Homozygous carriers of a novel IGFALS mutation are 1.5 SD shorter than heterozygous relatives and tend to have lower bone mineral density

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Introduction

Acid Labile Subunit (ALS), is a 85 kDa protein which forms a ternary complex with IGF-I (or IGF-II) and IGFBP-3 (or IGFBP-5) in the circulation. The main function of ALS is to prolong the serum half life of these IGF-IGFBP-3/-5 complexes. To date, 16 different mutations in the IGFALS gene have been identified in 22 affected patients. Homozygous inactivating mutations in *IGFALS* cause low serum levels of ALS, IGFs, and, especially, IGFBP-3, being associated with a moderately short stature.

Objective and hypotheses

There are limited data on differences in height, bone mineral density (BMD) and pubertal delay between homozygous and heterozygous carriers of *IGFALS* defects.

We report clinical and laboratory features and BMD of homozygous and heterozygous carriers of a novel *IGFALS* mutation in a large Kurdish family.

Patients and Methods

Index cases were two first degree cousins presenting with short stature, low IGF-I, very low IGFBP-3 and normal basal GH, caused by a homozygous (c.1462G>A, p.Asp488Asn) mutation in *IGFALS*. This novel mutation introduces a new N-glycosylation site, which may lead to misfolding of the protein leading to its relatively rapid intracellular degradation. Eight homozygous patients (6 <18 yrs), 11 heterozygotes (7 <18 yrs) and one non-affected family member (height: -0.9 SDS) were studied (Figure 1). Informed consent was obtained from all study participants. Age at menarche (females) and age at accelerating growth, testicular growth and shaving (males) were recorded. Height and biochemical findings were expressed as SDS, and BMD (Horizon DXA, Hologic) as z score (NHANES). Ternary complex formation was investigated by size-exclusion chromatography.

Figure 1

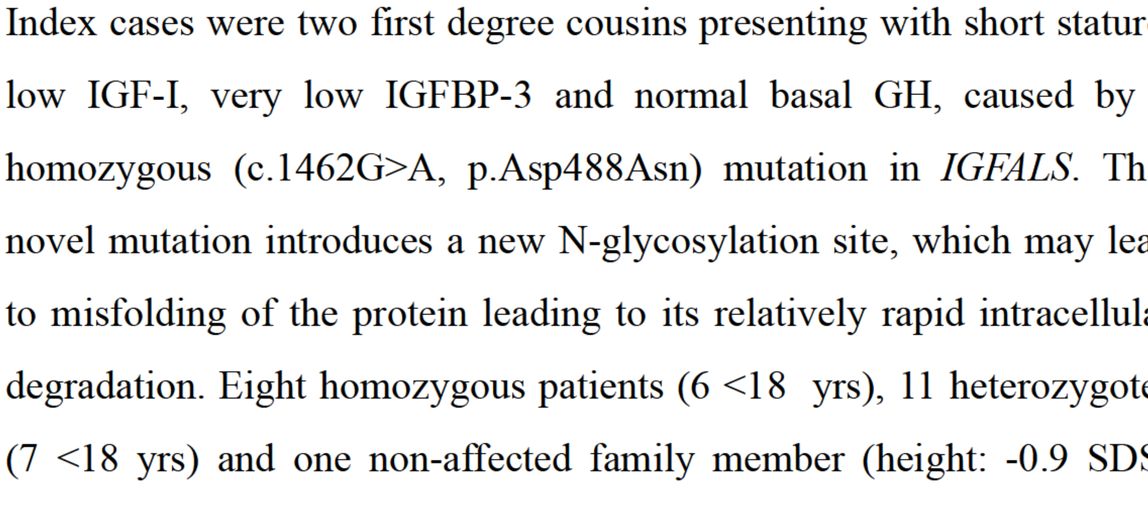

Figure 1. Pedigree of the family. The filled boxes refer to affected subjects, dotted boxes to heterozygous carriers and empty boxes to unaffected subjects.

Results

Homozygotes were 1.5 SD shorter than heterozygous carriers, who were 1.7 SD shorter than the population's mean. Development of puberty could be evaluated in two homozygotes (both delayed) and 6 heterozygotes (4 delayed). Serum IGF-I, IGFBP-3 and ALS showed the expected pattern for complete and partial ALS deficiency, respectively. BMD tended to be lower in homozygous carriers (NS), possibly partially caused by height differences. Ternary complex formation was markedly diminished in sera from homozygous patients, whereas heterozygotes showed an intermediate pattern (Figure 2).

Table 1

Table 1. Comparison of anthropometric, laboratory and bone mineral density (BMD) features of homozygous and heterozygous individuals

Mean (SD)	Homozygotes (n=8)	Heterozygotes (n=11)	P value
Age (yrs)	11.7 (5.2)	21.5 (16.1)	0.283
Height SDS	-3.3 (0.6)	-1.7 (1.0)	0.003
Height SDS range	-4.2 to -2.7	-3.2 to -0.1	
IGF-I SDS (age<18)	-2.2 (0.3) (n=6)	-0.7 (0.7) (n=5)	0.006
IGFBP-3 SDS(age<18)	-4.0 (0.7) (n=6)	0.1 (0.7) (n=5)	0.006
IGFBP-2 SDS	-1.04 (0.9)	-0.5 (1.4)	0.237
ALS SDS	-4.6 (1.5)	-1.5 (0.8)	<0.001
BMD z-score	-1.3 (1.2)	-0.6 (0.4)	0.110

Figure 2

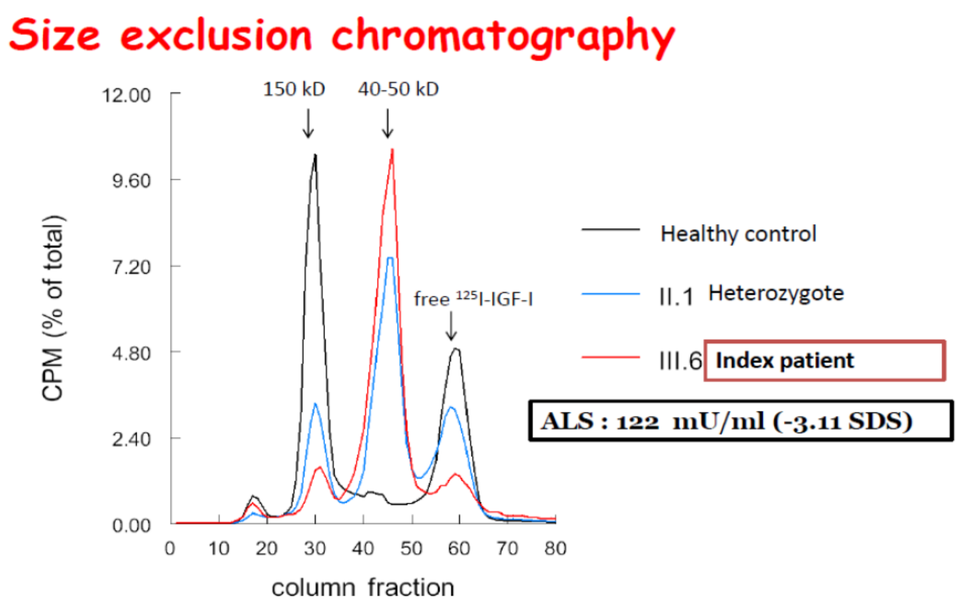

Figure 2. Size exclusion chromatography of an index patient, heterozygous carrier and healthy control

Conclusions

Homozygous carriers of the IGFALS mutation were 1.5 SD shorter than heterozygous carriers, BMD z-score tended to be lower and pubertal delay appeared frequent in both groups.

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