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Delayed diagnosis of congenital myasthenia due to associated mitochondrial enzyme defect

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Abstract

Clinical phenotypes of congenital myasthenic syndromes and primary mitochondrial disorders share significant overlap in their clinical presentations, leading to challenges in making the correct diagnosis. Next generation sequencing is transforming molecular diagnosis of inherited neuromuscular disorders by identifying novel disease genes and by identifying previously known genes in undiagnosed patients. This is evident in two patients who were initially suspected to have a mitochondrial myopathy, but in whom a clear diagnosis of congenital myasthenic syndromes was made through whole exome sequencing. In patient 1, whole exome sequencing revealed compound heterozygous mutations c.1228C > T (p.Arg410Trp) and c.679C > T (p.Arg227*) in collagen-like tail subunit (single strand of homotrimer) of asymmetric acetylcholinesterase (*COLQ*). In patient 2, in whom a deletion of exon 52 in Dystrophin gene was previously detected by multiplex ligation-dependent probe amplification, Sanger sequencing revealed an additional homozygous mutation c.1511_1513delCTT (p.Pro504Argfs*183) in docking protein7 (DOK7). These case reports highlight the need for careful diagnosis of clinically heterogeneous syndromes like congenital myasthenic syndromes, which are treatable, and for which delayed diagnosis is likely to have implications for patient health. The report also demonstrates that whole exome sequencing is an effective diagnostic tool in providing molecular diagnosis in patients with complex phenotypes.

Keywords: Congenital myasthenia; Mitochondrial respiratory chain; Mutation; *DOK7*; *COLQ*; Duchenne muscular dystrophy; Whole exome sequencing

1. Introduction

Congenital myasthenic syndromes (CMS) are a family of inherited neuromuscular disorders characterised by fatigable muscle weakness, ptosis, ophthalmoplegia, respiratory and skeletal muscle weakness [1]. This clinical profile overlaps considerably with other myopathies and can lead to diagnostic challenges [2]. Electromyography and muscle histology may provide nonspecific results, resulting in patients being misdiagnosed and untreated [2–4]. Establishing the specific molecular diagnosis in a family allows treatment to be individualised as drug responses vary widely between different forms of CMS [5,6].

The molecular diagnosis of genetically heterogeneous disorders like CMS and mitochondrial respiratory chain (MRC) disorders can be challenging, as traditional Sanger sequencing

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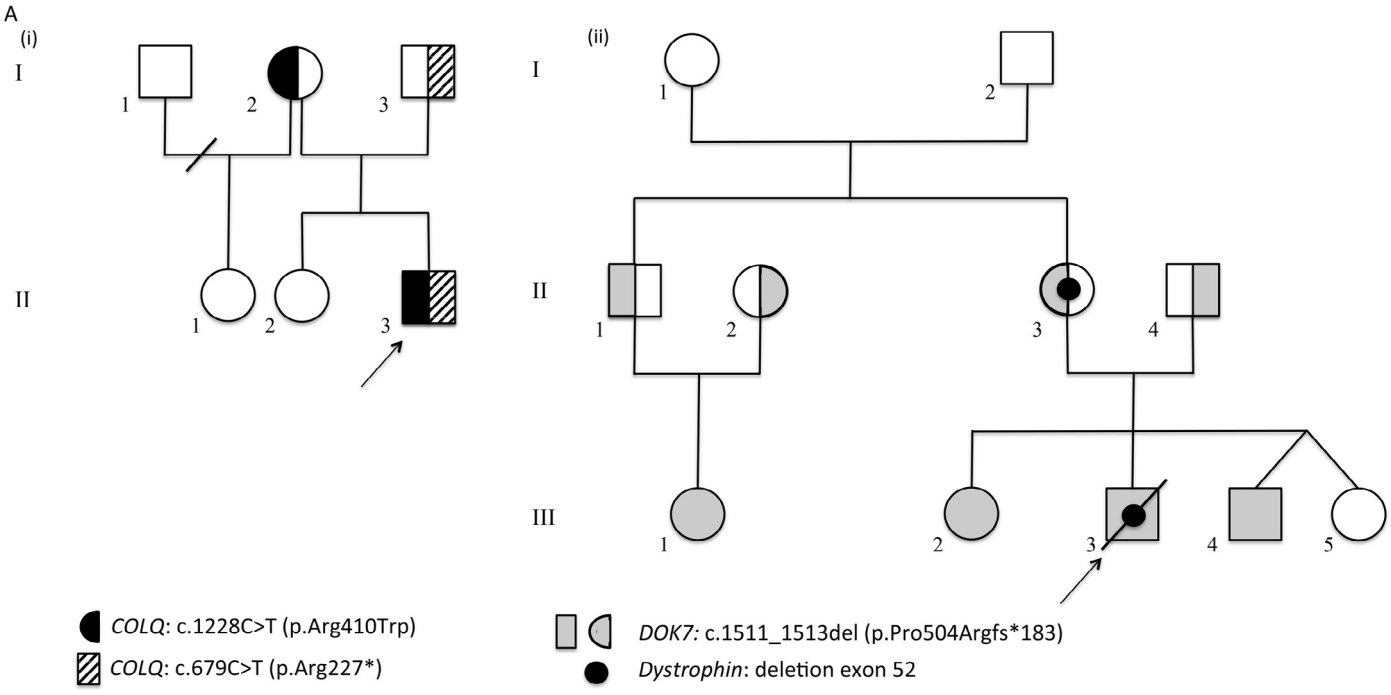
is often time consuming and expensive. Next generation sequencing (NGS) technology is now being applied as an efficient and cost-effective strategy for the diagnosis of Mendelian disorders, not only for screening of well characterised genes, but also for identification of novel disease genes and prenatal diagnosis [7,8].

We report two patients with mutations in genes associated with CMS in whom there was no molecular diagnosis but a suspicion of mitochondrial myopathy was initially considered, based on mitochondrial enzyme studies which showed complex I deficiency. The report illustrates the diagnostic difficulty in differentiating between these disorders that share phenotypic similarities.

2. Case reports

2.1. Patient 1

This boy's clinical phenotype in early childhood and the abnormality on repetitive nerve stimulation (RNS) were initially presumed to represent a form of congenital myasthenia and were previously reported [9]. He was the youngest of three children (Fig. 1A(i); II-3) to



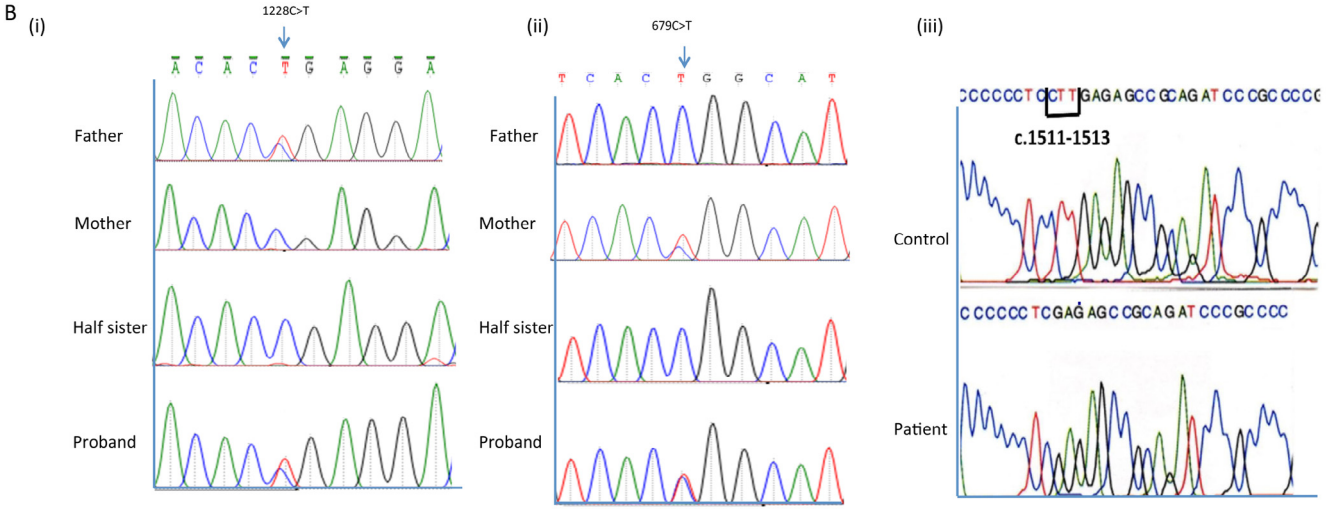


Fig. 1. (A) Pedigrees for family 1 (i) and 2 (ii). The proband is denoted by an arrow. (B) DNA sequence profile *COLQ* mutations for patient 1, parents and unaffected sister. (i) c.1228C > T (p.Arg410Trp) mutation heterozygous in the father and proband. (ii) c.679C > T (p.Arg227*) mutation heterozygous in the mother and proband. (iii) Sanger sequencing of *DOK7* near the end of exon 7 in a control and in patient 2 showing a homozygous c.1511_1513delCTT deletion in patient.