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Rare neurological channelopathies — networks to study patients, pathogenesis and treatment

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Abstract

Each of the thousands of rare neurological diseases requires a widely distributed network of centres, investigators and patients, so as to foster multidisciplinary investigations and involve sufficient numbers of patients in the discovery of disease pathogenesis and novel treatment. In this Review, we highlight the value of this collaborative approach in patient-oriented research into rare neurological channelopathies. Two networks, the Consortium for Clinical Investigations of Neurological Channelopathies (CINCH) and the Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA), provide a link between patients with rare channelopathies and investigators who are studying disease pathogenesis and developing novel treatments. Interactions between patients, researchers and advocacy groups promote shared agendas that benefit patient education and recruitment, research collaboration and funding, and training and mentoring of junior investigators who are attracted to the study of the diseases that provide the focus for the two networks. Here, we discuss how linkage of national and international centres has enabled recruitment of study participants, provided opportunities for novel studies of pathogenesis, and facilitated successful clinical trials.

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Author contributions

All authors researched data for the article, made substantial contributions to discussions of the content, wrote the article, and reviewed and/or edited the manuscript before submission.

Competing interests statement

The authors declare no competing interests.

FURTHER INFORMATION

Consortium for Clinical Investigations of Neurological Channelopathies (CINCH): <https://www.rarediseasesnetwork.org/cinch/>

Coordination of Rare Diseases at Sanford (CoRDS): <http://www.sanfordresearch.org/cords/>

Most neurological diseases are rare, and even common conditions such as stroke, epilepsy, headache and dementia have rare subsets and distinct and infrequent clinical scenarios that pose challenges to patients and investigators. A figure of 7,000 as the total number of rare diseases is widely mentioned in the literature^{1,2}, but our experience suggests that the actual number is probably 5–10-fold greater, as characterization of pathogenesis leads to a better understanding of genetic, immunological and other aetiologies, and to separation of clinical phenotypes into distinct disease entities.

Neurological channelopathies — ion channel disorders that manifest predominantly with neurological symptoms — represent a rapidly expanding group of rare diseases that illustrate the challenges and opportunities in investigating the pathogenesis of rare diseases, and suggest strategies to improve the design and study of treatments for specific conditions^{3,4}. Two consortia for the investigation of neurological channelopathies, initially supported by the Office of Rare Diseases Research and the National Institute of Neurological Disorders and Stroke (NINDS), were established as Rare Disease Centers in the Rare Diseases Clinical Research

Network (RDCRN). The Consortium for Clinical Investigations of Neurological Channelopathies (CINCH) and the Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA — previously known as the Clinical Research Consortium for Spinocerebellar Ataxias) both have channelopathies manifesting with cerebellar ataxia as a major focus of investigation. Although the precise prevalence is unknown, each of the target conditions is estimated to affect no more than 1 in 100,000 individuals, which qualifies for the rare disease designation as defined by the Rare Diseases Act of 2002 for any disease affecting fewer than 200,000 people in the USA. These two consortia established networks by linking centres with major expertise in the basic neuroscience and molecular aspects of the target diseases with experts in the clinical phenomenology of these conditions, and they illustrate the role of networks in collaborating with patient advocacy groups to advance the understanding and treatment of rare diseases.

In this Review, we outline the role of CINCH and CRC-SCA in bringing together the various stakeholders in neurological channelopathy research, and highlight the achievements of these consortia to date.

Target diseases for CINCH and CRC-SCA

CINCH

CINCH received NIH support in 2003 to study three neurological diseases: periodic paralysis, nondystrophic myotonia, and episodic ataxia (EA). Between 2004 and 2014, these three target diseases expanded to 18 genetically distinct diseases (TABLE 1).

Periodic paralyses, the first genetically characterized channelopathies, present with episodic skeletal muscle weakness or paralysis, resulting from muscle hypo-excitability triggered by exertion or certain foods⁵. Hyperkalaemic periodic paralysis is often accompanied by high potassium levels, and is caused by autosomal dominant mutations in *SCNA4* (REF. 6), which encodes a muscle sodium channel. Hypokalaemic periodic paralysis is invariably

accompanied by low potassium levels, and is caused by mutations in either *SCN4A* or the *CACNA1S* gene⁷, which encodes a muscle calcium channel. Andersen–Tawil syndrome is an unusual periodic paralysis that manifests with cardiac arrhythmia and dysmorphic features. Andersen–Tawil syndrome type 1 is caused by mutations in the *KCNJ2* gene, which encodes a potassium channel expressed in the heart and muscle⁸. However, *KCNJ2* mutations are estimated to account for only 60% of cases, indicating genetic heterogeneity. A mutation in a second potassium channel gene, *KCNJ5*, was recently identified in a patient with Anderson–Tawil syndrome and primary aldosteronism⁹.

Myotonia refers to sustained spontaneous repetitive electrical activity resulting from muscle hyperexcitability, with delayed relaxation of skeletal muscle fibres after voluntary contractions. Myotonia is attributed to altered chloride or sodium channel function, and is clinically classified on the basis of associated muscle wasting. Nondystrophic myotonia is characterized by stiffness and muscle hypertrophy that result from autosomal dominant or autosomal recessive mutations in the *CLCN1* gene¹⁰. *CLCN1* encodes the skeletal muscle chloride channel CLC-1, which is important for membrane repolarization. In addition, certain mutations in the *SCN4A* gene can cause nondystrophic myotonia instead of paralysis¹¹.

Myotonia is also a prominent feature of myotonic dystrophy types 1 and 2 (DM1 and DM2), for which the primary genetic defects are unstable nucleotide repeat expansions in the 3' untranslated region of the *DMPK* (DM1 protein kinase) gene, and intron 1 of the *CNBP* (cellular nucleic acid-binding protein) gene, respectively¹². DM1 and DM2 present with multiorgan manifestations, largely caused by RNA dysregulation and toxicity. Impaired chloride channel function is thought to be attributable to aberrant splicing of *CLCN1* in DM1 (REFS 13, 14), and downregulation of *CLCN1* expression in DM2 (REF 15).

EA is a clinical diagnosis based largely on discrete episodes of imbalance and incoordination with clear onset and resolution. EA has overlapping features with complicated migraine and epileptic seizures¹⁶. The condition is genetically heterogeneous, with eight distinct genetic loci having been identified to date^{16,17}, in addition to cases of sporadic and familial late-onset EA^{18,19}. EA subtype designation is dictated by genetic characteristics. For example, EA1 is defined by mutations in *KCNA1* (REF 20), and EA2 is defined by mutations in *CACNA1A*²¹. However, negative findings from genetic investigation of known EA-associated genes does not rule out a clinical diagnosis of EA, because we have not yet identified all the potential genetic defects that could contribute to this clinical manifestation. Genetic stratification facilitates longitudinal studies and clinical trials in cohorts that are homogenous in terms of genetic diagnosis and molecular pathogenesis.

CRC-SCA

CRC-SCA was founded in 2010, and its remit includes spinocerebellar ataxias (SCAs), in which neuronal ion channel functions are thought to have important roles in the phenotypic expression and underlying pathophysiology of the disease. SCAs are a clinically and genetically heterogeneous group of autosomal dominant disorders with the core

manifestation of slowly progressive nonepisodic ataxia due to cerebellar degeneration, accompanied to varying degrees by extracerebellar neurological manifestations.

In a 1982 paper²², Harding classified SCAs into three types — autosomal dominant cerebellar ataxia (ADCA) types I, II and III — on the basis of the presence or absence of extracerebellar neurological disorders. The ADCA III phenotype is limited to cerebellar ataxia, whereas individuals with ADCA I show additional involvement of pontomedullary systems, basal ganglia, cerebral cortex, spinal tracts and/or peripheral nerves. ADCA II is characterized by additional involvement of the retina.

The number of loci linked to dominantly inherited SCA now exceeds 30, and several SCA syndromes have turned out to be caused by mutations in genes encoding ion channels (TABLE 1). SCA6, for example, is caused by a glutamine-encoding CAG repeat expansion in the *CACNA1A* gene, which encodes the Ca_v2.1 voltage-gated calcium channel²³. Importantly, EA2 and another episodic disorder, familial hemiplegic migraine type 1 (FHM1), are also caused by mutations of *CACNA1A*²¹, hence, they are allelic disorders of SCA6. SCA13 and SCA19/22 are caused by mutations in the voltage-gated potassium channel-encoding genes *KCNC3* (REF. 24) and *KCND3* (REFS 25,26), which had not previously been recognized to be important in cerebellar function. SCA15/16/29 results from mutations in *ITPR1*, which encodes the inositol 1,4,5-trisphosphate receptor, type 1 (REFS 27–29), a ligand-gated ion channel that mediates calcium release from the endoplasmic reticulum.

Organization of the networks

A request for applications for funding for RDCRN from the Office of Rare Disease Research prompted experts in the basic neuroscience of the neurological channelopathies and SCAs to create CINCH and CRC-SCA to formalize collaborations with clinical investigators who were assembling populations of patients with these rare diseases.

Each site was led by a neurologist with expertise and special interest in channelopathies and SCAs, and was staffed by a clinical coordinator. All clinical data from the studies were stored centrally at the Data Management and Coordinating Center (DMCC), which provided administrative core and statistical support for all consortia of the RDCRN. Advocacy groups including the National Ataxia Foundation (NAF), the Muscular Dystrophy Association (MDA) and the Periodic Paralysis Association (PPA), as well as international groups such as the Italian Telethon and similar organizations in the UK, Canada and elsewhere, were invited to join the effort. Within the framework of the RDCRN, patient registries, semiannual investigator meetings and funding for pilot studies facilitated consortia integration, research funding and interactions. Research coordinators were also enlisted and developed their own network with other rare disease consortia (BOX 1).

Roles of the networks

Training and career development

Both CINCH and CRC-SCA invested in a strong training component to mentor and nurture junior investigators with an interest in pursuing patient-oriented research in rare neurological channelopathies. Specifically, the consortia made trainees central to the development and performance of all aspects of the research plan by providing a didactic curriculum of instruction, establishing a mentoring team for each trainee, promoting cross-site interaction and learning as well as trainee interaction with patient groups, and fostering trainee publications and career-development grant preparation. With the assistance of the DMCC and the patient advocacy groups, along with the investigators at various sites, the trainees received instructions in protocol and consent design, trial design for small samples, development of outcome measures, working with the FDA, and recruitment of study participants.

Recruitment of research participants

Patient advocacy groups — including the PPA, the MDA and the NAF for CINCH, and the NAF for CRC-SCA — provide essential support for networks. Patient referrals are facilitated by these groups, which also provide financial and logistical support for research activities, such as organizing patient registries and investigator meetings. Registries established with the help of the RDCRN infrastructure can facilitate recruitment, but other sources have proved even more effective than the RDCRN registries. For example, for CINCH, by far the most important single factor in identification and recruitment of patients was the involvement of European sites — in the UK, France and Italy, for example — that served as reference centres for the entire country³⁰.

For CRC-SCA, two patient registries, one established by the RDCRN and the other by the NAF, are now combined into a single NAF-sponsored registry, which is managed by the Coordination of Rare Diseases at Sanford (CoRDS). The registry includes information on patients with a variety of ataxias, including SCA6, SCA13, SCA19/22 and SCA15/16/29, and the EAs.

Both consortia brought in multiple investigators from multiple institutions in different geographical regions to facilitate patient enrolment. The principal investigator at each study site would work with a trainee and a study coordinator to recruit study participants, document physical findings and assess outcome measures. A major challenge for the initiation of the clinical studies was to obtain the approval from multiple institutional review boards for a unified protocol and informed consent across all sites, given that regulatory constraints and concerns differed among institutions and countries. The establishment of the infrastructure for the networks was particularly powerful to facilitate the natural history studies that are necessary for future clinical trials.

Improving diagnosis

A shared focus of CRC-SCA and CINCH is to improve diagnosis through comprehensive phenotypic and genotypic characterization of these conditions. In addition to population data

and *in silico* predictive data, the clinicians and scientists of these two consortia have access to rich clinical databases linked to genetic data. These databases can be used for segregation analysis and to determine whether genetic variants arose *de novo*, as well as to provide information on pathogenicity to meaningfully classify genetic variants identified in study participants. In this section, we describe how projects initiated by CRC-SCA and CINCH have provided new insights into SCA13 and the EAs, respectively.

A major challenge that we face is dealing with genetic variants of unknown significance, a classification that is unsatisfactory to both the specialist provider and the patient. This limitation restricts the ability of the provider to establish a diagnosis and discuss the natural history of the disease, as well as to provide genetic counselling. It also limits therapeutic options and impedes disease management and patient participation in clinical trials. New guidelines for reporting genetic variants in a clinical context highlight the complexity surrounding the interpretation of genetic variants as pathogenic or benign³¹.

CRC-SCA has pursued expansion of both the genotype and the phenotype of SCA13 (REFS 32–35). Through extensive sequencing of the coding region of the SCA13-associated gene *KCNC3* as part of a diagnostic work-up for sporadic ataxias, we have assembled a database of single nucleotide polymorphisms (SNPs) and alternative alleles for this gene. Our access to index patients and their relatives has greatly enhanced our ability to interpret the relevance of the genetic variants that we discover.

A specific example illustrates our experience. We evaluated a multigenerational pedigree with ataxia associated with the c.1771A>G, p.Ser591Gly allele of *KCNC3* (M. F. Waters, unpublished work). This allele is interesting in that it appears frequently in ataxia databases, making it an appealing choice as the cause of a single disease. On the basis of limited population sequencing, the allele appears with a frequency of approximately 1% and, thus, could account for the majority of cases of SCA13, reminiscent of the Phe508del allele in cystic fibrosis as the causative mutation in about 75% of cases³⁶. However, in a three-generation pedigree with three affected individuals that was referred to CRC-SCA, the allele was not found in all the affected family members, and was present in several asymptomatic individuals beyond the typical age of onset. These findings indicate that the genetic variant does not reliably segregate with the disease phenotype and, therefore, does not meet a key criterion for assigning pathogenicity. Furthermore, functional studies revealed no difference in biophysical properties between the wild-type and the mutant channels. The ability to recruit patients with a rare condition and to conduct appropriate clinical, genetic and cellular studies enabled the CRC-SCA investigators to conclude that this allele is likely to be benign.

Currently, EA1 and EA2 are the best-characterized EA syndromes; the other EAs were defined by genetic characterization of single families or probands. To study genotype–phenotype correlations and natural history in EA, the CINCH investigators assembled a cohort of physician-referred or self-referred patients with EA³⁷. Each participant underwent a detailed clinical history (including family history) and physical examination. Individuals who reported discrete episodes of recurrent and transient ataxia were given the opportunity to enter the CINCH longitudinal studies. Those reporting muscle twitching were assigned an ‘EA1-like’ phenotype, whereas those with nystagmus were assigned an ‘EA2-like’

phenotype. The remaining participants were assigned as 'other EA. DNA samples from individuals in the EA1-like and EA2-like subgroups were screened for mutations in the *KCNA1* and *CACNA1A* genes, respectively, and those in the 'other EA' subgroup underwent screening in both genes.

Most patients in the EA1-like cohort were found to have mutations in *KCNA1*; only six of the 39 individuals with EA1-like features tested negative for these mutations³⁷. In the cohort with an EA2-like phenotype, mutations were rarely detected in individuals with symptom onset after age 20 years¹⁶. In addition to heterozygous point or indel (base insertion or deletion) mutations, genomic rearrangements in the *CACNA1A* gene have been found in patients who exhibit EA2-like features but test negative for mutations on conventional sequencing^{38,39}. Mutation detection in 'other EA' has been low, suggesting that novel disease-associated genes are yet to be discovered in EA syndromes. Detailed clinical characterization, facilitated by CINCH, has helped us to define EA syndromes with distinctive clinical features that await further genetic characterization.

The mutation-negative study participants merit whole-exome or whole-genome sequencing, which provides an approach to genome-wide interrogation that is more cost-effective than sequential examination of specific genes by conventional Sanger sequencing. Recent studies have demonstrated the utility and high yield of unbiased whole-exome sequencing in the diagnosis of cerebellar ataxia^{40,41}. The availability of family histories and the active participation of family members further strengthen our ability to filter genetic variants to shorten the list of candidate variants and interpret their relevance.

A natural history study on EA1 conducted by the CINCH investigators revealed phenotypic variability across different families with distinct mutations³⁷, and the clinical spectrum is even broader for EA2 than for EA1. EA2 is allelic to FHM1 (REF 21) and SCA6 (REF 23), and these conditions display a dramatic spread in the age of onset (from early childhood for EA2 to late in life for SCA6). SCA6 typically presents with slowly progressive ataxia, although some patients experience episodic features in the early stage of the disease.

The infrastructure of CINCH, with a broad referral network, has facilitated the recruitment of study participants with distinctive forms of EA for gene discovery. EA5 is defined by mutations in the *CACNB4* gene⁴², which encodes an auxiliary subunit of the voltage-gated P/Q-type calcium channel. The pore-forming and voltage-sensing subunit of this channel is encoded by the EA2-associated gene *CACNA1A*. EA6 is caused by heterozygous mutations in the *SLC1A3* gene, which encodes a glial glutamate transporter. EA6 was first characterized in a child who exhibited episodic and progressive ataxia with complicated migraine, seizures and alternating hemiplegia⁴³, and was subsequently identified in another family with episodic ataxia and migraine⁴⁴. More recently, a novel heterozygous mutation in *SLC1A3* was identified in a patient and his cousin, who developed progressive ataxia at age 30 years and 39 years, respectively⁴⁰. EA7 has been linked to chromosome 19q13 (REF 45); other related clinical disorders have not yet been mapped but are being actively investigated^{46,47}.

Understanding pathogenesis

A major focus for investigators affiliated with CRC-SCA and CINCH has been to understand how mutations in ion channel genes can lead to ataxia. Ion channels are important determinants of excitability of nerve and muscle, and the channelopathies expose the vital roles of these molecules in maintaining normal function. The study of pathogenic genetic variants in ataxia-causing neurological channelopathies has also provided valuable new insights into the pivotal roles of voltage gated cation channels in cerebellar development and degeneration. The clinical manifestations of the channelopathies are influenced by the way in which the pathogenic variants alter the biochemical and biophysical properties of the ion channels. In addition, the temporal and spatial regulation of ion channel gene expression is important, as is the anatomical context. Therefore, characterization of defects at the network and organismal level, as well as at the molecular level, is necessary to fully elucidate the functional consequences of specific mutations in ion channel genes. Animal models of the channelopathies have an important role in this research.

Investigation of the pathological mechanisms of channelopathies has been a major focus for trainees in CINCH and CRC-SCA. Many trainees were involved in laboratory research and cross-sectional clinical studies, which enabled them to publish results relatively quickly, while more-lengthy longitudinal studies were being developed and implemented.

Developing treatment

The challenges of designing treatment and performing clinical trials for rare diseases have long been recognized, and initially discouraged investment in the effort. However, increased understanding of the pathogenesis of many of these diseases has provided a stimulus for drug-development and economic models that justify the opportunity costs and provide returns on investment, thereby making rare diseases an attractive research target.

The CINCH and CRC-SCA networks set out to develop and study the natural history of outcome measures that would be amenable to study in clinical trials. In addition, the consortia considered approaches that would facilitate randomized controlled trials in widely distributed patient cohorts of rare diseases. These approaches include patient-reported and recorded outcomes that can be followed longitudinally in patients at home via telemedicine technology^{48,49}, and ‘N-of-1’ or crossover studies in which individual patients serve as their own control^{50,51}. CINCH enabled a relatively large crossover trial of the sodium channel blocker mexiletine to be conducted in patients with the very rare disease nondystrophic myotonia (incidence <1 in 100,000). This drug was shown to be beneficial to the primary measure of efficacy (a self-reported myotonic severity outcome), as well as to quality of life and virtually every other secondary outcome⁵².

The publication of the mexiletine trial highlighted the importance of rare disease networks⁵³. Obtaining regulatory approval from the EMA or FDA poses substantial challenges for the rare disease community; however, networks enable adequate numbers of study participants to be brought together, so that the pivotal trials that are required to secure this approval can be conducted. Using this approach, the CINCH investigators were able to establish the efficacy of dichlorphenamide in two trials in the exceedingly rare disease hypokalaemic

periodic paralysis^{14,54}. FDA approval of this drug for periodic paralyses, which was granted in 2015, was based on these pivotal studies.

Owing to advances in understanding the variation in phenotypes in many genetic diseases, it is becoming increasingly clear that the gold-standard randomized placebo-controlled trial is unsuitable for both rare and common diseases in which a host of genetic factors can influence pharmacological responses. The N-of-1 trial is likely to be essential to deal with such variation. By finding the optimal treatment for each patient, these trials should pave the way to precision or personalized medicine, and rare diseases research can provide valuable lessons towards achieving this goal.

Accomplishments and challenges

A timeline of research in SCA is provided in FIG. 1. The operation of CRC-SCA began in September 2010, based on NIH Challenge Grant funding (5RC1NS068897). This 2-year funding (2010–2012) allowed CRC-SCA to join the NIH RDCRN. CRC-SCA evaluated 345 patients with SCA (60 with SCA1, 75 with SCA2, 138 with SCA3, and 72 with SCA6) at nine US centres, and published the core result in 2013 (REF 55). The clinical characteristics of these patients showed strong agreement with the data collected by the European SCA investigators^{56,57}. For example, both cohorts revealed that SCA1 was the fastest-progressing and SCA6 was the slowest-progressing disease among these SCAs, and that the age at onset for SCA6 was significantly later than that for the other SCAs. These studies provided key results to evaluate the feasibility of transatlantic clinical trials in SCAs. The European and US groups also collaborated in a genetic modifier study, and found that the age at onset of patients with SCA2, SCA3, SCA6 and SCA7 was influenced by CAG repeat-containing genes other than those primarily linked to each disease⁵⁸. CRC-SCA has received further funding from the NAF to continue enrolment for and maintenance of their natural history database, and to prepare for a biomaterial repository.

The publication of data from a CRC-SCA natural history study has prompted inquiries from pharmaceutical and biotechnology industries regarding the availability of patient cohorts for future clinical trials. However, trials of drugs designed to slow down disease progression demand a larger sample size than is available within a single cohort. CRC-SCA and their European counterpart have initiated an international collaboration to overcome this problem. Clinical research consortia for SCAs in Asia, Latin America and other countries have also communicated with CRC-SCA regarding potential participation in this international collaboration^{58–60}.

The NAF awarded the Pioneer Grant (US\$100,000 for 1 year) in 2013 to support the natural history database for CRC-SCA, which is now housed at the University of California, Los Angeles. The NAF also arranged conference calls and face-to-face meetings of the CRC-SCA investigators and coordinators. Although CRC-SCA strongly encouraged investigators to collect further longitudinal data, the rate of new patient enrolment and frequency of follow-up visits have been low, primarily due to a lack of financial support for such research activities. However, CRC-SCA has added a further nine sites to the existing nine sites in the

past 3 years, and these sites are ready to enrol new participants to the natural history database as soon as new funding becomes available.

The remarkable similarity between the CRC-SCA and the European natural history data allows readiness for transatlantic clinical trials to be intensified in anticipation of future opportunities. A key focus is on biomarkers: under the leadership of Gulin Oz at the University of Minnesota; four CRC-SCA sites are developing magnetic resonance spectroscopy biomarkers for key SCAs under NIH funding (grant 1R01NS080816). CRC-SCA is also planning to establish a SCA biorepository in collaboration with the pharmaceutical industry.

CINCH was a part of the NIH RDCRN from 2003 to 2013 (FIG. 2). CINCH recruited and trained 25 trainees who authored 58 publications; all remain involved in rare diseases, including channelopathy research, and all but two are in full-time academic work. With active involvement of trainees, CINCH organized NINDS-funded symposia attended by experts from around the world and patient support groups. Position papers on periodic paralyses⁵, episodic ataxias¹⁶ and nondystrophic myotonias⁶¹ from these symposia summarized the current understanding of these conditions and the clinical equipoise concerning established and experimental treatment. Because of the episodic nature of the symptoms of the target diseases, the CINCH investigators incorporated and validated an interactive voice response diary to capture recurrent transient symptom frequency, duration and severity⁶².

The CINCH infrastructure enabled this consortium to successfully compete for funding for treatment trials, including FDA-funded Phase II trials of mexilitine for nondystrophic myotonia⁵² and 4-aminopyridine for EA2, as well as the pivotal trial of dichlorphenamide in periodic paralyses, funded by the NIH and the MDA, that led the FDA to approve this drug as the first treatment for primary hyperkalaemic and primary hypokalaemic periodic paralysis in August 2015. The CINCH investigators have conducted a prospective study of objective and patient-reported outcomes in nondystrophic myotonia⁶³ in preparation for multinational trials to investigate mexilitine in patients with this condition⁶⁴.

Despite all the accomplishments, CRC-SCA and CINCH have encountered unanticipated challenges. For example, CRC-SCA planned to enrol 800 research participants, but the actual number was only 345.

This shortfall in enrolment was partly due to a longer-than-anticipated delay in obtaining the approval of institutional review boards at all sites, but was largely attributable to overestimation of study participation. Other contributing factors included lack of convenient transportation for participants to reach the study sites, limited outreach, and the non-therapeutic nature of the study. The CINCH investigators faced a setback with the Phase II trial in EA2, which had to be terminated when the lead study site failed to reach a contractual agreement with the supplier of the study drug after 3 years of negotiation.

Conclusions

The two consortia reviewed in this article, CINCH and CRC-SCA, illustrate the value of research networks in bringing together basic scientists, clinical scientists, and advocacy groups and the patients they represent, in order to build collaborations, enlist patient participation in research efforts, foster patient and public education, and support the infrastructure for research activities. The accomplishments of the networks include identification of additional genetic mutations affecting subsets of patients, characterization of the phenotypes of many rare diseases, definition of the disease pathogenesis and, most importantly, discovery of new treatments for the target diseases. However, perhaps predictably, a decade of research identified many new diseases in need of further study and many new questions for investigators. The collaborations promoted a sense of collective optimism that each rare disease can be better characterized, and can become a focus for the development of treatment assessment strategies, eventually leading to successful implementation of treatment trials.

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Key points

- Consortium for Clinical Investigations of Neurological Channelopathies (CINCH) and Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) are multicentre networks that engage patients who have rare neurological channelopathies with investigators, as well as advocacy groups
- Shared goals of the networks are to improve diagnosis, characterize the natural history, understand disease mechanisms, develop outcome measures that can be assessed in clinical trials, and devise novel treatment
- Patients, advocacy groups and investigators are partners in network activities, including teleconferences for study organization and training, steering committee meetings, and annual face-to-face research workshops and scientific symposia
- CINCH and CRC-SCA have invested in mentoring of junior investigators to pursue patient-oriented research on rare channelopathies
- The two networks have created and maintained patient registries, stratified patients on the basis of genetic characteristics, collected longitudinal clinical data to identify disease-relevant outcome measures, and conducted Phase I and II trials
- The two networks illustrate the collaborative approach that is necessary for the growing list of rare neurological channelopathies in need of treatment and further investigation

Box 1. | The CINCH and CRC-SCA networks

CINCH and CRC-SCA are multicentre networks with a shared focus on neurological channelopathies that cause ataxia. On the map, the CINCH centres are shown in red and the CRC-SCA centres are shown in blue (see the figure).

CINCH

The University of Rochester, Rochester, New York, USA is the lead centre, with affiliated sites at:

- Brigham and Women's Hospital, Harvard School of Medicine, Boston, Massachusetts, USA
- London Health Sciences Center, London, Ontario, Canada
- National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, USA
- National Hospital for Neurology and Neurosurgery, University College London, UK
- IRCCS Policlinico San Donato — Università degli Studi di Milano, Milan, Italy

- University of California, Los Angeles, California, USA
- University of California, San Francisco, California, USA
- University of Kansas Medical Center, Kansas City, Kansas, USA
- University of South Florida, Tampa, Florida, USA
- University of Texas Southwestern Medical Center, Dallas, Texas, USA

CRC-SCA

The University of Florida, Gainesville, Florida, USA is the lead centre, with affiliated sites at:

- Baylor College of Medicine, Houston, Texas, USA
- Columbia University, New York, New York, USA
- Emory University, Atlanta, Georgia, USA
- Harvard University MGH, Boston, Massachusetts, USA
- Johns Hopkins University, Baltimore, Maryland, USA
- Stanford University, Palo Alto, California, USA
- University of Alabama at Birmingham, Alabama, USA
- University of California, Los Angeles, California, USA
- University of California, San Francisco, California, USA
- University of Chicago, Chicago, Illinois, USA
- University of Colorado, Denver, Colorado, USA
- University of Michigan, Ann Arbor, Michigan, USA
- University of Minnesota, Minneapolis, Minnesota, USA
- University of Rochester, Rochester, New York, USA
- University of South Florida, Tampa, Florida, USA
- University of Texas Southwestern, Dallas, Texas, USA
- University of Utah, Salt Lake City, Utah, USA

CINCH, Consortium for Clinical Investigations of Neurological Channelopathies; CRC-SCA, Clinical Research Consortium for Spinocerebellar Ataxias.

Figure 1|. Timeline of molecular and clinical research in SCA.

SCA research began with the classification of autosomal dominant cerebellar ataxias in 1982. Key clinical events are in grey boxes, and key molecular events in SCA research are in purple boxes. Mapping of the first SCA locus (SCA1) in 1989 and identification of an expanded polyglutamine-encoding CAG repeat in the *ATXN1* gene 4 years later heralded the molecular era, leading the way to the identification of an ever-increasing number of mutations and genes (italicized) that define SCA. Polymorphic repeat expansions are indicated in parentheses alongside many of the genes; those without parentheses are affected

by point mutations or small indel mutations. Sporadic empirical clinical trials resulted largely in disappointing or uncertain results in the past, but the recent molecular advances facilitated coordinated efforts to investigate natural history, genetic modifiers and biomarkers of the SCAs. These studies have renewed hope for international multicentre clinical trials, which would be necessary for securing a large enough sample size to test disease-modifying therapeutics. CAG, Cooperative Ataxia Group; CRC-SCA, Clinical Research Consortium for Spinocerebellar Ataxias; ESMI, European Spinocerebellar Ataxia Type 3/Machado–Joseph Disease Initiative; ICARS, International Cooperative Ataxia Rating Scale; JPND, European Union-supported Joint Program in Neurodegenerative Disease; SCA, spinocerebellar ataxia.

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Figure 2|. Timeline of molecular and clinical research in neurological channelopathies.

The purple boxes show key discoveries of human channelopathies that were the focus of CINCH, with the defective genes in italics. The identification of mutations in the *SCN4A* gene in hyperkalaemic periodic paralysis marked the first demonstration that genetic defects in an ion channel gene could cause human disease. The discovery of mutations in the *CLCN1* gene in myotonia congenita was followed by the genetic characterization of other nondystrophic myotonia syndromes. EA1 and EA2 (allelic to SCA6) are channelopathies that affect the CNS. Andersen–Tawil syndrome manifests with periodic paralysis and

cardiac arrhythmia. Founding of the patient support groups and key clinical trials are shown in grey boxes. CINCH, Consortium for Clinical Investigations of Neurological Channelopathies; EA, episodic ataxia; RCT, randomized control trial; SCA6, spinocerebellar ataxia type 6.

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Table 1|**Neuromuscular and ataxia channelopathies**

Disease type	Known diseases in 2004	Known diseases in 2014
<i>CINCH target diseases</i>		
Periodic paralysis	<ul style="list-style-type: none"> • Hypokalaemic • Hyperkalaemic • Andersen–Tawil syndrome 	<ul style="list-style-type: none"> • Hypokalaemic (types 1 and 2) • Hyperkalaemic • Andersen–Tawil syndrome (types 1 and 2)
Nondystrophic myotonia	Chloride channelopathies: <ul style="list-style-type: none"> • Myotonia congenita (autosomal dominant and autosomal recessive) 	Chloride channelopathies: <ul style="list-style-type: none"> • Myotonia congenita (autosomal dominant and autosomal recessive) • Myotonic dystrophy type 1 (DM1) • Myotonic dystrophy type 2 (DM2) Sodium channelopathies: <ul style="list-style-type: none"> • Myotonia fluctuans • Myotonia permanens
Episodic ataxia (EA)	<ul style="list-style-type: none"> • EA1 • EA2 	EA1–7
<i>CRC-SCA target diseases</i>		
Spinocerebellar ataxia (SCA)	SCA6	SCA6, SCA13, SCA15/16/29 and SCA19/22

CINCH, Consortium for Clinical Investigations of Neurological Channelopathies; CRC-SCA,

Clinical Research Consortium for Spinocerebellar Ataxias.