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Novel *Alu* Retrotransposon Insertion Leading to Alström Syndrome

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Abstract

Alström Syndrome is a clinically complex disorder characterized by childhood retinal degeneration leading to blindness, sensorineural hearing loss, obesity, type 2 diabetes mellitus, cardiomyopathy, systemic fibrosis, and pulmonary, hepatic, and renal failure. Alström Syndrome is caused by recessively inherited mutations in the *ALMS1* gene, which codes for a putative ciliary protein. Alström Syndrome is characterized by extensive allelic heterogeneity, however founder effects have been observed in some populations. To date, more than 100 causative *ALMS1* mutations have been identified, mostly frameshift and nonsense alterations resulting in termination signals in ALMS1. Here we report a complex Turkish kindred in which sequence analysis uncovered an insertion of a novel 333 basepair *Alu* Ya5 SINE retrotransposon in the *ALMS1* coding sequence, a previously unrecognized mechanism underlying mutations causing Alström Syndrome. It is extraordinarily rare to encounter the insertion of an *Alu* retrotransposon in the coding sequence of a gene. The high frequency of the mutant *ALMS1* allele in this isolated population suggests that this recent retrotransposition event spread quickly, and may be used as a model to study the population dynamics of deleterious alleles in isolated communities.

Keywords

Alström Syndrome; ALMS1; *Alu* Ya5; Insertion Mutation; Short Interspersed Nuclear Elements (SINE)

INTRODUCTION

Alström Syndrome (ALMS; OMIM 203800) is a multi-systemic autosomal recessive disorder with a broad spectrum of clinical signs (Alström, et al. 1959; Marshall et al. 2007). Patients with ALMS typically present in the first months of life with progressive retinal cone-rod dystrophy that leads to blindness by the end of the second decade. Bilateral sensorineural hearing impairment develops during childhood or adolescence. Other hallmarks of ALMS that develop in early childhood include truncal obesity, significant insulin resistance, hyperinsulinemia, type 2 diabetes mellitus (T2DM), and hypogonadism in both male and female patients. Dilated cardiomyopathy (DCM) and congestive heart failure (CHF) may develop suddenly in infants, whereas the gradual onset of restrictive

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cardiomyopathy can occur during adolescence or adulthood. Multi-organ fibrosis ultimately leads to major organ failure and premature death (Marshall et al. 2005, 2007). Serious manifestations of the fibrosis that affect patients' prognosis and survival include pulmonary fibrosis and restrictive lung disease, steatosis leading to cirrhosis and hepatic failure, and progressive glomerulosclerosis and renal failure. Other symptoms, not always present, include urological abnormalities, advanced bone age, adult short stature and scoliosis, hypothyroidism, mixed dyslipidemia, and hypertension. The clinical features emerge at different times throughout childhood making correct diagnosis in children problematic. To address the difficulty in obtaining an accurate molecular diagnosis due to phenotypic variability and the progressive nature of the clinical features, a set of diagnostic criteria has been developed to allow for the patient's age (Marshall et al. 2007). The differential diagnosis includes the more common Bardet-Biedl Syndromes (BBS), a genetically heterogeneous disorder that manifests principally in later-onset rod-cone dystrophy, postaxial polydactyly, central obesity, developmental disabilities and cognitive impairment, hypogonadism, and structural and functional renal abnormalities (Waters and Beales 2010).

ALMS is caused by mutations in ALMS1, a large gene on chromosome 2p13 comprised of 23 exons. *ALMS1* encodes a protein of 4,169 amino acids (Collin et al. 2002; Hearn et al. 2002). The ALMS1 protein localizes to centrosomes and basal bodies of ciliated cells and is ubiquitously expressed in all tissues reported to be pathologically affected in patients, implicating ALMS as one of the emerging diseases falling under the class of ciliopathies. In general, the clinical picture of ciliopathies is variable with a wide range and growing number of clinically distinct phenotypes and causative genes (Baker and Beales 2010). Although the exact biological function of ALMS1 remains elusive, the pathophysiology of ALMS is thought to involve aberrant intracellular trafficking and ciliary dysfunction (Collin et al. 2005; Li et al. 2007). There are over a hundred recognized mutations causing Alström Syndrome, most of which occur in exons 8,10, and 16 of *ALMS1* (Marshall et al. 2007b; Joy et al. 2002; Pereiro et al. 2011).

In the present study, we report a novel mutation characterized by the insertion of a large *Alu* Ya5 SINE retrotransposon into the coding sequence of *ALMS1*. This is the first report of a pathogenic *ALMS1* mutation resulting from an *Alu* insertion.

MATERIALS AND METHODS

Clinical assessment of patients

The patients were diagnosed with ALMS at the Pediatric Department of Dicle University, based upon the clinical features and the diagnostic criteria for children aged 3–14 years proposed by Marshall et al. (2007). Written informed consent to participate was obtained from the parents, and the patients and siblings gave their verbal consent. The study protocol was conducted in accordance with the tenets of the Declaration of Helsinki, and the institutional review boards of the participating institutions approved the study protocols. No financial remuneration was given to patients or families for participation in this study.

Patient assessment included ophthalmologic, audiologic, and general physical examinations according to standard hospital protocols. Serum chemistries and routine urinalysis were performed using traditional methods in licensed clinical laboratories.

Extraction of Genomic DNA for sequencing

We collected peripheral blood samples from the patients, their unaffected siblings, and their parents, after obtaining appropriate informed consent. Genomic DNA from the propositus and his extended family was amplified with ALMS1 exon 16-specific primers as described

previously (Collin et al. 2002). Products were purified and sequenced using the 3730×l DNA Analyzer (Applied Biosystems).

Accession Numbers

The GenBank accession number for the *ALMS1* sequence reported in this paper is NM_015120.4)

RESULTS

Clinical Presentation of Patients

Here, we describe two patients from a highly consanguineous kindred residing in a small village near Kızıltepe, Mardin in southeastern Turkey. The fathers are brothers (V-1 and V-3) and the mothers are sisters (V-2 and V-4). Additionally, the great grandparents of the affected children descend from a common ancestral couple (I-1, and I–2) (Fig. 1).

Patient #1—The proband (VI-6), a 13 year-old boy, was one of 10 children from a first degree consanguineous marriage. Three of his brothers (VI-1–3) died at 6–7 months of age, and one brother (VI-5) died at 12 months - all of unknown etiology, as medical evaluation was not available to the family. The proband had progressive vision loss since birth and was totally blind with no light perception. He also had bilateral sensorineural hearing loss. He exhibited truncal obesity, with a BMI of 28.9 (>95% for age and gender), short stature (<25 centile), kyphosis, pes planus, thin hair, thick ears, mild hypertension, and hypogonadism (low testicular volume, delayed puberty, Tanner grade 1). He had normal intelligence and no digital anomalies. This patient did not have the advanced bone age that is typical for children with ALMS, but instead had retarded growth with a bone age 12.5 years (Fig. 2).

The patient had insulin resistance, hyperinsulinemia (194 pmol/L) and T2DM (fasting glucose: 45.1 mmol/L; HbA1C: 14.4%), He had no metabolic acidosis and was urine ketone-negative. He was hyperlipidemic with a total cholesterol of 17.6 mmol/L, an HDL of 0.62 mmol/L, VLDL of 7.3 mmol/L, and triglycerides > 16 mmol/L. He had sub-clinical hypothyroidism (TSH: 7.8 μIU/ml, free T4: 913.7 nmol/L). He did not have cardiomyopathy as an infant, but left ventricular hypertrophy without cardiac failure was detected by echocardiography at 11 years of age. He had hepatosplenomegaly and renal failure (urea: 59.2mmol/L, creatinine: 266.9umol/L, parathormone: 216 ng/L, urine density: 1005). He died from complications of CHF, hypertension, intracranial hemorrhage, and multiple organ failure (renal, hepatic, and pulmonary) after an episode of severe acute gastroenteritis at age 14 years.

Patient #2—This girl (VI–14), age 6 years, is a first cousin of Patient #1. She is one of seven children from a first degree consanguineous marriage. She had 5 unaffected siblings, and one sibling (VI–12) who died at the age of 6 months of undocumented causes. Her birth and perinatal period was normal, but photodysphoria and nystagmus were noticed at birth. Vision loss and obesity (BMI 29.2; >97th centile) manifested in early childhood. She has normal hearing. Her glucose, hepatic, pulmonary, urological, cardiac, and renal functions are normal. Her intelligence is within normal range and she lacks digital anomalies. She has hypertriglyceridemia (4.11mmol/L) (Fig. 2).

Detection of *ALMS1* Mutations

Upon genetic evaluation, both patients were homozygous for an identical insertion of 333 bp in exon 16 of *ALMS1*. Comparison of the insertion sequence to the catalog of repetitive sequences in Repbase (Repbase, Genetic Information Research Institute, http://www.girinst.org/; Jurka et al. 2005) revealed that it belongs to the class of *Alu* Ya5

elements, an evolutionary recent transposition competent *Alu* family in the human lineage (Comeaux et al. 2009). In comparison to the wild-type *ALMS1* allele (Fig. 3a), the *ALMS1*^{Alu} allele (Fig. 3b) bears a target site duplication, which reflects the *Alu* insertion mechanism via target-site primed reverse transcription insertion (Perez-Stable et al. 1984). The target site correlates exactly with the proposed consensus 5'-TT^AAAA-3' of a primary nicking site for *Alu* insertions (Jurka, 1997). The long uninterrupted stretch of adenosines (76 nts) suggests that the *Alu* sequence was inserted by a recent retrotransposition event.

Interestingly, we did not identify a 100% identical sequence anywhere in the human genome assembly, indicating a hitherto unknown polymorphism of active *Alu* Ya5 elements. Another distinguishing feature of the *ALMS1*^{Alu} allele is a truncation of 34 nucleotides at the 5' end, likely a result of incomplete reverse transcription during transposition. Therefore, this particular element is likely no longer transcription- and retrotransposition-competent.

Heterozygous carriers were identified by haplotype analysis with chromosome 2p13-specific microsatellite markers and confirmed by PCR genotyping for the presence of the *Alu* allele (forward, TGATGATAGCAGAGGGGAAC; reverse, GGAAAGGATGTTGGTGGTAGT). The wild-type allele produces a PCR product size of 313 bps, while the *Alu* allele produces a PCR product size of 646 bps. As heterozygous carriers have been identified in both branches of the pedigree, at least one of the great-great-grandparents (I-1, or I-2) was likely also heterozygous for the ALMS1^{Alu} allele. No clinical features of ALMS were reported in previous generations of this pedigree and no other affected individuals have yet been identified in this village.

Frequency of the *ALMS1*^{Alu} Allele

DNA from 29 unaffected individuals from the Kiztepe village and 50 additional unaffected individuals from a random, unrelated Turkish population was tested for the presence of ALMS1^{Alu} allele. We did not identify the insertion in any individuals in the “pan-Turkey” cohort. In contrast, in the local village population, the frequency of the mutation was 6.9% (2 out of 29 tested were heterozygous carriers of ALMS1^{Alu}).

DISCUSSION

Mobile genetic elements, or transposons, are powerful modulators of genome variation and the biological implications of their activity are considerable, ranging from genomic instability in cancers to regulation of gene expression during development to speciation (Jurka et al. 2005; Comeaux et al. 2009; Perez-Stable et al. 1984). In mammalian genomes, all transposons belong to the group of retrotransposons which generate new copies and multiply by reverse-transcription of their RNA and integration of this cDNA into new genomic locations. Among the many types of retrotransposons present in humans, the short interspersed nuclear elements (SINEs) of the *Alu* class, originally derived from a signal recognition particle, 7SL RNA, have a high mutagenic potential in humans, and represent the largest group of repetitive sequences, accounting for approximately 20% of the human genome (Lander et al. 2001). Alu elements have propagated to an estimated 1–2×10^6 copies in primate genomes, and have generally achieved a balance between detrimental consequences for the individual and beneficial outcomes for genetic variation and speciation.

These *Alu* transpositions affect the genome in several ways, such as causing insertion mutations, recombination between elements, gene adaptation, and alterations in gene expression. Throughout 65 million years of primate evolution, these elements have spread over the entire genome by retrotransposition, contributing significantly to the size of the genome. Over the evolutionary timescale, most Alu subfamilies have lost their ability for

retrotransposition and reside within the genomes as phenotypically neutral elements that are located in the intergenic, intronic, and untranslated regions, but rarely in the coding regions of genes and genomes (Batzer and Deininger 2002). However, some have preserved their retrotransposition capability, and have been shown to be the causative alteration in some diseases (Callinan and Batzer 2006; Claverie-Martín et al.,2003, 2005).

The *Alu* element identified in these patients belongs to the still-active Ya5 family, and thus features of the insertion suggest a very recent retrotransposition event. Interestingly, this is one of very few examples for an *Alu* element causing a direct disruption of an open reading frame by insertion in a coding exon.

The mutagenic potential of these retrotransposons has led to the development of host genome defense mechanisms aimed to suppress “retrotransposons life cycle”, mainly at the stage of transcription via DNA methylation of their promoters (Yoder et al. 1997). At the molecular level, *Alu*-mediated recombination can lead to deletion of genomic loci flanked by identical *Alu* repeats and is common in some hereditary cancers (Moolhuijzen et al.; Konkel and Batzer 2010). Another phenomenon, exon skipping, occurs when *Alu* insertions interfere with the assembly of the splicing machinery upon premRNA. Finally and infrequently, as in the case reported here, *de novo Alu* insertions may disrupt a coding exon of an essential gene, leading to an inheritable disease in people homozygous for the disrupted allele.

In summary a novel mutation was identified to be caused by a recent *Alu* insertion in the coding sequence of human *ALMS1* in a Turkish family with Alström Syndrome. The large insertion leads to a disruption of the open reading frame and thus represents a unique disease-causing variant among *ALMS1* mutations and extends the spectrum of mutations causative for Alström Syndrome. Additionally, this new observation provides valuable evidence for the devastating mutagenic potential of transposition-competent *Alu* elements.

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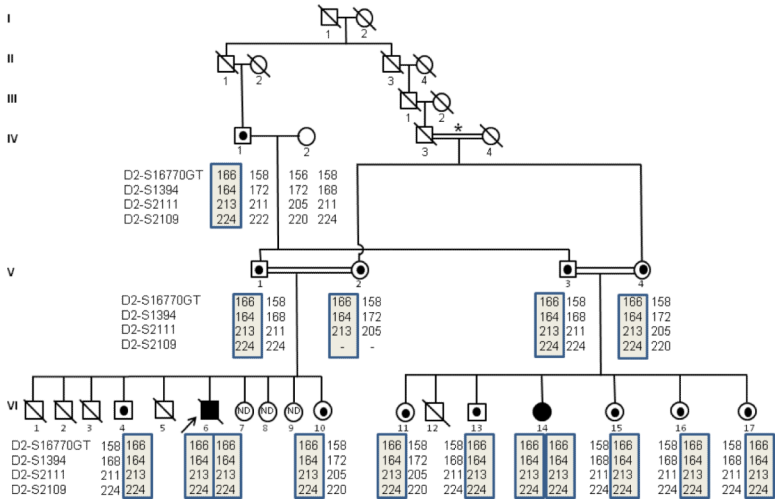
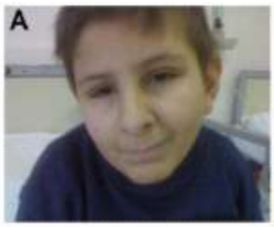


Fig. 1.

A six generation Turkish family segregating for the *ALMS*^{Alu} allele. Squares indicate male family members, circles indicate female family members. A strike-through indicates deceased. Double slashed lines indicate marriage consanguinity, with the relationship between IV-3 and IV-4, marked by an asterisk, being first degree. Black solid symbols indicate patients who are homozygous for the *ALMS*^{Alu} allele. Heterozygous carriers of the Alu insertion are depicted by a black dot in the center of the symbol. ND indicates that the individual was unaffected, and not genotyped. The propositus (VI-6) is indicated by an arrow. The fathers (V-1 and V-3) are brothers and mothers (V-2 and V-4) are sisters). Additionally, the great grandparents of the affected children descend from a common ancestral couple (I-1, and I-2). This pedigree pinpoints that original transposition event occurred not less than 7 generations ago (I-1and I-2), and the allele has persisted in the families since then.



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Clinical Features	Patient 1 (VI-6)	Patient 2 (VI-14)
Vision loss (age)	Beginning at birth; totally blind at 11y	Beginning at birth; partial vision at 6 y
Hearing loss	Yes	Normal hearing
Obesity (BMI)	Truncal obesity (28.9 kg/m2)	Truncal obesity (29.2 kg/m2)
Cardiac	Congestive heart failure at age 11y	Normal
Hepatic	Hepatosplenomegaly	Hepatosplenomegaly
Renal	Renal failure	Normal
Diabetes	Yes	No
Hypogonadism	Yes	NA
Hypertension	Yes	No
Lipid profile	Mixed hyperlipidemia	Hypertriglyceridemia
Skeletal	Kyphosis; delayed bone age; pes planus	Kyphosis
Digestion	Gastroesophageal reflux	No
Other	Pruritis	No

Fig. 2.

Summary of clinical features of the patients with Alström Syndrome. A. Proband (VI-6) at 13 years of age. B. Proband's cousin (VI-14) at 6 years of age. C. Summary of clinical presentation of the two patients. NA-not assessed.

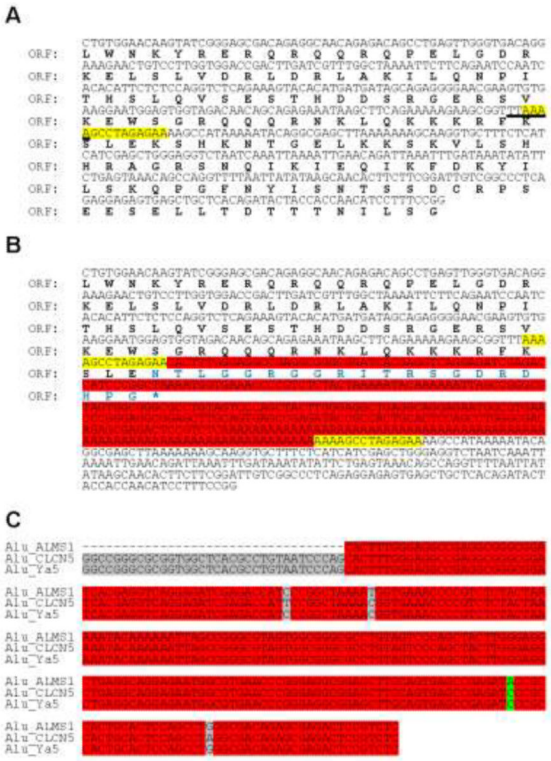

Fig. 3.

Alu retrotransposon insertion in the ALMS1 locus. Panel a shows the region in exon 16 where the insertion was discovered. The site targeted by the *Alu* insertion is highlighted in yellow. Open reading frame (ORF) is shown in bold. The target site (underlined) exactly matches the proposed consensus 5'-TT^AAAA-3' of a primary nicking site for *Alu* insertions (Jurka, 1997). Panel b shows the nucleotide sequence of the 333 base pair *Alu* insertion mutation introducing a premature stop codon, denoted with an asterisk. The *Alu* element is highlighted in red, and target site duplication in yellow. The alternative C-terminus of the ORF is in blue font. Panel c shows the sequence alignments of the *Alu* discovered in this study (*Alu ALMS1*), the *Alu* element at the CLCN5 locus (*Alu* CLCN5) confirmed as a recent de novo germline transposition, and the *Alu* Ya5 sequence from Repbase (RepBase ID: AluYa5). Truncation of 34 nucleotides at the 5' end of the *Alu ALMS1* element, which contains the A-box of the *Alu* bipartite promoter, is likely due to incomplete reverse-transcription of original RNA copy. Identical bases are highlighted in red. Interestingly, C-->A transversion (highlighted in green) is a unique SNP in publicly available human genomic databases and likely reflects a rare polymorphism among active Alu elements.