Revisiting the Clinical, Histochemical and Molecular Spectrum of Adult-Onset adPEO Associated with the C10Orf2 (PEO1) Mutation (S36.008)

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Objective: To definitively define the clinical and molecular understanding of mtDNA disorders by deep phenotyping a large, well-characterized cohort of adult patients with PEO1 (C10Orf2)-linked adPEO. Background: To date, C10orf2 (also called PEO1, encoding the Twinkle helicase) is a nuclear encoded mitochondrial gene that have been implicated in mitochondrial DNA (mtDNA) replication disorders. Pathogenic mutations in the C10orf2 gene have been associated with a myriad of clinical presentations. Recessive C10orf2 mutations characteristically result in severe, early onset, multisystem disorders of mtDNA maintenance; whilst the majority of adult-onset cases are characterised by autosomal dominant PEO presenting with ptosis, ophthalmoparesis and muscle restricted multiple mtDNA deletions. Other clinical features including myopathy, cataracts and possible cardiac involvement have been described. Method: We reviewed the detailed clinical, histochemical and genetic analysis of 90 patients (including 33 previously reported cases) who harboured a dominant mutation in C10orf2 attending specialized mitochondrial disease referral centres in the UK. Results: The most common clinical findings were PEO and ptosis followed by proximal weakness and fatigue. Interestingly not all patients had PEO at the time of molecular diagnosis and often there were only minor histochemical abnormalities detected. Molecular screening identified a further 14 novel C10orf2 mutations not previously determined. Conclusions: This is the largest case series, and review of the literature, to date, confirming the clinical and molecular features associated with dominant C10orf2 mutations. Our findings confirm that dominant mutations in C10orf2, in general, behave stereotypically and manifest as a relatively benign clinical phenotype, compared to the other mtDNA maintenance disorders.