

# Polycystic ovary syndrome, a phenotypic manifestation of mtDNA variants

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## Letter to the Editor

In a recent study Ding et al. investigated 80 females with polycystic ovary syndrome (PCOS) for the presence of mtDNA variants in blood lymphocytes. They found a mtDNA variant in 12 of the 82 patients [1]. However, only 4 of these mtDNA variants were assessed as pathogenic [1]. We have the following comments and concerns.

The authors found that PCOS was due to a definitive variant in the mtDNA in four of the 80 patients [1]. In another six patients, PCOS was associated with probably pathogenic mtDNA variants [1]. Pathogenicity of the mtDNA variants was assessed by application of the Yarham-score [2]. Did the authors use results from their own study or from the literature to score the variants?

Strong arguments against pathogenicity of the variants presented in table 3 are that all were homoplasmic, that four control subjects also carried three of these variants, that the conservation index was below 70% for three variants, that no cybrid studies and no single fiber studies had been carried out, and that no evidence for a biochemical defect in muscle homogenates or immune-histochemical alterations of the muscle biopsy was provided.

Was the family history positive for a mitochondrial

disorder (MID) or features suggesting MID in any of the 12 index cases carrying an mtDNA variant? Did any of the first-degree relatives manifest with cerebral, endocrine, muscle, nerve, gastrointestinal, cardiac, renal, muscle, nerve, or hematological disease? Particularly mothers of patients carrying definite and probable mtDNA mutations should manifest clinically in the majority of the cases, since mtDNA variants are transmitted via a maternal trait of inheritance in 75% of the cases. Only in 25% of the offspring de novo mtDNA point mutation occur [3].

One patient with a pathogenic variant presented as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome [1]. Which phenotypic manifestations did this particular patient develop since diagnosis? Was there vomiting, headache, stroke-like episodes, seizures, myopathy, cardiomyopathy, or cognitive decline? Which organs were affected in addition to the ovaries? One patient was reported as having Lebers' hereditary optic neuropathy (LHON) [1]. Were organs affected other than the retinal ganglion cells and the ovaries? Did visual impairment recover in this particular after some time? Did the two patients in whom the definitive mtDNA variant manifested as arterial hypertension also manifest in other organs or tissues? MIDs are most frequently mitochondrial multi-organ disorder (MIMODS) [4].

Lactic acidosis is a frequent manifestation of MIDs [5]. Was lactate determined in the included patients? How often was lactic acidosis found? Did lactic acidosis also occur in patients who did not carry a mtDNA variant?

Were the 80 patients with PCOS also investigated for pituitary adenoma, occasionally reported in patients with a MID [6]? Did control subjects also have normal serum testosterone values? Was testosterone determined in controls?

Overall, this excellent study could be more meaningful, if affected and unaffected family members of the index cases were prospectively investigated for subclinical or manifesting MID. Patients with a MID require thorough work-up for MIMODS even of clinically unaffected organs.

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