Osteopetrosis with Renal Tubular Acidosis

Alternative Names
Guibaud-Vainsel Syndrome
Carbonic Anhydrase II Deficiency
Marble Brain Disease
Carbonic Anhydrase II
CA2
CA II
Carbonic Anhydrase II, Erythrocyte, Electrophoretic Variants of Carbonic Anhydrase B

WHO International Classification of Diseases
Congenital malformations, deformations and chromosomal abnormalities

OMIM Number
259730

Mode of Inheritance
Autosomal recessive

Gene Map Locus
8q22

Description
Osteopetrosis with renal tubular acidosis, or carbonic anhydrase type II (CAII) deficiency, is a rare autosomal recessive disorder manifested clinically with osteopetrosis, renal tubular acidosis (RTA), cerebral calcification, and growth retardation.

Molecular Genetics
The molecular basis for this isoenzyme defect has been characterized, and the defect has been identified as a mutation in the gene encoding the isoenzyme of CAII, located at chromosome 8q22. Absence of this isoenzyme has been observed in circulating erythrocytes and renal tubular cell membranes of affected patients. Defects in H+ secretion have previously been suggested as the cause for their RTA. In detailed studies, some patients are said to have proximal RTA, others distal RTA, and yet others, a combination of proximal and distal RTA.

Epidemiology in the Arab World

Egypt
Nagai et al. (1997) described a 3.5-year-old Egyptian boy, born for unrelated parents, with osteopetrosis, cerebral calcification, a persistent anion gap type of metabolic acidosis (plasma pH 7.26), and a mild degree of hypokalemia. In addition, the patient had the following findings: impaired renal re-absorption of HCO3, decreased NH4+ excretion, low urine-blood PCO2 difference in alkaline urine, a high urinary citrate level unless he was severely acidic, and a failure to achieve maximally low urine pH. These findings indicated that the renal acidification mechanisms of the patient were impaired in both the proximal and distal tubule as a result of CAII deficiency.

Kuwait
Bourke et al. (1981) reported two Kuwaiti Bedouin sibs with osteopetrosis with renal tubular acidosis. The major clinical manifestation in both was periodic hypokalemic paresis, while one sib showed basal ganglion calcification and mental subnormality. Abdel-Al et al. (1994) diagnosed 19 Arab children (six boys and 13 girls) in ten sibships as having osteopetrosis over a 5-year period in various hospitals in Kuwait. Eighteen patients had an isolated autosomal recessive form and one had autosomal recessive osteopetrosis associated with renal tubular acidosis. The mean age of diagnosis was 24 months. Parental consanguinity was high amongst them (68%). Anemia, hepatosplenomegaly, failure to thrive, recurrent infections and neurological manifestations were common. Associated congenital abnormalities were found in 26%. Deafness, hydrocephalus and dental caries were
relatively less common. Abdel-Al et al. (1994) noted a high mortality rate (37%) owing to infection.

Saudi Arabia
Ohlsson et al. (1980) described four children from three Saudi Arabian families suffering from osteopetrosis, distal renal tubular acidosis and cerebral calcification associated clinically with mental retardation, stunted growth, abnormal teeth and a similar facial appearance. The syndrome was inherited as an autosomal recessive. Ohlsson et al. (1980) attributed the growth retardation to renal tubular acidosis but no metabolic link was evident between the other major features of the disorder. In addition, Ohlsson et al. (1980) could not define the fundamental defect in their patients. However, the disorder was radiologically indistinguishable from the classical recessive (malignant) and dominant (benign) forms of osteopetrosis but its other characteristics lead Ohlsson and colleagues (1980) to conclude that their patients exhibited a separate disease entity. In 1986, Ohlsson and colleagues described four new Saudi Arabian cases of the carbonic anhydrase II deficiency syndrome from two families. The disease was inherited as autosomal recessive and exhibited osteopetrosis with renal tubular acidosis and cerebral calcification. Additional features also included mental retardation, growth failure, typical facial appearance, and abnormal teeth. Two patients showed evidence of restrictive lung disease. One of the patients reported represented the first neonate reported to be affected with this syndrome. Intrauterine growth was normal, but metabolic acidosis was already evident in the neonatal period. Radiographic evidence of osteopetrosis was probably absent at birth but appeared during the late neonatal period. Carbonic anhydrase II deficiency was demonstrated in erythrocyte hemolysates from the older two siblings of this neonate, and a 50% normal level of carbonic anhydrase II was demonstrated in the erythrocyte hemolysate from their father.

In 1988, Al Rajeh et al. described two sisters with osteopetrosis associated with renal tubular acidosis and cerebral calcification, inherited as an autosomal recessive disorder. Features of the two patients included deficiency of carbonic anhydrase II. Significant reduction in blood levels of carbonic anhydrase II was also found in both parents and another sister, suggestive that these individuals are heterozygotic carriers.

Al-Rasheed et al. (1998) observed, over a 10-year period, 28 Arab children with autosomal recessive osteopetrosis in two hospitals in Riyadh. Eighteen (64%) had osteopetrosis associated with metabolic acidosis probably due to a renal tubular defect; nine (32%) had a malignant infantile form of osteopetrosis and one had a mild form with delayed onset. Parental consanguinity was 56% and 40% among patients with and without acidosis respectively. Somatic and psychomotor retardation and recurrent bone fractures were common in both groups. Dental caries, cerebral calcification and optic atrophy were more frequent in patients with acidosis, while anemia, hepatosplenomegaly and deafness were more common in patients without acidosis.

Tunisia
Fathallah et al. (1994) analyzed the genomic DNA of 10 Tunisian patients for the presence of a splice junction mutation at the 5' end of intron 2 in the carbonic anhydrase II gene (CAII) previously described in six CAII-deficient patients presumed to be of Arab origin. All the patients were homozygous for this mutation and were mentally retarded, a characteristic feature of the phenotype of patients with an Arabic background. Fathallah et al. (1994) concluded that this mutation is found exclusively in patients with an Arabic background and it may be confined to this ethnic group. In 1997, Fathallah et al. traced the origin of this disorder in 24 Tunisian patients from 14 families with CAII deficiency. All families had histories of osteopetrosis, renal tubular acidosis, mental retardation, and CA II deficiency. Fathallah et al. (1997) conducted a filiation study to trace these families back to a common Arabic tribe that settled in the Maghreb (North Africa) in the tenth century. By sequence-tagged site analysis, Fathallah et al. (1997) showed cosegregation of the Taq (-) allele with the mutation in 12 families out of 14. This observation supported a founder effect to explain the common CAII deficiency allele in the Tunisian population. In the remaining two families, a genomic recombination or gene conversion occurred between the TaqI restriction marker and the mutation causing the disease. Fathallah et al. (1997) suggested the presence of a hot spot for recombination or gene conversion at the CA II locus because of the relatively high recombination frequency observed.

References
Al Rajeh S, el Mouzan MI, Ahlberg A, Ozaksoy D. The syndrome of osteopetrosis, renal

Contributors
Ghazi O. Tadmouri: 3.5.2005