CHAPTER 1

A molecular pathomechanism of spinal muscular atrophy

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Spinal muscular atrophy (OMIM 253300, 253550, 253400) – caused by *SMN1* gene mutations – is one of the most frequent autosomal recessive genetic disorders, its incidence being estimated at 1 per 5,000 to 10,000 births [1-3]. The disorder leads to a loss of lower motor neurons, resulting in muscle-wasting and atrophy. However, the age at the onset of the disease and the severity of clinical symptoms are very variable, a *continuum* in fact being observed from the congenital form through to asymptomatic cases [4-6]. Such was the degree of clinical variability that discussion was evoked previously as to whether spinal muscular atrophy was one disease with a wide phenotypical spectrum, or actually many different diseases. However, we now know that all forms (SMA0, SMA1, SMA2, SMA3 and SMA4) are associated with mutations of the *SMN1* gene located in the SMA region [7]. This region present on the long arm of chromosome 5 (5q12.3) is composed of two similar segments – the telomeric and the centromeric. The *SMN1* gene is found on

the telomeric segment, while its equivalent, the *SMN2* gene, is on the centromeric. In addition, there are several other genes in this region, like *H4F5*, *NAIP* and *p44*, as well as many repeat sequences and pseudogenes, making this unstable genetically [8, 9, 10].

Moreover, spinal muscular atrophy is very homogenous at the molecular level, with over 95% of the mutations responsible for SMA (96.5% in the Polish population) entailing biallelic loss of exon 7 of the *SMN1* gene [7, 11]. Such marked homogeneity of the molecular basis in turn begged questions regarding the phenotypic variability of the disease and potential phenotype modifiers. Initially, a link was invoked with the size of the deletion in the SMA region [7]. Specifically, it seemed that large deletions including neighboring genes such as the *NAIP* gene might cause the severe form of the disease. However, deletion size is now seen as the effect of a different molecular mechanism underpinning *SMN1* loss, rather than a real cause of SMA variability. Burghes proposed that the se-

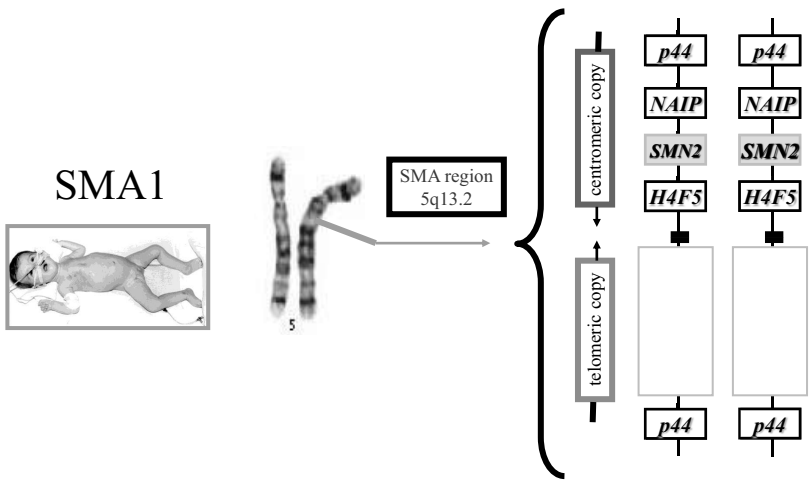

Fig. 1A. Different mechanisms responsible for *SMN1* gene loss a real deletion in the SMA region causes the loss of neighboring genes

vere form of the disease was caused by true deletions in the SMA region, while mild forms reflected the conversion of SMN forms [12] [Figs. 1a and 1b]. True deletions in the SMA region cause the actual loss of the *SMN1* gene. In this mechanism, neighboring genes like the *NAIP* gene are often also deleted, and only a single copy of the equivalent *SMN2* gene per allele persists. The conversion, also called correction of sequence, is a kind of recombination between two closely homologous regions of DNA (located on one chromosome or more). Conversion of the *SMN1* gene to *SMN2* results in the loss of the *SMN1* gene itself, while neighboring genes are preserved and the total number of *SMN2* gene copies increases. And the number of *SMN2* copies is the main modifier of phenotypic variability in SMA.

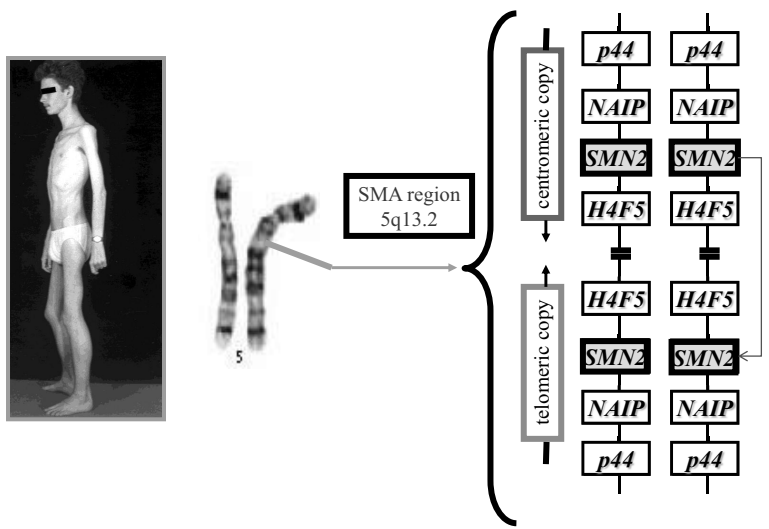

Fig. 1b. Different mechanisms responsible for *SMN1* gene loss- *SMN1*-to-*SMN2* conversions lead to the loss of the former, as well as to an increase in the total number of *SMN2* genes. The neighboring genes persist.