Association study of fibroblast growth factor genes and brain volumes in schizophrenic patients and healthy controls

Afke F. Terwisscha van Scheltinga[a], Steven C. Bakker[a], Neeltje E.M. van Haren[a], Heleen B.M. Boos[a], Hugo G. Schnack[a], Wiepke Cahn[a], Martine Hoogman[b], Marcel P. Zwiers[c], Guillen Fernandez[c], Barbara Franke[d], Hilleke E. Hulshoff Pol[a] and René S. Kahn[a]

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[a]Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Centre Utrecht, Utrecht, [b]Department of Language and Genetics, Max Planck Institute for Psycholinguistics, [c]Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour and [d]Department of Human Genetics and Psychiatry, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

Correspondence to Afke F. Terwisscha van Scheltinga, MD, PhD, Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Centre Utrecht, Huispostnummer A00.241, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands
Tel: +31 88 755 5555; fax: +31 88 755 5466; e-mail: afketvs@gmail.com

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Fibroblast growth factors (FGFs) play crucial roles in brain development and neuroprotection and have been implicated in the susceptibility to schizophrenia (Terwisscha van Scheltinga *et al*., 2010). FGF mutant mice studies suggest that disturbances of FGFs affect brain structure *in vivo*. Brain structure is associated robustly with schizophrenia and is highly heritable. We systematically screened single nucleotide polymorphisms (SNPs) in the FGF system for association with intracranial volume, a developmental phenotype affected by FGFs, and with brain volume, a schizophrenia endophenotype.

Intracranial volume (corrected for age and sex) and total brain volume (corrected for age, sex, and intracranial volume) were measured on a 1.5 T MRI scanner in 162 schizophrenic patients and 151 healthy controls, as described before (Terwisscha van Scheltinga *et al*., 2013). We selected SNPs located in 83 genes, including 22 FGFs, five FGF receptors, and 56 interacting proteins. After quality control, a set of 915 SNPs genotyped with the Illumina HumanHap550 beadchip (Illumina, San Diego, California, USA) was analyzed for effects on these volumes using analysis of variances. Over-representation of multiple high-ranking SNPs in CACNA1D (calcium channel, L-type, α1D subunit, also called Cav1.3) was tested using a Fisher exact test and with permutation analysis (randomly permuting intracranial volume 10 000 times while leaving genotype data unchanged).

After Bonferroni correction, no single SNP was associated significantly with intracranial volume or brain volume. For intracranial volume, there was a significant over-representation of SNPs in CACNA1D among the highest-ranking SNPs (expected number of CACNA1D SNPs with $P < 0.1 = 7$, observed = 20; over-representation P-value Fisher exact $= 1.0 \times 10^{-5}$, permutation P-value = 0.004). When taking into account disease status, CACNA1D SNPs were not significantly over-represented because some SNPs had effects predominantly in patients and others in controls. However, there were no main effects of the CACNA1D SNPs on disease status, or a gene-based over-representation. Although there was some linkage disequilibrium between the high-ranking SNPs, together they explained more variance in intracranial volume (10.7%) than each separately (2.4–3.7%).

These results suggest that multiple SNPs in CACNA1D, each with small effects, influence intracranial volume in patients as well as controls. Activation of FGF receptors opens these calcium channels, thereby affecting axon outgrowth (Archer *et al*., 1999). Interestingly, the largest reported genome-wide association study for schizophrenia found multiple hits in calcium channels (Ripke *et al*., 2013). We attempted to replicate our findings in an independent sample of 892 healthy controls, with 1.5 or 3 T MRI scans, genotyped on the Affymetrix GeneChip 6.0 (Affymetrix, Santa Clara, California, USA) [see Bralten *et al*. (2011) for a sample description]. Of the 57 SNPs in CACNA1D, only 18 were overlapping with the Illumina SNPs used in the initial sample. No over-representation was observed in this second sample (expected number of CACNA1D SNPs with $P < 0.1 = 7$, observed = 6). This could mean that our initial finding was based on stochastic variation. However, different study characteristics (healthy controls only, different MRI scanners, and SNP sets) might also explain the nonreplication. Taken together, SNPs in the FGF system do not seem to exert major effects on brain volume in schizophrenic patients and healthy controls.

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Conflicts of interest

There are no conflicts of interest.

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