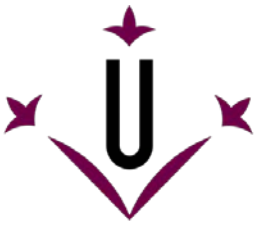

TITLE:

The interaction between the ZNF804A gene and cannabis use on the risk of T psychosis in a non-clinical sample

RUNNING TITLE: *ZNF804A* and cannabis use interaction on schizotypy

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ABSTRACT

Objective. The *ZNF804A* gene and cannabis use are risk factors for psychosis, both of which have also been associated with schizotypic traits. This study aimed to test whether *ZNF804A* (rs1344706) modulates the relation between cannabis use and schizotypy levels in a general population sample.

Method. The sample consisted of 389 Spanish non-clinical subjects (43% males, mean age=21.1(2.19)). Schizotypy was evaluated with the three factors of the Schizotypal Personality Questionnaire-Brief (SPQ-B): Cognitive-Perceptual (CP), Interpersonal (I) and Disorganized (D). Subjects were classified as cannabis users or non-users. Multiple linear regressions were conducted to test the effect of genetic and environment factors and their interaction on SPQ-B scores. Sex and anxiety scores (evaluated with SCL) were included as covariates.

Results. The analyses showed a significant linear relationship between the *ZNF804A* and SPQ-I: homozygotes AA showed higher scores (p=0.001). An interaction between cannabis use and rs1344706 on SPQ-CP was observed: among individuals AA, cannabis users presented higher scores than non-users, while among individuals CC, cannabis users presented lower scores compared to non-users (p=0.005).

Conclusion. These results add evidence on that the *ZNF804A* modulates schizotypy and suggest that schizotypy levels are influenced by an interaction between the exposure to cannabis and the *ZNF804A* genotype.

Keywords: *ZNF804A*, cannabis, psychosis, schizotypy, gene-environment interaction

Significant outcomes:
- Our study supports the notion that the gene *ZNF804A* has an effect on a psychosis vulnerability marker such as schizotypy in healthy individuals.
- The association between cannabis use and schizotypy is modulated by the *ZNF804A* gene.

Limitations:
- Cross-sectional design and self-referred measures of schizotypy and cannabis use may constitute an inherent source of bias.
- Non-existent previous studies testing ZNF804Axcannabis interaction, the sample size and the non-availability of a replication sample make necessary further studies to confirm the results.

1. Introduction

Psychotic disorders, including schizophrenia (SZ), are among the most severe and impairing conditions, with lifetime prevalence around 3% (1). Psychotic disorders are multifactorial disorders determined by genetic, environmental risk factors and the interaction between these factors (2,3).

As regards to genetic factors, twin and family studies have estimated that the heritability of SZ is between 64% and 81% (4,5). Moreover, genome-wide association studies (GWAS) have reported a substantial polygenic component that contributes to the risk for these disorders (6,7). These studies have allowed identifying several new candidate gens for SZ and one of the most relevant is the *ZNF804A* gene. Subsequently, this association has been further explored and replicated, which has enhanced the understanding of its involvement in SZ (7–11).

ZNF804A (2q32.1) is expressed throughout the foetal and adult human brain, especially in the medial temporal lobe and brain cortices (12,13). Despite the exact functions of ZNF804A still remains unclear, proteins with zinc finger domains are known to play a variety of roles, including binding to DNA, transcriptional regulation, gene expression and DNA–protein interactions (11,14,15). In this regard, molecular and bioinformatic studies suggest that ZNF804A likely has pivotal roles in cell physiology by its involvement in neurodevelopment regulation (8), synaptic plasticity (16) and also with brain structure and function (12,17). More specifically, *ZNF804A* has been reported to be involved in early neurite outgrowth and in regulating spine maintenance and the ability of neurons to respond to activity-dependent stimuli (16).

As a putative transcription factor, *ZNF804A* has a large number of potential targets both in the developing foetus and the adult brain, including genes that are involved in neuronal migration, neurite outgrowth and synaptic transmission (18). Interestingly,

some of the genes regulated by *ZNF804A*, such as the Dopamine Receptor D2 (*DRD2*) or Catechol-O-Methyltransferase (*COMT*), are directly involved in dopaminergic transmission and have been associated with schizophrenia (19). Therefore, current evidence suggests that dysregulation of ZNF804A could contribute to the altered neuronal and synaptic structures that are associated with psychotic and other neurodevelopmental disorders (20).

Within *ZNF804A* gene, the rs1344706 single-nucleotide polymorphism (SNP) has been repeatedly associated with psychosis (6,9,10,21) and the A variant has been identified with an increased risk for these disorders. In addition, two independent studies have shown that the risk allele of rs1344706 is associated with reduced expression of *ZNF804A* RNA, both in brain tissue of foetus and in individuals with schizophrenia, bipolar disorder or major depression disorder(12,13).

Two studies have also associated the rs1344706 with a vulnerability marker for psychosis, such as schizotypy (22,23). Schizotypy is a set of personality traits encompassing behaviours, cognitions and emotions that resemble the signs and symptoms of psychotic disorders in the general population. Schizotypy encompasses perceptual impairments and unusual views or ideas, a loss of normal emotional, physical and social functions and odd behaviour and speech, among other traits(24). Due to the clinical resemblance between schizotypy and psychotic symptoms it has been suggested that overlapping aetiological factors might underlie the two phenotypes (25). Therefore the study of the genetic underpinnings of vulnerability traits in non-clinical samples constitutes a useful framework within which to investigate aetiological factors of psychotic disorders (26).

One of the environmental risk factors most strongly implicated with the emergence of psychotic symptoms and disorders is the use of cannabis (27,28). Cannabis can induce psychotic symptoms through the activation of the endocannabinoid system, which is an

endogenous system that modulates dopamine neurotransmission (29). Interestingly, cannabis use has also been associated with schizotypy, being the positive and the disorganized dimensions of schizotypy the most strongly related (30–33). However, only a relatively small proportion of cannabis users develop psychotic symptoms, which means that other factors might explain the interaction between cannabis and psychosis risk (34). In this context, epidemiological studies have found that the risk for psychosis associated with cannabis use is increased in individuals with genetic vulnerability to psychosis (positive family history) (35). Similarly, familial correlation of schizotypal scores varies depending on the exposure to cannabis, which confirms the importance of gene-cannabis interaction in the expression of psychosis vulnerability markers (36,37).

As regard to gene-cannabis interaction, some studies have shown the interaction between dopaminergic neurotransmission related genes (*COMT* and *AKT1*) and cannabis use on psychosis risk (35). Taking into consideration these previous studies, and the regulatory roles of *ZNF804A*both neurodevelopmental processes and gene expression, it is therefore of interest to study the interaction between *ZNF804A* and cannabis use in order to increase the knowledge of the underlying mechanism by which cannabis increases the risk for psychosis. Despite that both *ZNF804A* gene and cannabis use have been independently described as genetic and environmental risk factors not only for psychosis but also for a psychotic vulnerability marker such as schizotypy, there are no studies assessing the GxE between *ZNF804A* gene and the cannabis use in psychosis.

Therefore, this study aimed to investigate the impact of cannabis use on schizotypal personality traits conditional to the genetic variability at *ZNF804A*gene in a general population sample. We hypothesized that the SNP rs1344706 within the *ZNF804A*gene would modulate the relationship between a well known environmental risk factor for psychotic disorders such as cannabis and the schizotypy levels in adult healthy subjects.

2. Method

2.1. Sample

The sample consisted of 389 subjects from the Spanish general population who were recruited in 2004-05 at the campus of the Jaume I University in Castelló (Spain).

Exclusion criteria were the presence of any major medical illness affecting brain function, neurological conditions, and personal history of head injury or psychiatric medical treatment. These areas were screened by trained psychologists by using a short interview designed for this study that included selected items of psychiatric diagnosis structured scales such as Structured Clinical Interview for DSM-IV (SCID-I) (38) and Familiar Interview for Genetic Studies (FIGS) (39). Specific questions about psychiatric assistance, psychotropic medication, hospital admissions and suicide attempts were asked to the participants.

Ethical approval was obtained from local research ethics committees. All participants provided written consent after being informed about the study procedures and implications. All procedures were carried out according to the Declaration of Helsinki.

2.2. Measures

The schizotypal personality was measured with Schizotypal Personality Questionnaire-Brief (SPQ-B) (40). The SPQ-B consists of 22-items self-report scale and comprises three identifiable factors (cognitive-perceptual (CP), interpersonal (I) and disorganized (D)). The CP and the I factors included 8 items each one and the D factor 6 items, and the final score of each factor was calculated as the sum of all the items of each factor. These factors include the evaluation of the presence of odd ideas, paranoia, lack of close personal relationship, suspiciousness and odd behaviour and speech. The participants

were screened for their anxious symptomatology by means of the 23-item scale of the revised version of the Symptom Check List, SCL-90-R (41). Clinical information was available for 100% of individuals.

Life-time cannabis use was assessed with one question regarding the frequency of consumption “never”, “sometimes”, “monthly”, “weekly” or “daily”. This variable was then dichotomized in: cannabis use (daily, weekly, and monthly) or non-cannabis use (sometimes or never). This information was available for 98.9% of individuals.
Similarly, participants were asked about the use of other illicit drugs (i.e. amphetamine-type stimulants, cocaine, heroin and other opioids, or ecstasy) and were classified as other drugs users (daily, weekly, and monthly) or other drugs non-users (occasionally or never).

2.3. Molecular analyses

Genomic DNA from each individual was extracted from buccal mucosa samples by means of a cotton swab using the BuccalAmp DNA (Epicentre® Biotechnologies, Madison, WI). The SNP (rs1344706) at*ZNF804A* gene was determined using Applied Biosystems TaqMan 5’ exonuclease assays. Polymerase chain reaction plates were read on ABI PISM 7900HT instrument with SDS 2.4 software (Applied Biosystems). The genotyping call rate for the SNP was 100%.

2.4. Statistical analyses

All data were processed using PASW statistics (SPSS Inc., Chicago Illinois, USA) and Stata v. 14 (StataCorp, 2013).

The Student's t test and ANOVA test were used to compare the means of continuous variables between two or more groups, respectively. Chi-squared test were performed to analyze the distribution of qualitative variables between groups.

Multiple linear regressions were conducted to test the effect of genetic and environment factors and their interaction on SPQ-B scores. First, the main effect of the independent variables (rs1344706 and cannabis use) was tested in the same model on each SPQ dimension (SPQ-CP, SPQ-I, SPQ-D). Second, the interaction between rs1344706 and cannabis use on each SPQ-dimension was analyzed. Sex, SCL anxiety scores and the use of other drugs were included as covariates.

The presence of Hardy-Weinberg equilibrium was examined using the chi-squared test with PLINK v1.07 (42).

Considering that three models were tested (effect of cannabis and genotype on the three SPQ dimensions), significant p-value threshold was established at 0.017 (0.05/3).

3. Results

3.1 Sample description

Participants (n=389) were university students (43% males) with a mean age at interview of 21.11 years (sd=2.19). The SPQ-Band SCL-anxiety mean scores (sd) were as follows: SPQ-CP 1.57(1.49), SPQ-I 2.76(2.12), SPQ-D 1.15(1.23) and SCL-A 4.20(4.99).

The 29% of individuals were classified as cannabis users and 12% of individuals were classified as other drugs users.

The genotypic frequencies were in Hardy-Weinberg equilibrium and allelic frequencies were similar to those described for European population in 1000 Genomes Project (MAF=38%). The genotypic frequencies were as follows: 31.2% AA, 47.0% AC and 21.8% CC.

There were no statistically significant differences between cannabis users and non-users on age, genotype, SCL scores and the SPQ-CP and SPQ-I. However, there were significant differences on sex (60% of the cannabis non-users were females (χ^2=5.8 p=0.016)) and SPQ-D (cannabis users had higher SPQ-D scores than non-users (t=-2.38 p=0.017 R2=0.21)).

3.2 Effects of cannabis use and *ZNF804A* genotype on SPQ-B

Regarding the Interpersonal schizotypy factor, a significant linear relationship between the genotype and the schizotypal scores was observed: homozygotes AA showed higher Interpersonal schizotypal scores (β=-0.16 SE=0.14 p=0.001 R^2=0.13). The mean (sd) SPQ-I scores for each genotype were as follow: AA (3.19 (0.19)), AC (2.65 (0.15)) and CC (2.36 (0.22)). No effect of cannabis use nor the interaction between genotype x cannabis was detected on SPQ-I.

In reference to the Cognitive-Perceptual factor, no effect of the main factors (genotype and cannabis) was observed. However, the interaction analysis showed the interplay between cannabis use and rs1344706 on SPQ-CP (β=0.21 SE=0.44 p=0.005 R^2=0.19): depending on the *ZNF804A* genotype the exposure to cannabis is associated differently to Cognitive Perceptual schizotypal scores (Figure 1). Heterozygous individuals showed similar SPQ-CP scores regardless of their cannabis use, while in the two homozygous groups (AA or CC) the cannabis use showed contrary effects. Among individuals AA, cannabis users presented higher scores than non-users, while among CC cannabis users presented lower scores compared to non-users.

In order to better detail the interaction analysis, we tested the effect of the genotype on SPQ-CP score separately in the group of cannabis users and non-users. Linear regression analyses showed that there is a significant effect of the genotype on SPQ-CP only in the group of cannabis users (β=-0.20 SE=0.20 p=0.025 R^2=0.04). Then, within cannabis users group, AA homozygotes have the highest SPQ-CP ratings while within cannabis non-users there are no significant differences among genotypic groups.

Finally, no significant effect of the genotype, cannabis use or the interaction was observed on SPQ-D.

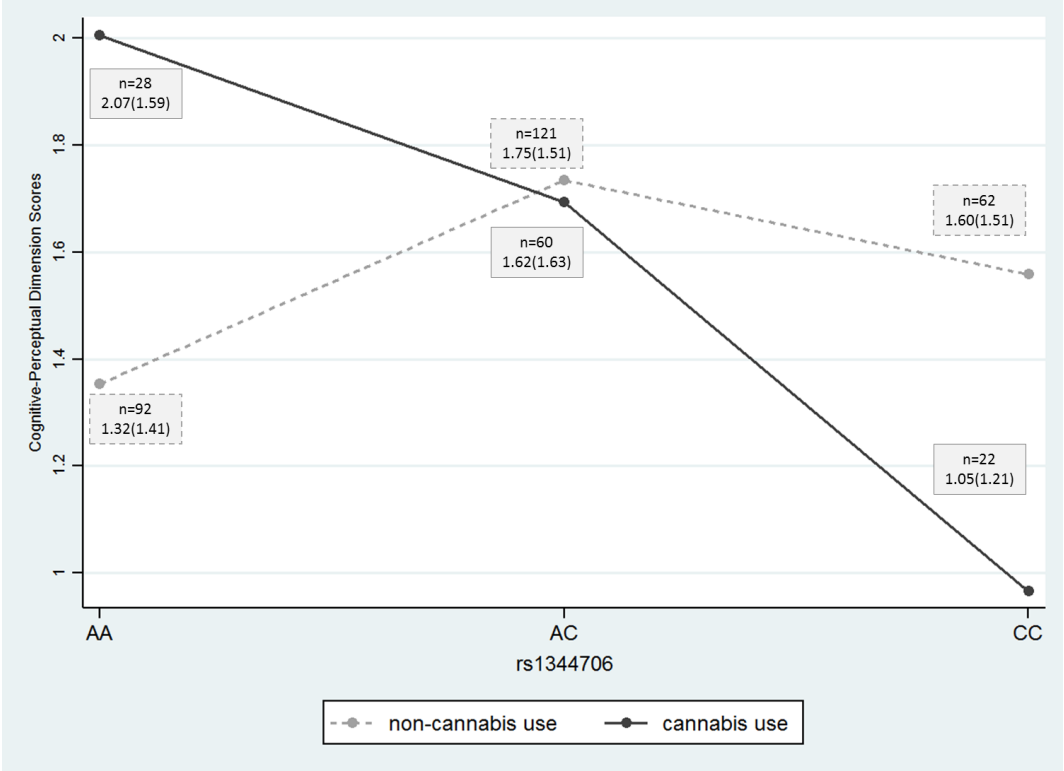

Figure 1. Among cannabis users, individuals AA showed higher scores in SPQ-CP (SD) dimensions than CC, while non-users showed the opposite trend (AA lower scores than CC). n= number of individuals.

4. Discussion

This study adds evidence on that *ZNF804A* gene may exert certain effect on psychosis proneness, measured as schizotypal traits in healthy subjects. In addition, our findings suggest, for the first time, that genetic variability at the *ZNF804A* gene may modulate the relationship between the cannabis use and psychotic proneness.

On the one hand, we have observed an association between the rs1344706 with SPQ-I. Particularly, we found that homozygotes AA showed higher Interpersonal schizotypal scores. This result is in line with different studies reporting the association of this variant with schizophrenia risk (e.g., 6,10), and it is also consistent with two previous studies that found this variant associated with schizotypy in general population sample (22,23). In regard to the two prior non-clinical population based studies, Yasuda et al. (2011) reported that A carriers showed higher disorganization dimension, but they did not describe differences in the other schizotypal factors. In the second study, although the direction of association was opposed to what expected, Stefanis et al. (2013) reported an association between paranoid and disorganized dimensions and rs1344706. Differences in the results among our study and the two previous studies might be explained by different sample characteristics, such as differences in sample size, ethnic origin or age and sex distributions. For instance, Yasuda's study consisted of 176 Japanese individuals with a mean age of 36.8 (sd=11.5) years. In Stefanis' study, although the subject's mean age (21 years, sd=1.9) was similar to our study, 100% of the subjects were men undergoing military service. Despite these differences, our results add onto the body of evidence that the *ZNF804A* gene might be involved in the pathogenesis of schizophrenia.

On the other hand, we have not observed an effect of cannabis use *per se* and either of the genotype on schizotypy ratings. However, the GxE interaction analyses have shown that the cannabis use seems to act as a modifier of the association between the

rs1344706 genotype and Cognitive Perceptual schizotypal scores. Among cannabis users, individuals AA showed higher scores in SPQ-CP dimensions than CC, while non-users showed the opposite trend. As observed when the effect of the genotype on SPQ-CP score was tested separately in the group of cannabis users and non-users, the rs1344706 genotype is linearly related with SPQ-CP scores only in the group of cannabis users.

For the interpretation of this GxE interplay, it is essential to understand the biological function of *ZNF804A* gene and the effect of a polymorphic variant in it. As mentioned, *ZNF804A* is presumably involved in the development and function of neural and synaptic structures (43), that regulates the expression of other genes, some of which have been directly or indirectly previously associated with schizophrenia (19,44).

To this respect, it was first considered whether the risk allele affects the expression of ZNF804A or even other genes. Two studies converge in showing that the SNP rs1344706 has a cis-acting effect on *ZNF804A* expression in the human foetal brain (12,13), a critical period in neurodevelopment. Specifically, these studies showed reduced expression associated with the risk allele; however, allelic direction still remains controversial due to contradictory results from other studies (45,46). Nonetheless, it can be hypothesized that the dysregulation of *ZNF804A* expression could have an effect on important neurodevelopmental processes that ultimately might increase the risk to develop psychosis in adolescence. However, since rs1344706 maps to an intronic region, the mechanisms causing these expression changes remains poorly understood. In this sense, a recent study suggested that the *MYT1L* and *GATA2* genes, which are involved in oligodendrocyte and neuronal differentiation and have been previously associated with schizophrenia, are strong candidates for regulating *ZNF804A* expression via rs1344706 (47). However, further effort is needed in determining the proteins that interact with the rs1344706 motif in order to elucidate the mechanism by which this SNP affects the *ZNF804A* expression.

Some limitations of this study must be acknowledged. First, the cross-sectional design is not the optimal to test causal associations and the retrospective measures may constitute an inherent source of bias. However, the genetic and environmental variables were selected based on previous findings and the analyses had a directional hypothesis also defined according to evidence (48,49). Second, participants were self-referred for the study, which may have introduced a selection bias into our sample. Despite these limitations, we would like to outline the design of this study as an intrinsic strength, because the assessment of the association between cannabis use and schizotypy aims to overcome the presence of multiple confounding factors inherent to psychosis; such as medication or the heterogeneous symptomatology of the disorder.

Further analyses in independent samples are required to replicate the present results and also to improve the knowledge of the etiological mechanism underlying the risk for psychosis, both in general population and in clinical samples.

In conclusion, our study supports the notion that the gene *ZNF804A* has an effect on a psychosis vulnerability marker such as schizotypy in healthy individuals from the population, and shows for the first time that this effect can be modulated by cannabis use.

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6. References

1. Perala J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsa E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry [Internet]. 2007;64:19–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17199051
2. Tsuang MT, Faraone S V. The case for heterogeneity in the etiology of schizophrenia. Schizophr Res [Internet]. 1995 Oct [cited 2017 Mar 10];17(2):161–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8562491
3. European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI). Identifying Gene-Environment Interactions in Schizophrenia: Contemporary Challenges for Integrated, Large-scale Investigations. Schizophr Bull [Internet]. 2014 May 24 [cited 2014 Jun 10];40(4):729–36. Available from: http://schizophreniabulletin.oxfordjournals.org/content/40/4/729.long
4. Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet [Internet]. NIH Public Access; 2009 Jan 17 [cited 2014 Jun 2];373(9659):234–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3879718&tool=pmcentrez&rendertype=abstract
5. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry [Internet]. 2003 Dec [cited 2015 Feb 26];60(12):1187–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14662550
6. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature [Internet]. 2009 Aug 6 [cited 2014 May 25];460(7256):748–52. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3912837&tool=pmcentrez&rendertype=abstract
7. Gratten J, Wray NR, Keller MC, Visscher PM. Large-scale genomics unveils the genetic architecture of psychiatric disorders. Nat Neurosci [Internet]. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved.; 2014 May 27 [cited 2014 May 27];17(6):782–90. Available from: http://dx.doi.org/10.1038/nn.3708
8. Riley B, Thiselton D, Maher BS, Bigdeli T, Wormley B, McMichael GO, et al. Replication of association between schizophrenia and ZNF804A in the Irish Case-Control Study of Schizophrenia sample. Mol Psychiatry [Internet]. 2010 Jan [cited 2014 Dec 11];15(1):29–37. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2797562&tool=pmcentrez&rendertype=abstract
9. Steinberg S, Mors O, Børglum AD, Gustafsson O, Werge T, Mortensen PB, et al. Expanding the range of ZNF804A variants conferring risk of psychosis. Mol Psychiatry [Internet]. 2011 Jan 5 [cited 2017 Feb 10];16(1):59–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20048749
10. Williams HJ, Norton N, Dwyer S, Moskvina V, Nikolov I, Carroll L, et al. Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. Mol Psychiatry [Internet]. 2011 Apr 6 [cited 2017 Feb 10];16(4):429–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20368704
11. Hess JL, Glatt SJ. How might ZNF804A variants influence risk for schizophrenia

and bipolar disorder? A literature review, synthesis, and bioinformatic analysis. Am J Med Genet B Neuropsychiatr Genet [Internet]. 2014 Jan [cited 2014 Nov 27];165B(1):28–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24123948

12. Hill MJ, Bray NJ. Evidence That Schizophrenia Risk Variation in the *ZNF804A* Gene Exerts Its Effects During Fetal Brain Development. Am J Psychiatry [Internet]. American Psychiatric AssociationArlington, VA; 2012 Dec [cited 2017 Mar 8];169(12):1301–8. Available from: http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.2012.11121845
13. Tao R, Cousijn H, Jaffe AE, Burnet PWJ, Edwards F, Eastwood SL, et al. Expression of *ZNF804A* in Human Brain and Alterations in Schizophrenia, Bipolar Disorder, and Major Depressive Disorder. JAMA Psychiatry [Internet]. American Medical Association; 2014 Oct 1 [cited 2017 Mar 8];71(10):1112. Available from: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2014.1079
14. Brayer KJ, Segal DJ. Keep Your Fingers Off My DNA: Protein–Protein Interactions Mediated by C2H2 Zinc Finger Domains. Cell Biochem Biophys [Internet]. Humana Press Inc; 2008 Mar 6 [cited 2017 Mar 8];50(3):111–31. Available from: http://link.springer.com/10.1007/s12013-008-9008-5
15. Laity JH, Lee BM, Wright PE. Zinc finger proteins: new insights into structural and functional diversity. Curr Opin Struct Biol [Internet]. 2001 Feb [cited 2017 Mar 10];11(1):39–46. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0959440X00001676
16. Deans PJM, Raval P, Sellers KJ, Gatford NJF, Halai S, Duarte RRR, et al. Psychosis Risk Candidate ZNF804A Localizes to Synapses and Regulates Neurite Formation and Dendritic Spine Structure. Biol Psychiatry [Internet]. Elsevier; 2016 Sep 15 [cited 2017 Mar 8];84(0):399–415. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27837918
17. Hess JL, Glatt SJ. How might *ZNF804A* variants influence risk for schizophrenia and bipolar disorder? A literature review, synthesis, and bioinformatic analysis. Am J Med Genet Part B Neuropsychiatr Genet [Internet]. 2014 Jan [cited 2017 Mar 8];165(1):28–40. Available from: http://doi.wiley.com/10.1002/ajmg.b.32207
18. Hill MJ, Jeffries AR, Dobson RJB, Price J, Bray NJ. Knockdown of the psychosis susceptibility gene ZNF804A alters expression of genes involved in cell adhesion. Hum Mol Genet [Internet]. Oxford University Press; 2012 Mar 1 [cited 2017 Mar 10];21(5):1018–24. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddr532
19. Girgenti MJ, LoTurco JJ, Maher BJ, Schaefer C, Wyatt R. ZNF804a Regulates Expression of the Schizophrenia-Associated Genes PRSS16, COMT, PDE4B, and DRD2. Jennings B, editor. PLoS One [Internet]. Public Library of Science; 2012 Feb 27 [cited 2017 Mar 13];7(2):e32404. Available from: http://dx.plos.org/10.1371/journal.pone.0032404
20. Penzes P, Cahill ME, Jones KA, VanLeeuwen J-E, Woolfrey KM. Dendritic spine pathology in neuropsychiatric disorders. Nat Neurosci [Internet]. 2011 Mar [cited 2014 Jul 13];14(3):285–93. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3530413&tool=pmcentrez&rendertype=abstract
21. O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat Genet [Internet]. Nature Publishing Group; 2008 Sep [cited 2014 May 26];40(9):1053–5. Available from: http://dx.doi.org/10.1038/ng.201
22. Yasuda Y, Hashimoto R, Ohi K, Fukumoto M, Umeda-Yano S, Yamamori H, et al. Impact on schizotypal personality trait of a genome-wide supported psychosis variant of the ZNF804A gene. Neurosci Lett [Internet]. 2011 May 20 [cited 2015 Jun 16];495(3):216–20. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/21457757
23. Stefanis NC, Hatzimanolis A, Avramopoulos D, Smyrnis N, Evdokimidis I, Stefanis CN, et al. Variation in psychosis gene ZNF804A is associated with a refined schizotypy phenotype but not neurocognitive performance in a large young male population. Schizophr Bull [Internet]. 2013 Nov [cited 2015 Jul 13];39(6):1252–60. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3796069&tool=pmcentrez&rendertype=abstract
24. Raine A. Schizotypal personality: neurodevelopmental and psychosocial trajectories. Annu Rev Clin Psychol [Internet]. 2006 Jan [cited 2015 Dec 10];2:291–326. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17716072
25. Fanous AH, Neale MC, Gardner CO, Webb BT, Straub RE, O'Neill FA, et al. Significant correlation in linkage signals from genome-wide scans of schizophrenia and schizotypy. Mol Psychiatry [Internet]. 2007 Oct [cited 2016 Jan 13];12(10):958–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17440434
26. Barrantes-Vidal N, Grant P, Kwapil TR. The Role of Schizotypy in the Study of the Etiology of Schizophrenia Spectrum Disorders. Schizophr Bull [Internet]. 2015 Mar 25 [cited 2015 Apr 8];41 Suppl 2(suppl 2):S408-16. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4373635&tool=pmcentrez&rendertype=abstract
27. MINOZZI S, DAVOLI M, BARGAGLI AM, AMATO L, VECCHI S, PERUCCI CA. An overview of systematic reviews on cannabis and psychosis: Discussing apparently conflicting results. Drug Alcohol Rev [Internet]. 2009 Nov 18 [cited 2017 Mar 10];29(3):304–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20565524
28. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet [Internet]. 2007 Jul [cited 2017 Mar 10];370(9584):319–28. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673607611623
29. Covey DP, Mateo Y, Sulzer D, Cheer JF, Lovinger DM. Endocannabinoid modulation of dopamine neurotransmission. Neuropharmacology [Internet]. 2017 Apr 25 [cited 2017 May 12]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0028390817301831
30. Fridberg DJ, Vollmer JM, O'Donnell BF, Skosnik PD. Cannabis users differ from non-users on measures of personality and schizotypy. Psychiatry Res [Internet]. 2011 Mar [cited 2017 Mar 13];186(1):46–52. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0165178110004671
31. Schubart CD, van Gastel WA, Breetvelt EJ, Beetz SL, Ophoff RA, Sommer IEC, et al. Cannabis use at a young age is associated with psychotic experiences. Psychol Med [Internet]. 2011 Jun 7 [cited 2017 Mar 13];41(6):1301–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20925969
32. Cohen AS, Buckner JD, Najolia GM, Stewart DW. Cannabis and psychometrically-defined schizotypy: use, problems and treatment considerations. J Psychiatr Res [Internet]. 2011 Apr [cited 2017 Mar 13];45(4):548–54. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022395610002578
33. Szoke A, Galliot A-M, Richard J-R, Ferchiou A, Baudin G, Leboyer M, et al. Association between cannabis use and schizotypal dimensions – A meta-analysis of cross-sectional studies. Psychiatry Res [Internet]. 2014 Sep [cited 2017 Mar 13];219(1):58–66. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0165178114003771
34. Decoster J, van Os J, Myin-Germeys I, De Hert M, van Winkel R. Genetic variation underlying psychosis-inducing effects of cannabis: critical review and future directions. Curr Pharm Des [Internet]. 2012 [cited 2017 Mar 10];18(32):5015–23.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/22716139
35. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to Pot - A Review of the Association between Cannabis and Psychosis. Front psychiatry [Internet]. Frontiers Media SA; 2014 [cited 2017 Mar 14];5:54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24904437
36. van Winkel R, GROUP Investigators G. Further Evidence That Cannabis Moderates Familial Correlation of Psychosis-Related Experiences. PLoS One [Internet]. Public Library of Science; 2015 [cited 2017 Mar 14];10(9):e0137625. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26384217
37. Genetic Risk and Outcome in Psychosis (GROUP) Investigators. Evidence That Familial Liability for Psychosis Is Expressed as Differential Sensitivity to Cannabis. Arch Gen Psychiatry [Internet]. 2011 Feb 7 [cited 2017 Mar 14];68(2):138. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20921112
38. First MB, Gibbon M, Spitzer RL, Williams JBW BL. Entrevista clínica estructurada para los trastornos de la personalidad del eje II del DSM-IV (SCID-II).
39. E. M. Family Interview for Genetic Studies (FIGS): A Manual for FIGS. Bethesda, MD Clin Neurogenetics Branch, Intramural Res Program, Natl Inst Ment Heal. 1992;
40. Raine A, Benishay D. The SPQ-B: A Brief Screening Instrument for Schizotypal Personality Disorder. J Pers Disord [Internet]. Guilford Publications Inc.; 1995 Dec 10 [cited 2015 Jun 3];9(4):346–55. Available from: http://guilfordjournals.com/doi/abs/10.1521/pedi.1995.9.4.346
41. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychol Med [Internet]. 1983 Aug [cited 2017 Mar 13];13(3):595–605. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6622612
42. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet [Internet]. 2007 Sep [cited 2014 Jul 10];81(3):559–75. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1950838&tool=pmcentrez&rendertype=abstract
43. Chang H, Xiao X, Li M. The schizophrenia risk gene ZNF804A: clinical associations, biological mechanisms and neuronal functions. Mol Psychiatry [Internet]. 2017 Mar 14 [cited 2017 May 15]; Available from: http://www.nature.com/doifinder/10.1038/mp.2017.19
44. Umeda-Yano S, Hashimoto R, Yamamori H, Okada T, Yasuda Y, Ohi K, et al. The regulation of gene expression involved in TGF-β signaling by ZNF804A, a risk gene for schizophrenia. Schizophr Res [Internet]. 2013 May [cited 2017 Mar 13];146(1–3):273–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0920996413000649
45. Williams HJ, Norton N, Dwyer S, Moskvina V, Nikolov I, Carroll L, et al. Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. Mol Psychiatry [Internet]. 2011 Apr 6 [cited 2017 Mar 13];16(4):429–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20368704
46. Guella I, Sequeira A, Rollins B, Morgan L, Myers RM, Watson SJ, et al. Evidence of allelic imbalance in the schizophrenia susceptibility gene ZNF804A in human dorsolateral prefrontal cortex. Schizophr Res [Internet]. 2014 Jan [cited 2017 May 15];152(1):111–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24315717
47. Hess JL, Quinn TP, Akbarian S, Glatt SJ. Bioinformatic analyses and conceptual synthesis of evidence linking *ZNF804A* to risk for schizophrenia and bipolar disorder. Am J Med Genet Part B Neuropsychiatr Genet [Internet]. 2015 Jan [cited 2017 Mar 13];168(1):14–35. Available from: http://doi.wiley.com/10.1002/ajmg.b.32284
48. Cardon LR, Bell JI. Association study designs for complex diseases. Nat Rev

Genet [Internet]. 2001 Feb 1 [cited 2017 Mar 13];2(2):91–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11253062

49. Dick DM, Agrawal A, Keller MC, Adkins A, Aliev F, Monroe S, et al. Candidate gene-environment interaction research: reflections and recommendations. Perspect Psychol Sci [Internet]. NIH Public Access; 2015 Jan [cited 2017 Mar 14];10(1):37–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25620996