A homozygous IER3IP1 mutation causes microcephaly with simplified gyral pattern, epilepsy, and permanent neonatal diabetes syndrome (MEDS).

Public Summary:
Wolcott-Rallison syndrome (WRS) and the recently delineated microcephaly with simplified gyration, epilepsy, and permanent neonatal diabetes syndrome (MEDS) are clinically overlapping autosomal recessive disorders characterized by early onset diabetes, skeletal defects, and growth retardation. While liver and renal symptoms are more severe in WRS, neurodevelopmental characteristics are more pronounced in MEDS patients, in which microcephaly and uncontrolled epilepsy are uniformly present. Mutations in the EIF2AK3 gene were described in patients with WRS and defects in this gene lead to increased susceptibility to apoptotic cell death. Mutations in IER3IP1 have been reported in patients with MEDS and similarly, loss of activity results in apoptosis of neurons and pancreatic beta cells in patients. Here we report on a homozygous mutation of the IER3IP1 gene in four patients from two unrelated consanguineous Egyptian families presenting with MEDS who display burst suppression patterns on EEG. All patients presented with mildly elevated liver enzymes, microalbuminuria, and skeletal changes such as scoliosis and osteopenia, leading to repeated bone fractures. We expand the phenotypic spectrum of MEDS caused by IER3IP1 gene mutations and propose that WRS and MEDS are overlapping clinical syndromes, displaying significant gene-dependent clinical variability.

Scientific Abstract:
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