIC SURVEY**

Fortunately, recent technological developments in genomics, combined with increased knowledge regarding the role of non-coding regions of the genome, are now enabling researchers to more fully investigate the genetic basis of SCD resulting from cardiac arrhythmia disorders. Genetic studies in this area show particular promise, as these inherited conditions can serve as models capable of yielding valuable molecular insights relevant to SCD more widely.

In France, the Genetic Survey of Sudden Cardiac Death (GenSuD) project is working towards exactly this goal. Using data from the world’s largest clinical biobanks for Brugada syndrome, early repolarisation syndrome and SCD, the project’s overarching mission is to reconstitute the genetic model of ventricular fibrillation (the mechanism by which SCD usually occurs) and identify novel genetic factors modulating SCD risk.

To achieve this, GenSuD has been divided into three specific aims. First, the scientists are applying whole-exome sequencing to seek out previously unidentified genes that are causally related to familial forms of arrhythmias (‘susceptibility genes’). Second, the researchers are employing a targeted next-generation sequencing approach to estimate the involvement of all known susceptibility genes for arrhythmia syndromes in the burden of SCD. Third, the team is extending a previous genome sequencing-association study on selected index cases of the condition in order to stratify the risk of SCD in this highly exposed population.

GenSuD is a groundbreaking study in a number of ways. Notably, it is the first project of its kind to address the contribution of both rare and common genetic variants in the susceptibility to cardiac arrhythmias, and to comprehensively analyse the implication of known arrhythmia-susceptibility genes in yet unexplained SCD in the young adult.

**STRENGTHENING RESEARCH NETWORKS**

Perhaps most innovative of all, however, is GenSuD’s large-scale collaborative approach. The project is comprised of three project partners: l’institut du thorax, le Paris-Centre de recherche cardiovasculaire, and l’institut de recherche sur les maladies cardiovasculaires, du métabolisme et de la nutrition. Each partner is a world-leader in various aspects of SCD genetics. This collaborative approach relies heavily on the activity of a national clinical network against inherited cardiac arrhythmias, which involves 16 recruiting centres across France.

In addition, GenSuD is supported by an international collaborative consortium involving 13 centres with expertise in Brugada syndrome spanning Europe, the US and Japan. The network has been working together for almost two decades in order to produce the critical mass necessary to carry out population-based genetic investigations.

Taken together, the GenSuD researchers have an extremely wide range of complementary knowledge areas and skills, spanning genetics, genomics, bioinformatics, statistical genetics, epidemiology and cardiovascular physiology, all of which will be needed if GenSuD is to achieve its ambitious goals. Overall, it is hoped that GenSuD will reinforce links and strengthen working
relationships between SCD researchers, both within France and further afield.

**ELUCIDATING BRUGADA SYNDROME**

Work aimed at achieving the project’s third goal – the identification of genetic polymorphisms modulating arrhythmia phenotypes – is currently being carried out at l’institut du thorax in Nantes. This is where GenSuD’s two co-principal investigators, Drs Richard Redon and Jean-Jacques Schott are based.

Initially, together with Professor Connie Bezzina’s group at the Academic Medical Centre of Amsterdam, l’institut du thorax group coordinated a GWAS involving 312 index cases and 1,115 control individuals, and succeeded in identifying three common haplotypes associated with susceptibility to Brugada syndrome. These were all subsequently replicated on independent case-control sets from Europe and Japan. "We found that their cumulative effect on disease susceptibility was unexpectedly large, with an estimated odds ratio of 21.5 in the presence of more than four risk alleles versus less than two," elaborates Schott.

However, due to the relatively small size of the case-control set, it is probable that there are other susceptibility genes that went undetected. The team is therefore currently in the process of building upon these findings by recruiting an additional 2,000 Brugada syndrome patients through collaborating centres, creating the most significant Brugada syndrome cohort ever collected and dramatically increasing statistical power. Once this task has been completed, a full genome sequencing-associating study can be undertaken to obtain unprecedented genetic and biological insights.

**A CUSTOM KIT**

Other GenSuD tasks are also being carried out in parallel. For example, project partners recently began investigating the extent to which susceptibility genes for cardiac arrhythmia disorders play a role in SCD burden among young people. Researchers are using a custom kit that enables the systematic sequencing of more than 100 genes potentially associated with inherited cardiac arrhythmias or cardiomyopathies. "We are currently applying this kit to a group of 200 young victims of out-of-hospital SCD," elaborates Redon. "This work will enable us to estimate the contribution of undiagnosed mutations in every gene previously involved in cardiac arrhythmias to the burden of SCD."

**A BRIGHT FUTURE**

Overall, the GenSuD researchers are optimistic that the project’s findings will contribute to improving the diagnosis, risk stratification and preventative treatment of individuals at high risk of SCD. The impacts of such developments, in terms of burden reduction for both patients and health systems, are likely to be significant.

Furthermore, the collaborative link forged and reinforced by this project will pave the way for future research endeavours in this area. "Long-lasting collaborations facilitate the emergence of innovative programmes based on informal agreements and grant sharing," confirms Redon. Indeed, in the future, the GenSuD researchers hope to build upon the success of this project by establishing and coordinating a European consortium dedicated to elucidating the genetic epidemiology of unexplained SCD.

**GENSuD: A GENETIC SURVEY ON SUDDEN CARDIAC DEATH**

**OBJECTIVES**

- To explore familial forms of cardiac arrhythmias
- To identify new genetic factors modulating disease risk
- To address the relative involvement of all known arrhythmia-susceptibility genes in the population burden of sudden cardiac death (SCD)

**KEY COLLABORATORS**

Professor Connie Bezzina, AMC Amsterdam, Netherlands • Dr Jean-François Deleuze, CEA-CNG, France • Professor Xavier Jouven, Paris Cardiovascular Research Center, Georges Pompidou European Hospital, France • Dr Pascale Guicheney, Institute of Cardiometabolism And Nutrition, Inserm-UPMC UMR 5116, France • The Rhythmogen network

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**DR RICHARD REDON** is an international expert in analysing structural variation in the human genome. He has recently been developing new approaches to address the genetics of complex disorders. He is currently leading a large collaborative study aiming to identify genetic risk factors associated with sudden cardiac death.

**DR JEAN-JACQUES SCHOTT** has been investigating the molecular basis of cardiovascular diseases since the mid-1990s. His recent research on degenerative diseases led to the identification of the first predisposition genes to common and rare forms of mitral valve defects. He is currently leading the genetic cardiovascular team at l’institut du thorax.