SHANK2 MUTATIONS:

Synapse homeostasis in Autism Spectrum Disorders (ASD)

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BACKGROUND

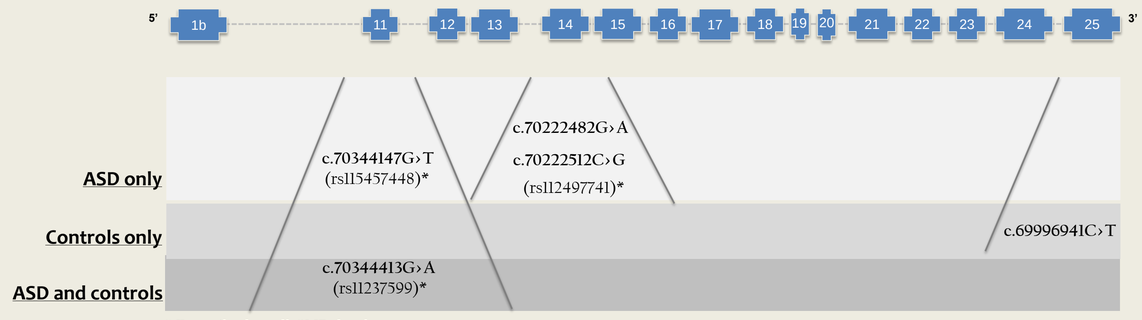
ASD are a heterogeneous group of neurodevelopmental disorders presenting a complex inheritance pattern. The genetic causes of ASD are diverse, but the majority of genes previously implicated participate in the development and function of neuronal circuits[1]. Mutations in genes encoding synaptic cell adhesion molecules and scaffolding proteins, such as neuroligins (*NLGN*), neurexins (*NRXN*) and the *SHANK* family, have been recurrently reported in patients with ASD[2,3]. *SHANK2* encodes a scaffolding protein located in the postsynaptic density (PSD) of glutamatergic synapses, and mutations in *ProSAP1/SHANK2* have been recently associated with both ASD and intellectual disability [1,3].

METHODOLOGY

In the context of an European effort to better understand the role of the *NRXN-NLGN-SHANK* pathway in ASD, we sequenced exons 1b and 11 to 25 of the *ProSAP1/SHANK2* for coding mutations in 1) Portuguese ASD patients (N=10); 2) control subjects (N=10) with no obvious psychiatric disease history, although not specifically screened for ASD.

RESULTS

Sequencing of *ProSAP1/SHANK2* identified a paternally inherited non-synonymous variant (Gly489Val), with no pathogenic effect according to *in silico* predictive analysis, in one ASD patient. Three synonymous changes were found, two of them previously described as polymorphisms in dbSNP (Figure 1). An intriguing finding was one non-synonymous variant (Pro1745Leu) present in a control subject, with a possibly damaging effect predicted by *in silico* studies (Table 1). While this subject may be in the autistic spectrum, it is also possible that the variant has low penetrance.



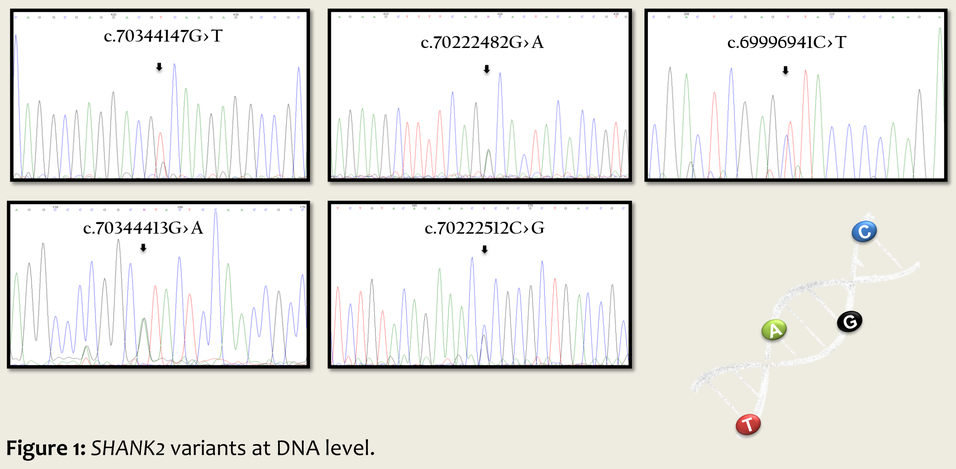


Figure 1: *SHANK2* variants at DNA level.

Table 1: *SHANK2* variants found in ASD patients and controls.

	DNA variant		Aminoacid change		Functional impact* (*In silico*)	Inheritance
	Exon	Nucleotide				
ASD only	11	c.70344147G>T	Gly489Val	Non Synonymous	Benign	Paternal
	14	c.70222512C>G	Thr595Thr	Synonymous	ND	ND
	14	c.70222482G>A	Arg605Arg	Synonymous	ND	*De novo*
Control only	25	c.69996941C>T	Pro1745Leu	Non Synonymous	Probably damaging	ND
ASD & controls	11	c.70344413G>A	Ala400Ala	Synonymous	ND	ND

* Determined using PolyPhen-2 prediction of functional effects of human nsSNPs software.

FINAL REMARKS

***In vitro* studies in neuronal cell cultures revealed that multiple sequence changes in *SHANK2* are responsible for reduced synapse density at dendrites. A better knowledge of how genetic variants, such as those identified, interfere with synaptic homeostasis and modulate ASD risk will help understand the complex inheritance pattern of ASD.**

REFERENCES:

[1] Berkel S. *et al.* Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. (2010) Nature Genetics 42, 489–491; [2] Pinto D. *et al.* Functional impact of global rare copy number variation in autism spectrum disorders. (2010) Nature 466: 368-372 [3] Leblond C.S. *et al.* Genetic and Functional Analyses of SHANK2 Mutations Support a Multiple Hit Model of Autism Spectrum Disorders. (2011) The 12th International Congress of Human Genetics and the American Society of Human Genetics 61st Annual Meeting October 11-15, 2011 Montreal, Canada.