M13. CONTRIBUTION OF THE 14-3-3 GENE FAMILY TO AUTISM SPECTRUM DISORDER

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Background We recently identified a heterozygous 1-bp insertion in the YWHAZ gene (c.659_660insT, p.L220Ffs*18) in two brothers with Autism Spectrum Disorder (ASD) (Toma et al. Mol Psychiatry 2014;19:784). This gene encodes 14-3-3ζ, one of the seven isoforms of the 14-3-3 protein family. In this study we aimed to (1) functionally characterize the disruptive mutation identified in YWHAZ; and (2) evaluate the possible implication in ASD of all members of this gene family (SFN, YWHAQ, YWHAG, YWHAZ, YWHAB, YWHAH, YWHAE).

Methods Normal and truncated 14-3-3ζ were expressed as fusion proteins in E. coli, where their solubility was tested. Furthermore, Biacore experiments were performed to assess the affinity of the truncated 14-3-3ζ with the well-known interactor Ser19-phosphorylated tyrosine hydroxylase (TH-Ser19P). To test the possible involvement of common and rare variants of the 14-3-3 genes in ASD we performed, respectively, (a) a case-control association study in 727 ASD patients and 714 controls, by using tagSNPs covering the seven genes; and (b) resequencing of all these genes in 285 ASD patients.

Results Truncated 14-3-3ζ presented a decreased solubility and lost its affinity with TH-Ser19P. No common variants were found associated with ASD in our study. The mutation screening identified two potentially damaging variants in the SFN gene.

Discussion These results suggest a possible dominant negative effect of the truncated 14-3-3ζ. The genetic study of the 14-3-3 gene family did not identify other risk variants in the YWHAZ gene. Although potential mutations were identified in SFN, further experiments are needed to test its possible contribution to ASD.

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