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COQ4 mutation leads to childhood-onset ataxia improved by CoQ1O administration

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Abstract

Loss of function mutations in *COQ4* lead to fatal neonatal mitochondrial disorders with CoQ10 deficiency. In two siblings with childhood-onset, slowly progressive ataxia from a consanguineous mating from Turkey, whole exome sequencing identified homozygous missense mutations in COQ4 (Gly55Val). Blood levels of CoQ10 were either below or at the low end of the normal range. The more severely affected of the siblings was given a high dose of CoQ10 (2000 mg/day) for one month, following which significant improvement in neurological signs and symptoms was noted. Our report indicates that COQ4 mutations are a rare cause of ataxia and that CoQ10 supplementation is a personalized treatment for this form of ataxia.

Keywords

Ataxia; CoQ4 Mutation; CoQ10 Deficiency; Genetics; Therapy

Introduction

Ataxia is a clinical feature of hundreds of disorders, and even pure cerebellar ataxia without other symptoms can be caused by mutations in at least 40 dominant [1] and 45 recessive genes [2]. Whole exome and whole genome sequencing has recently allowed the

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identification of novel genes involved in numerous rare Mendelian disorders including ataxia, but many cases of isolated or recessive ataxia still remain unexplained [3,4]. When there are two or more affected individuals from a consanguineous mating, gene identification using homozygosity mapping is an efficient way to identify new genes for rare disorders [5,6]. In rare cases, gene identification can lead to personalized therapy, as exemplified here.

Patients and Methods

Patients

The index case is a 26 year-old male with slowly progressive ataxia and spasticity. His parents are first cousins. The proband had walking difficulty at the age of 8, followed by partial epilepsy four years later and lost the ability to ambulate by age 16. Neurological examination revealed cognitive deterioration, dysarthria, inability to walk even with support but able to stand with support, severe spasticity in the lower limbs, mild spasticity in the upper limbs, moderate weakness in proximal leg muscles, dysmetria and dysdiadochokinesia. His oculomotor movements and sphincter were normal with symmetrical deep tendon reflexes in both limbs. However, Babinski sign was positive bilaterally. A brain MRI of index case at time of evaluation showed cortical and subcortical T2 hyperintensity, not limited to a specific vascular territory, as described in a previous report describing *COQ4* mutations [5] (Fig. 1). He was treated with carbamazepine (600 mg twice daily) and clonazepam (2 mg, twice daily).

The proband's 27 year-old sister's symptoms also started when she was 8 years old but progressed more slowly than the proband. She developed partial epilepsy when she was 12 years old. Physical examination demonstrated dysarthria, spastic-ataxic gait, mild spasticity in all four extremities, although more prominently in the lower extremities. She could walk without support. Dysmetria and dysdiadokokinesis were present. Eye movements were normal. Her cognition was impaired. Babinski sign was positive bilaterally with no sphincter dysfunction.

Routine biochemistry, hemogram and metabolic tests were normal in both. Whole spine MRI did not reveal any pathology. However, brain magnetic resonance imaging (MRI) showed cerebral and cerebellar atrophy. She had been treated with levatiracetam (1000 mg, twice daily).

Recruitment

The index case was referred to medical genetics with an initial diagnosis of ataxia. Genetic counseling was offered and all individuals, which included the two affected individuals, 2 unaffected siblings and parents, gave their voluntary informed written consent to participate. The local study protocol was approved by the Ethics Committee at Erciyes University, Kayseri, Turkey. The genetic study has been reviewed and approved by the University of Michigan institutional review board. Following identification of the mutation in CoQ10 biosynthesis, the treating neurologist attempted a trial with CoQ10 supplementation in the more severely affected individual. After this was successful, approval for CoQ10 treatment

was granted from local health insurances, both patients were under long term treatment and were re-assessed after ~ 1 year.

CoQ10 levels

Plasma CoQ10 (Q10, 87853) was analyzed by the Mayo Clinic (Rochester, MN). Since samples were in transport more than 72 hours, only total (not reduced) plasma CoQ10 values were reliable and reported. CoQ10 levels of the sister, patient 2, although not treated with CoQ10, was measured at the same times as patient 1.

Next generation exome sequencing

DNA was isolated from whole blood using the Qiagen Gentra Puregene kit. Next generation exome sequencing was performed by the University of Michigan DNA core facility. Exome was captured by the SeqCap EZ Exome v3.0 kit (Roche, CA, USA), and paired ends were sequenced on HiSeq2000 to an average depth of 52 X. Variants of interest were validated and tested for segregation patterns, such as verification of heterozygosity, by Sanger sequencing.

Results

DNA samples from a sibling pair with childhood-onset ataxia were submitted for next generation exome sequencing. Common SNPs were used for linkage analysis using Merlin [7] with a pedigree loop included to account for the first cousin mating (Fig. 2A). Model parameters were for a fully penetrant rare recessive disease with a minor allele frequency of 0.0001. Only one region on distal chromosome 9 showed a LOD score above 1.0 under this model (Fig 2B). The region implicated contained 51 genes. We identified only one gene, *COQ4,* with a homozygous mutation that was predicted to be damaging, exon2:c.G164T :p.G55V. Both parents were heterozygous. This particular mutation has not been previously reported [8] and the glycine at this position is conserved in all vertebrates (Fig 2C). As *C0Q4* mutations lead to CoQ10 deficiency [9], plasma CoQ10 was measured. CoQ10 levels were below or at the low end of normal (Table 1). CoQ10 treatment has been suggested [9,10] and has helped in humans and animal models with CoQ10 deficiency [11] and in some of the more prevalant causes of ataxia [12]. The treating neurologist therefore offered treatment with high dose (2000 mg/day) CoQ10 to the more severely affected patient. After one month on therapy the patient was re-evaluated, and another blood sample of the index patient was drawn. The Scale for the Assessment and Rating of Ataxia (SARA) [13], a validated rating scale for ataxia, was used to quantify severity of cerebellar dysfunction. Following 1 month of treatment with CoQ10, although serum CoQ10 values were not improved, clinical evaluation and subjective report showed a marked improvement. The total SARA score improved from 30 to 10, with the biggest improvement in gait and station, from being wheelchair bound, unable to walk even with support, or standing unaided, to now being able to walk with a walker and standing without support. After ~ 1 year of maintained therapy with CoQ10, the patient remained much improved from baseline, with a SARA score of 17. Subsequently the affected sister was also initiated on CoQ10 with an improvement in the SARA score at the initiation of treatment of 31 to 12 following long term treatment.

Discussion

Our results suggest that certain mutations in COQ4 lead primarily to ataxia, in contrast to more damaging mutations that lead to lethal neonatal mitochondrial encephalomyopathy [9,10] with variable presentations, including one case with mainly neurological involvement [9] similar to our cases. Our results suggest that COQ4 deficiency can lead to ataxia that is responsive to CoQ10 treatment. Although only a single case, our results are consistent with animal models and prior evidence in patients with other CoQ10 deficiencies that demonstrate benefit from high dose CoQ10 therapy [14]. This case represents an early report of CoQ10 treatment for COQ4-deficiency ataxia. The SARA score improvement from 30 to 10 may be exaggerated by inexperience of the physician with the English form, and psychologically by the subjective clear improvement observed by all, the patient, his parents and the physician, The later scores (from 32 to 17 and 31 to 12) may be a more objective indicative of treatment response. We should also note that while blood CoQ10 levels were borderline low in both, it was not a good biomarker, as already initially, the level in the less severely affected sister was lower than in the more affected brother, and levels did not show improvement during treatment. Since blood was drawn in Turkey several days before analysis at the Mayo clinic, we can't rule out technical problems with measurements in these delayed samples. The question of value of blood CoQ10 as a biomarker in such cases of ataxia clearly warrants further studies under optimal conditions and larger sample sizes.

Of relevance, recently, a case of multiple system atrophy, a severe form of ataxia with autonomic system failure, with mutations in *COQ2* was reported who was treated with high-dose ubiquinol, a more bioavailable form of CoQ10. While plasma levels of CoQ10 improved in that case, phenotype, and SARA score of 40, in contrast to our cases reported here, did not improve [15]. More research is needed to determine whether similarities and differences are due to timing of the administration in relation to disease stage, different mutations, or other still unknown factors.

Conclusion

In Turkey, as in the US, CoQ10 is considered a supportive supplement rather than a prescription medication. This can limit access due to out-of-pocket costs associated with supplementation with high dose CoQ10. In these and similar cases such as vitamin deficiencies with demonstrated low blood levels, high dose supplementation should be considered a precise pharmacotherapy, and coverage should be available through prescription. The benefit of CoQ10 treatment may be suggested by the molecular etiology as well as blood levels, and clinical improvement with CoQ10 can significantly improve health and quality of life.

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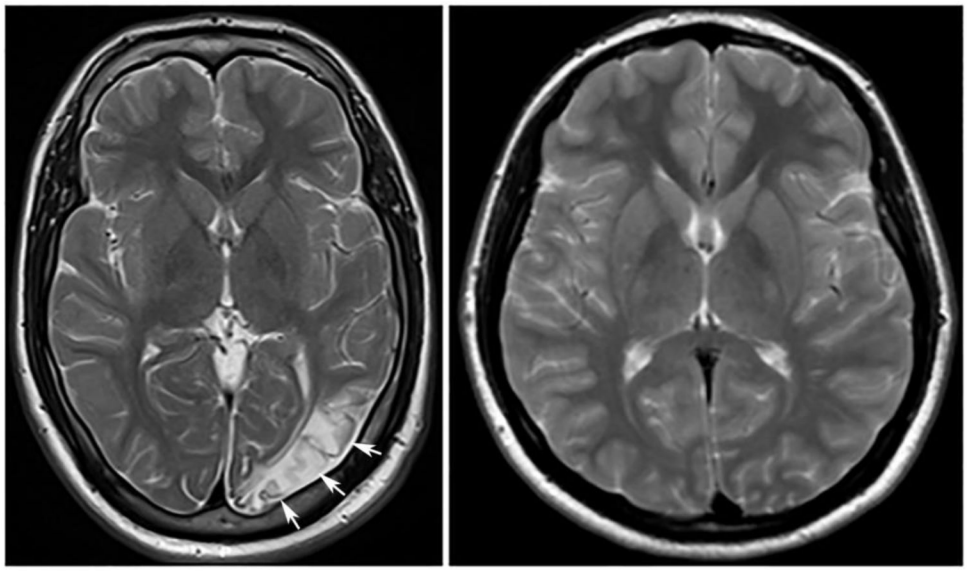

Fig. 1: MRI of index case

T2 weighted axial images of the patient (left) and age-matched control (right). Patient's image shows cortical and subcortical signal changes in the left occipital region (arrow) and mild atrophy.

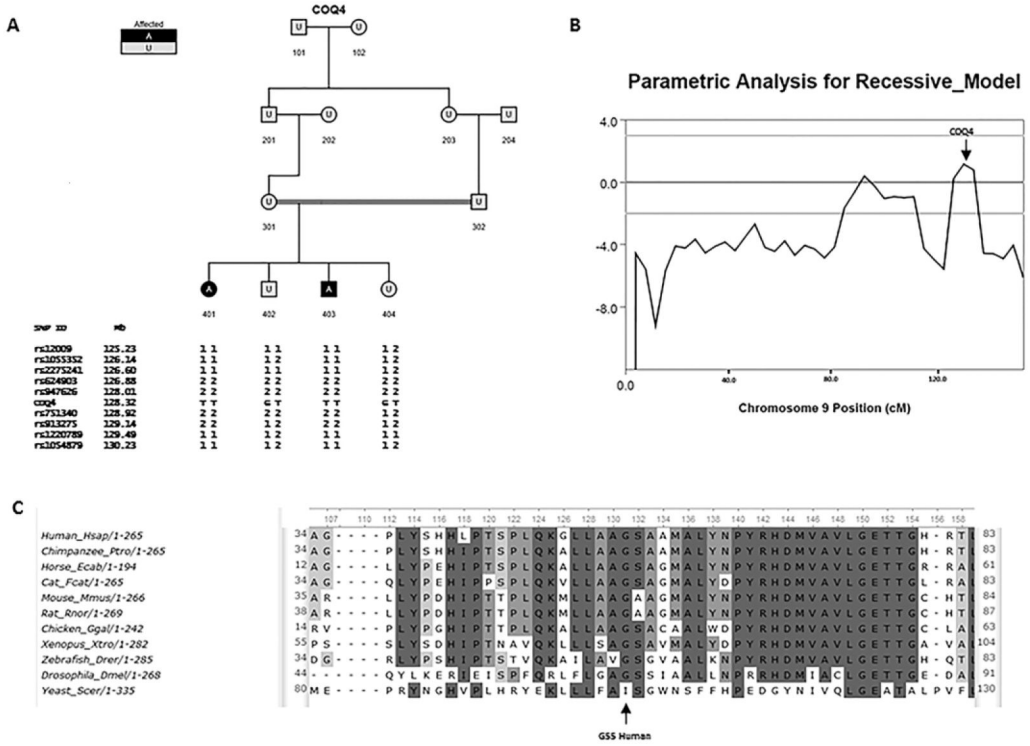

Fig 2. Family with Linkage Analysis and mutation in *COQ4*

A: Pedigree of consanguineous family, with genotypes of closely linked SNPs from linkage analysis shown next to COQ4 status (based on Sanger sequencing). **B:** Linkage analysis of chromosome 9, the only chromosome with LOD > 1, **C:** Cross species comparison of amino acid sequence alignment shows glycine at position 55 is conserved in all vertebrates.

Table 1:

Summary of clinical, laboratory and imaging findings of the reported patients

	Patient 1			Patient 2	
	Before treatment	**After 1 month COQ10 (2000mg per day)**	**After ~1 year of CoQ10 (2000mg per day)**	**Before treatment**	**After ~1 year of CoQ10 (2000mg per day)**
Consanguinity	Product of first cousin marriages				
Sex	Male			Female	
Age at onset (years)	8				
Age at evaluation (years)	25		27	26	28
SARA score at evaluation	30	10	17	17	12
Gait	Unable to walk, even supported	Clearly abnormal, > 10 steps not possible	Marked staggering, intermittent support of the wall required	Gait difficulty	Gait difficulty
Station	Able to stand >10 sec with constant support	Able to stand >10 sec without support	Able to stand >10s in natural position only with intermittent support	Normal	Normal
Nose finger test	Tremor > 5 cm	Tremor <2 cm	Tremor with an amplitude <2cm	Tremor <2 cm	Tremor <2 cm
Speech	Dysarthria	Dysarthria	Dysarthria	Dysarthria	Dysarthria
COQ10 in blood mcg/L (433–1532 is normal range)	500	461	NA	428 and 308	NA
MRI	Cerebral (especially parietal-occipital region) and cerebellar atrophy		NA	Cerebral and cerebellar atrophy	NA
Other features	Partial epilepsy, Cognitive deterioration		None	Partial epilepsy, Cognitive deterioration	None