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RESEARCH REPORT

Compound Heterozygous Inheritance of Mutations in *Coenzyme Q8A* Results in Autosomal Recessive Cerebellar Ataxia and Coenzyme Q_{10} Deficiency in a Female Sib-Pair

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Abstract Autosomal recessive ataxias are characterised by a fundamental loss in coordination of gait with associated atrophy of the cerebellum. There is significant clinical and genetic heterogeneity amongst inherited ataxias; however, an early molecular diagnosis is essential with low-risk treatments available for some of these conditions. We describe two female siblings who presented early in life with unsteady gait and cerebellar atrophy. Whole exome sequencing revealed compound heterozygous inheritance of two pathogenic mutations (p.Leu277Pro, c.1506+1G>A) in the coenzyme Q8A gene (*COQ8A*), a gene central to biosynthesis of coenzyme Q (CoQ). The paternally derived p.Leu277Pro mutation is predicted to disrupt a conserved motif in the substrate-binding pocket of the protein, resulting in inhibition of CoQ_{10} production. The maternal c.1506+1G>A mutation destroys a canonical splice donor site in exon 12 affecting transcript processing and subsequent protein translation. Mutations in this gene can result in primary coenzyme Q_{10} deficiency type 4, which is characterized by childhood onset of cerebellar ataxia and exercise intolerance, both of which were observed in this sib-pair. Muscle biopsies revealed unequivocally low levels of CoQ_{10}, and the siblings were subsequently established on a therapeutic dose of CoQ_{10} with distinct clinical evidence of improvement after 1 year of treatment. This case emphasises the importance of an early and accurate molecular diagnosis for suspected inherited ataxias, particularly given the availability of approved treatments for some subtypes.

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Introduction

Individuals with autosomal recessive cerebellar ataxia (ARCA) present with considerable clinical diversity but fundamentally have an inability to coordinate movement and balance due to cerebellar dysfunction. Individuals are typically diagnosed in childhood or as young adults (<30 years of age), with cerebellar atrophy visible by MRI (Montero et al. 2007). While categorisation of clinical entities has improved with the identification of the genetic basis for many of these conditions, there is still substantial

genetic heterogeneity, making diagnosis challenging and an efficient molecular diagnosis difficult. However, the importance of a precise genetic diagnosis (enabling discrimination between the many types of autosomal recessive ataxias) has been underlined by the realisation that a minority of these disorders can be effectively treated with pharmacotherapy, resulting in significant improvement in health.

The advent of next generation sequencing technologies has tremendously enhanced the efficiency of molecular diagnosis for complex and highly heterogeneous neurodevelopmental disorders such as the inherited ataxias, providing answers for families, facilitating family planning and occasionally presenting the prospect of treatment strategies. We have applied this approach to identify the genetic basis for an ARCA caused by a deficiency in CoQ_{10} synthesis, resulting in a treatment strategy for a family 9 years after symptom onset.

Cases

We describe a family with two girls who presented primarily with gait ataxia and cerebellar atrophy. There was no known consanguinity between the two Caucasian parents, and their family history was non-contributory. The proband (II.1) was born after an uncomplicated pregnancy and delivery at term. She sat, rolled and crawled at appropriate ages but only succeeded in walking, unsteadily, with a walker at 2 years and 6 months, and her gait remains unsteady at her current age of 11 years. She presented primarily with dysmetria (with no clonus); however there has been no discernable deterioration since her diagnosis. She is not dysmorphic, but does have reduced muscle bulk and tone. Her reflexes are normal, and she has no visual disturbance or nystagmus. MRI at 2 years and 2 months showed a small cerebellar vermis but normal height of the cerebellar hemispheres (Fig. 1a). A repeat MRI at 7 years and 9 months showed prominent cerebellar sulci, with a loss of height of the cerebellar hemispheres, and atrophy of the vermis (Fig. 1b). Both scans revealed a normal brainstem, including the pons.

The proband's sister (II.2) demonstrated a similar course, with truncal ataxia preventing walking until 3 years of age. At 2 years and 2 months, MRI revealed a small cerebellar vermis and increased spaces between the folia especially in the inferior cerebellum (Fig. 1c). The height of the cerebellar hemispheres was normal, and the brainstem and pons appeared normal. The proband also has a younger brother (III.3) who shows no clinical abnormalities at 3 years of age.

The metabolic workup for both girls has been extensive with no abnormalities in plasma cholesterol, plasma albumin, transferrin isoelectric focussing, plasma and urinary amino acids, urinary organic acids, cerebrospinal fluid (CSF) neurotransmitters and CSF lactate. Comparative genomic hybridisation (Agilent ISCA (v2)) revealed no significant imbalance. Liver mitochondrial enzymology was considered normal, and muscle mitochondrial enzymology revealed complex II + III to be low (reflecting the enzymatic deficiency later proposed by genetics – full mitochondrial analysis can be found in Supplementary Table 1). Electron microscopy analysis of the same muscle tissue showed no evidence of giant abnormal mitochondria. Other fine structures were unremarkable. Initial genetic investigations by Sanger sequencing ruled out mutations in

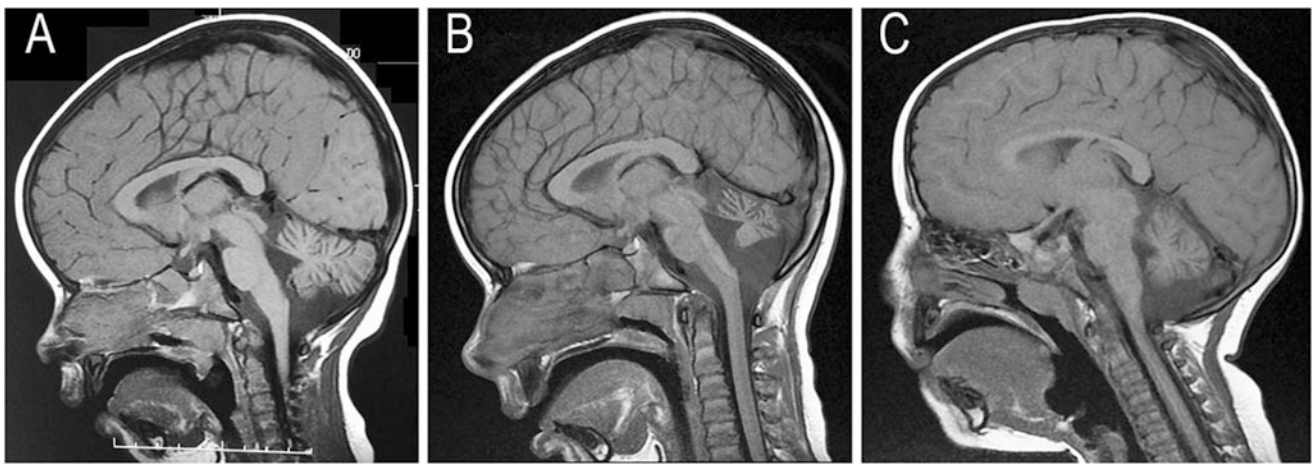

Fig. 1 T1-weighted midline sagittal MRI scans of the two siblings with *COQ8A* mutations. (**a**) Scan of the oldest sibling at 2 years and 2 months of age demonstrating a small cerebellar vermis; (**b**) follow-up scan of the older sibling at age 7 years and 9 months demonstrating progressive loss of volume of the cerebellar vermis and thinning of the folia consistent with an atrophic mechanism underlying her ataxic presentation; (**c**) scan of the younger sibling at age 2 years and 2 months demonstrating moderate volume loss in the cerebellar vermis and increased spaces between the folia

APTX, and no causative triplet repeat expansions were identified in *FRDA*, *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *TBP*, and *ATN1*. We subsequently performed whole exome sequencing on both affected siblings (Supplementary Methods).

Variation filtering identified the presence of two single nucleotide variants (SNVs) in *COQ8A* (coenzyme Q8A, previous symbol *ADCK3* (AARF domain-containing kinase 3); NM_020247.4, OMIM 606980) in both affected children (Table 1). Sanger sequencing of parental DNA confirmed compound heterozygous inheritance of these variants. Mutations in *COQ8A* result in coenzyme Q_{10} deficiency, primary, 4 (COQ10D4, OMIM 612016), an autosomal recessive disorder characterized by childhood onset of cerebellar ataxia and exercise intolerance (Lagier-Tourenne et al. 2008), which is phenotypically concordant with this family's presentation.

The paternally derived SNV encodes a non-synonymous missense change from leucine to proline (c.830T>C, p.Leu277Pro) in exon 6. This amino acid is conserved in vertebrates from human to lamprey (UCSC (Kent et al. 2002), PhyloP (Pollard et al. 2010); Supplementary Figure 1) and is located in an N-terminal motif that is conserved across all members of the AARF domain-containing kinase family: the KxGK motif (positions 276–279) (Lagier-Tourenne et al. 2008). The variant has been previously observed in heterozygote state in a single European individual in the gnomAD dataset (AF = 4.48–06) (Lek et al. 2016). This variant is predicted to be damaging by mutation impact prediction algorithms (PolyPhen-2, SIFT Blink, SNPs&GO, PROVEAN, full details in Supplementary Table 2).

The maternally derived SNV alters the canonical splice donor site in exon 12 (c.1506+1G>A); this mutation has not been reported previously and is absent in public variant databases. BDGP splice site and ASSP programmes predict that this variant will destroy the splice donor site of exon 12, which is expected to affect removal of intron 12 from all reported protein-coding isoforms. The effect of the c.1506+1G>A splice site mutation was determined using RNA sequencing (Supplementary Methods) on blood obtained from both parents. No significant abundance differences were observed between the parents for any annotated *COQ8A* protein-coding transcript (200,000 vs. 190,926 FPKM, $p = 0.43$ for canonical transcript NM_020247.4). However, all mRNA molecules originating from the maternal c.1506+1G>A allele retained all or part of intron 12; conversely, intron 12 was correctly spliced in all mRNAs originating from the mother's wild-type allele and both paternal alleles. RNAseq fragments derived from the maternal wild-type allele were twice as abundant as those from the c.1506+1G>A allele (52 vs. 25 fragments). Mutation haplotypes and parental inheritance were validated by PCR followed by Sanger sequencing (Fig. 2).

Following the discovery of the *COQ8A* variants, muscle and plasma total CoQ_{10} were measured using high-performance liquid chromatography with electrochemical detection, similarly to Tang et al. (2001). The muscle CoQ_{10} was mildly reduced in II.1 (16.3 ± 3.4 nmol/g tissue, reference range 20–70 nmol/g wet tissue) when compared to biopsies from myopathy patients not suspected of CoQ_{10} deficiencies and previously published reference intervals (Lopez et al. 2006). Plasma CoQ_{10} was reported as low-normal (0.68 µmol/L, 0.52 µmol/L in II.1 and II.2, respectively; reference range 0.45–1.71 µmol/L), which is consistent with the literature on biosynthetic CoQ_{10} defects (Molyneux et al. 2005, 2008; Yubero et al. 2014).

The siblings underwent treatment with oral CoQ_{10} (20 mg/kg/day, (Blumkin et al. 2014)) and follow-up was performed at 12 months. Use of a validated clinical tool for the assessment of ataxia (Trouillas et al. 1997) was instituted to objectively measure the effect of treatment. The scale is scored 0–100 with a score of 0 signifying no ataxic symptoms and 100 indicating a maximal score. The proband's baseline score was 40/100, and after treatment for 12 months, the score had reduced to 29/100 (full ataxia assessment is detailed in Supplementary Table 3). The parents of the child also reported an improvement in energy and classroom performance, observations that were reinforced when teachers, blinded to the deliberate omission of daily doses of CoQ_{10}, volunteered their observations of discernible deterioration in function over the school day. The younger sibling also demonstrated an improvement in ataxia score from 49/100 to 43/100 over the same time frame as her sister.

Discussion

Autosomal recessive ataxias due to primary CoQ_{10} deficiency are a heterogeneous group of disorders caused by mutations in genes involved in the CoQ_{10} biosynthetic

Table 1 *COQ8A* variant annotations

Gene	Chr	HGVS DNA ref	HGVS protein ref	Variant type	Predicted effect	Genotype
COQ8A	1	NM_020247.4:c.830T>C	NM_020247.4:p.(Leu277Pro)	Missense	Aa change	Heterozygous
COQ8A	1	NG_012825.2:c.1506+1G>A	NG_012825.2:p.(=)	Splice donor	Destroys splice site	Heterozygous

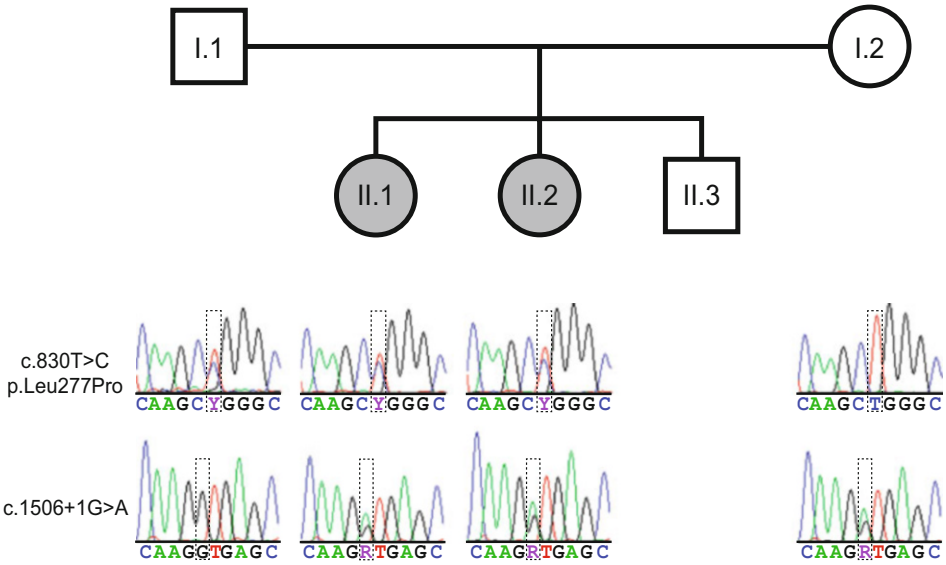

Fig. 2 Family pedigree and transmission of the c.830T>C and c.1506+1G>A mutations in the COQ8A gene. Sanger sequencing electropherograms for both loci are shown below the corresponding family member in the lower part of the figure

pathway (Desbats et al. 2015). Coenzyme Q_{10} acts as an electron carrier in the mitochondrial respiratory chain and serves as an antioxidant in the intracellular environment (Crane et al. 1993); hence there has been much clinical interest in its potential therapeutic benefits. Indeed, therapeutic doses of CoQ_{10} have been successful in ameliorating symptoms for some cases of primary CoQ_{10} deficiency ataxias (Mignot et al. 2013). We describe compound heterozygous mutations in *COQ8A*, a gene central to the CoQ_{10} biosynthetic pathway, in two female siblings who presented with gait ataxia and cerebellar atrophy. The older sibling had moderately decreased muscle CoQ_{10} and both underwent a trial of CoQ_{10}. Remarkably, both siblings showed improvement in their ataxia scores following 12 months of treatment, with functional improvements also evident in daily classroom performance.

Causative mutations in the *COQ8A* gene were first reported in childhood ataxia by Lagier-Tourenne in 2001 who proposed the term autosomal recessive cerebellar ataxia 2 (ARCA2) after observing cerebellar atrophy and exercise intolerance during childhood with an associated reduction of muscle CoQ_{10} (Lagier-Tourenne et al. 2008). *COQ8A* encodes an unorthodox protein kinase-like (uPKL) protein that localises to the mitochondrial matrix and is central to CoQ biosynthesis (Khadria et al. 2014; Stefely et al. 2016). The deletion of the yeast and *E. coli* homologues eliminates CoQ biosynthesis in these organisms (Poon et al. 2000; Do et al. 2001), and a mouse *COQ8A* knockout model exhibits an ataxic phenotype and pathological signatures that align with the human condition (including degeneration of cerebellar Purkinje cells and abnormal skeletal mitochondria morphology) (Stefely et al. 2016). The structure of the protein was originally described by Stefely et al. as an UbiB protein with an atypical protein kinase-like fold containing particular features inhibitory to protein kinase activity (Stefely et al. 2015). More recently, they provide evidence that the protein encoded by *COQ8A* functions similar to yeast Coq8p and further argue that it is in fact an uPKL with noncanonical activities which support CoQ biosynthesis (amongst other functions) (Stefely et al. 2016).

Atypical kinase COQ8A, mitochondrial, features a long N-terminal extension, which folds into α-helices to form a KxGQ motif which appears to play a central role in CoQ biosynthesis, as mutating the region results in autophosphorylation and inhibition of CoQ production in vivo (Stefely et al. 2015, 2016). The p.Leu277Pro mutation identified in this New Zealand family is located in one of the predicted alpha helical domains (GQα2), which contribute to the KxGQ motif. The well-described tendency of proline to distort and destabilise alpha helices in aqueous environments (Khan and Vihinen 2007) suggests that the mutation affects protein stability, as demonstrated for other known pathogenic mutations in the GQα2 helix (Stefely et al. 2015).

The second mutation, c.1506+1G>A, destroys the splice donor site in exon 12 resulting in retention of intron 12 leading to premature termination of COQ8A protein synthesis, ultimately resulting in reduced CoQ_{10} levels. Primary cell lines from an ACRA2 patient harbouring similar mutations to the case described here (splice and missense) showed reduced protein and total CoQ_{10} levels and exhibited ultrastructural changes to the mitochondria (Cullen et al. 2016).

Some patients with primary CoQ_{10} synthesis defects respond to supplementation with high-dose oral CoQ_{10} (Desbats et al. 2015); however, patients with *COQ8A* mutations show a somewhat varied response, with many not responding well (Lamperti et al. 2003; Aure et al. 2004; Lagier-Tourenne et al. 2008; Mollet et al. 2008; Anheim et al. 2010; Gerards et al. 2010; Horvath et al. 2012; Terracciano et al. 2012; Mignot et al. 2013; Blumkin et al. 2014; Liu et al. 2014; Barca et al. 2016; Hikmat et al. 2016; Malgireddy et al. 2016), as summarised in Supplementary Table 4. There have, however, been three reported cases of improvement, two of which are later onset than the girls presented here. The latest, reported by Barca et al., showed improvement in speech and gait in a 48-year man (onset at 20 years of age) after 1 year of treatment with 400 mg/day CoQ_{10} (Barca et al. 2016). This individual harbours a homozygous deletion (c.1511_1512delCT) that leads to a premature truncation of the protein (p. Ala504fs). This mutation is located 5 bp from the splice site mutation described in our New Zealand sib-pair, both of which reside in the protein kinase domain. Another study by Liu et al. reported improvement in a Pakistani sib-pair (age of onset: 10 years of age), who harbour a homozygous frameshift mutation (c.1844_1845insG) in the C-terminus of mitochondrial atypical kinase COQ8A, which is predicted to extend the open reading frame by 81 amino acids (Liu et al. 2014). These siblings showed significant improvements in myoclonic movements, ataxic gait and dysarthric speech 3 months after treatment with CoQ_{10} at 200 mg twice a day. The third reported case of improvement describes partial improvement in motor skills balance and strength at 5 years of age with 20 mg/kg/day oral CoQ_{10} (Blumkin et al. 2014). When the drug was ceased at 6 years of age (pre-empted by the patient who had an accompanying psychiatric condition), their condition deteriorated. This individual and her sister (milder presentation) harbour compound heterozygous mutations in the protein kinase domain (p.P502R), near the site disrupted by the splice site mutation described here, and a previously observed deletion at c.1750_1752delACC. There are also some self-reported improvements from patients on oral CoQ_{10} (Mollet et al. 2008; Liu et al. 2014). The sib-pair described here provides further evidence of the therapeutic benefits of CoQ_{10} for this condition in some families.

This case outlines the clinical and genetic heterogeneity of autosomal recessive ataxias and highlights the importance of early and accurate diagnosis (in this instance using whole exome sequencing). This seems particularly prudent given the possible response to a low-risk treatment option that could be given prior to severe central nervous system damage.

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Take-Home Message

Compound heterozygous *COQ8A* mutations cause treatment-responsive CoQ_{10} deficiency ataxia.

Contributions of Individual Authors

JCJ, KL and RGS designed and conducted experiments and wrote the manuscript; WW and BS conducted experiments; JT, DRL and RH clinically confirmed research results; SPR clinically evaluated patients and conducted the trial of CoQ_{10} treatment; SM, PMG and RM performed muscle and plasma CoQ_{10} analysis.

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Competing Interest Statement

JCJ, WW, BS, JT, DRL, RH, SM, PMG, RM, SPR, RGS and KL declare they have no conflict of interest.

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Details of Ethics Approval

The study was approved by the New Zealand Northern B Health and Disability Ethics Committee (ref 12/NTB/59), and parents provided written informed consent.

Patient Consent Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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