Pathogenic mitochondrial mt-tRNA(Ala) variants are uniquely associated with isolated myopathy.

Abstract:
Pathogenic mitochondrial DNA (mtDNA) point mutations are associated with a wide range of clinical phenotypes, often involving multiple organ systems. We report two patients with isolated myopathy owing to novel mt-tRNA(Ala) variants. Muscle biopsy revealed extensive histopathological findings including cytochrome c oxidase (COX)-deficient fibres. Pyrosequencing confirmed mtDNA heteroplasmy for both mutations (m.5631G>A and m.5610G>A) whilst single-muscle fibre segregation studies (revealing statistically significant higher mutation loads in COX-deficient fibres than in COX-positive fibres), hierarchical mutation segregation within patient tissues and decreased steady-state mt-tRNA(Ala) levels all provide compelling evidence of pathogenicity. Interestingly, both patients showed very high-mutation levels in all tissues, inferring that the threshold for impairment of oxidative phosphorylation, as evidenced by COX deficiency, appears to be extremely high for these mt-tRNA(Ala) variants. Previously described mt-tRNA(Ala) mutations are also associated with a pure myopathic phenotype and demonstrate very high mtDNA heteroplasmy thresholds, inferring at least some genotype:phenotype correlation for mutations within this particular
mt-tRNA gene.

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