

Alstrom syndrome in four sibs from northern Jordan

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Alstrom syndrome is a rare, autosomal recessive disorder, which was first described as a combination of atypical retinal degeneration, obesity, diabetes mellitus, and sensorineural hearing impairment.¹ Other features that have been described in Alstrom syndrome include hypertriglyceridemia, hepatic dysfunction,² slowly progressive chronic nephropathy, hypothyroidism, male hypogonadism, acanthosis nigricans, cataracts, dilated cardiomyopathy,³ and intellectual impairment.⁴ The wide-ranging and complex spectrum of phenotypes reported among 182 patients in a recent review on Alstrom syndrome broadens those previously described.⁵ The gene for Alstrom syndrome has been localized to the short arm of chromosome 2 (2p12-13.13).^{6,7} We report four sibs with Alstrom syndrome from north Jordan with variable manifestations and mental subnormality. This is the first report of Alstrom syndrome from one of the East Mediterranean Arab countries.

Case

Three siblings aged 24, 21, and 15 years were referred to the National Center for Diabetes, Endocrinology and Genetics in Amman for evaluation of their genetic disorder. They presented with diabetes mellitus type 2, low vision, impaired hearing, hypertension and obesity. The parents were second cousins and both had type 2 diabetes mellitus. Another sib in the family had similar features of obesity, impaired vision and hearing and diabetes, and died with chronic renal failure at the age of 26 years. The family pedigree is illustrated in Figure 1. The family had other relatives with first cousin parents who exhibited a similar phenotype, but these subjects were not available for examination and the description of the condition was not clear enough to point to a diagnosis of Alstrom syndrome. All three sibs had a history of early onset obesity since infancy. Although the parents could not precisely recall the birth weights of the sibs, they were able to remember that the weight of the eldest affected sib (case 1) was 10 kilograms at the age of 3 months, and that all the affected sibs were considered obese at the age of 4 to 5 months.

Linkage analysis was performed at the Clinical Genetics Service of St James University Hospital in Leeds, UK, using 4 markers at the region of the Alstrom gene on 2p12-13.13. PCR amplification (10 L reactions) was performed with 1 unit Fast Start Taq polymerase (Roche); 1x buffer supplied; dNTPs 4 mM each; primers 10 µM each (one labelled with fluorescein); 200 mM betaine; 250 ng genomic DNA; and using a Genamp thermal cycler (Applied Biosystems) with the following conditions: preheating at 95° for 5 minutes; 23 cycles of denaturation at 95° (30 seconds), annealing at 52° (30 seconds; D2S286) or 56° (30 seconds; D2S358, D2S2112, D2S2110), extension at 72° (5 minutes); followed by 72° (5 minutes) and 60° (60 minutes) incubations. The results showed that all three affected siblings (II-7, II-8, II-10) inherited the same maternal and paternal haplotypes while 5 unaffected siblings did not. Among the unaffected siblings three

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were heterozygotes (II-1, II-3, II-11), two were normal homozygotes (II-2, II-6) and one (married to her first cousin) refused to be tested (II-4). The eldest sibling (II-1) was married to his first cousin, and she proved to be a non-carrier by linkage analysis. Furthermore, one of the presumably unaffected siblings (II-9) (a 19-year-old female), when tested revealed the same haplotypes as her three affected siblings (Figure 1). On recruitment and assessment for Alstrom syndrome, she was found to have diabetes, dyslipidemia, and acanthosis nigricans. On ophthalmologic examination, she had posterior subcapsular cataracts and retinal pigmentary changes. She was thus considered to have Alstrom syndrome. The markers D2S2110 and D2S286 that flank the ALMS1 locus showed identical genotypes on the paternal and maternal high-risk haplotypes, compatible with autozygosity of the region around the ALMS1 locus (Figure 2).

Case 1 (II-7) was the eldest affected sib, a female aged 24 years with obesity (BMI 34), hypertension, diabetes mellitus type 2 and acanthosis nigricans. She had a history of nystagmus and photophobia in infancy and her vision was severely impaired, with alternating exotropia and left eye preference for fixation. Ophthalmologic findings revealed the presence of bilateral posterior subcapsular cataracts, bilateral retinal pigmented epithelial mottling, macular holes and oval optic discs with temporal pallor. Visually evoked potential assessment revealed delayed P100 latencies in both eyes consistent with demyelination of optic nerves. Other findings included moderate bilateral sensorineural hearing impairment on audiometry, small ASD (atrial septal defect) with no evidence of cardiomyopathy on echocardiography, and fatty liver on ultrasound examination. There was a moderate impairment of cognitive function (Wechsler intelligence scale: verbal intelligence quotient [IQ] 57, performance IQ 47, and full IQ 50). Laboratory findings revealed the presence of hypertriglyceridemia, a low HDL level, elevated serum transaminases, elevated HbA1c, hyperinsulinemia and primary hypothyroidism. She had a regular menstrual cycles with normal secondary sexual characters and within normal gonadotrophin levels and renal function tests. Brain magnetic resonance imaging and plain radiographs of the spine and extremities revealed no abnormal findings.

Case 2 (II-8) was a male, aged 22 years with a BMI of 28. He had features similar to his elder sister except for the absence of squint, the absence of ASD on echocardiography with a thickened mitral valve leaflets and a trace of aortic regurgitation, no elevation of liver enzymes and no hypothyroidism. He was of dull normal intelligence with an IQ of 85 on the Wechsler

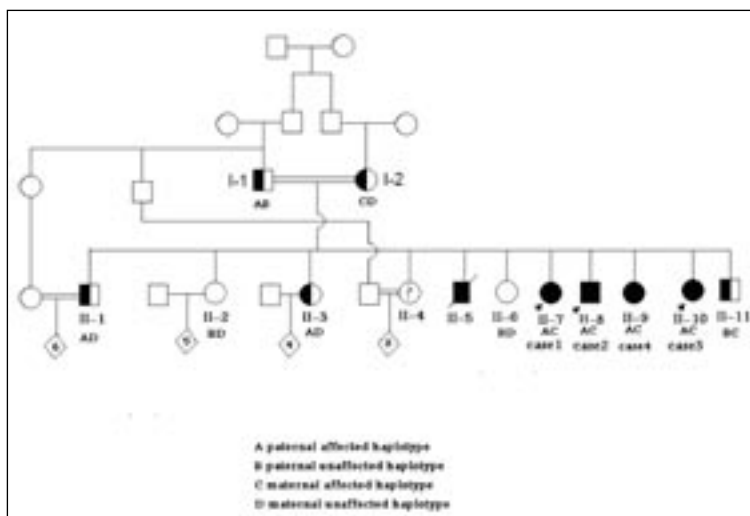


Figure 1. Pedigree of Alstrom syndrome.

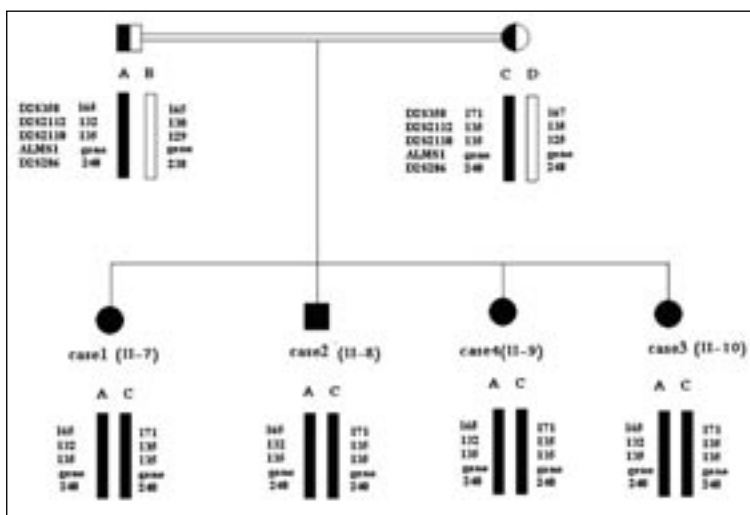


Figure 2. Allele segregation and mapping of candidate region of the gene for Alstrom syndrome.

Intelligence Scale for adult and Wechsler Memory scale (verbal IQ 92 and performance IQ 83).

Case 3 (II-10) was a female, aged 15 years with a BMI of 37. She displayed all the features as her elder sister except for the absence of ASD on echocardiography, absence of hypothyroidism and absence of squint. At the age of 15 years, she had primary amenorrhoea with within normal gonadotrophin levels. She showed evidence of mild impairment of cognitive function (Wechsler intelligence scale: verbal IQ 70, performance IQ 57, and full IQ 60).

Case 4 (II-9) was a female, aged 19 years and diagnosed as Alstrom syndrome by linkage analysis.

Assessment for Alstrom syndrome revealed the presence of obesity (BMI 33), hypertension, diabetes mellitus type 2, and acanthosis nigricans. Ophthalmologic findings revealed the presence of a bilateral posterior subcapsular cataract and the picture of bilateral retinal pigmented epithelial mottling. Laboratory findings showed hypertriglyceridemia, low HDL level, elevated serum transaminases, and elevated HbA1c level. She had regular menstrual cycles with normal secondary sexual characters. IQ assessment was not done.

Discussion

Alstrom syndrome is a rare autosomal recessive disorder with around 200 cases reported from various populations.⁵ There are reports describing Alstrom syndrome in the North African population.⁶ However, this is the first report of Alstrom syndrome in a family from Jordan and from the Eastern Mediterranean Arab countries. The main findings of the syndrome of obesity, severe visual impairment, sensorineural hearing loss, diabetes mellitus type 2, hypertension and dyslipidemia were present in four siblings in this family. Dilated cardiomyopathy has been frequently observed in Alstrom syndrome,³ but not in any of the four siblings in this report. A fifth sib in the family (II-5) died with renal failure at the age of 26 years. He was described as obese, with type 2 diabetes mellitus, and severe visual and hearing impairment. We diagnosed him as Alstrom syndrome in retrospect. The female siblings in the family showed an elevation of liver enzymes with an indication of fatty liver on abdominal ultrasound. Liver dysfunction has been reported in Alstrom syndrome with variable degrees of severity.²

Intellectual impairment has not been a constant feature of Alstrom syndrome and borderline to mild mental retardation has been described in a minority of patients.^{4,5} Cognitive evaluation of patients with Alstrom syndrome is usually difficult because of the associated visual and hearing impairments. Mental subnormality showed an intrafamilial variability in our family. Among the siblings in the present family both female probands had mental retardation with an IQ lower than 60 and with the performance IQ was more affected than the verbal IQ. Their affected brother had

an IQ of 85. The fourth sibling (II-9), diagnosed with Alstrom syndrome after performing linkage analysis for the family did not have IQ testing. Until her diagnosis, the family considered her as unaffected and as having a presumably normal intelligence.

All four sibs with Alstrom syndrome in this family had hypertriglyceridemia with no correlation between the triglyceride level and obesity, similar to the results cited among 37 patients with Alstrom syndrome and hypertriglyceridemia in another report.⁸ Alstrom syndrome was not diagnosed in this family until the affected sibs reached their second and third decades. The fourth sibling with Alstrom was not brought to medical attention until linkage analysis showed that she had the same haplotypes as the affected siblings. Such a late diagnosis or misdiagnosis of Alstrom syndrome is not unusual because of the rarity of the disease and because of variable presentation and clinical features.^{3,5,9,10} Genetic counseling offered to this family stressed on the advice of limiting further intermarriages in the future. Among the siblings already married to their first cousins, II-1 was a carrier and his wife was not by linkage analysis, while the other sibling (II-4) refused to be tested, presumably fearing that she and her husband were carriers of the gene. A recent study on the consanguinity rate in Jordan shows that the rate of first cousin marriages is showing a decline from 28.5% among all marriages contracted between 1950-1979 to 19.5% of all marriages contracted after 1980.¹¹

The recent identification of the ALMS1 gene and various mutations leading to Alstrom syndrome^{12,13} may provide useful insight into the basic pathogenesis of obesity, maturity onset diabetes mellitus, hyperinsulinemia, retinopathy and sensorineural hearing impairment. Genotype-phenotype correlation in Alstrom syndrome remains to be elucidated with the increase in number of cases undergoing mutation analysis. Both parents in this family have diabetes mellitus type 2, raising the question of whether carriers of Alstrom gene are more genetically susceptible to diabetes mellitus type 2.

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