



Case report

Spinal muscular atrophy due to a “de novo” 1.3 Mb deletion: Implication for genetic counseling

Luciana Rodrigues Jacy da Silva^a, Mileny Esbravatti Stephano Colovati^a, Bruno Coprerski^a, Carlos Eugênio Fernandez de Andrade^b, Edmar Zanoteli^c, Salmo Raskin^d, Mariana Moysés Oliveira^e, Maria Isabel Melaragno^e, Ana Beatriz Alvarez Perez^{a,*}

^a Medical Genetics Center, Department of Morphology and Genetics, Federal University of São Paulo, São Paulo, Brazil

^b Santa Marcelina Hospital, São Paulo, Brazil

^c Department of Neurology, Medical School of the University of São Paulo, São Paulo, Brazil

^d Genetika, Genetic Counseling and Genetics Laboratory, Curitiba, Brazil

^e Department of Morphology and Genetics, Federal University of São Paulo, São Paulo, Brazil

Received 29 June 2012; received in revised form 25 October 2012; accepted 15 January 2013

Abstract

We report a 3-year-old female with type I spinal muscular atrophy (SMA) born to a young and non-consanguineous couple. The child presented at two months of life with intense muscle weakness affecting predominantly proximal portions of the limbs, especially the legs, muscle hypotonia, fasciculation of the tongue, and severe respiratory muscle involvement. She remained in an intensive care unit with an assisted ventilation system from the fourth month of life. She died at 3 years of age from pulmonary infection. Molecular analysis confirmed the diagnosis of SMA but revealed that only the father was an asymptomatic carrier. Because *SMN1* is mapped in a complex region containing repetitive elements due to an inverted duplication of approximately 500 kb, we carry out an SNP array and detected a 1.3 Mb deletion including the *SMN1* and *SMN2* genes that explain the disease.

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Keywords: Spinal muscular atrophy; SNP array; Genetic counseling; *SMN* gene

1. Introduction

Spinal muscular atrophy (SMA I; MIM#253300) is a neuromuscular autosomal recessive disorder. Approximately 95–98% of individuals with clinical diagnosis of SMA are homozygous for an exon 7 deletion in both copies of the *SMN1* gene [1,2]. Approximately 2–5% of patients are compound heterozygotes for a deletion of at least *SMN1* exon 7 and an intragenic inactivating mutation of *SMN1* [1,3].

Nearly 2% of parents of an affected child are not carriers of a *SMN1* gene mutation, and in these SMA cases the other altered allele is hit by a “de novo” mutation [3,4]. Changes in expression of the centromeric copy of *SMN* (*SMN2*) are known to modify the phenotype [5–7].

Three mechanisms seem to play a crucial role in the occurrence of de novo mutations in SMA: (1) unequal crossing-over between homologous chromosomes, (2) intrachromosomal deletion, and (3) gene conversion [8–11]. Because of its duplicated structure, including *SMN* and *NAIP* homologues, the SMA region seems to be prone to unequal rearrangement or gene conversion [10,12,13]. It appears that unequal recombination causing larger deletions are associated with more severe phenotypes, whereas intrachromosomal deletions and gene conversions are associated with milder SMA [11,14].

* Corresponding author. Address: Medical Genetics Center, Department of Morphology and Genetics, Federal University of São Paulo, Rua Coronel Lisboa 966, Vila Clementino, CEP-04020-041 São Paulo, Brazil. Tel./fax: +55 11 5085 0188.

E-mail address: anabia.morf@epm.br (A.B.A. Perez).

The detection of a de novo rearrangement resulting in the loss of the telomeric copy of the *SMN* gene in an SMA family indicates a recurrence risk reduced from 25% to a substantially lower percentage, the only risk in this situation coming from recurrent de novo mutation or germ-line mosaicism in physical structure that might predispose to de novo rearrangements.

2. Case report

We report here a 3-years-old female diagnosed with type I SMA, born from a young and non consanguineous couple who has a previous healthy daughter. She presented at two months of life an intense muscle weakness affecting predominantly proximal portions of the limbs, especially the legs, muscle hypotonia, fasciculation of the tongue, mild facial muscle weakness sparing the ocular motility, and intense respiratory muscle involvement. The child remained in an intensive care unit with assisted ventilation from the fourth month of life. She died at 3 years of age from pulmonary infection. The molecular study by quantitative PCR revealed deletion of exon 7 in homozygosis of *SMN1* gene and only two copies of exons 7 and 8 of the *SMN2* gene, consistent with the severity of the case. The analysis of *SMN1* and *SMN2* genes in the patient's parents revealed that the father has one normal copy of the

SMN1 gene and one *SMN1* allele with a deletion of exon 7, as well as two copies of the *SMN2* gene. The analysis performed in the mother revealed two wild copies of *SMN1* gene and one copy of *SMN2*, demonstrating that she is not a carrier of SMA. The genome-wide study performed in the patient using the Affymetrix GeneChip® Genome-Wide Human SNP Array 6.0 showed arr 5q13.2(69,074,964–70,391,173)×1 (GRCh/hg19) revealing a 1.3 Mb deletion including *SMN1* and *SMN2* genes (Fig. 1a). The same study performed in the parents did not show copy number abnormalities in the same region (Fig. 1b and c).

3. Discussion

The *SMN1* is mapped in a complex region containing a variety of pseudogenes and repetitive elements due to an inverted duplication of the region of approximately 500 kb [1,14]. This unstable region is subject to “de novo” rearrangements, including gene duplication, conversion and deletions, mainly due to the high (>95%) homology of the low copy repeats present in this region act as substrates for non-allelic homologous recombination (NAHR), leading to loss or gain of dosage sensitive genes [12,13,15]. The NAHR can occur when two low copy repeats are located on the same chromosome in the same orientation, leading to deletion



Fig. 1. Array data from the patient (a) showing a 1.3 Mb deletion including the *SMN1* and *SMN2* genes (arrows) and from her mother (b) and father (c) indicating that the patient's deletion is a “de novo” event.

and/or duplication or when they are in opposite orientation, resulting in inversion of this region [12,13]. It has been suggested that the presence of low copy repeats in this region can contribute to instability in the region and unequal recombination events in the SMA [11].

There is no previous report of whole genome array study showing a deletion in the 5q13 region. We propose that “de novo” rearrangements in SMA may occur more frequently than previously suspected considering the genomic architecture of the 5q13 region and array studies must be considered in estimating the recurrence especially in cases of non consanguineous parents. The evaluation of deletion may change the risk for the recurrence of the disease in genetic counseling. Thus, the proband received the paternal mutation of the gene *SMN1* (deletion of exon 7) from her father and in the allele received from her mother occurred a “de novo” 1.3 deletion including *SMN1* gene. The SNP array revealed normal in the parents for the region 5q13.2. In this case, the recurrence risk for SMA is lower than the 25% usually estimated.

References

- [1] Lefebvre S, Burglen L, Reboullet S, et al.. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* 1995;80(1):155–65.
- [2] McAndrew PE, Parsons DW, Simard LR, et al.. Identification of proximal spinal muscular atrophy carriers and patients by analysis of SMN1 and SMN2 gene copy number. *Am J Hum Genet* 1997;60(5):1411–22.
- [3] Wirth B. An update of the mutation spectrum of the survival motor neuron gene (*SMN1*) in autosomal recessive spinal muscular atrophy. *Hum Mut* 2000;15(3):228–37.
- [4] Ogino S, Wilson RB. Genetic testing and risk assessment for spinal muscular atrophy (SMA). *Hum. Genet.* 2002;111(6):477–500.
- [5] Prior TW, Swoboda KJ, Scott HD, Hejmanowski AQ. Homozygous *SMN1* deletions in unaffected family members and modification of the phenotype by *SMN2*. *Am J Med Genet A* 2004;130A(3):307–10.
- [6] Swoboda KJ, Prior TW, Scott CB, et al.. Natural history of denervation in SMA: relation to age, *SMN2* copy number, and function. *Ann Neurol* 2005;57(5):704–12.
- [7] Zanuteli E, Maximino JR, Reed UC, Chadi G. Spinal muscular atrophy: from animal model to clinical trial. *Funct Neurol* 2010;25(2):73–9.
- [8] McLean MD, Roy N, MacKenzie AE, et al.. Two 5q13 simple tandem repeat loci are in linkage disequilibrium with type I spinal muscular atrophy. *Hum Mol Genet* 1994;3(11):1951–6.
- [9] Melki J, Lefebvre S, Burglen L. De novo and inherited deletions of the 5q13 region in spinal muscular atrophies. *Science* 1994;264(5164):1474–7.
- [10] Burghes AH. When is a deletion not a deletion? When it is converted. *Am J Hum Genet* 1997;61:9–15.
- [11] Wirth B, Schmidt T, Hahnen E, et al.. De novo rearrangements found in 2% of index patients with spinal muscular atrophy: mutational mechanisms, parental origin, mutation rate, and implications for genetic counseling. *Am J Hum Genet* 1997;61(5):1102–11.
- [12] Lupski JR, Stankiewicz P. Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. *PLoS Genet* 2005;1(6):e49.
- [13] Gu W, Zhang F, Lupski JR. Mechanisms for human genomic rearrangements. *Pathogenetics* 2008;1:4.
- [14] Hahnen E, Forkert R, Marke C, et al.. Molecular analysis of candidate genes on chromosome 5q13 in autosomal recessive spinal muscular atrophy: evidence of homozygous deletions of the *SMN* gene in unaffected individuals. *Hum Mol Genet* 1995;4(10):1927–33.
- [15] Schmutz J, Martin J, Terry A. The DNA sequence and comparative analysis of human chromosome 5. *Nature* 2004;431(7006):268–74.