Wolcott-Rallison Syndrome: A new mutation and report of two cases

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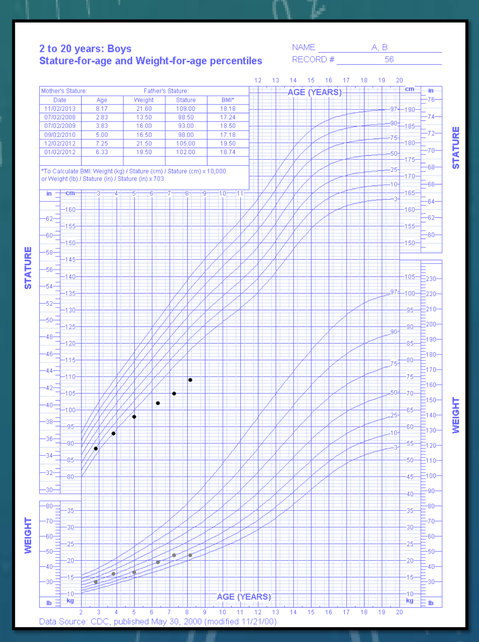
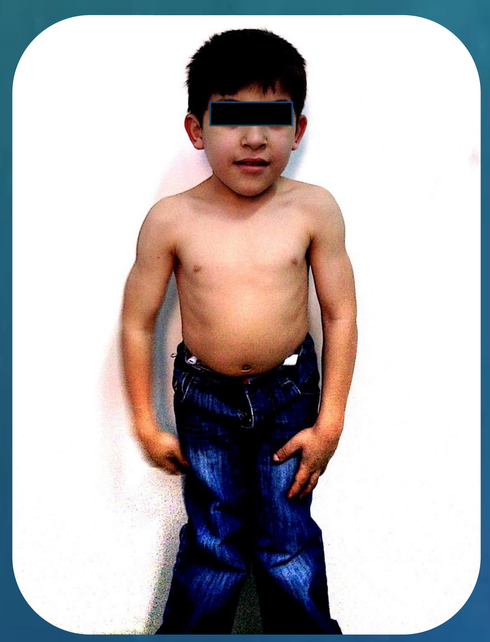
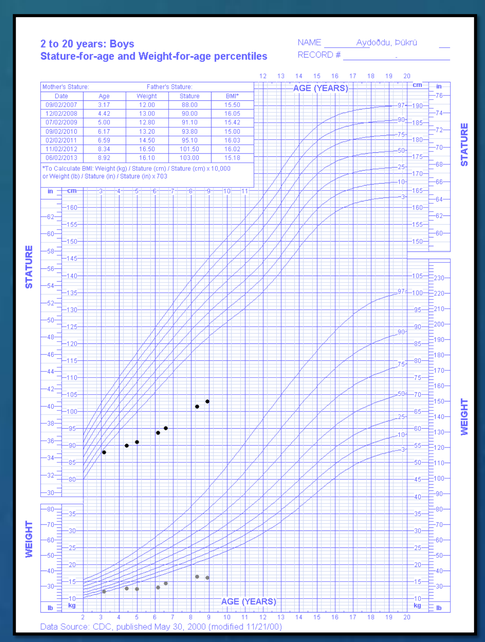
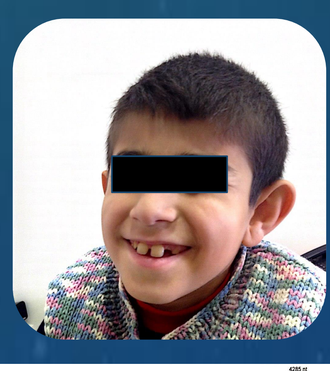
Background: Wolcott-Rallison Syndrome (WRS) is a rare, autosomal recessive disease and characterized by early-onset diabetes, spondyloepiphyseal dysplasia, short stature, osteopenia, acute liver failure, and neurological deficit. It results from mutation in a gene of the eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3). **Objective and hypotheses:** We report two WRS patients diagnosed in infantile period.

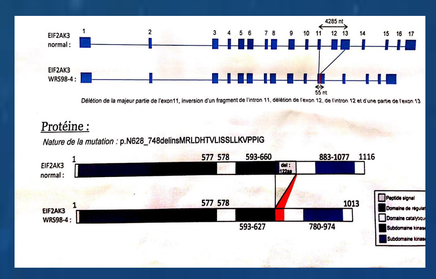
Methods: PCR techniques were used to amplify the 17 exons of the EIF2AK3 gene and DNA direct assay techniques were used for gene mutation analysis. **Patient 1:** A boy was admitted to our clinic for diabetic ketoacidosis at the age of 15 months. Liver biopsies were performed due to elevated transaminases at 2 years and 2 months, and 7 years, and were consistent with chronic hepatitis. Epiphyseal dysplasia on X-rays of both hands was observed. At the age of 8.5 years, height 109 cm (-3.82 SDS), weight 21.6 kg (-1.6 SDS), genu valgum deformity, difficulty in walking and running were remarkable on physical examination. Last Hb1C level was 9.7% with intensive insulin therapy. **Patient 2**, a boy was diagnosed with diabetes at the age of 17 months. Elevated transaminases were notable at 3 y, difficulty in walking was remarkable at 5 y. At 7 years of age, intracranial abscess developed which was successfully treated with posaconasole and hyperbaric oxygen. At the age of 9.5 years, physical examination showed height of 103 cm (-5.2 SDS), weight of 16.1 kg (-5.6 SDS), orthodontic problems, genu valgum deformity, difficulty in walking and running. **Results:** While two homozygous mutations (E926K and K939R) in EIF2AK3 gene were detected in patient 1, internal deletion in the gene which has never been reported was identified in patient 2.











Patient 1: Note the growth deceleration, and genu varum deformity

Patient 2: Note the growth deceleration, dysmorhpic face, and internal deletion in the gene

Conclusion: Major skeletal abnormalities of WRS are osteoporosis/osteopenia, thoracolumbar kyphosis, and bowing of the femur. In addition, pancreas exocrine insufficiency, hypothyroidism, and various central nervous system anomalies (cerebellar cortical dysplasia, cerebral atrophy, pachygyria) have been reported. WRS should be suspected in any child who presents with permanent, nonimmune neonatal/infantile diabetes associated with skeletal dysplasia, short stature, episodes of acute liver failure, or pancytopenia.