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SUDDEN UNEXPECTED DEATH IN ADULTS WITH M. 3243A>G MUTATION

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Background Heterogeneity of clinical phenotype associated with the m.3243A>G mutation is a significant diagnostic and prognostic challenge to clinicians. Current literature regarding disease progression in relation to this mutation focuses on individuals who are moderately or severely affected by the disease. Here we present two sudden unexpected deaths in individuals who were largely asymptomatic.

Method Multiple tissues were investigated including muscle, brain and heart. The degree of respiratory chain deficiency was determined using histochemical techniques and m.3243A>G mutation load by pyrosequencing.

Result A high level of m. 3243A>G mutation load was detected in cardiomyocytes, brain and skeletal muscle. Mild left ventricular hypertrophy was identified in one case. There were 15–60% of COX deficient cardiomyocytes in both cases. Interestingly, the extensive respiratory chain deficiency observed in brain tissues from both of these individuals is similar to a patient severely affected by MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes).

Conclusion We propose that sudden unexpected death in asymptomatic individuals with high tissue heteroplasmy represents a new, but rare, phenotype. The exact mechanism of death is undetermined although cardiac cause is a strong possibility. This adds a further challenge to the increasingly complex counselling of asymptomatic carriers of the m.3243A>G mutation.