

Heterozygous mutations in BCS1L gene: A clinical case of Bjornstad syndrome

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ABSTRACT

Introduction: BCS1L, a 419-amino acid chaperone protein, is a member of the family called AAA-ATPases associated with various cellular activities. The AAA-family ATPases mediate the folding, unfolding, assembly and degradation of proteins. BCS1L is responsible for incorporating the Fe/S Rieske protein into complex III. Mutations in the BCS1L gene are the cause of Bjornstad syndrome (congenital sensorineural hearing loss and pili torti), GRACILE syndrome (growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death), complex III deficiency and patients with all of these features.

Patients and Methods: A 3-year old girl was evaluated for developmental problems, congenital deafness, and a possible mitochondrial disorder. Prior electron transport chain enzymology performed on muscle was non-diagnostic. Her exam showed sparse hair that was found to be pili torti upon microscopic examination. Her examination was significant for growth failure (all parameters < 1st percentile), lack of language function, preserved strength but unable to walk or manipulate objects with her hands that appeared to be due to apraxia and reduced muscle stretch reflexes.

Results: Her laboratory evaluation was significant for, elevated lactic acid and generalized amino aciduria. Molecular analysis of direct sequencing of BCS1L gene revealed two novel heterozygous mutations in the BCS1L gene, resulting in Bjornstad syndrome with features of GRACILE syndrome.

Discussion: Bjornstad syndrome is an autosomal recessive disorder, associated with sensorineural hearing loss and pili torti. The mother of the clinical case had only one of novel heterozygous mutation observed in the child while the father carried the other heterozygous mutation. All exons and adjoining introns of BCS1L gene were PCR amplified and sequenced. Results of this clinical case with the molecular analysis of the family are presented.

INTRODUCTION

Bjornstad syndrome is an autosomal recessive condition characterized by sensorineural hearing loss and pili torti. The BCS1L, gene responsible for the syndrome has been mapped to chromosome 2q34-36. BCS1L a chaperone protein is a member of the ATPases associated with various cellular activities. BCS1L protein is located in the inner mitochondrial membrane and is presumed to facilitate the insertion of Rieske Fe/S protein into precursors to complex III during assembly of the respiratory chain. Complex III then becomes assembled with complexes IV and I into respirasome supercomplex that facilitates the electron transfer required for the ATP generation.

Mutations in BCS1L gene has been reported to be associated with neonatal tubulopathy, encephalopathy, and liver failure: also with severe disorder termed Gracile Syndrome with aminoaciduria, cholestasis, iron overload, lactic acidosis and early death. Mutations reported in BCS1L with less severity in manifestations are associated with the Bjornstad syndrome. Family study of patient MZ with gene sequencing of BCS1L is presented.

CLINICAL SUMMARY

MZ (Figure1) is a 3 year old girl, born at term followed by a pregnancy notable only by oligohydramnios. MZ seemed healthy for the first eight months of life, although her mother suspected she had low motor tone and possibly poor hearing. MZ lost her hair in the first few months and failure to gain weight lead to a diagnosis of failure to thrive, but it was determined to be due to gastroesophageal reflux. Lactic acidosis was identified at nine months of life and elevated liver transaminase levels were detected soon after. A g-tube was placed because of a failure to gain weight. Despite efforts at nutritional support, MZ did not gain weight and had little language development but would communicate by pointing. MZ demonstrated slow acquisition of motor milestones but just after her third birthday lost the ability to stand unassisted. MZ did have some regression in June 2006 as she was beginning to pull to a standing position but lost that skill.



Figure 1. MZ a 3-yr old girl affected with Pili torti, elevated lactic acid and generalized aminoaciduria

Further testing demonstrated elevated tricarboxylic cycle intermediates and continued lactic acidosis. A muscle biopsy was performed and demonstrated a citrate synthase greater than twice the control value, with the components of the respiratory chain (complex I+III, II+III and IV) 47%-62% control when adjusted for citrate synthase activity, thought possibly consistent with relative mtDNA depletion. Muscle histology was normal. A liver biopsy showed multifocal ground-glass hepatocellular changes that was interpreted as GSD with mild periportal fibrosis and apoptosis". CF gene testing and PW/Angelman methylation were normal. At the time she was first evaluated by one of the authors (BHC) there were pending studies: fibroblasts for ETC enzymology, fumarase activity, alpha ketoglutarate dehydrogenase activity and copper transport and uptake. POLG1 sequencing was not performed.

Physical examination demonstrated height, weight and head circumference < 5th percentile. She is a bright-eyed and alert child. The most striking feature is the lack of hair. There were several strands of hair (maybe 20) with the longest hair shaft being less than an inch long. The hair shaft would fracture by touching the shaft. She did not have any expressive language function but her visual attentiveness suggested an interest in what was occurring, but there was no indication she had a understanding of spoken language. The cranial nerve exam was normal aside from what appeared to be lack of ability to hear. The motor bulk was reduced but her strength was normal for bulk. Muscle stretch reflexes were slightly reduced. She was not able to sit or walk independently and her arm movements coordinated like that of an 8-12 month old child. There was no organomegaly, cataracts, thickened skin or other systemic or dysmorphic findings.

Because of the history of growth retardation, hearing loss, lactic acidosis, fragile hair shafts (microscopic examination of the hair did confirm trichothiodystrophy), and hepatic disease, BCS1L gene sequencing was performed on MZ and her parents.

RESULTS

Lab evaluations are indicative of elevated lactic acid and generalized aminoaciduria. Genomic DNA was amplified using primers flanking the exon –intron BCS1L gene boundaries from MZ and Parents(B1 and B2). Double stranded DNA sequencing was performed using the ABI Big Dye method in an ABI 3100 DNA analyzer. Sequence variants were identified with Gene Window and Celera databases. MZ was a compound heterozygote for two novel variants R183H and GNovel R. MZ's mother was heterozygous /Wild type for variant GNovel R while father was heterozygous /Wild type for variant R183H. (Figure 2.)

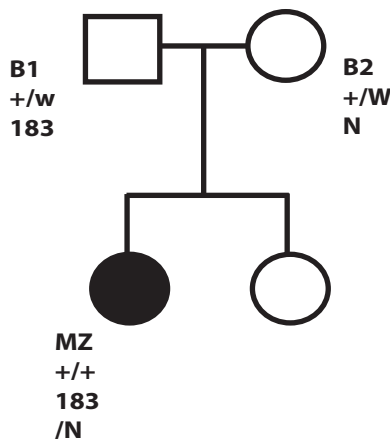
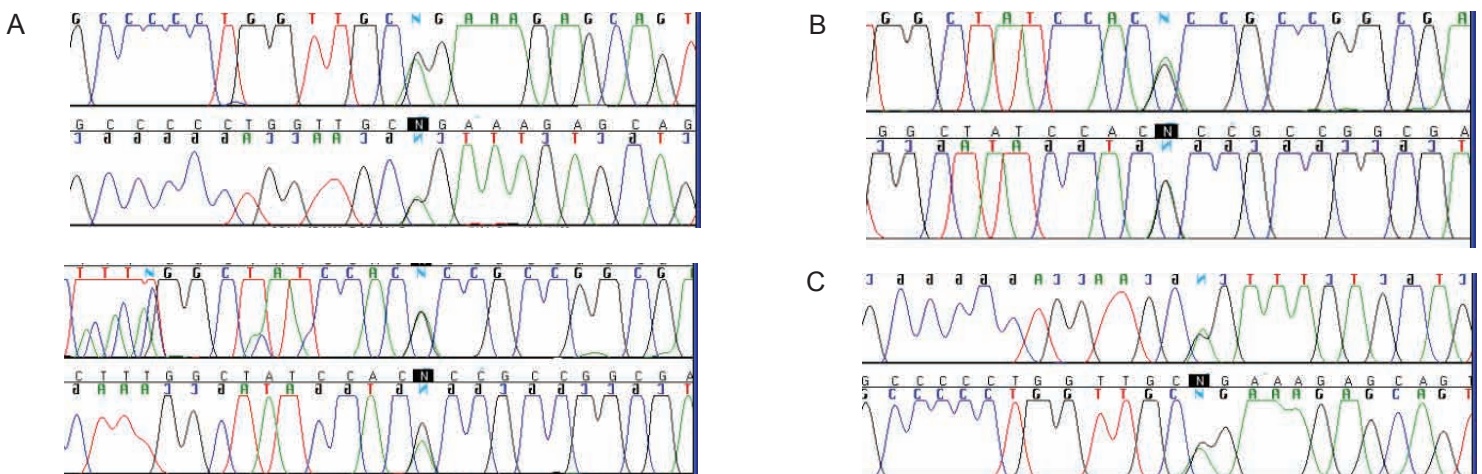


Figure 2. Pedigree of MZ family with sequence electropherograms of (a) MZ with variants 183/Novel (b) B1 Dad heterozygous 183/WT (c) B2 Mom heterozygous Novel/+ indicating the location of nucleotide change.



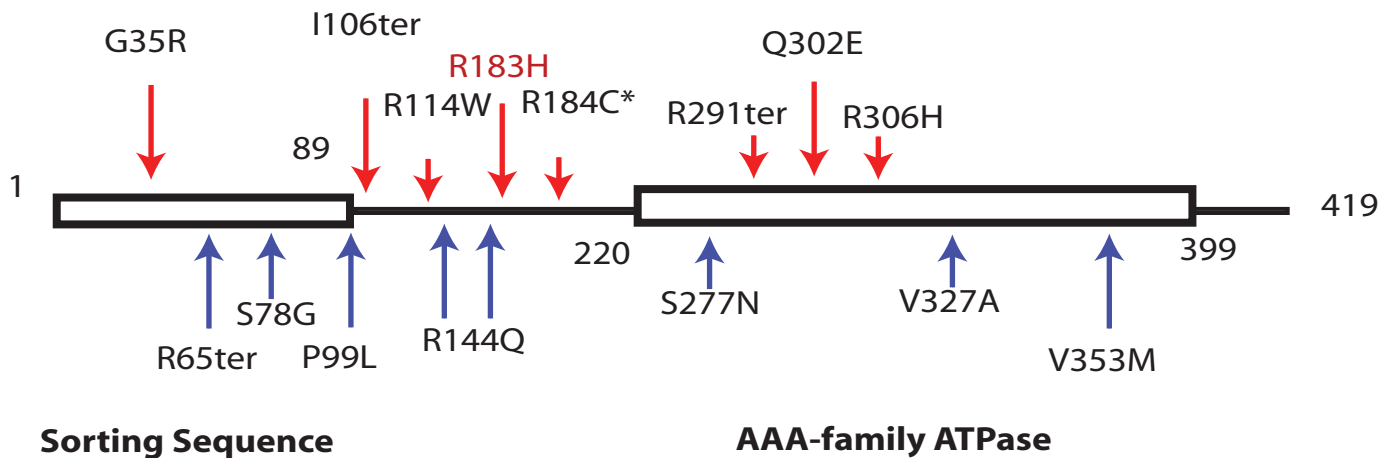


Figure 3. Schematic representation of the BCS1L protein with the mitochondrial sorting sequence domain (residues 1 to 89) and the conserved AAA-family ATPase domain (residues 220 to 339). Mutations that cause the Bjornstad syndrome are shown red arrows, mutations that complex III deficiency are indicated with an asterisk and mutations that cause complex III or the GRACILE syndrome are shown in blue arrows. Variant R183H found MZ is located in red.

CONCLUSIONS

- Both sequence variants detected in MZ and parents indicate the presence of these variants in a compound heterozygous state result in a milder complex III deficiency of Bjornstad syndrome with growth retardation, developmental delay and profound hypotonia.
- These novel variants both result in missense residues-change in codon 183 is from Arginine to histidine changing it to hydrophobic residue while the variant Gnovel R an glycine to arginine change results in hydrophilic residue-these two events would result in changing the folding patterns, protein-protein interactions of the chaperone protein involved in the COXIII formation
- MZ's sister is unaffected clinical and has not been tested for her carrier status. Both parent's carrier status is indicated with presence of one normal copy of BCS1L gene.
- Presence of overlapping features with Gracile syndrome also with lack of severity in clinical findings has been shown with accumulation of mitochondrial respiratory intermediates that lacked Rieske Fe/S protein and decreased electron-transport –chain activity.

REFERENCES

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