CASE REPORT OF UKRAINIAN SMA FAMILY WITH RARE 5Q13 LOCUS REARRANGEMENTS

Alona Yurchenko[1], Erika Patskun[2], Nataliya Hryshchenko[3]

[1]Kiev National University, Educational and Scientific Center "Institute of Biology and Medicine", Kyiv, Ukraine
[2]Municipal Non-profit Enterprise "Transkarpathian Clinical Regional Hospital named after A.Novak", Uzhgorod, Ukraine
[3] Institute of Molecular Biology and Genetics National Academy of Sciences of Ukraine, Kyiv, Ukraine
alenaurchenko001@gmail.com

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disorder which is characterized by the degeneration of alpha motor neurons and progressive peripheral muscle weakness. The great majority of SMA patients have homozygous deletion in *SMN1* gene of 5q13 locus and the SMA carriers have the heterozygous deletion with typical "1+0" *SMN1* genotype. The highly homologous *SMN2* gene is located in the same locus, and SMA patients have 1 to 6 copies of this gene. *SMN2* would partially compensate a deficiency of the SMN protein in SMA patients. An increased *SMN2* copies result in an increased amount of the protein and lead to milder SMA phenotype [1].

A routine screening for SMA carriers is performed using quantitative PCR (qPCR) or Multiplex Ligation-Dependent Probe Amplification technology. These methods cannot determine the silent SMA carriers, who have *SMN1* duplication (2 copies) in 5q13 locus and *SMN1* deletion on the homological chromosome ("2+0" *SMN1* genotype). In some populations *SMN1* duplication is associated with rare haplotype of intragenic *SMN1* polymorphisms (g.27134G and g.27706_27707delAT) due to "founder" effect [2]. Analysis of these markers in a combination with dosage-sensitive methods would be used to determine "2+0" silent carriers improving the overall SMA carrier detection rate. However, the frequency of the "founder" *SMN1* haplotype is different in the populations, leading to different informativeness of the "2+0" haplotype determination [3].

A 10-year-old SMA patient (proband) from a large Transcarpathian unrelated family has homozygous *SMN1* deletion, but his phenotype is atypically mild as compared with other SMA patients with same *SMN1* mutation: he had proximal lower limb amyotrophy but saved the ability to walk independently. One of his elder sisters had proximal lower limb weakness (has never been examined) but other relatives had no specific SMA phenotypic symptoms. The molecular testing showed that proband's mother had heterozygous deletion in *SMN1* representing a typical *SMN1* genotype ("1+0"). The father had two *SMN1* copies which required further clarification.

The aim of our study was to determine an origin of the patient's paternal 5q13 rearrangement. We performed the qPCR of *SMN1* and *SMN2* genes as well as a segregation analysis of 5q13 region polymorphic markers LAS96 and 2AE9.1 in all available family members. The results are presented in the table 1.

Family member	*SMN1* copies / genotypes	*SMN2* copies/ genotypes	2AE9.1 alleles	LAS96 alleles	SMA status
proband	**0 / 0+0**	**4 / 2+2**	**2-2**	**6-6**	**SMA**
mother	1 / 1+0	3 / 1+2	2-4	3-6	SMA carrier
father	2 / 2+0	2 / 0+2	2-4	6-6	SMA carrier
sibs 1	3 / 1+2	1 / 1+0	4-4	3-6	Non carrier
sibs 2	**0 / 0+0**	**4 / 2+2**	**2-2**	**6-6**	**SMA**
sibs 3	3 / 1+2	1 / 1+0	4-4	3-6	Non carrier
sibs 4	1 / 1+0	3 / 1+2	2-4	3-6	SMA carrier
sibs 5	1 / 1+0	3 / 1+2	2-4	3-6	SMA carrier

Table 1. 5q13 rearrangement study in the family members

It would be noted that proband`s sibs 2 (13 years old female without specific SMA sings) had the same *SMN1* homozygous deletion. According to obtained result, it was found that the father is the carrier of rare *SMN1* ("2+0"). The chromosome with *SMN1* duplication inherited within the family (father, sibs 1 and sibs 3) hadn't g.27134G allele indicating the origin of the rearrangement is not due to mentioned above "founder" effect. The proband`s parents have *SMN2* heterozygous duplication (mother: "2 + 1", father: "2 + 0"). Consequently, the proband and sibs 2 inherited *SMN2* duplication from both of parents and have 4 *SMN2* copies.

We can conclude that two children inherited the *SMN1* deletion from both the parents; but the father is a silent carrier of a rare *SMN1* genotype. The proband and sibs 2 inherited from the parents 4 *SMN2* copies, that could explain their mild SMA phenotypes. The parental *SMN1* duplication has a recurrent origin possibly due to *de novo* mutation.

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