No effect of schizophrenia risk genes *MIR137*, *TCF4*, and *ZNF804A* on macroscopic brain structure

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ABSTRACT

Single nucleotide polymorphisms (SNPs) within the *MIR137*, *TCF4*, and *ZNF804A* genes show genome-wide association to schizophrenia. However, the biological basis for the associations is unknown. Here, we tested the effects of these genes on brain structure in 1300 healthy adults. Using volumetry and voxel-based morphometry, neither gene-wide effects—including the combined effect of the genes—nor single SNP effects—including specific psychosis risk SNPs—were found on total brain volume, grey matter, white matter, or hippocampal volume. These results suggest that the associations between these risk genes and schizophrenia are unlikely to be mediated via effects on macroscopic brain structure.

1. Introduction

A recent meta-analysis of GWAS studies of schizophrenia found the strongest evidence for an association with the single nucleotide polymorphism (SNP) rs1625579 in an intron of the *MIR137* (http://www.genecards.org/cgi-bin/carddisp.pl?gene=mir137) gene (Ripke et al., 2011). This association was later replicated in a GWAS study, providing increasing evidence for a role for *MIR137* in the aetiology of schizophrenia (Ripke et al., 2013). Interestingly, *MIR137*, which encodes a microRNA, regulates several other schizophrenia risk genes, notably *ZNF804A* (http://www.genecards.org/cgi-bin/carddisp.pl?gene=ZNF804A) and *TCF4* (http://www.genecards.org/cgi-bin/carddisp.pl?gene=TCF4) (Kim et al., 2012; Guella et al., 2013; Kwon et al., 2013; Wright et al., 2013). In silico, cellular, and luciferase based approaches have provided evidence that MIR137 downregulates both ZNF804A (Kim et al., 2012) and TCF4 (Guella et al., 2013; Kwon et al., 2013) expression.

DNA sequence variation in *ZNF804A* and *TCF4* has been robustly associated with schizophrenia risk. SNP rs1344706, in intron two of *ZNF804A*, was the first variant to reach unequivocal genome-wide significance for schizophrenia (O'Donovan et al., 2008), with a later meta-analysis confirming the association and extending it to a broader psychosis phenotype (Williams et al., 2011). For *TCF4*, Stefansson et al. (2009) first reported an association between SNP rs9960767, in intron 3 of the gene, and schizophrenia, with several other SNPs in the gene subsequently being associated with the disorder (Ripke et al., 2011; Steinberg et al., 2011). *ZNF804A* and *TCF4* are believed to encode transcription factors, but little is known about the mechanistic pathways via which they might increase risk for schizophrenia. Similarly, the risk SNPs are located in non-coding regions of the genes and it is not yet clear how they modulate disease risk. At the molecular level, they may impact on transcript expression or splicing (Hill and Bray, 2012; Guella et al., 2013; Tao et al., 2014); at the systems level, the risk alleles may influence brain function or structure (Esslinger et al., 2009; Quednow et al., 2011; Rasetti et al., 2011; van Erp et al., 2014).

Structural MRI studies show that schizophrenia is associated with a reduction in total brain volume of around 2.6%, with larger effects for grey matter than white matter, and with the reductions prominent in frontal and temporal cortices and hippocampus (Fornito et al., 2009; Ellison-Wright and Bullmore, 2010; Haijma et al., 2013). For the SNPs under investigation in this study, only SNP rs1625579 in the *MIR137* gene has been associated with smaller hippocampal volumes in patients with schizophrenia (Lett et al., 2013). Therefore, we focused our investigations on total brain volume, grey matter, white matter, and hippocampal volume only.

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Given the unambiguous genetic epidemiological evidence for the involvement of these three genes in the risk of schizophrenia, we investigated whether allelic variation in these genes impacts on macroscopic brain structure in a cohort of 1300 healthy adults. We assessed single SNP as well as gene-wide effects on our volumes of interest. We also investigated the *joint* effect of these three genes on these brain volumes (given the regulatory effects of *MIR137* on *ZNF804A* and *TCF4* (Wright et al., 2013)). Additionally, using voxel-based morphometry (VBM), we studied whether risk SNPs rs1344706 in *ZNF804A*, rs9960767 in *TCF4*, and rs1625579 in *MIR137* were associated with variation in grey and white matter volume.

2. Methods

This study is part of the Brain Imaging Genetics (BIG) project which comprises healthy volunteer subjects, mostly university students, who participate in diverse imaging studies at the Donders Centre for Cognitive Neuroimaging (DCCN), Nijmegen, The Netherlands (Franke et al., 2010; Stein et al., 2012). At the time of this study, anatomical (T1-weighted) MRI scans and genetic data were available from 1300 self-reported healthy subjects, usually as part of their involvement in diverse smaller-scale studies at the DCCN. All had given their consent to participate in BIG. Demographic information about the cohort can be found in Table 1. The study was approved by the regional medical ethics committee (CMO Arnhem-Nijmegen).

Genetic analyses, including genotyping, genetic imputation and quality control were performed as described previously (Guadalupe et al., 2014). Three different genes, *MIR137*, *TCF4*, and *ZNF804A* and approximately 25 kilobase flanking regions were analysed. A total of 1211 SNPs were included in the analysis (168 for *MIR137*, 146 for *TCF4*, and 897 for *ZNF804A*).

Magnetic resonance imaging (MRI) data were acquired at the Donders Centre for Cognitive Neuroimaging at 1.5T and 3T Siemens MRI scanners. Data acquisition and analysis have been described previously (Franke et al., 2010; Cousijn et al., 2012).

Statistical analysis on the volumetric data was performed using the – linear command implemented in PLINK software V1.07 (http://pngu. mgh.harvard.edu/~purcell/plink/) (Purcell et al., 2007). The method of analysis we performed was analogous to the method reported by Bralten et al. (2011, 2013) and Cousijn et al. (2012). The analysis consisted of a SNP-by-SNP linear regression and the estimation of the effect of the complete gene. Additionally, we assessed the effect of the three genes combined. The SNP-by-SNP linear regression for association with brain volumes (GM, WM, TBV and hippocampal volume) was performed using sex, age, and TBV as covariates. The analysis of GM was adjusted by WM volume and vice-versa. Multiple testing correction was performed by running 10,000 max(T) permutation tests using the "mperm" command and obtaining an empirical *p*-value for each SNP. The association statistics of the observed and permuted data were saved using the "mperm-save-all" command and then added to create a Σstatistic per run for all SNPs at the same time (10,001 in total, one for the observed data and 10,000 for the permuted data). The empirical *p*-value was then estimated by the number of times the observed Σstatistic was bigger than the permuted Σstatistic divided by the total number of permutations (10,000). Results were considered significant at $p < 0.05$.

Additionally, VBM analyses were carried out for the schizophrenia risk SNPs rs1344706 in *ZNF804A*, rs9960767 in *TCF4*, and rs1625579 in *MIR137*. We also included in this analysis any other SNP showing significant association (empirical *p*-value corrected for multiple testing) with any of the volumes. A full-factorial ANCOVA with these SNPs as factor and participants' age, gender, TBV (where appropriate), and scan protocol as covariates was carried out. Statistics were corrected for nonstationarity and were applied at p(whole brain uncorrected) < .001 and subsequent cluster statistics at p(FWE) < .05. A Bonferroni correction was applied to correct for multiple comparisons.

3. Results

The gene-wide analysis of the individual genes as well as the three genes combined did not yield any significant results for association with TBV, GM volume, WM volume, or hippocampal volume (Table 2).

In the SNP-by-SNP analysis, one SNP in *MIR137*, rs9440302, was found to have a significant association with hippocampal volume (Supplementary Fig. 1), with an empirical *p*-value of 0.0166 (p_{emp} was estimated adjusting for 168 SNPs). Therefore, this SNP was also included in the VBM analysis). We looked specifically at the effects of SNPs rs1344706 in *ZNF804A*, rs9960767 in *TCF4*, and rs1625579 in *MIR137* on GM, WM, TBV and hippocampal volume but no significant effects were detected for these risk SNPs. The corrected *p*-values from the SNP-by-SNP analysis for these risk SNPs can be found in Supplementary Table 1. Corrected and uncorrected *p*-values for all studied SNPs can be found in Supplementary Table 2. When excluding left-handed subjects from our analyses, we found the same results.

Whole-brain VBM analyses revealed no effect of SNPs rs1344706 in *ZNF804A*, rs9960767 in *TCF4*, and rs1625579 in *MIR137* on GM or WM volumes. For SNP rs9440302 in *MIR137*, whole-brain analyses as well as a region of interest analysis within a hippocampal ROI (WFU pickatlas, Tzourio-Mazoyer et al., 2002) showed no effects.

4. Discussion

Here we studied the effects of schizophrenia risk genes *MIR137*, *TCF4*, and *ZNF804A* on macroscopic brain variation in healthy volunteers. No gene-wide effects or effects of specific risk SNPs were found on grey matter, white matter, total brain volume, and hippocampal volume. Additionally, when looking at the combined effect of the three risk genes, no effects could be detected. Given the large sample size used in this study (power to detect an effect size $\geq 5\%$ with $n = 1300$; a SNP MAF = 19%; $D' = 0.5$ with the causal variant; $\alpha = 0.05$ is 80%), these findings provide convincing evidence that SNPs in these genes do not impact on macroscopic brain structure in young healthy volunteers.

This is the first study, to our knowledge, assessing the effects of SNPs in *TCF4* on TBV, GM, WM, and hippocampal volume. We also extended and replicated our earlier finding that variation in *ZNF804A* does not affect these parameters (increasing our sample size 46%: $n = 892$ vs $n = 1300$ see Cousijn et al., 2012; also Bergmann et al., 2013; Sprooten et al., 2012). Regarding *MIR137*, SNP rs1625579 has been previously associated with smaller hippocampal volumes in patients with schizophrenia (Lett et al., 2013), but we did not observe this effect

Table 1
Demographic information, volumes in ml.

Total *N*	1300
Mean age (years)	22.9 (3.8)
Sex F/M	57.4/42.6%
Handedness (R)	93.6%
Mean TBV (SD)	1257.8 (125.5)
Mean GM volume (SD)	775.1 (81.4)
Mean WM volume (SD)	482.7 (62.1)
Mean Hippocampus volume (SD)	4.0 (0.4)

Table 2
Gene-wide *p*-values for the three genes separately and combined.

	TBV	GM	WM	Hippocampus
ZNF804A	0.4666	0.7560	0.9986	0.3868
MIR137	0.9271	0.8644	0.9971	0.1552
TCF4	0.9419	0.3158	0.4460	0.7306
All three genes combined	0.5543	0.8287	0.9089	0.3502

in our sample of healthy controls. We did observe an association between SNP rs9440302 within *MIR137* and hippocampal volume, with the A allele being associated with larger hippocampal volumes. However, we could not replicate this finding using VBM, so future studies are needed to determine whether this is a robust association. Moreover, this SNP has not been associated with risk for schizophrenia and we found the probability of an association between this SNP and risk SNP rs1625579 to be very low ($r^2 = 0.203$), indicating that they probably work independently.

Genetic neuroimaging studies in healthy volunteers provide important information about potential pathways between genetic variation and schizophrenia, by investigating the effects of risk genes on brain structure or brain function unconfounded by effects of the illness or its treatment. In this study, we have shown that genetic variation in schizophrenia risk genes *MIR137*, *TCF4*, and *ZNF804A* does not lead to alterations in TBV, GM, WM, or hippocampal brain volumes as measured with structural MRI in healthy young adults. Whilst we cannot rule out that effects might be found using different imaging methods such as diffusion tensor imaging, or that there might be effects in clinical populations or neurodevelopmental effects in childhood, it seems more likely that the pathophysiological correlates of allelic variation in these genes occur in other ways, such as via modulation of brain function or functional connectivity.

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Contributors

HC, PJH, and AAV designed the study. GF, SEF, BF, MZ, and AAV made the data available. ME and AAV carried out the analyses. HC wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.08.007.

References

Bergmann, O., Haukvik, U.K., Brown, A.A., Rimol, L.M., Hartberg, C.B., Athanasiu, L., Melle, I., Djurovic, S., Andreassen, O.A., Dale, A.M., Agartz, I., 2013. ZNF804A and cortical thickness in schizophrenia and bipolar disorder. Psychiatry Res. 212 (2), 154–157.

Bralten, J., Arias-Vasquez, A., Makkinje, R., Veltman, J.A., Brunner, H.G., Fernandez, G., Rijpkema, M., Franke, B., 2011. Association of Alzheimer's gene SORL1 with hippocampal volume in young, healthy adults. Am. J. Psychiatry 168 (10), 1083–1089.

Bralten, J., Franke, B., Waldman, I., Rommelse, N., Hartman, C., Asherson, P., Banaschewski, T., Ebstein, R.P., Gill, M., Miranda, A., Oades, R.D., Roeyers, H., Rothenberger, A., Sergeant, J., Oosterlaan, J., Sonuga-Barke, E., Steinhausen, H.C., Faraone, S.V., Buitelaar, J.K., Arias-Vasquez, A., 2013. Candidate genetic pathways for attention-deficit/hyperactivity disorder (ADHD) show association to hyperactive/impulsive symptoms in children with ADHD. J. Am. Acad. Child Adolesc. Psychiatry 52 (11), 1204–1212.

Cousijn, H., Rijpkema, M., Harteveld, A., Harrison, P.J., Fernandez, G., Franke, B., Arias-Vasquez, A., 2012. Schizophrenia risk gene ZNF804A does not influence macroscopic brain structure: an MRI study in 892 volunteers. Mol. Psychiatry 17 (12), 1155–1157.

Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia. A meta-analysis. Schizophr. Res. 117 (1), 1–12.

Esslinger, C., Walter, H., Kirsch, P., Erk, S., Schnell, K., Arnold, C., Haddad, L., Mier, D., Opitz von Boberfeld, C., Raab, K., Witt, S.H., Rietschel, M., Cichon, S., Meyer-Lindenberg, A., 2009. Neural mechanisms of a genome-wide supported psychosis variant. Science 324 (5927), 605.

Fornito, A., Yucel, M., Patti, J., Wood, S.J., Pantelis, C., 2009. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. Schizophr. Res. 108, 104–113.

Franke, B., Vasquez, A.A., Veltman, J.A., Brunner, H.G., Rijpkema, M., Fernandez, G., 2010. Genetic variation in CACNA1C, a gene associated with bipolar disorder, influences brainstem rather than gray matter volume in healthy individuals. Biol. Psychiatry 68 (6), 586–588.

Guadalupe, et al., 2014. Measurement and genetics of human subcortical and hippocampal asymmetries in large datasets. Hum. Brain Mapp. http://dx.doi.org/10.1002/hbm.22401.

Guella, I., Sequeira, A., Rollins, B., Morgan, L., Torri, F., van Erp, T.G., Myers, R.M., Barchas, J.D., Schatzberg, A.F., Watson, S.J., Akil, H., Bunney, W.E., Potkin, S.G., Macciardi, F., Vawter, M.P., 2013. Analysis of miR-137 expression and rs1625579 in dorsolateral prefrontal cortex. J. Psychiatr. Res. 47 (9), 1215–1221.

Haijma, S.V., Van Haren, N., Cahn, W., Koolschijn, P.C.M.P., Hulshoff Pol, H.E., Kahn, R.S., 2013. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr. Bull. 39 (5), 1129–1138.

Hill, M.J., Bray, N.J., 2012. Evidence that schizophrenia risk variation in the ZNF804A gene exerts its effects during fetal brain development. Am. J. Psychiatry 169 (12), 1301–1308.

Kim, A.H., Parker, E.K., Williamson, V., McMichael, G.O., Fanous, A.H., Vladimirov, V.I., 2012. Experimental validation of candidate schizophrenia gene ZNF804A as target for hsa-miR-137. Schizophr. Res. 141 (1), 60–64.

Kwon, E., Wang, W., Tsai, L.H., 2013. Validation of schizophrenia-associated genes CSMD1, C10orf26, CACNA1C and TCF4 as miR-137 targets. Mol. Psychiatry 18 (1), 11–12.

Lett, T.A., Chakravarty, M.M., Felsky, D., Brandl, E.J., Tiwari, A.K., Goncalves, V.F., Rajji, T.K., Daskalakis, Z.J., Meltzer, H.Y., Lieberman, J.A., Lerch, J.P., Mulsant, B.H., Kennedy, J.L., Voineskos, A.N., 2013. The genome-wide supported microRNA-137 variant predicts phenotypic heterogeneity within schizophrenia. Mol. Psychiatry 18 (4), 443–450.

O'Donovan, M.C., Craddock, N., Norton, N., Williams, H., Peirce, T., Moskvina, V., Nikolov, I., Hamshere, M., Carroll, L., Georgieva, L., Dwyer, S., Holmans, P., Marchini, J.L., Spencer, C.C., Howie, B., Leung, H.T., Hartmann, A.M., Moller, H.J., Morris, D.W., Shi, Y., Feng, G., Hoffmann, P., Propping, P., Vasilescu, C., Maier, W., Rietschel, M., Zammit, S., Schumacher, J., Quinn, E.M., Schulze, T.G., Williams, N.M., Giegling, I., Iwata, N., Ikeda, M., Darvasi, A., Shifman, S., He, L., Duan, J., Sanders, A.R., Levinson, D.F., Gejman, P.V., Cichon, S., Nothen, M.M., Gill, M., Corvin, A., Rujescu, D., Kirov, G., Owen, M.J., Buccola, N.G., Mowry, B.J., Freedman, R., Amin, F., Black, D.W., Silverman, J.M., Byerley, W.F., Cloninger, C.R., 2008. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat. Genet. 40 (9), 1053–1055.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81 (3), 559–575.

Quednow, B.B., Ettinger, U., Mossner, R., Rujescu, D., Giegling, I., Collier, D.A., Schmechtig, A., Kuhn, K.U., Moller, H.J., Maier, W., Wagner, M., Kumari, V., 2011. The schizophrenia risk allele C of the TCF4 rs9960767 polymorphism disrupts sensorimotor gating in schizophrenia spectrum and healthy volunteers. J. Neurosci. 31 (18), 6684–6691.

Rasetti, R., Sambataro, F., Chen, Q., Callicott, J.H., Mattay, V.S., Weinberger, D.R., 2011. Altered cortical network dynamics: a potential intermediate phenotype for schizophrenia and association with ZNF804A. Arch. Gen. Psychiatry 68 (12), 1207–1217.

Ripke, S.S.A., Kendler, K.S., Levinson, D.F., Sklar, P., Holmans, P.A., Lin, D.Y., Duan, J., Ophoff, R.A., Andreassen, O.A., Scolnick, E., Cichon, S., St Clair, D., Corvin, A., Gurling, H., Werge, T., Rujescu, D., Blackwood, D.H., Pato, C.N., Malhotra, A.K., Purcell, S., Dudbridge, F., Neale, B.M., Rossin, L., Visscher, P.M., Posthuma, D., Ruderfer, D.M., Fanous, A., Stefansson, H., Steinberg, S., Mowry, B.J., Golimbet, V., De Hert, M., Jönsson, E.G., Bitter, I., Pietiläinen, O.P., Collier, D.A., Tosato, S., Agartz, I., Albus, M., Alexander, M., Amdur, R.L., Amin, F., Bass, N., Bergen, S.E., Black, D.W., Børglum, A.D., Brown, M.A., Bruggeman, R., Buccola, N.G., Byerley, W.F., Cahn, W., Cantor, R. M., Carr, V.J., Catts, S.V., Choudhury, K., Cloninger, C.R., Cormican, P., Craddock, N., Danoy, P.A., Datta, S., de Hann, L., Demontis, D., Dikeos, D., Djurovic, S., Donnelly, P., Donohoe, G., Duong, L., Dwyer, S., Fink-Jensen, A., Freedman, R., Freimer, N.B., Friedl, M., Georgieva, L., Giegling, I., Gill, M., Glenthøj, B., Godard, S., Hamshere, M., Hansen, M., Hansen, T., Hartmann, A.M., Henskens, F.A., Hougaard, D.M., Hultman, C.M., Ingason, A., Jablensky, A.V., Jakobsen, K.D., Jay, M., Jürgens, G., Kahn, R.S., Keller, M.C., Kenis, G., Kenny, E., Kim, Y., Kirov, G.K., Konnerth, H., Konte, B., Krabbendam, L., Krausucki, R., Lasseter, V.K., Laurent, C., Lawrence, J., Lencz, T., Lerer, F.B., Liang, K.Y., Lichtenstein, P., Lieberman, J.A., Linszen, D.H., Lönnqvist, J., Loughland, C.M., Maclean, A.W., Maher, B.S., Maier, W., Mallet, J., Malloy, P., Mattheisen, M., Mattingsdal, M., McGhee, K.A., McGrath, J.J., McIntosh, A., McLean, D.E., McQuillin, A., Melle, I., Michie, P.T., Milanova, V., Morris, D.W., Mors, O., Mortensen, P.B., Moskvina, V., Muglia, P., Myin-Germeys, I., Nertney, D.A., Nestadt, G., Nielsen, J., Nikolov, I., Nordentroft, M., Norton, N., Nöthen, M.M., O'Dushlaine, C. T., Olincy, A., Olsen, L., O'Neill, F.A., Ørntoft, T., Owen, M.J., Pantelis, C., Papadimitriou, G., Pato, M.T., Peltonen, L., Pickard, B., Pimm, J., Pulver, A.E., Puri, V., Quested, D., Quinn, E.M., Rasmussen, H.B., Réthelyi, J.M., Ribble, R., Rietschel, M., Riley, B.P., Ruggeri, M., Schall, U., Schulze, T.G., Schwab, S.G., Scott, R.J., Shi, J., Sigurdsson, E., Silverman, J.M., Spencer, C.C., Stefansson, K., Strange, A., Strengman, E., Stroup, T.S., Suvisaari, J., Tereniuis, L., Thirumalai, S., Thygesen, J.H., Timm, S., Toncheva, D., van den Oord, E., van Os, J., van Winkel, R., Veldink, J., Walsh, D., Wang, A.G., Wiersma, D., Wildenauer, D.B., Williams, H.J., Williams, N.M., Wormley, B., Zammit, S., Sullivan, P.F., O'Donovan, M.C., Daly, M.J., Gejman, P.V., 2011. Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 43 (10), 969–976.

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kähler, A.K., Akterin, S., Bergen, S.E., Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K., Sanchez, N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D., Bulik-Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet, V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P., Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson, E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage, M., Walters, J.T., Multicenter Genetic Studies of Schizophrenia Consortium, Levinson, D.F., Gejman, P.V., Kendler, K.S., Laurent, C., Mowry, B.J., O'Donovan, M.C., Owen, M.J., Pulver, A.E., Riley, B.P., Schwab, S.G., Wildenauer, D.B., Dudbridge, F., Holmans, P., Shi, J., Albus, M., Alexander, M., Campion, D., Cohen, D., Dikeos, D., Duan, J., Eichhammer, P., Godard, S., Hansen, M., Lerer, F.B., Liang, K.Y., Maier, W., Mallet, J., Nertney, D.A., Nestadt, G., Norton, N., O'Neill, F.A., Papadimitriou, G.N., Ribble, R., Sanders, A.R., Silverman, J.M., Walsh, D., Williams, N. M., Wormley, B., Endophenotypes International Consortium, Psychosis, Arranz, M.J., Bakker, S., Bender, S., Bramon, E., Collier, D., Crespo-Facorro, B., Hall, J., Iyegbe, C., Jablensky, A., Kahn, R.S., Kalaydjieva, L., Lawrie, S., Lewis, C.M., Lin, K., Linszen, D.H., Mata, I., McIntosh, A., Murray, R.M., Ophoff, R.A., Powell, J., Rujescu, D., Van Os, J., Walshe, M., Weisbrod, M., Wiersma, D., Wellcome Trust Case Control Consortium 2, Donnelly, P., Barroso, I., Blackwell, J.M., Bramon, E., Brown, M.A., Casas, J.P., Corvin, A.P., Deloukas, P., Duncanson, A., Jankowski, J., Markus, H.S., Mathew, C.G., Palmer, C.N., Plomin, R., Rautanen, A., Sawcer, S.J., Trembath, R.C., Viswanathan, A.C., Wood, N.W., Spencer, C.C., Band, G., Bellenguez, C., Freeman, C., Hellenthal, G., Giannoulatou, E., Pirinen, M., Pearson, R.D., Strange, A., Su, Z., Vukcevic, D., Donnelly, P., Langford, C., Hunt, S.E., Edkins, S., Gwilliam, R., Blackburn, H., Bumpstead, S.J., Dronov, S., Gillman, M., Gray, E., Hammond, N., Jayakumar, A., McCann, O.T., Liddle, J., Potter, S.C., Ravindrarajah, R., Ricketts, M., Tashakkori-Ghanbaria, A., Waller, M.J., Weston, P., Widaa, S., Whittaker, P., Barroso, I., Deloukas, P., Mathew, C.G., Blackwell, J.M., Brown, M.A., Corvin, A.P., McCarthy, M.I., Spencer, C.C., Bramon, E., Corvin, A.P., O'Donovan, M.C., Stefansson, K., Scolnick, E., Purcell, S., McCarroll, S.A., Sklar, P., Hultman, C.M., Sullivan, P.F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45 (10), 1150–1159.

Sprooten, E., McIntosh, A.M., Lawrie, S.M., Hall, J., Sussmann, J.E., Dahmen, N., Konrad, A., Bastin, M.E., Winterer, G., 2012. An investigation of a genomewide supported psychosis variant in ZNF804A and white matter integrity in the human brain. Magn. Reson. Imaging 30 (10), 1373–1380.

Stefansson, H., Ophoff, R.A., Steinberg, S., Andreassen, O.A., Cichon, S., Rujescu, D., Werge, T., Pietilainen, O.P., Mors, O., Mortensen, P.B., Sigurdsson, E., Gustafsson, O., Nyegaard, M., Tuulio-Henriksson, A., Ingason, A., Hansen, T., Suvisaari, J., Paunio, T., Borglum, A.D., Hartmann, A., Fink-Jensen, A., Nordentoft, M., Hougaard, D., Norgaard-Pedersen, B., Bottcher, Y., Olesen, J., Breuer, R., Moller, H.J., Giegling, I., Rasmussen, H. B., Timm, S., Mattheisen, M., Bitter, I., Rethelyi, J.M., Magnusdottir, B.B., Sigmundsson, T., Olason, P., Masson, G., Gulcher, J.R., Haraldsson, M., Fossdal, R., Thorgeirsson, T.E., Thorsteinsdottir, U., Ruggeri, M., Tosato, S., Franke, B., Strengman, E., Kiemeney, L.A., Melle, I., Djurovic, S., Abramova, L., Kaleda, V., Sanjuan, J., de Frutos, R., Bramon, E., Vassos, E., Fraser, G., Ettinger, U., Picchioni, M., Walker, N., Toulopoulou, T., Need, A.C., Ge, D., Yoon, J.L., Shianna, K.V., Freimer, N.B., Cantor, R.M., Murray, R., Kong, A., Golimbet, V., Carracedo, A., Arango, C., Costas, J., Jonsson, E.G., Terenius, L., Agartz, I., Petursson, H., Nothen, M.M., Rietschel, M., Matthews, P.M., Muglia, P., Peltonen, L, St Clair, D., Goldstein, D.B., Stefansson, K., Collier, D.A., 2009. Common variants conferring risk of schizophrenia. Nature 460 (7256), 744–747.

Stein, J.L., Medland, S.E., Vasquez, A.A., Hibar, D.P., Senstad, R.E., Winkler, A.M., Toro, R., Appel, K., Bartecek, R., Bergmann, O., Bernard, M., Brown, A.A., Cannon, D.M., Chakravarty, M.M., Christoforou, A., Domin, M., Grimm, O., Hollinshead, M., Holmes, A.J., Homuth, G., Hottenga, J.J., Langan, C., Lopez, L.M., Hansell, N.K., Hwang, K.S., Kim, S., Laje, G., Lee, P.H., Liu, X., Loth, E., Lourdusamy, A., Mattingsdal, M., Mohnke, S., Maniega, S.M., Nho, K., Nugent, A.C., O'Brien, C., Papmeyer, M., Putz, B., Ramasamy, A., Rasmussen, J., Rijpkema, M., Risacher, S.L., Roddey, J.C., Rose, E.J., Ryten, M., Shen, L., Sprooten, E., Strengman, E., Teumer, A., Trabzuni, D., Turner, J., van Eijk, K., van Erp, T.G., van Tol, M.J., Wittfeld, K., Wolf, C., Woudstra, S., Aleman, A., Alhusaini, S., Almasy, L., Binder, E.B., Brohawn, D.G., Cantor, R.M., Carless, M.A., Corvin, A., Czisch, M., Curran, J.E., Davies, G., de Almeida, M.A., Delanty, N., Depondt, C., Duggirala, R.,

Dyer, T.D., Erk, S., Fagerness, J., Fox, P.T., Freimer, N.B., Gill, M., Goring, H.H., Hagler, D. J., Hoehn, D., Holsboer, F., Hoogman, M., Hosten, N., Jahanshad, N., Johnson, M.P., Kasperaviciute, D., Kent Jr., J.W., Kochunov, P., Lancaster, J.L., Lawrie, S.M., Liewald, D. C., Mandl, R., Matarin, M., Mattheisen, M., Meisenzahl, E., Melle, I., Moses, E.K., Muhleisen, T.W., Nauck, M., Nothen, M.M., Olvera, R.L., Pandolfo, M., Pike, G.B., Puls, R., Reinvang, I., Renteria, M.E., Rietschel, M., Roffman, J.L., Royle, N.A., Rujescu, D., Savitz, J., Schnack, H.G., Schnell, K., Seiferth, N., Smith, C., Steen, V.M., Valdes Hernandez, M.C., Van den Heuvel, M., van der Wee, N.J., Van Haren, N.E., Veltman, J.A., Volzke, H., Walker, R., Westlye, L.T., Whelan, C.D., Agartz, I., Boomsma, D.I., Cavalleri, G.L., Dale, A.M., Djurovic, S., Drevets, W.C., Hagoort, P., Hall, J., Heinz, A., Jack Jr., C.R., Foroud, T.M., Le Hellard, S., Macciardi, F., Montgomery, G.W., Poline, J.B., Porteous, D.J., Sisodiya, S.M., Starr, J.M., Sussmann, J., Toga, A.W., Veltman, D.J., Walter, H., Weiner, M.W., Bis, J.C., Ikram, M.A., Smith, A.V., Gudnason, V., Tzourio, C., Vernooij, M.W., Launer, L.J., DeCarli, C., Seshadri, S., Andreassen, O.A., Apostolova, L.G., Bastin, M.E., Blangero, J., Brunner, H.G., Buckner, R.L., Cichon, S., Coppola, G., de Zubicaray, G.I., Deary, I.J., Donohoe, G., de Geus, E.J., Espeseth, T., Fernandez, G., Glahn, D.C., Grabe, H.J., Hardy, J., Hulshoff Pol, H.E., Jenkinson, M., Kahn, R.S., McDonald, C., McIntosh, A.M., McMahon, F.J., McMahon, K.L., Meyer-Lindenberg, A., Morris, D.W., Muller-Myhsok, B., Nichols, T.E., Ophoff, R.A., Paus, T., Pausova, Z., Penninx, B.W., Potkin, S.G., Samann, P.G., Saykin, A.J., Schumann, G., Smoller, J.W., Wardlaw, J.M., Weale, M.E., Martin, N.G., Franke, B., Wright, M.J., Thompson, P.M., 2012. Identification of common variants associated with human hippocampal and intracranial volumes. Nat. Genet. 44 (5), 552–561.

Steinberg, S., de Jong, S., Andreassen, O.A., Werge, T., Borglum, A.D., Mors, O., Mortensen, P.B., Gustafsson, O., Costas, J., Pietilainen, O.P., Demontis, D., Papiol, S., Huttenlocher, J., Mattheisen, M., Breuer, R., Vassos, E., Giegling, I., Fraser, G., Walker, N., Tuulio-Henriksson, A., Suvisaari, J., Lonnqvist, J., Paunio, T., Agartz, I., Melle, I., Djurovic, S., Strengman, E., Jurgens, G., Glenthoj, B., Terenius, L., Hougaard, D.M., Orntoft, T., Wiuf, C., Didriksen, M., Hollegaard, M.V., Nordentoft, M., van Winkel, R., Kenis, G., Abramova, L., Kaleda, V., Arrojo, M., Sanjuan, J., Arango, C., Sperling, S., Rossner, M., Ribolsi, M., Magni, V., Siracusano, A., Christiansen, C., Kiemeney, L.A., Veldink, J., van den Berg, L., Ingason, A., Muglia, P., Murray, R., Nothen, M.M., Sigurdsson, E., Petursson, H., Thorsteinsdottir, U., Kong, A., Rubino, I.A., De Hert, M., Rethelyi, J.M., Bitter, I., Jonsson, E.G., Golimbet, V., Carracedo, A., Ehrenreich, H., Craddock, N., Owen, M.J., O'Donovan, M.C., Ruggeri, M., Tosato, S., Peltonen, L., Ophoff, R.A., Collier, D.A., St Clair, D., Rietschel, M., Cichon, S., Stefansson, H., Rujescu, D., Stefansson, K., 2011. Common variants at VRK2 and TCF4 conferring risk of schizophrenia. Hum. Mol. Genet. 20 (20), 4076–4081.

Tao, R., Cousijn, H., Jaffe, A.E., Burnet, P.W.J., Edwards, F., Eastwood, S.L., Shin, J.H., Lane, T.A., Walker, M.A., Maher, B.J., Weinberger, D.R., Harrison, P.J., Hyde, T.M., Kleinman, J.E., 2014. Expression of ZNF804A in human brain and alterations in schizophrenia, bipolar disorder and major depressive disorder. A novel transcript fetally regulated by the psychosis risk variant rs1344706. JAMA Psychiatry http://dx.doi.org/10.1001/jamapsychiatry.2014.1079 (AOL 6 August).

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289.

van Erp, T.G., Guella, I., Vawter, M.P., Turner, J., Brown, G.G., McCarthy, G., Greve, D.N., Glover, G.H., Calhoun, V.D., Lim, K.O., Bustillo, J.R., Belger, A., Ford, J.M., Mathalon, D. H., Diaz, M., Preda, A., Nguyen, D., Macciardi, F., Potkin, S.G., 2014. Schizophrenia miR-137 locus risk genotype is associated with dorsolateral prefrontal cortex hyperactivation. Biol. Psychiatry 75 (5), 398–405.

Williams, H.J., Norton, N., Dwyer, S., Moskvina, V., Nikolov, I., Carroll, L., Georgieva, L., Williams, N.M., Morris, D.W., Quinn, E.M., Giegling, I., Ikeda, M., Wood, J., Lencz, T., Hultman, C., Lichtenstein, P., Thiselton, D., Maher, B.S., Malhotra, A.K., Riley, B., Kendler, K.S., Gill, M., Sullivan, P., Sklar, P., Purcell, S., Nimgaonkar, V.L., Kirov, G., Holmans, P., Corvin, A., Rujescu, D., Craddock, N., Owen, M.J., O'Donovan, M.C., 2011. Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. Mol. Psychiatry 16 (4), 429–441.

Wright, C., Turner, J.A., Calhoun, V.D., Perrone-Bizzozero, N., 2013. Potential impact of miR-137 and its targets in schizophrenia. Front. Genet. 4, 58.