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RAPID COMMUNICATION

Calmodulinopathies: the need for a registry

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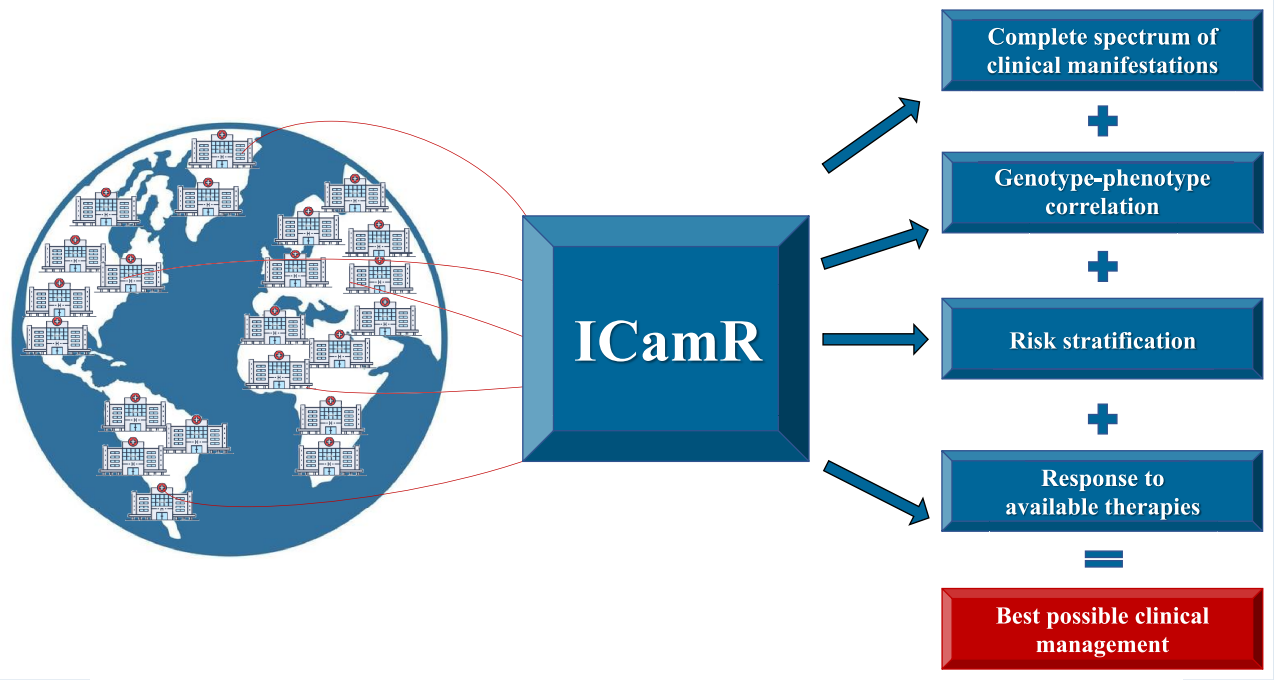
Abstract

Calmodulinopathies are very rare genetic disorders associated with a high risk for sudden cardiac death. Disease-causing variants in 1 of the 3 identical *CALM* genes cause severe forms of long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or idiopathic ventricular fibrillation, and there are many unanswered questions concerning management and underlying mechanisms. What is currently known depends largely on the initial publications from the ICamR (International Calmodulinopathy Registry). However, progress is delayed because the accrual of patients in ICamR is slow. As we did long ago for long QT syndrome, this is a call for action, requesting doctors all over the world to enroll even their isolated cases in the Registry. This is the only way to obtain, for an adequate number of patients, the data necessary to define the spectrum of clinical manifestations and the genotype-phenotype correlation essential for an improved risk stratification and best therapeutic management. If you are willing to contribute, please contact us.

Graphical Abstract



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Our dream: a multitude of doctors and hospitals from all over the world will enroll their patients with Calmodulin variants, even single cases, in the ICamR (International Calmodulinopathy Registry). The Registry, in turn, will deliver to the cardiology community a gestalt of novel data and information on the patients' features to allow the best possible clinical management.

Keywords Long QT Syndrome • Channelopathies • Genetics • Sudden cardiac death • Registries • Calmodulinopathies

Rare diseases are an unending source of problems. They are difficult to diagnose ('*never seen one before*'), they tend to be serious and often lethal, they are difficult to manage ('*this is my first case, there is nothing in the guidelines*').[1] All true, but there is a way out, and that's because we faced these problems before, and we learnt.

Fifty years ago, the knowledge about the Long QT Syndrome (for which the acronym LQTS was created in 1975[2]) was extremely limited. There was a smorgasbord of therapies, a clear sign that no one knew what to do, and just a handful of patients were treated with β-blockers. What was available in the literature until then was just a small number of case reports, without any insight on the nature of what appeared to be a highly lethal disorder. A 1975 publication[2] broke the spell by forcefully proposing two therapeutic interventions, β-blockers as the main therapy for all patients and left cardiac sympathetic denervation for those not fully protected by β-blockers. As still very little was known, Arthur Moss and Peter Schwartz, together with Richard Crampton, established the International Registry for the Long QT Syndrome in 1979[3] with the objectives to learn more about the underlying mechanisms, the natural history of the disease and the response to therapy. However, progress was slow, as the number of patients enrolled in the registry was growing piecemeal.

To address that problem, more than 40 years ago, in 1983 to be precise, one of us (P.J.S.), with the support of the European Society of Cardiology, published a short article inviting cardiologists from all over the world to enrol their patients in the LQTS Registry.[4] It was stated that '*A valid assessment of therapeutic efficacy in an uncommon disease cannot be based on 'personal experience'; cooperative efforts are necessary*.' After mentioning the existence of the International LQTS Registry, it was also written that '*Over 200 patients have already been enrolled, but many more are needed to draw meaningful and valid conclusions*.'

That article triggered a major response and large numbers of LQTS patients were rapidly enrolled. The registry was a success beyond any expectation, not only providing full answers to our original questions but also allowing the identification of the LQTS-causing genes because it was the Registry that, with its large pedigrees of clearly affected and non-affected individuals, provided molecular biologists and geneticists the material essential for their discoveries.[3]

Another example of the important findings obtained through Registries is what has happened with catecholaminergic polymorphic ventricular tachycardia (CPVT).[5,6] History often repeats itself and nowadays, when confronted with life-threatening arrhythmias in a child with a calmodulin variant, we face the same problems of 50 years ago with LQTS.

Three reports, published between 2012 and 2014, unexpectedly linked calmodulin mutations to CPVT,[7] to LQTS with a strikingly high mortality in infancy,[8] and to idiopathic ventricular fibrillation.[9] This 'calmodulin explosion' made clear that variants on the three identical calmodulin genes (*CALM1, CALM2, CALM3*) were causing extremely severe phenotypes with a high incidence of sudden cardiac death before age 5.

Calmodulin, a protein critically involved in the regulation of all major cardiac ion channels and the most important cellular calcium sensor, plays a key role in preserving cardiac electrical stability. It has the unique feature of being encoded by three genes in three different chromosomes all characterized by their extreme conservation. Indeed, *CALM* variants are poorly tolerated and cause severe clinical phenotypes, often associated with increased risk for life-threatening arrhythmias.[10]

In 2015, to address the same issues we had in the past with LQTS, we created the International Calmodulinopathy Registry (ICamR) with the support of European Research Network ERN GUARD-Heart. The first report, based on 70 patients, appeared in 2019[11] and the second in 2024,[12] with data on 140 patients. There has been progress, but many questions are still open because more patients need to be enrolled.

ICamR has already provided useful information. It has shown the apparent value of triple therapy (β-blockers, mexiletine, and left cardiac sympathetic denervation). It has called attention to the presence of complex phenotypes, notably with neurologic components and/or cardiac structural abnormalities. Impressively, it played a major, and quite positive, role in a notorious trial for infanticide.[13]

A significant increase in the number of patients enrolled in ICamR will allow to address several relevant questions, scientific and clinical. A better understanding of the genotype-phenotype correlation will provide elements for risk stratification as well as clarification of the striking and puzzling distribution of the variants of the patients with life-threatening events, which, in 85% of cases, are located in a specific part of *CALM* genes, namely the EF-hand IV.[10] Larger numbers will allow to clarify the syndromic aspects and especially the relationship between *CALM* mutations and neurological manifestations and will allow to assess whether our impression that in some cases, often before age 5 and without changing therapy, cardiac electrical stability increases together with an impressive reduction of major cardiac events is correct.

All registries face problems. Among the obstacles to the enrolment in ICamR one certainly is that variants on the Calmodulin genes are very rare; another is that most doctors forgot their Latin ('gutta cavat lapidem') and may not realize the importance of their even single patients. Progress requires action. Practising cardiologists need to be aware of the Registry and to realize the importance, for science and for the patients, of a rapid increase in the enrolment of patients in ICamR. Whenever they are informed by the genetic laboratories that one of their patients has a calmodulin variant, they have the opportunity of contributing by contacting us for enrolling their patients in the Registry. This would not interfere in any way with their choices of management (even though we can usually be of help by providing information and suggestions) and with their right to publish individually their cases, but would significantly increase our ability of understanding, sooner rather than later, how to best deal with this very often dramatic disease.

Furthermore, as variant adjudication is often challenging in rare disease, also variants of uncertain significance should be reported as their carefully annotated presence in the Registry will facilitate their exit from 'genetic purgatory'. If patients presenting with features characteristic of a *CALM*-related disease are identified where genetic screening is not available we would be willing and ready to perform the necessary genetic screening. We will provide information on how to enrol the patients in ICamR and, subsequently, every year will request a follow-up. The registry does not interfere with any management decision concerning the enrolled patients, who continue to be the responsibility of their attending physician.

This text appears simultaneously in Circulation: Genomic and Precision Medicine, Europace, and JACC EP. This unprecedented action reflects the generous and farsighted decision of their Editors-in-Chief to whom goes our gratitude for they having given priority to the interest of science and of the affected patients. We will also be very grateful to the physicians around the world who will enrol their patients with Calmodulin mutations by contacting one of us.

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Data availability

The 'data availability' clause does not apply as this is an opinion manuscript without data.

References

1. Crotti L, Brugada P, Calkins H, Chevalier P, Conte G, Finocchiaro G *et al.* From gene-discovery to gene-tailored clinical management: 25 years of research in channelopathies and cardiomyopathies. *Europace* 2023;**25**:euad180.
2. Schwartz PJ, Periti M, Malliani A. The long QT syndrome. *Am Heart J* 1975;**89**: 378–90.
3. Moss AJ, Schwartz PJ. 25th anniversary of the international long-QT syndrome registry: an ongoing quest to uncover the secrets of long-QT syndrome. *Circulation* 2005;**111**: 1199–201.
4. Schwartz PJ. The idiopathic long QT syndrome. The need for a prospective registry. *Eur Heart J* 1983;**4**:529–31.
5. Roston TM, Vinocur JM, Maginot KR, Mohammed S, Salerno JC, Etheridge SP *et al.* Catecholaminergic polymorphic ventricular tachycardia in children: analysis of therapeutic strategies and outcomes from an international multicenter registry. *Circ Arrhythm Electrophysiol* 2015;**8**:633–42.
6. Peltenburg PJ, Kallas D, Bos JM, Lieve KVV, Franciosi S, Roston TM *et al.* An international multicenter cohort study on β-blockers for the treatment of symptomatic children with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2022;**145**:333–44.
7. Nyegaard M, Overgaard MT, Søndergaard MT, Vranas M, Behr ER, Hildebrandt LL *et al.* Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. *Am J Hum Genet* 2012;**91**:703–12.
8. Crotti L, Johnson CN, Graf E, De Ferrari GM, Cuneo BF, Ovadia M *et al.* Calmodulin mutations associated with recurrent cardiac arrest in infants. *Circulation* 2013;**127**: 1009–17.
9. Marsman RF, Barc J, Beekman L, Alders M, Dooijes D, Van Den Wijngaard A *et al.* A mutation in CALM1 encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence. *J Am Coll Cardiol* 2014;**63**:259–66.
10. Schwartz PJ, Crotti L, Nyegaard M, Overgaard MT. Role of calmodulin in cardiac disease: insights on genotype and phenotype. *Circ Genom Precis Med* 2024;**17**: e004542.
11. Crotti L, Spazzolini C, Tester DJ, Ghidoni A, Baruteau AE, Beckmann BM *et al.* Calmodulin mutations and life-threatening cardiac arrhythmias: insights from the international calmodulinopathy registry. *Eur Heart J* 2019;**40**:2964–75.
12. Crotti L, Spazzolini C, Nyegaard M, Overgaard MT, Kotta MC, Dagradi F *et al.* Clinical presentation of calmodulin mutations: the international calmodulinopathy registry. *Eur Heart J* 2023;**44**:3357–70.
13. Schwartz PJ, Crotti L, Nyegaard M, Overgaard MT. Calmodulin, sudden death, and the folbigg case: genes in court. *Eur Heart J* 2024;**45**:1801–3.