



# Creatine Transporter Defect Masquerading as Lujan Syndrome

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## Clinical Image

Lujan syndrome (OMIM #309520; AKA Lujan-Fryns syndrome, X-linked Intellectual Disability-Marfanoid habitus) is an X-linked disorder with intellectual disability, general asthenia, and long narrow face with high palate, small mandible and hyper nasal voice [1-3]. Although the affected males in the original family reported by Lujan had is sense mutation in MED12, only minorities of other males with this phenotype have been found to harbor mutations in this gene. This report describes 3 brothers with the Lujan syndrome phenotype who have a pathogenic mutation in SLC6A8 and biochemical findings typical of creatine transporter defect (OMIM 300352) [4]. The family was studied under the protocol reviewed and approved by the Self Regional Healthcare Institutional Review Board (SRHIRB). The mother provided informed consent for participation in the research and for publication of the photographs. The oldest brother (II-1) in kindred K9377 had normal prenatal growth (birth weight 3.8 kg), walked at 18 months, had delayed speech, and developed seizures prior to age 5 years. At age 24 years, he had height of 188 cm (97<sup>th</sup> centile), span of 190 cm (80<sup>th</sup> centile), weight of 80 kg (60<sup>th</sup> centile) and head circumference of 59.5 cm (95<sup>th</sup> centile). The face was expressionless with prominent forehead and protruding ears, and the palate was tall and narrow. Musculoskeletal findings included long upper limbs, mild pectus excavatum, reduced mobility of large joints, looseness of small joints of hands, and poor coordination of fine and gross movements (Figure 1). The IQ was estimated at 40 to 60, and he was admitted to residential facility for the intellectually disabled in adult life. The II-4 had normal birth weight (3.4 kg), walked at 21 months, had speech delay, and required special education from kindergarten onward. At age 20 years, the height was 178 cm (65<sup>th</sup> centile) span 187 cm (70<sup>th</sup> centile) and head circumference

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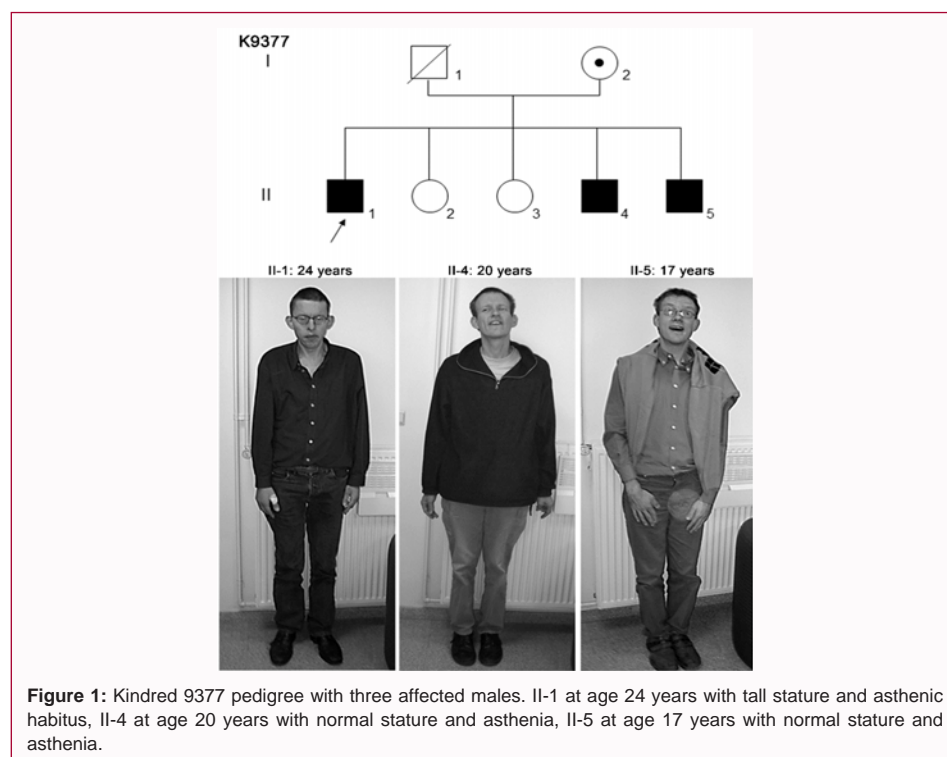
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**Figure 1:** Kindred 9377 pedigree with three affected males. II-1 at age 24 years with tall stature and asthenic habitus, II-4 at age 20 years with normal stature and asthenia, II-5 at age 17 years with normal stature and asthenia.

58 cm (80<sup>th</sup> centile). The forehead, and mandible were prominent, the ears protruded, and the palate was narrow and tall. The joints of the hands were hyper mobile, and he walked slowly but with reasonable coordination. He was able to make simple conversation and was docile and socially withdrawn. The II-5 weighed 4.3 kg at birth, walked at 16 months, and had delayed and deficient speech. At 17 years, the height was 173 cm (40<sup>th</sup> centile) span 184 cm (60<sup>th</sup> centile) and head circumference 56.4 cm (60<sup>th</sup> centile). He had synophrys, protruding ears, pectus excavatum, and decreased range of movement at large joints, hyper mobile hand joints, and mild in coordination. His speech was less fluent than his brothers. A hemizygous missense variant [NM\_005629.3:c.532A>G; NP\_005620.1:p.(Thr178Ala)] in SLC6A8, the gene responsible for creatine transporter defect was detected in all three patients by whole exome sequencing and confirmed by Sanger sequencing of cDNA. This alteration is not present in the Human Gene Mutation Database (HGMD) nor is it listed in any of the public SNP databases (Ex AC, gnom AD, db SNP, 1000 genomes, Exome Variant Server, Clin Var). Multiple in silico algorithms predict it to be damaging (Mutation Taster, SIFT, PolyPhen2 Hum Div, PROVEAN), and the threonine residue at position 178 is highly conserved across species (GERP RS=3.95; Si Phy (29 Mammals =6.15). Furthermore, the SLC6A8 gene is highly intolerant of missense variants (Z=3.31). The elevated urinary creatine in all three patients (1638, 1399, and 1315 mmol creatine/mol creatinine: normal range 5 to 512 mmol creatine/mol creatinine) strongly supports the pathogenicity. The mother was heterozygous for the alteration, but neither sister carried the gene variant. The mother and two sisters had random X-inactivation in peripheral blood. Creatine transporter defect is one of the more common X-linked intellectual disability syndromes [4]. Typically, prenatal growth is normal but stature decreases postnatally, eventually falling below the 3<sup>rd</sup> centile in one third of cases. Decreased muscle mass, hypotonia, language impairment, and aberrant behavior are other usual manifestations,

and they were present in the affected males in the family reported here. The progressive neurological, intestinal, and psychiatric manifestations noted in some males with creatine transporter defect were not observed in this family [5]. Other X-linked intellectual disability syndromes with general asthenia include Snyder-Robinson syndrome (OMIM 309583), Allan-Herndon syndrome (OMIM 300523), CK syndrome (OMIM 300831), Christianson syndrome (OMIM 300243), Arts syndrome (OMIM 301835), and spastic paraplegia 2 (OMIM 312920). The genes for all of these X-linked disorders have been identified.

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## References

1. Lujan JE, Carlin ME, Lubs HA. A form of X-linked mental retardation with marfanoid habitus. *Am J Med Genet.* 1984;17(1):311-22.
2. Fryns JP, Buttiens M. X-linked mental retardation with marfanoid habitus. *Am J Med Genet.* 1987;28(2):267-74.
3. Schwartz CE, Tarpey PS, Lubs HA, Verloes A, May MM, Risheg H, et al. The original Lujan syndrome family has a novel missense mutation (p.N1007S) in the MED12 gene. *J Med Genet.* 2007;44(7):472-7.
4. Salomons GS, van Dooren SJ, Verhoeven NM, Cecil KM, Ball WS, Degrauw TJ, et al. X-linked creatine-transporter gene (SLC6A8) defect: a new creatine-deficiency syndrome. *Am J Hum Genet.* 2001;68(6):1497-1500.
5. Kleefstra T, Rosenberg EH, Salomons GS, Stroink H, van Bokhoven H, Hamel BC, et al. Progressive intestinal, neurological and psychiatric problems in two adult males with cerebral creatine deficiency caused by an SLC6A8 mutation. *Clin Genet.* 2005;68(4):379-81.