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Compound heterozygosity for a large CNV deletion and a rare missense mutation in the FSTL5 gene of a patient affected by schizophrenia. Rita Gardella[1], Andrea Legati[2], Chiara Magri[3], Michele Traversa[4], Massimo Gennarelli[5], Emilio Sacchetti[6] and Sergio Barlati[7]

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A progress in the genetics of SC has derived from the discovery that some large and rare copy number variations (CNVs) are associated to the disease (Tam *et al.*, 2009). Although CNVs represent convincing risk factors, their presence also in unaffected individuals indicates that additional genetics and/or environmental factors are likely implicated in the development of the disease, as exemplified by the two-hit hypothesis (Girirajan *et al.*, 2010; Worstman *et al.*, 2011). For instance, the second hit might be another CNV or a point mutation affecting the same or a functionally correlated gene.

In a genome-wide CNV analysis of an Italian SC cohort we have identified a patient with an heterozygous large deletion (about 2300 kb) on chromosome 4q32.1-32.2 (Magri *et al.*, 2010). The deletion encompassed the *FSTL5* gene (ref. NM_020116), removing 14 of the 16 exons and causing the loss of nearly all the coding sequence. Sequencing of all the *FSTL5* coding exons of the patient revealed a T>C transition at position 1358 of the cDNA, in exon 12, resulting in a methionine to threonine substitution at position 453 (M453T) of the 847 amino acid sequence. This substitution was predicted to be "probably damaging" by *Polyphen* and "disease-causing" by *MutationTaster* software. As the M453T mutation was not reported in the *dbSNP132* database, we screened the DNA of 164 SC patients and 246 healthy controls for the presence of the mutation. The M453T substitution was identified in heterozygosity in a second patient and in one control. Given its rarity, the occurrence of the M453T substitution in a SC patient carrier of a *FSTL5* deletion suggests that this missense mutation could contribute to the clinical phenotype, likely acting through a recessive effect disclosed by the hemizygous condition.

The *FSTL5* gene is one of the five members (*FSTL1–5*) of the follistatin-like gene family, whose common feature is to encode for secreted extracellular glycoproteins with partial homology to follistatin, a well-known modulator of activin and other TGF-β superfamily members (Welt *et al.*, 2002). So far, the function of *FSTL5* has been poorly characterized. Its high level of expression in the spinal cord tissue of early embryonic mice suggested a possible role in the development of the neurodorsal spinal cord and/or in the axonal guidance of dorsal root ganglion (Masuda *et al.*, 2006). However, as retrieved from the *Atlas* and *MGD* databases, *FSTL5* expression is not limited to the spinal cord and it has been observed indifferent areas of the developing and adult central nervous system (CNS). Moreover, the FSTL5 protein has been reported to be secreted by cultured cortical neurons (Thouvenot *et al.*, 2008). These findings suggest that FSTL5 might play a relevant role in the CNS.

Although functional studies would be required, the co-occurrence in the same SC patient of two rare alterations in the *FSTL5* gene (a large CNV deletion and the M453T substitution) suggests that these two events may be important for the development of the disorder. Thus, our data supports the two-hit model as one of the mechanisms implicated in SC and highlights *FSTL5* as a candidate gene in the development of the disease. The mutational analysis of larger patient samples might help to better understand the role of *FSTL5* in SC.

References

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