

## **Final Progress Report: RSDSA and RSDhope Grant**

Researcher's Name: Richard G. Boles, M.D.  
E-mail Address: [rboles@chla.usc.edu](mailto:rboles@chla.usc.edu)  
Institution: Childrens Hospital Los Angeles  
Project Title: Maternally inherited mitochondrial DNA sequence variants and CRPS-I  
Date: June 30, 2010

### **1. What were the (specific) original objectives of this study?**

- a. To determine the degree of maternal inheritance in CRPS-I.
- b. To determine the prevalence of specific functional-disorder-related mitochondrial DNA (mtDNA) polymorphisms in CRPS-I.

### **2/3. Which objectives have been accomplished - summarize these accomplishments**

- a. The manuscript of the case series of 8 children with CRPS-I and maternally inherited mitochondrial dysfunction is now published in *Archives of Diseases in Childhood*.
- b. We have further developed and validated our Quantitative Pedigree Analysis methodology (see previous Progress Report).
- c. We have found that the same mtDNA polymorphisms associated with cyclic vomiting syndrome are also associated with CRPS-I and multiple additional functional disorders (see attached manuscripts, including a manuscript submitted to *Lancet*).
- d. Co-enzyme Q10 is effective and well tolerated in the treatment of cyclic vomiting syndrome, (published in *BMC Neurology*). This suggests that "co-Q" may be helpful in the treatment of CRPS-I, which is indeed my anecdotal clinical observation in several cases, especially combined with mega-dosages of B vitamins and high-dosage amitriptyline.
- e. We have preliminary data demonstrating probable maternal inheritance in 9/40 (22%) of CRPS-I cases referred through RSDSA/RSDHope, versus 1/40 (2%) of controls ( $P = 0.004$ ) (see attached abstract presented at Mitochondria 2009 in the Washington D.C. area).
- f. We have data demonstrating an association of mtDNA polymorphism 16519T with CRPS-I cases referred through RSDSA/RSDHope (21/49 = 43% of mtDNA haplogroup H CRPS-I subjects versus in 63/231 = 27% of HgH population controls;  $P = 0.031$ ; odds ratio 2.0, 95% CI 1.1-3.8) (see attached abstract presented at Mitochondria 2009 in the Washington D.C. area). 16519T is also associated with other functional disorders (see attached manuscripts and published articles) and thus this project provides supporting molecular data that CRPS-I is fundamentally related to the other functional disorders.
- g. Clinical data from the CRPS-I cases referred through RSDSA/RSDHope reveals that virtually all subjects suffer from multiple functional disorders in addition to CRPS-I. Many patients suffer from more than ten different functional disorders, frequently including the same as the ones that our group found are associated with 16519T.

### **4. Which objectives have not been accomplished?**

None. However, the clinical data is voluminous and a statistician is still analyzing it to see if any additional findings of the study can be found within.

### **5. Describe any problems in meeting these objectives**

The study was delayed because of personnel issues as discussed in the previous Progress Report.

### **6. Any budgetary questions**

None.

## 7. Future plans for this project

The attached manuscript was recently submitted to *Lancet*. Some of the CRPS-I data from this study are included in that manuscript. Recently, the P.I. received a good score on the first submission of an NIH grant application to sequence the full mtDNA in large numbers of subjects with cyclic vomiting syndrome and migraine. If funded, any disease-associated mtDNA sequence variants found as part of that study will be assayed for in the current bank of CRPS-I DNA samples.

Once the clinical data has been fully analyzed, likely a manuscript related to CRPS-I will be drafted for publication. This manuscript will probably focus on the high co-morbid functional disease burden in CRPS-I patients, as well as the finding of probable maternal inheritance in a sizable minority.

## 8. Publications or scientific presentations resulting from this project

Publications Resulting From This Project:

- Boles RG, Kerr JR, Zaki EA, Das K, Biswas S, Gardner A. “Functional” and dysautonomic-related conditions: Are we but blind men feeling different parts of an energy-depleted elephant? Submitted to *Lancet*.

Related Publications:

- Higashimoto T, Baldwin E, Gold JI, Boles RG (2008): Reflex sympathetic dystrophy: Complex regional pain syndrome type I in children with mitochondrial disease and maternal inheritance. *Arch Dis Child* 93:390-7.
- Camilleri M, Carlson P, Zinsmeister AR, McKinzie S, Busciglio I, Burton D, Zaki EA, Boles RG (2009): Mitochondrial DNA Polymorphisms, Functional Gastrointestinal Disorders and Gastrointestinal Motor and Sensory Functions. *Am J Physiol - Gastrointest Liver Physiol*. *Am J Physiol Gastrointest Liver Physiol* 296:G510-6.
- Zaki EA, Freilinger T, Klopstock T, Baldwin EE, Heisner K, Adams K, Dichgans M, Wagler S, Boles RG (2009): Two Common Mitochondrial DNA Polymorphisms Are Highly Associated With Migraine Headache and Cyclic Vomiting Syndrome. *Cephalalgia* 29:719-28.
- Boles RG, Zaki EA, Lavenbarg T, Hejazi R, Foran P, Freeborn J, Trilokekar S, McCallum R (2009): Are pediatric and adult-onset cyclic vomiting syndrome (CVS) biologically different conditions? Relationship of adult-onset CVS with the migraine and pediatric CVS-associated common mtDNA polymorphisms 16519T and 3010A. *Neurogastroenterol Motil*. Epub ahead of print.
- Boles RG, Lovett-Barr MR, Preston A, Li BU, Adams K (2010): Treatment of cyclic vomiting syndrome with coenzyme Q10 and amitriptyline, a retrospective study. *BMC Neurology* 10:10.

## 9. Statement written for the general public summarizing the highlights of this report

The term “functional disorders” refers to conditions that cause symptoms, but no abnormal findings on testing, such as from blood or imaging scans. Examples include migraine, cyclic vomiting syndrome (CVS), chronic fatigue syndrome, fibromyalgia, and irritable bowel, as well as CRPS-I (RDS). The first finding of this RSDSA and RSDHope-funded study is that CRPS-I patients usually suffer from multiple functional disorders, including the ones listed above.

Second, in this study the Boles group found that disease is primarily inherited in the mother’s family in 22% of CRPS-I families. Maternal inheritance suggests that the genetic mutation causing disease is encoded on the mitochondrial DNA (mtDNA), because the mtDNA is inherited exclusively from the mother.

Third, in this study the Boles group found that the mtDNA sequence variant called 16519T is common in CRPS-I patients. Previously, they had found that 16519T is common in CVS and in migraine patients. The data implies that 16519 doubles the risk that a person will develop CRPS-I. Overall, their data suggests that a

sizable minority of CRPS-I patients have disease in part due to mitochondrial dysfunction (low cellular energy levels), which in turn is in part due to DNA sequences inherited from the mother.

Their findings suggest that therapies aimed at increasing mitochondrial energy metabolism might be helpful in at least some patients with CRPS-I, perhaps more so in those in which functional disorders are common in relatives that share the same mtDNA sequence (siblings, mother, mother's siblings, sister's children, and the children of female patients). Dr. Boles has anecdotal observations (based on clinical experience, not vigorously studied) that CRPS-I does improve markedly in many children and young adults from families demonstrating maternal inheritance (older patients and those from families without maternal inheritance have not been studied). The therapy that appears to be effective consists of a combination of the following elements:

- Amitriptyline (enough to achieve a therapeutic blood level).
- Co-enzyme Q10 (starting with 200 mg twice a day (in adults and children over 80 pounds) from gel capsules or liquid preparations, and monitoring for a high blood level)
- B vitamins (including 100-400 mg of riboflavin a day)
- Exercise in moderation and/or physical therapy (to a degree short of causing substantial pain or fatigue; immobilization generally worsens the pain and disability)
- Frequent feedings to avoid fasting.

This regimen has potential side effects, and must be prescribed and followed by an appropriate physician. Therapy is complicated, and generally requires months to show full effects. For patients under age 30 years, referral to my Mitochondrial Functional Disorders Program at Childrens Hospital Los Angeles is a potential option. For more information, contact Dr. Boles at [rboles@chla.usc.edu](mailto:rboles@chla.usc.edu).

Sincerely,



Richard G. Boles, M.D.  
Director, CCS Center for Metabolic and Mitochondrial Disorders  
Division of Medical Genetics  
Childrens Hospital Los Angeles  
Associate Professor of Pediatrics  
Keck School of Medicine at USC