Recurrent *IGFALS* gene mutations p.E35Gfs*17 and p.[L409F;A475V]: Hot spot or founder effect?

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BACKGROUND

Some *IGFALS* variants have been reported in more than one ALS-deficient family raising the question whether they originated from a single common ancestor allele (founder effect) or alternatively, as independent mutational events (hot spot). Since c.103dupG (p.E35Gfs*17) is located in a stretch of 5 consecutive guanine residues, where both G-duplication and deletion have been described in several families, we speculate that this region could be a hot spot. In contrast, c.[1225C>T;1424C>T] (p.[L409F;A475V]) variants, both present in the same allele in two unrelated families, could result from a founder effect.

HYPOTHESIS AND OBJECTIVE

To test the hypothesis of a founder effect for c.[1225C>T;1424C>T] and a hot spot origin for c.103dupG, we studied polymorphic variants surrounding *IGFALS* gene and uniparental lineage markers in families harboring these variants.

SUBJECTS and METHODS

- ✓Thirty individuals from 5 families were included in the study (Figure 1). Two families harbored the c.[1225C>T;1424C>T] (p.[L409F;A475V]) variants while 5 families were carriers of c.103dupG (p.E35Gfs*17) variant. One family presented both mutations.
- ✓Seventeen SNPs were characterized by sequencing *IGFALS* gene exons 1 and 2, intron 1, 950 bp of 5´flanking region and 40 bp of 3´UTR. Only 9 informative SNPs were used to define the specific microhaplotype associated to each variant (Table 1).
- ✓Three STRs flanking the *IGFALS* gene locus (D16S3434 and D16S3024) were analyzed by PCR amplification using a fluorescently (FAM) labeled primer, capillary electrophoresis and Genescan. The D16S3434 presented 4 to 15 CA repeats and the D16S3024 19 to 31 CA repeats.
- ✓Patri- and matrilineal lineages were analyzed by means of 23 Y-STRs typing and mtDNA-D-Loop sequencing.

TABLE 1: SNPs information according to NCBI dbSNP database

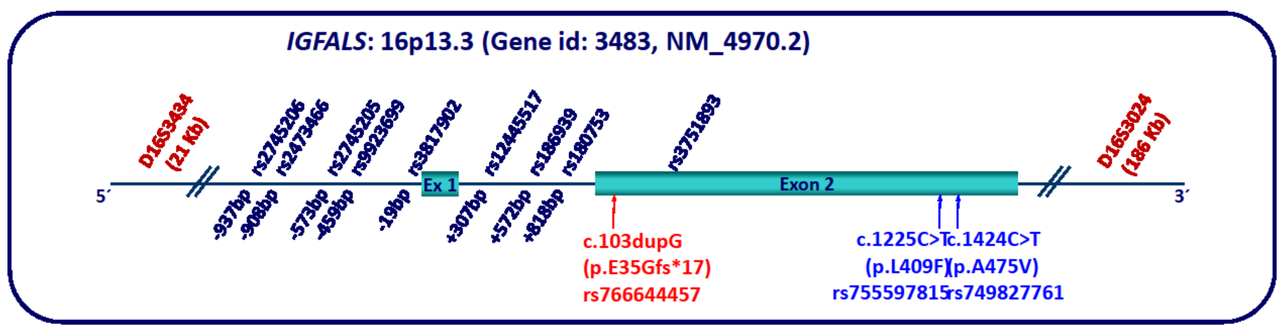
NCBI dbSNP id	HGVS Name (NM_004970.2:)	Alleles	NCBI dbSNP MAF/ Minor allele count
rs2745206	c.-937A>G	A/G	A=0.3281/1643
rs2473466	c.-908C>T	C/T	T=0.4381/2194
rs2745205	c.-573G>C	G/C	G=0.3323/1664
rs9923699	c.-459A>G	A/G	A=0.3325/1665
rs3817902	c.-19A>G	A/G	A=0.350/762
rs12445517	c.16+307C>T	C/T	T=0.448/976
rs186939	c.16+572C>G	C/T	C=0.347/755
rs180753	c.17-418G>C	G/C	G=0.3317/1661
rs3751893	c.210T>C (p.D70D)	T/C	T=0.215/469

http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?geneId=3483

Population frequency of analyzed variants according to Exome Aggregation Consortium Database (EXAC)

Variant		EXAC	
HGVS Name	NCBI dbSNP id (UCSC)	(nº alleles/ total alleles)	Frequency (Populations)
c.103dupG (p.E35Gfs*17)	rs766644457 (16:1842315 T/TC)	1/98800	0,00001012 (European)
c.1225C>T (p.L409F)	rs755597815 (16:1841194 G/A)	2/115968	0,00001725 (South Asian)
c.1424C>T (p.A475V])	rs749827761 (16:1840995 G/A)	10/96244	0.0001039 (Latino, E. Asian, S. Asian, European)

Exome Aggregation Consortium (ExAC), Cambridge, MA. (URL: http://exac.broadinstitute.org) [September, 2015].



SUMMARY AND CONCLUSIONS

✓Four families carrying the c.103dupG variant presented the same STRs and SNPs microhaplotype $(CA)_{12}$/gtcggtgcc/$(CA)_{21}$, while all the c.[1225C>T;1424C>T] carriers of the other 2 families presented a different microhaplotype $(CA)_{15}$/acgaaccgt/$(CA)_{22}$ or $(CA)_{23}$. Phylogenetic analysis revealed that all male lineages can be attributed to European or Eurasian haplogroups (40% E1b1b; 40% R1b and 20% Q) while mtDNA lineage belonged to Native American (57%), African (14%) and European (28%) haplogroups.

✓Based on the limited number of families studied, the finding of two particular microhaplotypes, suggests that both variants, the c.103dupG and the c.[1225C>T;1424C>T], originated from two independent mutational events supporting the hypothesis of a founder effect.

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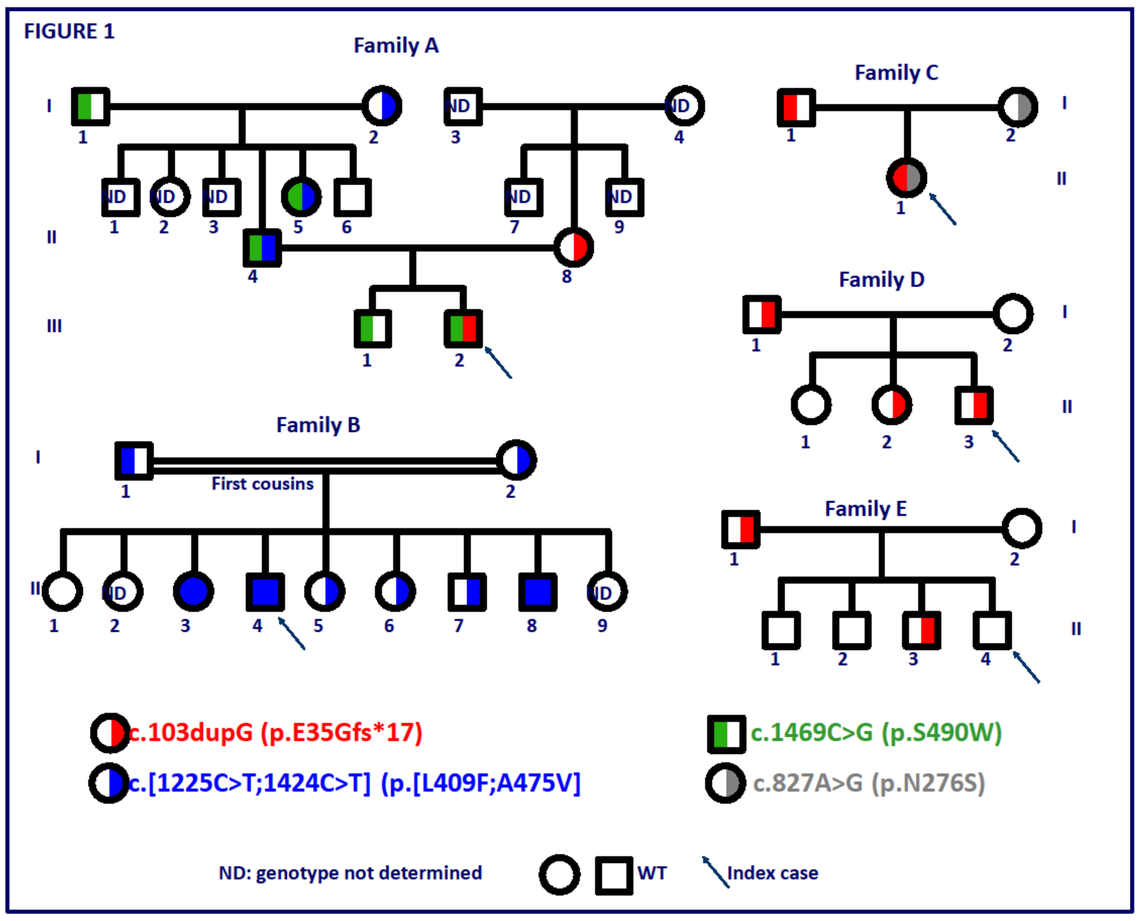
FIGURE 1



RESULTS

Variant	Family	Individual	*IGFALS* (NM_004970.2) associated polymorphisms									
			D16S3434 (nºrep)	rs2745206	rs2473466	rs2745205	rs9923699	rs3817902	rs12445517	rs186939	rs180753	rs3751893	D16S3024 (nºrep)
c.103dupG (p.E35Gfs*17)	A	II.8, III.2	12	G	T	C	G	G	T	G	C	C	21
	C	I.1, II.1	12	G	T	C	G	G	T	G	C	C	21
	D	I.1, II.2, II.3	12	G	T	C	G	G	T	G	C	C	21
	E	I.1, II.4	12	G	T	C	G	G	T	G	C	C	21
c.[1225C>T;1424C>T] (p.[L409F;A475V])	A	I.2, II.4, II.5	15	A	C	G	A	A	C	C	G	T	22
	B	I.1, I.2, II.3, II.4, II.5, II.6, II.7	15	A	C	G	A	A	C	C	G	T	23
WT	A	II.6	15	A	C	G	A	A	C	C	G	C	31
		I.2, II.6	13	G	T	C	G	G	T	G	C	C	28
		II.8, III.1	12	G	T	C	G	G	T	G	C	C	24
	B	I.1, II.1	10	A	C	G	A	A	C	C	G	C	24
		I.2, II.1, II.5, II.6, II.7	12	G	T	C	G	G	T	G	C	C	26
	C	I.1	4	G	C	C	G	G	C	G	C	C	29
		I.2	13	G	T	C	G	G	T	G	C	C	24
	D	I.1, I.2, II.1, II.2, II.3	12	G	T	C	G	G	T	G	C	C	22
		I.2, II.1	12	G	T	C	G	G	T	G	C	C	25
	E	I.1, II.1, II.2, II.4	13	G	T	C	G	G	T	G	C	C	25
		I.2, II.1, II.2	14	G	T	C	G	G	T	G	C	C	22
		I.2, II.3, II.4	14	G	T	C	G	G	T	G	C	C	25

Individual	*IGFALS* variant		Patri- and matrilineal lineages			
			Y chromosome		mtDNA	
	Name	Allele	Haplogroup predictor	YHRD	Haplogroup	Ethnicity
A /II.4	c.[1225C>T;1424C>T] (p.[L409F;A475V])	Maternal	Q (100%)	Eurasian-European	L2a1	African
	c.1469C>G (p.S490W)	Paternal				
A/II.8	c.103dupG (p.E35Gfs*17)	?			C1b	Amerindian
B/I.1	c.[1225C>T;1424C>T] (p.[L409F;A475V])	Maternal	E1b1b (91,8%)	Eurasian (Caucasian Uralic –Yukaghir)		
B/I.2	c.[1225C>T;1424C>T] (p.[L409F;A475V])	Maternal			T2g	Eurasian
C/I.1	c.103dupG (p.E35Gfs*17)	?	E1b1b (100%)	European-Eastern european	C1d	Amerindian
C/II.1	c.103dupG (p.E35Gfs*17)	?			A2	Amerindian
D/I.1	c.103dupG (p.E35Gfs*17)	?	R1b (100%)	European (Eastern or western european)	C1d	Amerindian
E/I.1	c.103dupG (p.E35Gfs*17)	?	R1b (100%)	European (South-Eastern or western European), Euro-asiatic (Altaic or Indo-iranian), Afro-asiatic (Semitic)	H1ba	Eastern Europe and NW Siberia

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