High Prevalence Mutations in *ALMS1* in Spanish Alström Patients

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Research

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Abstract

Background:

Alström syndrome (ALMS) is a rare disease with an estimated prevalence lower than 1 in 1,000,000. It is associated with mutations in the Alström syndrome 1 (*ALMS1)* gene, which codifies for a structural protein of the basal body and centrosomes. Symptomatology involves nystagmus, type 2 diabetes mellitus (DM2), obesity, dilated cardiomyopathy (DMC), neurodegenerative disorders and multi-organ fibrosis.

Methods:

We included the clinical data of 13 patients from 12 families, all of them from Spain. We studied the allelic frequency for the different mutations present in this cohort and we perform a haplotype analysis for the most prevalent allele.

Results:

Two alleles were detected in high frequency: p.(Tyr1714Ter) (0,25) and p.(Ser3872TyrfsTer19) (0,167). The segregation analysis of the mutation p.(Tyr1714Ter) in 3 families shows that it is linked to a rare missense polymorphism. Also, we detect an ancestral haplotype for *ALMS1* in three families.

Conclusion:

Mutation p.(Tyr1714Ter) co-segregates with a rare single nucleotide polymorphism (SNP) that could be arise by a founder effect in the Iberian Peninsula.

Introduction

Alström Syndrome (ALMS; OMIM #203800) is considered an ultra-rare disorder, with an estimated prevalence lower than 1 in 1,000,000 in European-descent populations and over 800 cases described worldwide, of which 13 patients have been diagnosed in Spain [1–4]. As in the case of other rare syndromes, consanguineous and/or geographically isolated populations refer higher frequency values [5–7].

ALMS is also a pleiotropic and multisystemic disorder that is characterized by high inter- and intra-familial variability, regarding the phenotype displayed and the age of onset and severity of symptoms [1,2]. Cardinal features include childhood obesity, insulin resistance, cone-rod retinal dystrophy, sensorineural hearing loss, type 2 diabetes mellitus (DM2), hypertriglyceridemia and dilated cardiomyopathy (DMC). Other features include hepatic, renal and pulmonary dysfunction, absence seizures or multi-organ fibrosis. The first clinical feature, corresponding to visual dysfunction, usually develops during the first year of life or even within a few weeks after birth with photophobia and nystagmus [2]. The remaining signs evolve slowly during childhood, although the most severe features can be detected before the first decade [1].

The clinical diagnosis of ALMS is based on the presence of primary and secondary features, considering the age of onset throughout development [8]

ALMS is a monogenic disorder caused by mutations in *ALMS1* gene (MIM #606844) and that represents an unusual phenomenon among ciliopathies. *ALMS1* is located on chromosome 2 (region 2p13.1), consists of 224 kilobases (kb) and contains 23 coding exons [9,10]. Several splicing isoforms have been reported, which could produce different protein isoforms with specific functions [9,11–13].

To date, over 270 pathogenic variants have been involved in ALMS development, of which 96% are nonsense or frameshift changes (insertions and deletions) that could originate truncated, non-functional proteins if translated [1,14]. Remarkably, causal changes in the 5' half of the *ALMS1* gene coding region (exons 1-7) are practically unreported, which suggests that mutations in this region could be embryonically lethal [2]. On the contrary, most of deleterious variants are clustered in exons 8 (6.1 kb), 10 (1.9 kb) and 16 (1.2 kb), which are considered mutational hotspots as they comprise 85-97% of the total mutational load for *ALMS1* in the different cohorts reported [1,7]. Hence, direct sequencing of these three exons represented the standard strategy when ALMS is suspected. However, the progressive implementation of high-throughput sequencing (HTS) techniques, such as whole-exome sequencing and targeted gene panels, is replacing the classical approach to ALMS molecular diagnosis [15–17].

Although the vast majority of mutations in *ALMS1* have been described once, several populations shown a founder effect like English or Turkish population [7,18]

The knowledge of the mutational load in this gene could be of great interest to understand the phenotype correlation and the molecular basis of this disorder.

Families And Methods

Cohort description

Thirteen patients from 12 unrelated families clinically diagnosed with AS were included in this study. Here we report the genetic characterization of 5 males and 8 females. Table 1.

Table 1.
Summary the genotype of patients, his LOVD ID and the author that described the case

			Allele 1		Allele 2	
Families	Lovd number patiente	Author	*ALMS1* Mutation 1 c.DNA	ALMS1 Mutation 1 Protein	ALMS1 Mutation 2 c.DNA	ALMS1 Mutation 2 Protein
GBB-28	-	-	c.2785G>T (Exon8)	p.(Glu929Ter)	c.2785G>T (Exon8)	p.(Glu929Ter)
RP-1232	-	-	c.4249del (Exon8)	p.(Arg1417GlyfsTer55)	c.4249del (Exon8)	p.(Arg1417GlyfsTer55)
FRPN36	1661	Piñeiro 2012	c.5142T>G (Exon8)	p.(Tyr1714Ter)	c.1844C>G (Exon 8)	p.(Ser615Ter)
GAS-37	1805	Marshall 2015	c.5142T>G (Exon 8)	p.(Tyr1714Ter)	c.4271T>G (Exon 8)	p.(Leu1424Ter)
GAS-38	1805	Marshall 2015	c.5142T>G (Exon 8)	p.(Tyr1714Ter)	c.4271T>G (Exon 8)	p.(Leu1424Ter)
GBB-46	-	-	c.5142T>G (Exon 8)	p.(Tyr1714Ter)	c.5142T>G (Exon 8)	p.(Tyr1714Ter)
GBB-44	1754	Marshall 2015	c.5142T>G (Exon 8)	p.(Tyr1714Ter)	c.11615_11616del (Exon 17)	p.(Ser3872TyrfsTer19)
UG-26225	-	-	c.5420_5423del (Exon 8)	p.(His1808GlufsTer20)	c.5420_5423del (Exon 8)	p.(His1808GlufsTer20)
RP-2186	177	Marshall 2015	c.7568_7569del (Exon 9)	p.(His2523ArgfsTer11)	c.4474G>T (Exon 8)	p.(Glu1492Ter)
GAS-39	1747	Marshall 2015	c.10754dup (Exon 16)	p.(Lys3585LysfsTer15)	-	-
RP-793	1663	Piñeiro 2012	c.10787_10788del (Exon 16)	p.(Val3596GlufsTer4)	c.10787_10788del (Exon 16)	p.(Val3596GlufsTer4)
GBB-45	-	-	c.11615_11616del (Exon 17)	p.(Ser3872TyrfsTer19)	c.11615_11616del (Exon 17)	p.(Ser3872TyrfsTer19)
RP-2177	-	-	c.11615_11616del (Exon 17)	p.(Ser3872TyrfsTer19)	c.805C>T (Exon 5)	p.(Arg269Ter)

ERG: Electroretinogram; DM2: Type 2 Diabetes Mellitus; DCM: Dilated Cardiomyopathy; CHF: Congestive Heart Failure.

Clinical history from families were obtained through collaboration with medical doctors and the National Association of Alström syndrome Spain. Main clinical characteristics are described in Table 2.

Table 2.
Phenotype summary based on diagnostic criteria for Alström syndrome according to Marshall et al. (2007) for 11 of the 13 cases. Clinical histories of patients GAS-39 was not achieved. **x**: presence of symptom. -: absence of symptom.

Families	Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)	Obesity and/or insulin resistance and/or DM2	History of DCM/CHF	Hearing loss	Hepatic dysfunction	Renal failure	Short stature	Males: hypogonadism; Females: irregular menses and/or hyperandrogenism	Thyroid Disorders	**Mutations**
GBB-28	x	x	x	-	-	-	-	-	-	p.(Glu929Ter (Glu929Ter)
RP-1232	x	x	x	x	-	-	-	x	x	p.(Arg1417Gl p.(Arg1417Gl
FRPN36	x	x	-	x	x	-	x	-	-	**p.(Tyr1714Te** (Ser615Ter)
GAS-37	x	x	x	x	x	-	x	x	x	**p.(Tyr1714Te** (Leu1424Ter)
GAS-38	x	x	-	x	x	-	x	x	x	**p.(Tyr1714Te** (Leu1424Ter)
GBB-46	x	x	-	x	x	-	x	-	x	**p.(Tyr1714Te (Tyr1714Ter)**
GBB-44	x	x	x	x	x	-	-	-	-	**p.(Tyr1714Te** (Ser3872Tyrf
UG-26225	x	x	x	-	-	-	-	-	x	p.(His1808Gl p.(His1808Gl
RP-2186	x	x	x	-	-	-	-	-	-	p. (His2523Argf (Glu1492Ter)
RP-793	x	x	x	x	-	-	x	-	x	p. (Val3596fsGl (Val3596Glut
RP-2177	x	-	x	x	-	-	-	-	-	p.(Ser3872Ty p.(Arg269Ter

ERG: Electroretinogram; DM2: Type 2 Diabetes Mellitus; DCM: Dilated Cardiomyopathy; CHF: Congestive Heart Failure.

This study was approved by the Galician Ethical Committee for Clinical Research (Spain 2006/08) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients or their guardians.

Mutations in these families were described elsewhere [1] and, as part of the Spanish ciliopathy cohort they have been studied by our group [3,4].

Mutations were previously described in these patients but we reanalyzed the cohort and confirmed on an independent PCR reaction and identified in both forward and reverse strands. All the mutations in these patients lead to premature stop codon, resulting in a truncated ALMS1.

Methods:

DNA extraction and Sanger Sequencing:

DNA was extracted from peripheral blood from participants and available family members. We used the Flexigene DNA kit 250 (Qiagen, Hilden, Germany), following the manufacturer's protocol.

Then DNA extraction, we analysed the exonic DNA of *ALMS1*. We amplified the DNA by polymerase chain reaction (PCR) in a MJ MiniTM Gradient Thermal Cycler (Bio-Rad, Hercules, CA) with primers described by Collin et al [9]. Then we purify PCR products using ExoSAP (Thermo-Fisher, USA) in a final volume of 6µL. The products were sequenced directly using the BigDye® Terminator v1.3 Cycle Sequencing Kit (Life technologies, Foster City, CA) in a 10-µl reaction. Sequencing products were precipitated, dried and resolved in an ABI PRISM 3130 (Life technologies, Foster City, CA) genetic analyser.

Finally, for nucleotide and amino acid numbering of mutations the reference sequence for *ALMS1* (ENST00000613296.5/NM_015120.4) was used.

Results

From 12 families we have 13 patients, 5 males and 8 females. All of them have a positive molecular diagnosis, and according to a recessive model, biallelic mutations.

In all cases except in one family, we established two pathogenic mutations. Six of them showed a homozygous mutation pattern, but none referred consanguinity. Families with the same mutation did not refer any relationship between them and came from different locations far away from each other.

Twelve different mutations were detected (Table 1), being homozygous six patients from families: GBB-45, GBB-46, RP-793, RP-1232, GBB-28 and UG-26225. One mutation is located in exon 5, seven mutations are located in exon 8, one in exon 9, two in exon 16 and one in exon 17 of *ALMS1*, all of them leading to a stop codon. Mutation p.(Tyr1714Ter) in exon 8 has a high frequency between our pool of patients 23.1%, appearing 5 times in 4 patients (one homozygous and three compound heterozygous). Mutation p.(S3872TyrfsTer19) have been detected four times in three patients, one homozygous, raising a 15.4% frequency. Most of the mutations were not shown in the ExAc database, no population information was available. Some of the mutations have been load into LOVD database from REWBA project, from the labs where the molecular analysis was performed.

For the data found, mutation p.(Tyr1714Ter) has been described 5 times [1,14] including three of our samples. Mutations p.(Ser3872TyrfsTer19) and p.(Val3596GlufsTer4) have been described 3 times [1,8], one heterozygous sample for p.(Ser3872TyrfsTer19) reported is one of our patients.

All patients included in this study, present some of kind of visual disorders. Obesity, insulin resistance or DM2 were present in 91% of the cases. DMC was found in 8 of 11 patients (73%). Hearing loss was reported in 8 of 11 patients (73%). (Table 2).

A second group of symptoms with low incidence was reported too: Hepatic dysfunction (45%), short stature (45%), thyroid disorders (55%) and hypogonadism/irregular menses 27. (Table 2).

Relative allele frequencies:

We detected two specific alleles with high frequency in *ALMS1*: p.(Tyr1714Ter) and p.(Ser3872TyrfsTer19), being only homozygous one family for each of those mutations. Relative frequencies of these alleles in the cohort were 0.231 and 0.154 respectively. (Figure 1).

Segregation study:

In patients carrying the p.(Tyr1714Ter) mutation we detected a single nucleotide polymorphism (SNP) with a low frequency (0.017) in European population. This SNP (rs45608038) is located in the Exon 8 of *ALMS1*. (Supp.Table 1). Thus, we evaluated in 3 families if the presence of this SNP segregates with the mutation p.(Tyr1714Ter), we concluded that this SNP is linked to the mutation. (Figure 2).

Haplogroup classification:

To complete the analysis and determinate if this was a common allele, we included the SNPs described by Scheinfeldt [19] to classify the haplogroup of these patients. The three patients carrying p.(Tyr1714Ter) show the ancestral haplotype described for *ALMS1*. Thus, we conclude that it is probably a founder mutation. (Table 3).

Table 3.
SNP analysed, exon in which they are found, genotype of the study individuals with the mutation p.(Tyr1714Ter) and shared common allele. *: causal mutation. ¯: rare variant linked to causal mutation.

Protein Mutation	SNPs	Exon	GBB-44	FRPN36	GBB-46	Common allele
p.(Phe730=)	rs7598901	8	T/T	T/T	T/T	T
p.(Gly1415Val)	rs6546837	8	G/G	C/G	G/G	G
p.(Ile1876Val)	rs6546838	8	A/A	G/A	A/A	A
p.(Ser2112Arg)	rs6724782	8	T/T	A/T	T/T	T
p.(Arg2285Leu)	rs6546839	8	G/G	C/G	G/G	G
p.(Arg2827Ser)	rs2056486	10	G/G	G/G	G/G	G
p.(Asn2857Ser)	rs10193972	10	A/A	G/A	A/A	A
p.(Asn1787Asp)¯	rs45608038	8	A/G	A/G	G/G	G
p.(Tyr1714Ter)*	rs772136379	8	T/G	T/G	G/G	G

Discussion

Alström Syndrome is a complex disease that affect multiple organs and induce metabolic disorder. Its huge heterogeneity symptomatology inter-patients and its low incidence in the worldwide population is a great difficulty to perform phenotype genotype correlations.

Until now, more than 270 mutations have been described for *ALMS1* related to ALMS. A great percentage of cases harbour private mutations.

In our cohort, we analysed 13 patients with causal ALMS mutations. Most of them have been described previously [4]. We have detected two mutations with high prevalence within our cohort. Both mutations, p.(Ser3872TyrfsTer19) and p.(Tyr1714Ter), generate a premature stop codon resulting in a truncated protein. They are located in exon 17 and 8 respectively. One of these mutations, p.(Tyr1714Ter), co-segregate with a low frequency SNP (rs45608038) in the 3 families analysed (Figure 2), which allows us to established a potential common origin of this allele in the Spanish patients. Also, based on the haplogroups described for *ALMS1*, this haplotype is grouped with the ancestral one [19] which have been detected in the South of Europe (France, Spain and Portugal) and have a high presence in the African continent. This fact could be interpreted as this ALMS allele was introduced in the Iberian Peninsula from the African continent.

Others SNPs were detected in the FRPN36 proband. Two of them (rs6546839 and rs6724782) are in high frequency in European population (24%) and latin population (40%). On the other hand, other two SNPs (rs6546838 and rs10193972) are described in the GWAS catalogue, the SNP rs6546838 is associate with an aberrant blood metabolite levels [20] while SNP rs10193972 is associate with the influence of general cognitive function [21].

In this report, we do not detect any correlation genotype-phenotype in the patients with mutation p.(Tyr1714Ter) and p.(Ser3872TyrfsTer19). Even in two brothers with the same genotype (p.(Tyr1714Ter)/p.(Leu1424Ter); GAS-37, GAS-38), the phenotype was not the same. In this case, GAS-37 report DMC but not his brother.

ALMS is a complex disorder and other factors could be influencing the development of the symptomatology. The prevalence of symptoms like DMC, hepatic dysfunction or hearing loss seems to be conditioned by other unknown agents. Numerous candidate ALMS1-interacting proteins have been reported, that could play a modulating function [22]

Until now, the exactly role of ALMS1 protein it is no clear, and has been detected in other tissues although the basal body location[22]. As pointed out by Braine 2017, some protein isoforms might have distinct intracellular locations and may perform different functions. However, most data support a role for ALMS1 beyond the ciliary function [23]. ALMS1 have been related with several cellular processes including endosomal trafficking, actin organisation and transcription, neuronal migration, maintenance of cellular quiescence, adipogenesis, spermatogenesis, maintenance of pancreatic β cell mass, adaptive thermogenesis, cell cycle arrest of cardiomyocytes and regulation of blood pressure and renal function [22,23].

ALMS is a very rare disease that shares clinical features with other ciliopathic syndromes, so clinical diagnosis is quite difficult in some cases. There are about 1,000 patients diagnosed with ALMS around the world. The difficulty to achieve a diagnosis and the lack for a global point of view, makes that some patients still be underdiagnose and seek for medical attendance when the symptoms get worse. An international effort is been made to enrol these patients into national and international associations that keep the patients updated and in touch with clinicians and investigation [24] and will facilitate future observational studies and clinical trials.

Conclusion

We detected two high prevalent *ALMS1* mutations: p.(Tyr1714Ter) and p.(Ser3872TyrfsTer19) in Spanish cohort. Mutation p.(Tyr1714Ter) co-segregates with a rare SNP that could be arise by a founder effect. Finally, three families with p.(Tyr1714Ter) mutation share the ancestral haplotype for *ALMS1* that it is predominant in African continent.

Abbreviations

ALMS: Alström syndrome.

CHF: Congestive Heart Failure.

DMC: dilated cardiomyopathy.

DM2: type 2 diabetes mellitus.

ERG: electroretinogram.

HTS: high throughput sequencing.

PCR: polymerase chain reaction.

SNP: single nucleotide polymorphism.

Declarations

Ethics approval and consent to participate:

This study adhered to the tenets of the Declaration of Helsinki and was approved by an ethics committee (*Comité Ético de Investigaciones Clínicas de Galicia*, Spain, 2006/08). Informed consent was obtained from all study participants or their guardians after the nature of the procedures to be performed in this study were fully explained.

Consent for publication

Not applicable.

Availability of data and materials:

The data that support the findings of this study are available from the corresponding author, D.V., upon reasonable request.

Competing interests:

The authors declare no conflict of interests.

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Authors' contributions:

BB-M, CL-S and DV designed the study. BB-M and CL-S performed the experiments. IP-R, TJ, FB-K and CA collected clinical and genetic data. BB-M, CL-S, CA and DV wrote the manuscript. All authors have read the draft and provided approval for publication.

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Figures

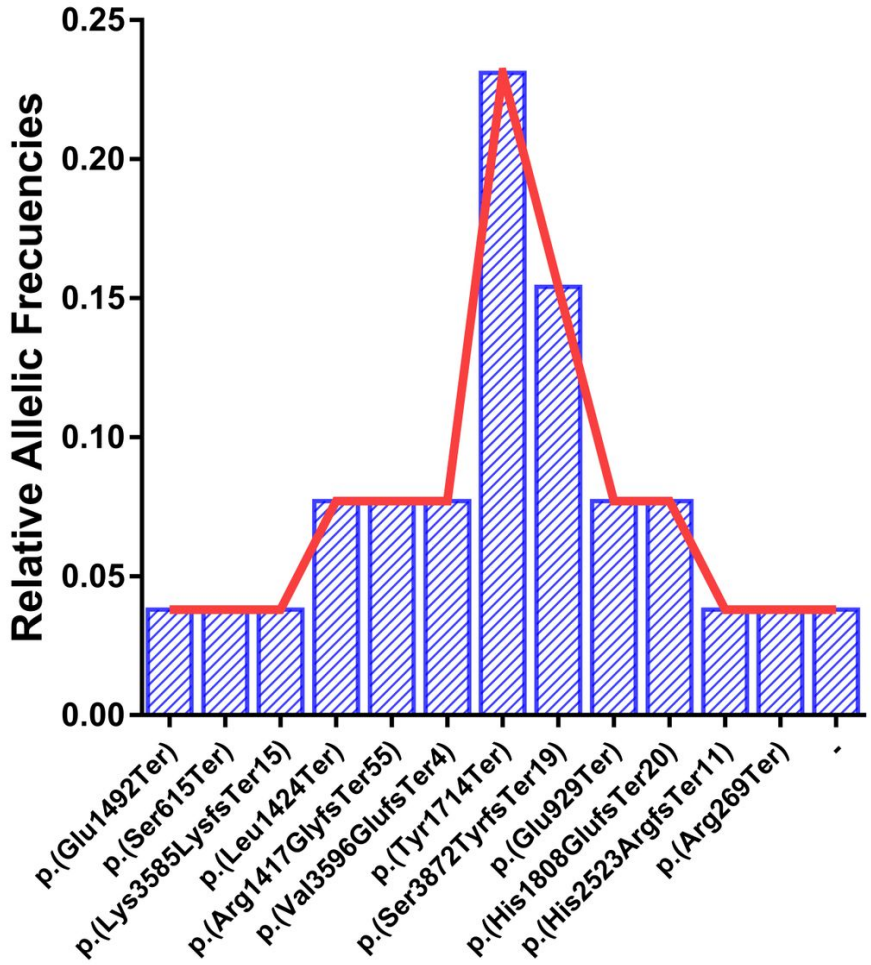

Figure 1

Different relative allele frequencies for the mutations detected in the cohort expressed as a fraction of total alleles (n=26).

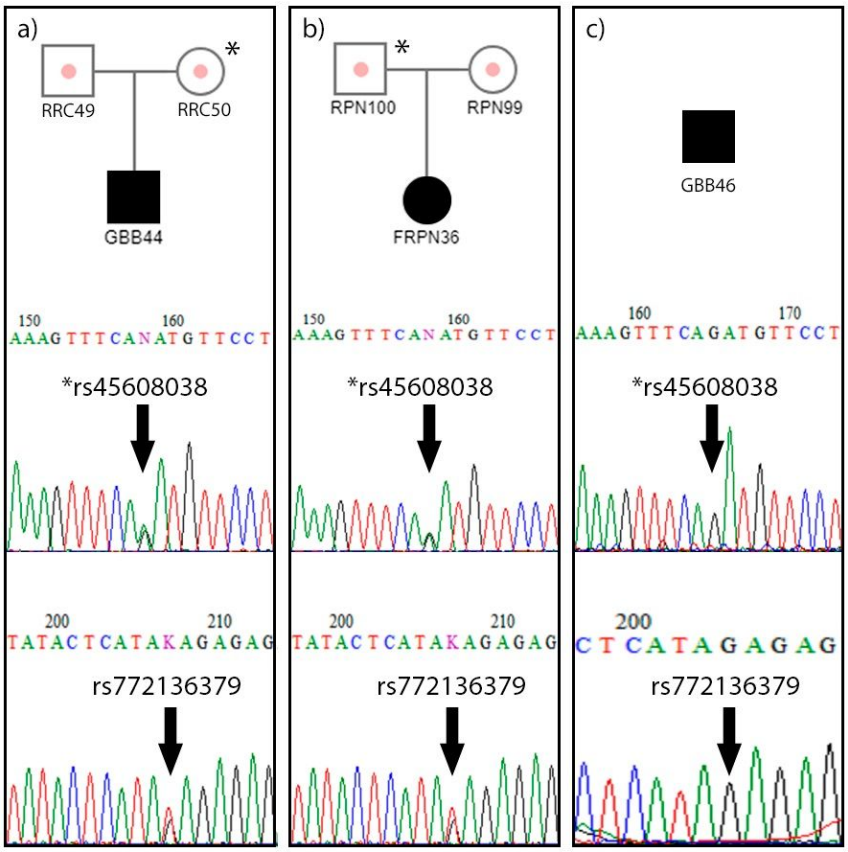

Figure 2

Representation of pedigree of 3 families. a) Representation of a mother carrier of the rare SNP and the causal mutation (heterozygosis). b) Representation of a father carrier of the rare SNP and the causal mutation (heterozygosis). c) Representation of proband with rare SNP and the causal mutation (homozygosis). *: rare SNP.

Supplementary Files

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- Supplementarydata.docx