Published in final edited form as:

Spiritual Clin Pract (Wash D C). 2017 March ; 4(1): 43–63. doi:10.1037/scp0000125.

Genetic Correlates of Spirituality/Religion and Depression: A Study in Offspring and Grandchildren at High and Low Familial Risk for Depression

Micheline R. Anderson[a], **Lisa Miller**[a], **Priya Wickramaratne**[b,c,d], **Connie Svob**[b,c], **Zagaa Odgerel**[b,c], **Ruixin Zhao**[b,c], and **Myrna M. Weissman**[b,c,d]

[a]Teachers College, Columbia University, New York, NY

[b]Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[c]Division of Epidemiology, New York State Psychiatric Institute, New York, NY, USA

[d]Mailman School of Public Health, Columbia University, New York, NY, USA

Abstract

Rationale—Possible genetic correlates of spirituality and depression have been identified in community samples. We investigate some of the previously identified candidates in a sample of families at both high and low-risk for depression.

Method—Offspring and grandchildren of individuals at high and low-risk for depression, participating in a multi-wave thirty-year longitudinal study, were assessed for seven SNPS drawn from four single gene candidates associated with systems implicated in both depression and spirituality: Serotonin (5-HT1B and 5-HT2A), Dopamine (DRD2), Oxytocin (OT) and Monoamine Vesicular Transporter (VMAT1).

Results—Dopamine (DRD2) Serotonin (5-HT1B), their Transporter (VMAT1) and Oxytocin (OXTR) were positively associated with a high level of importance of spirituality or religion (S/R) in the group at low familial risk for depression. DRD2 minor allele was associated with both lifetime major depressive disorder (MDD) and spirituality in the low-risk group for depression. No SNPs were related to S/R in the group at high familial risk for depression. OXTR was associated with lifetime MDD in the full sample.

Conclusion—Genes for dopamine, serotonin, their vesicular transporter, and oxytocin may be associated with S/R in people at low familial risk for depression. Genes for dopamine may be associated both with S/R and increased risk for depression in people at low-risk for depression, suggesting a common pathway or physiology to mild to moderate depression. MDD is associated with oxytocin across risk groups. In the high-risk group, phenotypic expression of S/R may be suppressed.

Correspondence: Micheline R. Anderson, Teachers College, Columbia University, 525 West 120th Street, New York, New York micheline.anderson@tc.columbia.edu.

Implications—The shared association of DRD2 by S/R and depression, generally found to be inversely related, calls for further research on their common physiological pathways, and the phenotypic expression of these pathways based upon use and environment. Prevention for offspring at high familial risk for depression might include support for the development of child spirituality.

A large literature over the past twenty years shows protective benefits of spirituality against depression (for reviews, see Van Ness & Larsen, 2002; Koenig, 2009). Depression and spirituality have been shown to share multiple physiological risk factors, including the preliminary suggestion of common genetic markers for risk (Smith, McCullough, & Poll, 2003). In this study we investigate a sub-set of those genetic markers that in previous studies have been linked both with depression and with spirituality (Perroud, 2009).

Whereas the majority of research has examined genetic links to depression and spirituality in community and convenience samples, the current study investigates these genes in a "high-risk" sample, namely a sample of adult offspring and grandchildren of people who had severe depression and matched controls (Weissman et al, 2016) offering a smaller sample size but a stronger "signal" for a link between any single gene and its phenotype. Previous research has shown that risk for depression differs by parental risk status–that is, individuals with a parent or grandparent diagnosed with depression are at least 2 to 3 times as likely to become depressed than children without a depressed parent (Klein et al, 2002; Lieb et al, 2002; Weissman et al, 2006). Further, this intergenerational risk is greatest for children with both a depressed grandparent and parent (Weissman et al, 2016).

As a field of inquiry single gene analysis has burgeoned over the past fifteen years (Ropers, 2010), offering etiological clues and markers for pathogenic processes but relatively small magnitude of an association with diagnosis. The largest effect sizes of genome-wide association studies (GWAS) account for a relatively small portion of the variance in both diagnosis of psychopathology and psychological traits (Park et al, 2011). That said, single gene analyses often indicate pathways that might be examined and common ground between seemingly divergent diagnoses or conditions. Likewise, the study of the genetic underpinnings of positive traits has thus far stemmed largely from candidate gene analysis (Moore et al, 2015).

The candidate genes that we investigate for a relationship between depression and spirituality in this high-risk sample were drawn from the previously published research on single gene candidates. Here we briefly review the literature associated with each single gene candidate that we assessed as potentially related to depression and spirituality and then present the results of the assessment that are driven by three research questions:

1. What are the single-gene correlates of spirituality?
2. What are the single-gene correlates of depression?
3. Are there differential associations by risk status?

Potential Candidate Single Genes for Spirituality and Depression

Oxytocin

Oxytocin (OT) is a nonapeptide signaling molecule that assists with human neuromodulation of social behavior, bonding, adaptation to stress, and reproduction. A large body of research exists on the oxytocin receptor gene (OXTR) and its association with social function, capacity for bonding, and related dysfunction indicated in pathology such as autism, depression, and schizophrenia (see Feldman, Monakhov, Pratt, & Ebstein, 2016 for review). The OXTR SNP rs2254298 (9073A>G), in particular, has been examined, with several studies demonstrating the link between its allelic variation and autism in Japanese, Israeli, and Caucasian samples (Jacob et al, 2007; Lerer et al, 2008; Liu et al, 2010). Costa et al (2009) examined genotypic distributions of rs2254298 and found that in a group of individuals with unipolar depression, there were a reduced number of A-allele carriers. In this same study, GG homozygotes showed high scores on subscales of need for approval, self-esteem, and adult separation anxiety, previously associated with depression.

As with other OXTR SNPs, the minor A allele of rs2254298 has also been associated with increased severity of symptoms in patients with anorexia nervosa and bulimia nervosa, as compared with healthy controls (Acevedo et al, 2015). In addition to allelic variation of the SNP, haplotypes with rs2254298 have shown associations with positive and negative affect and emotional loneliness in adults (Lucht et al, 2009), and high callous-unemotional traits, a developmental precursor to psychopathy, in children (Dadds et al, 2013).

OT has been associated with social behavior such as social affiliation, empathy, parental bonding, and stress regulation (for a review, see Aspé-Sánchez et al, 2016). Due to its apparent role in social affiliation and behavior, rs2254298 has also been examined as a moderator in the relation between religiosity and psychological distress, with the homozygote GG genotype driving an association between religiosity and increased psychological distress in a European American sample (Sasaki, Kim, & Xu, 2011). In another study by Sasaki and colleagues (2015), genetic moderation of the OXTR polymorphism influenced the impact of religious priming on self-control, such that individuals with the homozygote GG genotype showed greater increases in self-control than individuals with AA or AG genotypes after receiving religious cues in a social context. Finally, in a recent study on the effects of intranasal OT administration and self-reported spirituality, OT administration was shown to increase spirituality in males and this effect was moderated by OT-related genotypes (Van Capellen, Way, Isgett & Fredrichson, 2016).

Serotonin

To attract ongoing attention within psychopharmacologic research, the serotinergic system has been implicated in both pathology and personality, albeit the mechanisms of its role in the development of either are not straightforward. In imaging studies, it has been established that serotonin receptor binding potential is reduced in the brains of depressed individuals as compared with controls (Bhagwagar et al, 2004; Drevets et al, 1999, 2007; Murrough et al, 2011), reduced serotonin binding potential has been associated with serotonin receptor gene polymorphisms (Baldinger et al, 2015), and serotonin polymorphisms are associated with

Major Depressive Disorder (Kishi et al, 2013). However, the inverse of these findings has recently been supported (for review, see Kaufman et al, 2016), making apparent the complexity of the relationship between serotonin, 5-HT receptors, and depression, yet still lending support to the centrality of the system.

One SNP of interest, 5-HT2A receptor gene polymorphism rs6311, modulates HTR2A promoter activity, such that activity is greater in the presence of the A allele relative to the G allele (Parsons et al, 2004), and leads to greater transcriptive efficiency (Smith et al, 2013). Candidate gene-based and transmission disequilibrium association studies have shown that rs6311 may also have clinical significance and is associated with psychiatric disorders and related phenotypes, such as panic disorder (Unschuld et al, 2007), obsessive compulsive disorder in individuals with Tourette's Disorder (Dickel et al. 2007), and early onset Obsessive Compulsive Disorder in children and adolescents (Walitza et al, 2012). Giegling et al (2006) observed that haplotypes with the T allele of rs6311 and single functional (T) markers at rs6311 were protective against suicidal behavior, and CC-homozygotes reported more anger and aggression-related behavior. The association between genotypic variation and phenotypic expression of suicide, anger, and aggressive behavior was further supported in Saiz and colleagues' (2008) study in which the A allele was over-represented in non-impulsive suicide attempters, as compared to impulsive suicide attempters and healthy controls.

Although meta-analyses have conflicting conclusions on the association between rs6311 and unipolar and bipolar depression (Gu et al, 2013; Jin et al, 2013; Lin et al, 2014; Zhao et al, 2014), there has been meta-analytical support for other 5-HTR2A variants and MDD (Lin et al, 2014), risk for schizophrenia conferred by the -1438A/G polymorphism of rs6311 (Gu et al, 2013) and pilot data support for association with post-partum depression (El-Ibiary et al, 2013).

Like the 5-HT2A receptor gene, 5HT1B receptor genes modulate activity in the promoter region through influence on transcription of the gene. They do so by increasing the binding of transcription factors, thereby increasing the transcription of the downstream coding region (Huang et al, 1999). 5-HT1B receptor genes have been extensively studied and are associated with depression (Huang et al, 2003), impulsivity (Stoltenberg, Christ, & Highland, 2012; Varga et al, 2012;), ADHD (for review, see Caylak, 2012), aggression (Hakulinen et al, 2013) and alcoholism and substance use disorders (Fehr et al, 2000; Huang et al, 2003), particularly antisocial alcoholism (Lappalainen et al, 1998; Lee et al, 2009; Soyka et al, 2004).

Due to their role in transcription and expression of serotonin and its receptors, rs130058, rs11568817 and rs6298 have been examined as 5-HTR1B functional variants showing association with psychiatric disorder and maladaptive behaviors. In a Chinese Han population, rs11568817 was significantly associated with suicidal behavior in individuals experiencing major depression (Wang et al, 2009). Although conflicting findings exist, a recent meta-analysis concludes that there is a statistically significant association between rs130058 and rs11568817 and alcohol, cocaine, and heroin dependence (Cao, LaRocque, & Li, 2013).

Rs130058 has also been associated with phenotypes related to addiction and suicide, such as impulsive-aggressive behavior and anger and hostility in men (Zouk et al, 2007; Conner et al, 2010). In Conner et al's 2010 study, the T allele of rs130058 was overrepresented among suicide completers, suggesting that risk for suicide is conferred through the minor allele. Additionally, rs130058 and rs11568817 acted as a functional combination in the promoter region, accounting for significant variance in men's anger and hostility. Interestingly, in this 4-year longitudinal study, the genetic differences in haplotype variances and hostility and anger peaked at age 18 in men, declining thereafter. Age-related or developmental effects on this phenotypic manifestation might be of interest, as an additional study by Shoval et.al (2014) showed that the expression levels of participants in the serotinergic system, 5-HTR1B, increase sharply in adolescence.

Robust findings have been published that also identify both rs6298 and rs130058 as having respective roles in depressed patients' responses to antidepressant medication. Both SNPs interact with antidepressant type to show a differential association with side effects such as suicidal ideation as well as response time and efficacy (Lenze et al, 2013; Perroud et al, 2011; Villafuerte et al, 2009; Xu et al, 2012).

The serotonin system has also been implicated in studies of spirituality. While evidence exists that expression levels of 5-HTR1B receptors peak in adolescence (Shoval et al, 2014), studies show that spirituality surges in adolescence as well. Particular attention has been paid to the relation between self-transcendence and spiritual acceptance with reduced serotonin binding potential (Borg, Andree, Soderstom & Ferde, 2003), reduced serotonin transporter availability (resulting in elevated serotonin levels) in specific raphe nuclei (Kim et al, 2015), the short allele of the serotonin transporter gene 5-HTTLPR (Nilsson et al, 2007), and the polymorphism 5HT1A in patients with mood disorders (Lorenzi et al, 2005). The -1438A/G polymorphism of rs6311 has also shown association with self-transcendence in a Korean population (Ham et al, 2004).

Other personality traits, such as openness to experience, have also been shown to be associated with spirituality (Henningsgaard & Arnau, 2008; Sarouglou, 2002). Not only have cerebral levels of serotonin been associated with openness to experience and cognitive flexibility (Kalbitzer et al, 2009), but researchers are also beginning to examine 5-HTR2A polymorphisms as a means to understand the effect of gene and environment interaction on personality traits associated with spirituality. Rs6311 specifically has been shown to interact with the serotonin transporter gene (5-HTTLPR) and education level to predict novelty-seeking in a Spanish sample (Saiz et al, 2010). In a study among Russian wrestlers, rs6311 interacted with gender to predict openness to experience, as measured by the NEO-5 (Butovskaya et al, 2015). Additionally, an understanding of paradoxical expression–that a condition such as potentiation of serotonin transmission can both increase sensitivity to stressful experiences as well as increase openness to experiences–is important to understanding the relation among serotonin gene receptors, spirituality, and pathology.

Dopamine

Indicated in both psychopathology and well-being, the dopaminergic system is integral in motivation, learning, and reward processing. Of the dopamine receptor genes (DR), the D_2

dopamine receptor gene (DRD2) is one of the most widely studied, and abnormalities in the DRD2 gene have been implicated in Reward Deficiency Syndrome (Blum et al, 1990; 1996; 2012; 2014). Reward Deficiency Syndrome refers to a dearth of usual feelings of satisfaction that is a result of a disruption in the "brain reward cascade" brought about by a reduced number of dopamine receptors leading to insufficient binding and reduced extracellular dopamine, thus affecting mood and cravings in humans (Blum & Kozlowski, 1990). In addition to addiction, pathological gambling and other reward-seeking behaviors, DRD2 has also shown associations with suicidal behaviors (Mandelli & Serretti, 2013), Posttraumatic Stress Disorder (Voisey et al, 2009), higher levels of rumination in depressed individuals (Whitmer & Gotlib, 2012) and schizophrenia (Yao et al, 2014).

The most widely studied of the DRD2 SNPs, the Taq1A (rs1800497), is now known to be located in the nearby ANKK1 gene, approximately 10 kb downstream from the DRD2 gene, and results in an amino acid substitution (Neville, Johnstone, & Walton, 2004). Several studies have shown that individuals with the Taq1A minor A1 allele exhibit reduced striatal DRD2 binding when compared to subjects without the A1 allele (Eisenstein et al, 2016; Gluskin & Mickey, 2016; Noble, 2003), suggesting that it is indirectly involved in DRD2 expression or interacts with another DRD2 SNP. As with other DRD2 mutations, A1 allele carriers exhibit reduced receptor density, as compared with non-carriers (Nemoda, Szekely, & Sasvan, 2011). These existing functional differences in A1 allele carriers are suggested to confer risk for related psychopathology that has been identified in candidate gene-based association tests, such as depression in men (Roetker et al, 2012), increased risk for mood disorders (Zhang et al, 2014), borderline traits and impulsive self-damaging behaviors (Nemoda, 2010), PTSD (Li et al, 2016), alcohol dependence and alcoholism (Munafo, Matheson, & Flint, 2007; Smith et al, 2008), and opioid dependence (Chen et al, 2011).

In a review of the neurobiology of spirituality, Perroud (2009) suggests that similarities in the functional activity in spiritual and religious experience and the dopaminergic system indicate a relation between the two. Candidate gene and imaging studies are consistent with this idea. Using the TCI, Comings et al (2000) showed an association between DRD4 and spiritual acceptance, and suggested that this was a function of increased concentration of DRD4 receptors in cortical areas. In another sample, individuals with homozygous AA genotype experienced greater stress induced dopamine release and reported lower levels of openness to experience, reflecting what the authors interpreted to be a sensitive, vulnerable phenotype (Peciña, 2013). In the effort to understand gene-environment interactions, religiosity has also been identified as a moderator of the relation between the minor A1 allele of rs1800497 and delinquent/antisocial behavior in adolescents, such that individuals with the minor allele reported increased delinquency but only among males without religious belief (Beaver, Gibson, Jennings, & Ward, 2009).

Given the connection between receptor density, extracellular dopamine, and the neural network including the prefrontal cortex and the dorsal striatum, further support for the link between dopamine and spirituality is offered through imaging studies. A PET study of Yoga Nidra meditation demonstrated a significant increase of dopamine levels during the meditation practice (Kjaer et al, 2002). Additionally, the authors reported a significant decrease in binding in the ventral striatum. In another PET study, dysfunctions in the

dopaminergic system coincided with impairment in activating religious concepts among Parkinson's patients whose onset began on the left side of the body/right forebrain (Butler, McNamara, & Dorso, 2010). The result of this PET study is consistent with dopaminergic disruption in the right striatal prefrontal networks that occurs in Parkinson's disease. Also linking R/S and dopamine, it has been argued that the impetus for meditation and religious activities may be related to the activation of the dopaminergic system during these types of activities (Newberg & Iversen, 2003). However, the relation among surfeit dopamine, receptor deficiency, and binding potential remains unclear (Blum et al, 2014), particularly when considering the counterintuitive findings between healthy and clinical populations.

Vesicular Monoamine Transporters

Unlike the other SNPs examined, vesicular monoamine transporter (VMAT) genes are functionally related to proteins responsible for the transfer of monoamines such as dopamine, epinephrine and serotonin to synaptic vesicles. In particular, VMAT1 (SLC18A1) is exclusively found in neuroendocrine cells (Erickson et al, 1996).

In Lohoff et al (2014), fMRI data showed that the minor A allele altered amygdala and medial prefrontal cortex functioning as well as increased presynaptic transport of monoamines *in vitro.* Lohoff concluded that VMAT1 variants play a role in emotional processing as well as risk for psychopathology. These findings buttress association studies showing that the minor A allele of VMAT1 variant rs1390938 has been associated with lower risk of alcohol use dependence (Dutta et al, 2016; Vaht, Kiive, Veidebaum, & Harro, 2016), anxiety-related personality traits (Lohoff et al, 2008), maladaptive impulsivity, anxiety, depressiveness, and neuroticism (Vaht et al, 2016). Closely related VMAT2 (SLC18A2) SNPs have been associated with phenotypes such as depression in elderly men (Christiansen et al, 2007), alcohol dependence (Schwab et al, 2005), and post-traumatic stress disorder (Solovieff et al, 2014). The VMAT2 gene has also been implicated in discussion as "the God gene" (Hamer, 2004), due to the C allele's association with higher self-transcendence scores as compared with homozygous AA genotypes, and the relation of VMAT to the packaging and transportation of multiple monoamines, including dopamine and serotonin.

Method

Study samples

Study participants were 334 subjects (156 female and 178 male; mean age=31.5, SD= 16.0) comprised of offspring and grandchildren drawn from an ongoing thirty-year, three generational study of individuals at high and low-risk for depression. Mean ages for the two generations of study participants were as follows: Generation 2 (G2), M=47.5 SD=7.9 and Generation 3 (G3), M=19.3, SD=7.4 years.

Probands in Generation 1 (G1) had been originally recruited for the study of major depressive disorder and followed up for 30 years at six longitudinal waves. The study cohort has been described previously elsewhere (Weissman et al., 2016a; Weissman et al., 2016b). Subjects were diagnosed with major depression using the age-appropriate version of the

semi-structural diagnostic Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997; Mannuzza et al., 1986). Individuals with any history of bipolar, schizophrenia spectrum, or antisocial personality disorders were excluded. Altogether 450 individuals were available for the present study. Written informed consent was obtained from all subjects and the study protocol was approved by the Institutional Review Board at New York State Psychiatric Institute/Columbia University.

In the final study sample of 334 participants, 99.1% were Caucasian. Distribution of annual income ranged as follows: $5000 (7.1%), $15,000 (7.8%), $25,000 (10.6%), $35,000 (12.1%), $45,000 (12.8%), $55,000 (11.4%), $65,000 (7.8%), $80,000 (12.1%), $90,000(18.4%). Education levels ranged as follows: 18.6% had less than high school, 32.6% had high school, 48.8% had more than high school.

Religion and Spirituality

Religious denomination ranged as follows: 52.8% were Catholic, 21.3% Protestant, 6.0% belonged to other religious denominations, 7.1% were Agnostic/Atheist, 12.4% were personal religious, 3.6% were Jewish and 0.4% were Buddhist/Hindu/Muslim.

Measures on personal experience and practice of S/R included two questions. First, “How important to you is religion or spirituality?” with responses ranging from 1 (not important at all) to 4 (very important). Second, “How often, if at all, do you attend church, synagogue, or other religious or spiritual services?” with responses ranging from 1 (once a week or more) to 5 (never). The average rating within the study sample on the personal importance of S/R was M=2.74, SD=1.02 (approximating a rating of moderate importance), and the average rating on frequency of attendance was M= 2.91, SD=1.50 (with the average rate of church attendance approximating once or twice a year).

Rates of Depression

Of the 334 participants, 37.7% had a diagnosis of Life-Time MDD and 17.0% had an episode of MDD at most recent follow-up.

Genotyping—We genotyped in total 7 SNPs in five genes: HTR2A, HTR1B, OXTR, VMAT1 and DRD2 genes across the 2-generation samples (334 individuals). Genomic DNA was extracted from a saliva sample collected using Oragene DNA Self Collection Kit following the protocol provided by the manufacture (Oragene Genotek, Ontario, Canada). SNPs were genotyped using Taqman® SNP Genotyping assays with TaqMan® Genotyping Master Mix (Applied Biosystems, Foster City, CA) on an ABI 7900HT Fast Real-Time PCR System and analyzed using SDS 2.1 software (Applied Biosystems, Foster City, CA).

Analysis—The main analyses (Tables 2 and 3) were performed using methods for family based association tests within the framework of Generalized Estimating Equation models similar to that described in Chen and Yang (2010) using SAS (SAS Software Version 9.2, Cary, NC, Copyright 2008). Linear regression models were fitted to quantitative traits such as personal importance of S/R and logistic regression models were fitted to binary traits such as MDD. Personal importance of S/R and MDD are the respective outcomes; importance is

treated as a continuous variable, with values from 1–4. Higher score indicates greater personal importance of S/R. MDD is a binary variable with the values 0 (absence of Lifetime MDD) and 1 (presence of Lifetime MDD), respectively. For each of the 7 SNPs, the corresponding genotypes were coded as −1,0, 1 and treated as a linear predictor. All analyses were adjusted by age and gender. All models were assumed to be additive genetic models, with the homozygous minor allele genotype coded as −1, the heterozygous genotype coded as 0 and the homozygous major allele genotype coded as 1. Lack of independence among observations in the same pedigree was accounted for by treating each pedigree as a cluster, with an independence working correlation matrix used in the robust variance estimator.

Results

Study participants (N=334) were stratified into a high-risk group (N=109) and a low-risk group (N=225). The distribution of genotypes in the sample by risk status is summarized in Table 1. Rates of major and minor alleles for 5 of the 6 SNPs did not differ significantly between the low and high-risk groups. There was a significant difference in rates of major and minor alleles between the high and low risk group for DRD2 SNP rs1800497 (p=.053).

The results show that, adjusted by age and gender, there is a significant association between high personal importance of S/R and OXTR SNP rs2254298 (p=.024), 5HTR1B SNPs rs130058 (p=.001) and rs11568817 (p=.029), VMAT1 SNP rs1390938 (p=.033) and DRD2 SNP rs1800497 (p=.026) in the low-risk group. For rs130058 genotype, the minor A allele is associated with decreased personal importance of S/R. For the other four SNPs that were found to be associated with personal importance importance of S/R in the low risk group the minor allele was found to be associated with increased personal importance of S/R. In the high-risk group, rs2254298 is significantly associated with lifetime MDD (p=.049) and genotype GG is associated with higher risk of lifetime MDD. In the low-risk group, rs1800497 (p=.012) is significantly associated with lifetime MDD and genotype GG is associated with lower risk of lifetime MDD.

The interaction term of rs2254298*risk (OXTR by Risk Status) is not significant (p=.839) while rs1800497*risk (HTR1B by Risk Status) is significant (p=.041). So for rs2254298 (OXTR), we combine the two risk groups. The estimated parameter of rs2254298 is 0.7799 and its 95%CL is (0.045, 1.510). Therefore, there is still a significant association between lifetime MDD and rs2254298 (OXTR) in the whole sample (p=.036).

Discussion

We found associations between the personal importance of S/R and genes for dopamine (DRD2 SNP rs1800497), oxytocin (OXTR SNP rs2254298), serotonin (5HT1B SNPs rs130058 and rs11568817), and their vesicular transporter (VMAT1 SNP rs1390938) uniquely in the low-risk group. DRD2 was associated with both risk for depression and positively associated with S/R in the low-risk group. OXTR was associated with lifetime depression across both the high risk and the low risk group.

Research Question 1: What are the single-gene correlates of spirituality?

Findings on VMAT1, 5HT1B, OXTR, and DRD2 in the low-risk sample are consistent with previous literature that relates these genes with spirituality or closely related constructs. Interestingly, these genetic associations and their expression map onto three distinct domains related to spirituality: *mood, bonding, and transcendence.* As with VMAT and 5HT1B, which are linked to *mood,* spirituality has been linked with positive mood and thriving and as both conferring protective benefit against depression and other forms of psychopathology (Akrawi, Bartrop, Potter, & Touyz, 2015; Lucette, Ironson, Pargament, & Krause, 2016; Miller, 1998; in this sample, Miller et al 2014; Miller, Davies & Greenwald, 2000; Miller, Weissman, Gur & Adams, 2001). Spirituality, like OXTR, has been implicated in outcomes of *bonding* including prosocial behavior and empathy (Rew & Wong, 2006; Giordano, Prosek & Lankford, 2014). Dopamine receptor genes (here DRD2), like spirituality, have been linked to *transcendence* through previous studies (Comings et al, 2000; 2002).

Research Question 2: What are the single-gene correlates of depression?

DRD2 minor allele was found to be both a risk factor for depression and positively associated with higher levels of importance of S/R in the low-risk sample. Additionally, rates of minor allele frequency were significantly greater in the low-risk group than the high-risk group, suggesting the presence of a minor allele is more normative in the low-risk sample. This finding on DRD2 may lend support to previous research around a common pathway or physiology underlying both existentially oriented depression and spirituality (Miller, 2014; Miller & Barton, 2015; Barton, Barkin, & Miller, 2017). Experiential trait correlates that mirror this finding include the positive associations to both depression and spirituality found in openness to experience (Trull & Sher, 1994; Wolfstein & Trull, 1997; Henningsgaard & Arnau, 1998) and self-transcendence (for a review, see Cloninger, 2008).

DRD2 minor allele may increase risk for *either* depression or spirituality based upon environment, both that environment external to us and the internal environment that is in the use and practice of inner life (prayer, meditation, reflection, habitual inner ways of living). The physiological pathway supported by the DRD2 minor allele may show functional or morphological change due to spiritual practice. Offering some support for this hypothesis, neuroimaging shows common regions of parietal, precuneus and occipital cortex to be thicker in people with a *sustained* spirituality over five years and thinner in people with depression (Miller et al, 2014; Liu et al, this issue). Within the NIH pediatric imaging study, among those adolescents with mild-moderate levels of depression, those who also were high in transcendence (as measured by the Cloninger Self-Transcendence Scale) showed a differential cluster of depressive symptoms (less disrupted sleep and less anhedonia) and differential co-morbidity (less substance abuse and conduct disorder) then those low in self-transcendence (Miller & Barton, 2015).

The possibility that a sub-type of mild to moderate depression is associated with specifically the dopaminergic pathway mirrors a great body of clinical literature on the existential struggle (reward or lack of reward; ability to perceive transcendence and sense value) around developmental transitions and life events to find a felt sense of ultimate connection, meaning and purpose (Benson, Scales, Syvertsen, & Roehlkepartain 2012; Gottlieb, Still, & Newby-

Clark, 2007). It is possible that the epigenetic interaction of the minor allele of DRD2, with fellow bonding and mood related genes, is essential for report of spirituality (by conferring a greater capacity for transcendence). The fellow genes associated with spirituality (VMAT1, OXTR, and 5HT1BR) without the presence of minor allele DRD2 instead may confer a likelihood for a subtype identified by positive psychology as secular “virtuous humanists” (Barton & Miller, 2015).

Lending some support, a differential susceptibility and resilience of the dopaminergic system based upon environment was explored through a recent meta-analysis. Children with the “at-risk” DRD2 genotype (with the minor allele) fared worse in adverse environments but benefitted most in positive environments (Bakermans-Kranenburg & van Ijzendoorn, 2011). Similar findings supporting differential susceptibility have been found in studies examining the relation between DRD2 and aggression, intergenerational transmission of parenting, and response to prevention programs (Simons et al, 2011; Brody, Chen, & Beach, 2013; Beaver & Belsky, 2012). More generally, differential susceptibility also remains congruent with the theory of Reward Deficiency Syndrome (Comings & Blum, 2000), which suggests that the same individual at risk for addiction due to a less efficient dopaminergic system is responsive to spiritual intervention, perhaps due to the stimulation of the dopaminergic system. In light of surrounding research on openness to experience and self-transcendence, it may be susceptibility and sensitivity to the environment-a capacity for spiritual perception-that drives the relationship between depression and spirituality in the association with DRD2 SNP rs1800497. In this case, perhaps either depression or spirituality may be the resulting phenomenology of DRD2. Further research conducted at multiple levels of analysis is required to understand whether functional differences due to dopamine gene receptor polymorphic variation underlie a phenotype that is both susceptible to depression and yet protected through spirituality.

A more commonly researched associated between depression and bonding is reflected across the full sample, in both the high-risk and low-risk group (with particular strength in the high risk group), in the association between the oxytocin receptor gene (OXTR) rs2254298 and depression. This finding potentially suggests that the extensively researched pathway of OXTR to depression is a differential pathway to that of DRD2. To this body of research on OXTR, the current study replicates that OXTR interacts with familial risk for depression to predict psychopathology including depression and anxiety (Thompson et al, 2011). Difference by risk group could not be definitively be established due to a non-significance interaction term (OXTR x risk-group). That in the low-risk group alone OXTR was not significant, however, gains support from previous work by Brune (2012) who suggests a distinct physiological profile based upon environment to diverge from the OXTR gene over the course of the life-span. Drawing on a thorough review of existing literature on specifically the SNP rs2254298 (OXTR), Brune applies Belsky et al’s (2009) theory of *differential susceptibility*, to suggest that the phenotypic expression of genetic variants of rs2254298, whether favorable or unfavorable, are dependent on early environmental factors. The OXTR-specific gene-environment interaction has been directly tested in at least two studies. In a study by Thompson et al (2011), children with a heterozygous rs2254298 SNP in a high-risk group (with familial risk for depression) and children with the same variant in a low-risk group varied significantly in measures of psychopathology, in that children in the

high-risk group had significantly more depressive symptoms than those in the low-risk group. Further, when compared with children who were homozygous GG carriers in the low-risk group, low-risk children with a minor allele had the fewest depressive symptoms, suggesting that the GG carriers were less responsive to context than were the AG carriers.

In a low-income, African-American sample, Bradley and colleagues (2011) showed that OXTR SNP rs53576 moderated the relationship between childhood maltreatment and both attachment style and emotional dysregulation. In the sample, male and female G allele carriers were at increased risk for emotional dysregulation and attachment problems after experiencing childhood abuse. However, in other studies, these same vulnerable G allele carriers also sought out social support in times of stress (Kim et al, 2010). In fact, the G allele had, in less adverse conditions (not including maltreatment), been associated with higher levels of empathy and sensitive parenting (Rodrigues et al, 2009; Bakersman-Kranenburg & van Ijzendoorn, 2008). Thus, Bradley suggested that the counterintuitive finding, that G allele individuals were at most risk in this sample, aligned with the findings that the G allele conferred resilience in other studies, by application of Belsky's model.

Research Question 3: Are there differential associations based on risk status?

There appears to be a suppression of the phenotypic expression of spirituality in people at high risk for depression. In the high-risk group none of the candidate genes were associated with personal importance of S/R, despite consistent positive findings across four genes in the low-risk group. Differential risk and protective factors by familial risk for depression is consistent with other studies on clinical outcomes from this longitudinal sample. In Fendrich, Warner, & Weissman (1990), family risk factors of poor marital adjustment, divorce, parent-child discord, affectionless control and DSM-III diagnoses were predictive of depression and other diagnoses in offspring only in the low-risk group. In the high-risk group none of these usual family risk factors conferred risk for offspring diagnoses. In a 2006 study, Pilowsky and colleagues replicated this null finding in a subsequent generation of the same the study, among the children of these depressed parents 20 years later, showing that affectionless control remains predictive of MDD only in the low-risk group. These findings suggest that the impact of parental depression may outweigh other risk and protective factors in predicting clinical outcomes. In this study, it appears that in the high-risk group, familial ecology may in part suppress the phenotypic expression of genes otherwise associated with spirituality.

Our findings on potential suppression of the phenotype of spirituality speak to the intergenerational conference of risk for depression, and seem to point to opportunity for prevention and intervention in offspring. Previous prevention-intervention research shows that the intergenerational transmission of depression can be disrupted by preemptively supporting protective factors in offspring. (Beardslee, Gladstone, & O'Connor, 2011; Verdeli et al, 2004), raising the possibility that the fostering of spirituality in offspring of depressives might be preventative against a subsequent offspring depression.

Development of spirituality in offspring is partially dependent on the lived spirituality of a parental figure, as well as his or her tendency to clearly articulate and support spiritual beliefs and values (Boyatzis, Dollahite, & Marks, 2006). Parental expression and

transmission of spirituality may be mitigated by a mood disorder generating a depressogenic outlook (Gur, Miller, Warner, Wickramarantne, & Weissman, 2005). However, previous research on this same sample shows that the intergenerational transmission of religious denomination, (whether or not there is high level of parental spirituality) decreases the likelihood of transmission of depression and anxiety in offspring (in both high and low-risk groups) by 91% (Jacobs et al, 2012). Offspring of depressed parents, who are exposed in childhood to religious community, may find other adults who exhibit a strong spirituality, support for their own spirituality, and a "road map" to spiritual life derive the customary protective benefits of spirituality. Selective spiritual socialization (Miller et al, 2001), previously to have been identified in offspring of Opiate addicts, shows that youth tend to become concordant with the spirituality held by the healthiest committed parent figure in their lives, and in turn derive the protective benefits of spirituality. Prevention against the intergenerational transmission of depression may be derived from healthy adults who support offspring spirituality and/or engagement of youth in a community based upon religious or spiritual life (to include a community of service).

Limitations

The study design has the chief limitation of a single time assessment of religion and spirituality, drawn from the available data in this thirty-year longitudinal design. The single-item measure further conflates religion and spirituality, which are two distinct but related constructs and ways of living. A second customary limitation in single-gene research is that identification of single genes can point to pathways but does not fully explain the relationship between gene and behavior.

Conclusion

Spirituality and/or its expression as religiousness (S/R) may be a phenotype of DRD2, HT1B, VMAT1 and OXTR, in people at low risk for depression. Uniquely the minor allele of DRD2 (previously linked with reward and transcendence) is associated with both importance of S/R and increased risk for depression in people at low familial risk for depression, perhaps implicating a common pathway or mechanism dependent on environment (outer environment or practice of inner life). High familial risk for depression may suppress the phenotypic expression of these genes otherwise associated with spirituality. The association between MDD and bonding is associated with OXTR and found across both high and low risk for depression, suggesting a potentially differential pathway of depression..

References

Acevedo SF, Valencia C, Lutter M, McAdams CJ. Severity of eating disorder symptoms related to oxytocin receptor polymorphisms in anorexia nervosa. Psychiatry research. 2015; 228(3):641–648. [PubMed: 26106053]

Akrawi D, Bartrop R, Potter U, Touyz S. Religiosity, spirituality in relation to disordered eating and body image concerns: A systematic review. Journal of Eating Disorders. 2015; 3:29. http://doi.org/10.1186/s40337-015-0064-0. [PubMed: 26279837]

Aspé-Sánchez M, Moreno M, Rivera MI, Rossi A, Ewer J. Oxytocin and Vasopressin Receptor Gene Polymorphisms: Role is Social and Psychiatric Traits. Frontiers in Neuroscience. 2016; 28(9):510.

Bakermans-Kranenburg MJ, van IJzendoorn MH. Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. Social cognitive and affective neuroscience. 2008; 3(2):128–134. [PubMed: 19015103]

Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to rearing environment depending on dopamine-related genes: *New evidence and a meta-analysis*. Development and Psychopathology. 2011; 23(1):39–52. [PubMed: 21262038]

Baldinger P, Kraus C, Rami-Mark C, Gryglewski G, Kranz GS, Haeusler D, Hahn A, Spies M, Wolfgang W, Mitterhauser M, Rujescu D, Kasper S, Lanzenberger R. Interaction between 5-HTTLPR and 5-HT1B genotype status enhances cerebral 5-HT1A receptor binding. NeuroImage. 2015; 111(1):505–512. [PubMed: 25652393]

Barton YA, Barkin SH, Miller L. Deconstructing depression: A latent profile analysis of potential depressive subtypes in emerging adults. Spirituality in Clinical Practice. (in press).

Beardslee WR, Gladstone TR, O'Connor EE. Transmission and prevention of mood disorders among children of affectively ill parents: a review. Journal of the American Academy of Child & Adolescent Psychiatry. 2011; 50(11):1098–1109. [PubMed: 22023998]

Beaver KM, Gibson CL, Jennings WG, Ward JT. A gene X environment interaction between DRD2 and religiosity in the prediction of adolescent delinquent involvement in a sample of males. Biodemography and Social Biology. 2009; 55(1):71–81. [PubMed: 19835101]

Beaver KM, Belsky J. Gene-environment interaction and the intergenerational transmission of parenting: testing the differential-susceptibility hypothesis. Psychiatric Quarterly. 2012; 83(1):29–40. [PubMed: 21553075]

Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychological bulletin. 2009; 135(6):885. [PubMed: 19883141]

Benson PL, Scales PC, Syvertsen AK, Roehlkepartain EC. Is youth spiritual development a universal developmental process? An international exploration. The Journal of Positive Psychology. 2012; 7(6):453–470.

Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM, Cowen PJ. Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [11C]WAY-100635. Molecular Psychiatry. 2004; 9(4):386–392. [PubMed: 15042104]

Blum K, Chen AL, Giordano J, Borsten J, Chen TJ, Hauser M, Simpatico T, Femino J, Braverman ER, Barh D. The addictive brain: All roads lead to dopa-mine. Journal of Psychoactive Drugs. 2012; 44(2):134–143. [PubMed: 22880541]

Blum K, Cull JG, Braverman ER, Comings DE. Reward deficiency syndrome. American Scientist. 1996; 84(2):132–145.

Blum K, Febo M, McLaughlin T, Cronje FJ, Han D, Gold MS. Hatching the behavioral addiction egg: Reward Deficiency Solution System (RDSS)TM as a function of dopaminergic neurogenetics and brain functional connectivity linking all addictions under a common rubric. Journal of Behavioral Addictions. 2014; 3(3):149–156. [PubMed: 25317338]

Blum, K., Kozlowski, GP. Ethanol and neuromodulator interactions: a cascade model of reward. In: Ollat, H.Parvez, S., Parvez, H., editors. Alcohol and Behavior. Utrecht, Netherlands: VSP Press; 1990. p. 131-149.

Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, Nogami H, Briggs AH, Cohn JB. Allelic association of human dopamine D2 receptor gene in alcoholism. Journal of the American Medical Association. 1990; 263(15):2055–2060. [PubMed: 1969501]

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, Comings DE. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. Journal of the Royal Society of Medicine. 1996; 89(7):396–400. [PubMed: 8774539]

Borg J, Andree B, Sderstrom H, Farde L. The serotonin system and spiritual experiences. American Journal of Psychiatry. 2003; 160(11):1965–1969. [PubMed: 14594742]

Boyatzis CJ, Dollahite DC, Marks LD. The family as a context for religious and spiritual development in children and youth. The handbook of spiritual development in childhood and adolescence. 2006:297–309.

Bradley B, Westen D, Mercer KB, Binder EB, Jovanovic T, Crain D, … Heim C. Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: Moderation by oxytocin receptor gene. Development and Psychopathology. 2011; 23(02):439–452. [PubMed: 23786688]

Brody GH, Chen YF, Beach SR. Differential susceptibility to prevention: GABAergic, dopaminergic, and multilocus effects. Journal of Child Psychology and Psychiatry. 2013; 54(8):863–871. [PubMed: 23294086]

Brune M. Does the oxytocin receptor (OXTR) polymorphism (r2254298) confer 'vulnerability for psychopathology or 'differential susceptibility'? Insights from evolution. BMC Medicine. 2012:10–38. [PubMed: 22296610]

Butler P, McNamara P, Durso R. Deficits in the automatic activation of religious concepts in patients with Parkinsons Disease. Journal of the International Neuropsychological Society. 2010; 16:252–261. [PubMed: 19958570]

Butovskaya PR, Lazebnij OE, Fekhretdinova DI, Vasil'ev VA, Prosikova EA, Lysenko VV, Udina IG, Butovskaya ML. The relationship between polymorphism of four sertonic genes (5-HTTL, 5-HT1A, 5-HT2A, and MAOA) and personality in wrestlers and contro group. Molecular Genetics, Microbiology and Virology. 2015; 30(4):165–172.

Cao J, LaRocque E, Li D. Associations of the 5-hydroxytryptamine (serotonin) receptor 1B gene (HTR1B) with alcohol, cocaine, and heroin abuse. American Journal of Medicine. 2013; 162B(2): 169–176.

Caylak E. Biochemical and genetic analyses of childhood Attention Deficit/Hyperactivity Disorder. American Journal of Medicine and Genetics. 2012; 159B:613–627.

Chen D, Liu F, Shang Q, Song X, Miao X, Wang Z. Association between polymorphisms of DRD2 and DRD4 and opioid dependence: Evidence from the current studies. American Journal of Medicine and Genetics. 2011; 156:661–670.

Chen MH, Yang Q. GWAF: an R package for genome-wide association analyses with family data. Bioinformatics. 2010; 26:580–581. [PubMed: 20040588]

Christiansen L, Tan Q, Iachina M, Bathum L, Kruse TA, McGue M, Christensen K. Candidate gene polymorphisms in the serotonergic pathway: influence on depression symptomatology in an elderly population. Biological Psychiatry. 2007; 61(2):223–230. [PubMed: 16806099]

Cloninger CR. The psychobiological theory of temperament and character: comment on Farmer and Goldberg. Psychological Assessment. 2008; 20(3):292–299. [PubMed: 18778165]

Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. Progress in brain research. 2000; 126:325–341. [PubMed: 11105655]

Comings DE, Gade-Andavolu R, Gonzalez N, Wu S, Muhleman D, Blake H, … MacMurray JP. A multivariate analysis of 59 candidate genes in personality traits: the temperament and character inventory. Clinical Genetics. 2000; 58(5):375–385. [PubMed: 11140838]

Comings DE, Saucier G, MacMurray JP. Role of DRD2 and other dopamine genes in personality traits. Molecular genetics and the human personality. 2002:165.

Conner TS, Jensen KP, Tennen H, Furneaux HM, Kranzler HR, Covault J. Functional polymorphisms in the serotonin 1B receptor gene (HTR1B) predict self-reported anger and hostility among young men. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2010; 153(1):67–78.

Costa B, Pini S, Gabelloni P, Abelli M, Lari L, Cardini L, … Martini C. Oxytocin receptor polymorphisms and adult attachment styles in patients with depression. Psychoneuroendocrinology. 2009; 34(10):1506–14. [PubMed: 19515497]

Dadds MR, Moul C, Cauchi A, DobsonStone C, Hawes DJ, Brennan J, Urwin R, Ebstein RE. Polymorphisms in the oxytocin receptor gene are associated with the development of Psychopathy. Development and Psychopathology. 2013; 26(1):21–31. [PubMed: 24059750]

Dickel DE, Veenstra-VanderWeele J, Bivens NC, Wu X, Fischer DJ, Van Etten-Lee M, … Hanna GL. Association studies of serotonin system candidate genes in early-onset obsessive-compulsive disorder. Biological Psychiatry. 2007; 61(3):322–329. [PubMed: 17241828]

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, … Mathis C. PET imaging of serotonin 1A receptor binding in depression. Biological Psychiatry. 1999:1375–1387. [PubMed: 10578452]

Drevets WC, Thase M, Moses E, Price J, Frank E, Kupfer DJ, Mathis C. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nuclear Medicine and Biology. 2007; 34(7):865–877. [PubMed: 17921037]

Dutta N, Helton SG, Schwandt M, Zhu X, Momenan R, Lohoff FW. Genetic Variation in the Vesicular Monoamine Transporter 1 (VMAT1/SLC18A1) Gene and Alcohol Withdrawal Severity. Alcoholism: Clinical and Experimental Research. 2016; 40(3):474–481.

El-Ibiary SY, Hamilton SP, Abel R, Erdman CA, Robertson PA, Finley PR. A pilot study evaluating geneticand environmental factors for postpartum depression. Innovations in Clinical Neuroscience. 2013; 10(9–10):15–22.

Eisenstein SA, Bogdan R, Love-Gregory L, Corral-Frías NS, Koller JM, Black KJ, Moerlein SM, Perlmutter JS, Barch DM, Hershey T. Prediction of striatal D2 receptor binding by DRD2/ANKK1 TaqIA allele status. Synapse. 2016; 70(10):418–431. [PubMed: 27241797]

Erickson JD, Schafer MK, Bonner TI, Eiden LE, Weihe E. Distinct pharmacological properties and distribution in neurons and endocrine cells of two isoforms of the human vesicular monoamine transporter. Proceedings of the National Academy of Sciences. 1996; 93(10):5166–5171.

Fehr C, Grintschuk N, Szegedi A, Anghelescu I, Klawe C, Singer P, … Dahmen N. The HTR1B 861G> C receptor polymorphism among patients suffering from alcoholism, major depression, anxiety disorders and narcolepsy. Psychiatry Research. 2000; 97(1):1–10. [PubMed: 11104852]

Feldman R, Monakhov M, Pratt M, Ebstein RP. Oxytocin pathway genes: evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. Biological Psychiatry. 2016; 79:174–184. [PubMed: 26392129]

Fendrich M, Warner V, Weissman MM. Family risk factors, parental depression, and psychopathology in offspring. Developmental Psychology. 1990; 26(1):40.

Giegling I, Hartmann AM, Möller HJ, Rujescu D. Anger-and aggression-related traits are associated with polymorphisms in the 5-HT-2A gene. Journal of Affective Disorders. 2006; 96(1):75–81. [PubMed: 16814396]

Giordano AL, Prosek EA, Lankford CT. Predicting Empathy: The Role of Religion and Spirituality. Journal of Professional Counseling, Practice, Theory, & Research. 2014; 41(2):53.

Gluskin BS, Mickey BJ. Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human in vivo molecular imaging studies. Translational Psychiatry. 2016; 6(3):e747. [PubMed: 26926883]

Gottlieb BH, Still E, Newby-Clark IR. Types and precipitants of growth and decline in emerging adulthood. Journal of Adolescent Research. 2007; 22(2):132–155.

Gu L, Long J, Yan Y, Chen Q, Pan R, Xie X, Mao X, Hu X, Wei B, Su L. HTR2A–1438A/G polymorphism influences the risk of schizophrenia but not bipolar disorder or major depressive disorder: a meta-analysis. Journal of Neuroscience Research. 2013; 91:623–633. [PubMed: 23404241]

Gur M, Miller L, Warner V, Wickramaratne P, Weissman M. Maternal depression and the intergenerational transmission of religion. The Journal of nervous and mental disease. 2005; 193(5):338–345. [PubMed: 15870618]

Hakulinen C, Jokela M, Hintsanen M, Merjonen P, Pulkki-Raback L, Seppala I, … Keltikangas-Jarvinen L. Serotonin receptor 1B genotype and hostility, anger and aggressive behavior through the lifespan: the Young Fins study. Journal of Behavioral Medicine. 2013; 36:583–590. [PubMed: 22945537]

Ham BJ, Kim YH, Choi MJ, Cha JH, Choi YK, Lee MS. Serotonergic genes and personality traits in the Korean population. Neuroscience Letters. 2004; 354(1):2–5. [PubMed: 14698468]

Hamer, DH. The God gene: How faith is hardwired into our genes. Anchor; 2005.

Henningsgaard JM, Arnau RC. Relationships between religiosity, spirituality, and personality: a multivariate analysis. Personality and Individual Differences. 2008; 45:703–708.

Huang YY, Grailhe R, Arango V, Hen R, Mann JJ. Relationship of psychopathology to the human serotonin 1B genotype and reeptor binding kinetics in postmortem brain tissue. Neuropsychopharmacology. 1999; 21(2):238–246. [PubMed: 10432472]

Huang YY, Oquendo MA, Friedman JM, Greenhill LL, Brodsky B, Malone KM, … Mann JJ. Substance abuse disorder and major depression are associated with the human 5-HT1B receptor

gene (HTR1B) G861C polymorphism. Neuropsychopharmacology. 2003; 28(1):163–169. [PubMed: 12496953]

Jacob S, Brune CW, Carter CS, Leventhal BL, Lord C, Cook E. Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. Neuroscience Letters. 2007; 417(1):6–9. [PubMed: 17383819]

Jacobs M, Miller L, Wickramaratne P, Gameroff M, Weissman MM. Family religion and psychopathology in children of depressed mothers: Ten-year follow-up. Journal of Affective Disorders. 2012; 136(3):320–327. [PubMed: 22177740]

Jin C, Xu W, Yuan J, Wang G, Cheng Z. Meta-analysis of association between the -1438A/G (rs6311) polymorphism of the serotonin 2A receptor gene and major depressive disorder. Neurological Research. 2013; 35(1):7–14. [PubMed: 23317793]

Kalbitzer J, Frokjaer VG, Erritzoe D, Svarer C, Cumming P, Nielsen FA, … Knudsen GM. The personality trait openness is related to cerebral 5-HTT levels. NeuroImage. 2009; 45(2):280–285. [PubMed: 19135154]

Kaufman J, Birmaher B, Brent D, Rao UMA, Flynn C, Moreci P, … Ryan N. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child & Adolescent Psychiatry. 1997; 36(7):980–988. [PubMed: 9204677]

Kaufman J, DeLorenzo C, Choudhury S, Parsey RV. The 5-HT 1A receptor in major depressive disorder. European Neuropsychopharmacology. 2016; 26(3):397–410. [PubMed: 26851834]

Kjaer TW, Bertelsen C, Piccini P, Brooks D, Alving J, Lou HC. Increased dopamine tone during meditation-induced change of consciousness. Cognitive Brain Research. 2002; 13(2):255–259. [PubMed: 11958969]

Kim JH, Son YD, Kim JH, Choi EJ, Lee SY, Joo YH, … Cho ZH. Self-transcendence trait and its relationship with in vivo serotonin transport availability in brainstem raphe nuclei: An ultra-high resolution PET-MRI study. Brain Research. 2015; (1629):63–7.

Kim HS, Sherman DK, Sasaki JY, Xu J, Chu TQ, Ryu C, … Taylor SE. Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking. Proceedings of the National Academy of Sciences. 2010; 107(36):15717–15721.

Kishi T, Reigi Y, Fukuo Y, Okochi T, Matsunaga S, Umene-Nakano W, … Iwata N. The serotonin 1A receptor gene confer susceptibility to mood disorders: results from an extended meta-analysis of patients with major depression and bipolar disorder. European Archives of Psychiatry and Clinical Neuroscience. 2013; 263:105–118. [PubMed: 22752684]

Klein DN, Lewinsohn PM, Rohde P, Seeley JR, Durbin CE. Clinical features of major depressive disorder in adolescents and their relatives: impact on familial aggregation, implications for phenotype definition, and specificity of transmission. Journal of Abnormal Psychology. 2002; 111(1):98. [PubMed: 11866183]

Koenig HG. Research on religion, spirituality, and mental health: A review. Canadian Journal of Psychiatry. 2009; 54(5):283–91. [PubMed: 19497160]

Lappalainen J, Long JC, Eggert M, Ozaki N, Robin RW, Brown GL, … Goldman D. Linkage of Antisocial Alcoholism to the serotonin 5-HT1B receptor gene in 2 populations. Archives of General Psychiatry. 1998; 55:989–994. [PubMed: 9819067]

Lee SY, Lin WW, Huang SY, Kuo PH, Wang CL, Wu PL, … Lu RB. The relationship between serotonin receptor 1B polymorphisms A-161T and alcohol dependence. Alcoholism Clinical and Experimental Research. 2009; 33(9):1585–1589.

Leib R, Isensee B, Hofler M, Pfiste H, Wittchen H. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. Archives of General Psychiatry. 2002; 59:365–374. [PubMed: 11926937]

Lenze EJ, Dixon D, Nowotny P, Lotrich FE, Doré PM, Pollock BG, … Butters MA. Escitalopram reduces attentional performance in anxious older adults with high-expression genetic variants at serotonin 2A and 1B receptors. The International Journal of Neuropsychopharmacology. 2013; 16(2):279–288. [PubMed: 22717018]

Lerer E, Levi S, Salomon S, Darvasi A, Yirmiya N, Ebstein RP. Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. Molecular Psychiatry. 2008; 13:980–988. [PubMed: 17893705]

Li L, Bao Y, He S, Wang G, Guan Y, Ma D, Wang P, Huang X, Tao S, Zhang D, Liu Q, Wang Y, Yang J. The association between genetic variants in the dopaminergic system and posttraumatic stress disorder: a meta-analysis. Medicine. 2016; 95(11)

Lin JY, Jiang MY, Kan ZM, Chu Y. Influence of 5-HTR2A genetic polymorphisms on the efficacy of antidepressants and the treatment of major depressive disorder: a meta-analysis. Journal of Affective Disorders. 2014; 168:430–438. [PubMed: 25108775]

Liu J, Svob C, Wickmarantre P, Hao X, Talati A, Kayser J, Tenke C, Warner V, Yang J, Anderson M, Weissman MR. Neuroanatomical correlates of familial risk for depression and religiosity/spirituality. Spirituality in Clinical Practice. (in press).

Liu X, Kawamura Y, Shimada T, Otowa T, Koishi S, Sugiyama T, … Sasaki T. Association of the oxytocin receptor (OXTR) gene polymorphisms with autism spectrum disorder (ASD) in the Japanese population. Journal of Human Genetics. 2010; 55:137–141. [PubMed: 20094064]

Lohoff FW, Lautenschlager M, Mohr J, Ferraro TN, Sander T, Gallinat J. Association between variation in the vesicular monoamine transporter 1 gene on chromosome 8p and anxiety-related personality traits. Neuroscience Letters. 2008; 434(1):41–45. [PubMed: 18249496]

Lohoff FW, Hodge R, Narasimhan S, Nall A, Ferraro TN, Mickey BJ, … Nikolova YS. Functional genetic variants in the vesicular monoamine transporter 1 modulate emotion processing. Molecular Psychiatry. 2014; 19(1):129–139. [PubMed: 23337945]

Lorenzi C, Serretti A, Mandelli L, Tubazio V, Ploia C, Smeraldi E. 5-HT1A polymorphism and self-transcendence in mood disorders. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics. 2005; 137B(1):33–35.

Lucette A, Ironson G, Pargament KI, Krause N. Spirituality and Religiousness are Associated With Fewer Depressive Symptoms in Individuals With Medical Conditions. Psychosomatics. 2016

Lucht MJ, Barnow S, Sonnenfeld C, Rosenberger A, Grabe HJ, … Rosskopf D. Associations between the oxytocin receptor gene (OXTR) and loneliness and intelligence in normal subjects. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009; 33(5):860–866. [PubMed: 19376182]

Mandelli L, Serretti A. Gene environment interaction studies in depression and suicidal behavior: An update. Neuroscience and Biobehavioral Reviews. 2013; 37(10,1):2375–97. [PubMed: 23886513]

Mannuzza S, Fyer AJ, Klein DF, Endicott J. Schedule for Affective Disorders and Schizophrenia—Lifetime Version modified for the study of anxiety disorders (SADS-LA): rationale and conceptual development. Journal of Psychiatric Research. 1986; 20(4):317–325. [PubMed: 3806426]

Miller, BA. Intergenerational transmission of religiousness and spirituality. In: Miller, William R., Delaney, Harold D., editors. Judeo-Christian perspectives on psychology: Human nature, motivation, and change. Washington, DC, US: American Psychological Association; 2005. p. 227-244.p. xvip. 329

Miller L, Bansal R, Wickramaratne P, Hao X, Tenke CE, Weissman MM, Peterson BS. Neuroanatomical correlates of religiosity and spirituality: a study in adults at high and low familial risk for depression. JAMA psychiatry. 2014; 71(2):128–135. [PubMed: 24369341]

Miller L, Barton YA. Developmental Depression in Adolescents: A Potential Subtype Based on Neural Correlates and Comorbidity. Journal of Religion and Health. 2015; 54(3):817–828. [PubMed: 25877664]

Miller L, Davies M, Greenwald S. Religiosity and substance use and abuse among adolescents in the National Comorbidity Survey. Journal of the American Academy of Child & Adolescent Psychiatry. 2000; 39(9):1190–1197. [PubMed: 10986817]

Miller L, Weissman M, Gur M, Adams P. Religiousness and substance use in children of opiate addicts. Journal of Substance Abuse. 2001; 13(3):323–336. [PubMed: 11693455]

Miller WR. Researching the spiritual dimensions of alcohol and other drug problems. Addiction. 1998; 93:979–990. [PubMed: 9744129]

Moore RC, Eyler L, Mills PJ, O'Hara RM, Wachmann K, Lavretsky H. Biology of Positive Psychiatry. Positive Psychiatry: A Clinical Handbook. 2015:155.

Munafo MR, Matheson IJ, Flint J. Association of the DRD2 gene Taq1A polymorphism and alcoholism: a meta-analysis of case-control studies and evidence of publication bias. Molecular Psychiatry. 2007; 12:454–461. [PubMed: 17453061]

Murrough JW, Henry S, Hu J, Gallezot JD, Planeta-Wilson B, Neumaier JF, Neumeister A. Reduced ventral striatal/ventral pallidal serotonin 1b receptor binding potential in major depressive disorder. Psychopharmacology. 2011; 213:547–553. [PubMed: 20480149]

Nemoda Z, Lyons-Ruth K, Szekely A, Bertha E, Faludi G, Sasvari-Szekely M. Associations between dopaminergic polymorphisms and borderline personality traits among at risk adults and psychiatric inpatients. Behavioral Brain Functions. 2010; 6(1):1. [PubMed: 20047681]

Nemoda Z, Szekely A, Sasvari-Szekely M. Psychopathological aspects of dopaminergic gene polymorphisms in adolescence and young adulthood. Neuroscience and Biobehavioral Reviews. 2011; 35(8):1665–1686. [PubMed: 21527290]

Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: A novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Human Mutation. 2004; 23:540–545. [PubMed: 15146457]

Newberg AB, Iversen J. The neural basis of the complex task of meditation: neurotransmitter and neurochemical considerations. Medical Hypotheses. 2003; 61(2):282–291. [PubMed: 12888320]

Nillson KW, Damberg M, Öhrvik J, Leppert J, Anckarsäter H, Oreland L. Genes encoding for AP-2β and the Serotonin Transporter are associated with the Personality Character Spiritual Acceptance. Neuroscience Letters. 2007; 411(3):233–237. [PubMed: 17123722]

Noble EP. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. American Journal of Medical Genetics. 2003; 116B:103–125. [PubMed: 12497624]

Park JH, Gail MH, Weinberg CR, Carroll RJ, Chung CC, Wang Z, … Chatterjee N. Distribution of allele frequencies and effect sizes and their interrelationships for common genetic susceptibility variants. Proceedings of the National Academy of Sciences. 2011; 108(44):18026–18031.

Parsons MJ, D'Souza UM, Arranz MJ, Kerwin RW, Makoff AJ. The–1438A/G polymorphism in the 5-hydroxytryptamine type 2A receptor gene affects promoter activity. Biological Psychiatry. 2004; 56(6):406–410. [PubMed: 15364038]

Peciña M. DRD2 polymorphisms modulate reward and emotion processing, dopamine neurotransmission and openness to experience. Cortex. 2013; 49(3):877–890. [PubMed: 22424959]

Perroud, N. Religion/Spirituality and Neuropsychiatry. In: Huguelet, P., Koenig, HG., editors. Religion and Spirituality in Psychiatry. Cambridge, GBR: University Press; 2009.

Perroud N, Bondolfi G, Uher R, Gex-Fabry M, Aubry JM, Bertschy G, … Kosel M. Clinical and genetic correlates of suicidal ideation during antidepressant treatment in a depressed outpatient sample. Pharmacogenomics. 2011; 12(3):365–377. [PubMed: 21449676]

Pilowsky DJ, Wickramaratne P, Nomura Y, Weissman MM. Family discord, parental depression, and psychopathology in offspring: 20-year follow-up. Journal of the American Academy of Child & Adolescent Psychiatry. 2006; 45(4):452–460. [PubMed: 16601650]

Rew L, Wong YJ. A systematic review of associations among religiosity/spirituality and adolescent health attitudes and behaviors. Journal of Adolescent Health. 2006; 38(4):433–442. [PubMed: 16549305]

Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. Proceedings of the National Academy of Sciences. 2009; 106(50):21437–21441.

Roetker NS, Yonker JA, Lee C, Chang V, Basson JJ, Roan CL, … Atwood CS. Multigene interactions and the prediction of depression in the Wisconsin Longitudinal Study. BMJ Open Access. 2012; 2(4)

Ropers HH. Single gene disorders come into focus–again. Dialogues. Dialogues in Clinical Neuroscience. 2010; 12(1):95–102. [PubMed: 20373671]

Saiz PA, García-Portilla MP, Paredes B, Arango C, Morales B, Alvarez V, … Bobes J. Association between the A-1438G polymorphism of the serotonin 2A receptor gene and nonimpulsive suicide attempts. Psychiatric Genetics. 2008; 18(5):213–218. [PubMed: 18797395]

Saiz PA, Garcia-Portilla MP, Herrero R, Arango C, Corcoran P, Morales B, … Fernandez JM. Interactions between functional serotonergic polymorphisms and demographic factors influence personality traits in healthy Spanish Caucasians. Psychiatric Genetics. 2010; 20(4):171–178. [PubMed: 20421848]

Sarouglou V. Religion and the five factors of personality: A meta-analytic review. Personality and Individual Differences. 2002; 32:15–25.

SAS Software Version 9.2. Cary, NC, USA: Registered trademark of SAS Institute Inc; Copyright © 2008

Sasaki JY, Kim HS, Xu J. Religion and well-being: the moderating role of culture and the oxytocin receptor gene (OXTR). Journal of Cross-cultural Psychology. 2011; 42(8):1392–1405.

Sasaki JY, Mojaverian T, Kim HS. Religion priming and an oxytocin receptor gene (OXTR) polymorphism interact to affect self-control in a social context. Development Psychopathology. 2015; 27(1):97–109. [PubMed: 25640833]

Schwab SG, Franke PE, Hoefgen B, Guttenthaler V, Lichtemann D, Trixler M, … Wildenauer DB. Association of DNA polymorphisms in the synaptic vesicular amine transporter gene (SLC18A2) with alcohol and nicotine dependence. Neuropsychoparmacology. 2005; 30(12):2263–2268.

Shoval G, Ossnat B, Zalsman G, Mann JJ, Chechnik G. Transitions in the transcriptome of the serotonergic and dopaminergic systems in the human brain during adolescence. European Neuropsychopharmacology. 2014; 24:1123–1132. [PubMed: 24721318]

Simons RL, Lei MK, Beach SR, Brody GH, Philibert RA, Gibbons FX. Social environment, genes, and aggression evidence supporting the differential susceptibility perspective. American Sociological Review. 2011; 76(6):883–912.

Smith L, Watson M, Gates S, Ball D, Foxcroft D. Meta-analysis of the association of the Taq1A polymorphism with the risk of alcohol dependency: a HuGE gene-disease association review. American Journal of Epidemiology. 2008; 167(2):125–138. [PubMed: 17989061]

Smith RM, Papp AC, Webb A, Ruble CL, Munsie LM, Nisenbaum LK, … Sadee W. Multiple regulatory variants modulate expression of 5-hydroxytryptamine 2A receptors in human cortex. Biological Psychiatry. 2013; 73(6):546–554. [PubMed: 23158458]

Smith TB, McCullough ME, Poll J. Religiousness and depression: evidence for a main effect and the moderating influence of stressful life events. Psychological Bulletin. 2003; 129(4):614. [PubMed: 12848223]

Solovieff N, Roberts AL, Ratanatharathorn A, Haloosim M, De Vivo I, King AP, … Galea S. Genetic association analysis of 300 genes identifies a risk haplotype in SLC18A2 for post-traumatic stress disorder in two independent samples. Neuropsychopharmacology. 2014; 39(8):1872–1879. [PubMed: 24525708]

Soyka M, Preuss UW, Koller G, Zill P, Bondy B. Association of 5-HT1B receptor gene and antisocial behavior in alcoholism. Journal of Neural Transmission (Austria). 2004; 111(1):101–109.

Stoltenberg SF, Christ CC, Highland KB. Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. Progress in Neuropsychopharmacology & Biological Psychiatry. 2012; 39(1):182–191.

Thompson RJ, Parker KJ, Hallmayer JF, Waugh CE, Gotlib IH. Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression in and anxiety in adolescent girls. Psychoneuroendocrinology. 2011; 26:144–147.

Trull TJ, Sher KJ. Relationship between the five-factor model of personality and Axis I disorders in a nonclinical sample. Journal of Abnormal Psychology. 1994; 103(2):350. [PubMed: 8040504]

Unschuld PG, Ising M, Erhardt A, Lucae S, Kloiber S, Kohli M, … Uhr M. Polymorphisms in the serotonin receptor gene HTR2A are associated with quantitative traits in panic disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2007; 144(4):424–429.

Vaht M, Kiive E, Veidebaum T, Harro J. A functional vesicular monoamine transporter 1 (VMAT1) gene variant is associated with affect and the prevalence of anxiety, affective and alcohol use disorders in a longitudinal population-representative birth cohort study. International Journal of Neuropsychopharmacology. 2016; 19(7)

Van Capellen P, Way BW, Isgett SF, Fredrickson BL. Effects of oxytocin administration on spirituality and emotional responses to meditation. Social Cognitive and Affective Neuroscience. 2016:1–9. [PubMed: 26141925]

Van Ness PH, Larson DB. Religion, senescence, and mental health: The end of life is not the end of hope. The American Journal of Geriatric Psychiatry. 2002; 10(4):386–397. [PubMed: 12095898]

Varga G1, Szekely A, Antal P, Sarkozy P, Nemoda Z, Demetrovics Z, Sasvari-Szekely M. Additive effects of serotonergic and dopaminergic polymorphisms on trait impulsivity. American Journal of Medical Genetics. 2012; 159B(3):281–288. [PubMed: 22259185]

Verdeli H, Ferro T, Wickramaratne P, Greenwald S, Blanco C, Weissman MM. Treatment of depressed mothers of depressed children: pilot study of feasibility. Depression and Anxiety. 2004; 19(1): 51–58. [PubMed: 14978786]

Villafuerte SM, Vallabhaneni K, Œliwerska E, McMahon FJ, Young EA, Burmeister M. SSRI response in depression may be influenced by SNPs in HTR1B and HTR1A. Psychiatric Genetics. 2009; 19(6):281. [PubMed: 19829169]

Voisey J, Swagell CD, Hughes IP, Morris CP, van Daal A, Noble EP, … Lawford BR. The DRD2 gene 957C> T polymorphism is associated with posttraumatic stress disorder in war veterans. Depression and Anxiety. 2009; 26(1):28–33. [PubMed: 18833581]

Walitza S, Bové DS, Romanos M, Renner T, Held L, Simons M, … Grünblatt E. Pilot study on HTR2A promoter polymorphism, –1438G/A (rs6311) and a nearby copy number variation showed association with onset and severity in early onset obsessive–compulsive disorder. Journal of Neural Transmission. 2012; 119(4):507–515. [PubMed: 21874579]

Wang S, Zhang K, Xu Y, Sun N, Shen Y, Xu Q. An association study of the serotonin transporter and receptor genes with the suicidal ideation of major depression in a Chinese Han population. Psychiatry Research. 2009; 170(2):204–207. [PubMed: 19897250]

Weissman MM, Berry OO, Warner V, Gameroff MJ, Skipper J, Talati A, … Wickramaratne P. A 30-Year Study of 3 Generations at High Risk and Low Risk for Depression. JAMA Psychiatry. 2016; 73(9):970–977. [PubMed: 27532344]

Weissman MM, Wickramaratne P, Gameroff MJ, Warner V, Pilowsky D, Kohad RG, … Talati A. Offspring of Depressed Parents: 30 Years Later. American Journal of Psychiatry. 2016

Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. Offspring of depressed parents. The American Journal of Psychiatry. 2006; 163(6):1001–1008. [PubMed: 16741200]

Whitmer AJ, Gotlib IH. Depressive rumination and the C957T polymorphism of the DRD2 gene. Cognitive, Affective, & Behavioral Neuroscience. 2012; 12(4):741–747.

Wolfestein M, Trull TJ. Depression and openness to experience. Journal of Personality Assessment. 1997; 69(3):614–632. [PubMed: 9501488]

Xu Z, Zhang Z, Shi Y, Pu M, Yuan Y, Zhang X, Li L, Reynolds GP. Influence and interaction of genetic polymorphisms in the serotonin system and life stress on antidepressant drug response. Journal of Psychopharmacology. 2012; 26(3):349–359. [PubMed: 21937687]

Yao J, Pan Y-q, Ding M, Pang H, Wang B-j. Association between DRD2 (rs1799732 and rs1801028) and ANKK1 (rs1800497) polymorphisms and schizophrenia: A meta-analysis. American Journal of Medical Genetics, Part B. 2014; 168B:1–13.

Zhang W, Cao Y, Wang M, Ji L, Chen L, Deater-Deckard K. The dopamine D2 receptor polymorphism (DRD2 Taq1A) interacts with maternal parenting in predicting early adolescent depressive symptoms: evidence of differential susceptibility and age differences. Journal of Youth and Adolescence. 2015; 44(7):1428–40. [PubMed: 25941120]

Zhang L, Hu L, Xin L, Zhang J, Chen B. The DRD2 rs1800497 polymorphism increase the risk of mood disorder: Evidence from an updated meta-analysis. Journal of Affective Disorders. 2014; 158:71–77. [PubMed: 24655768]

Zhao X, Sun L, Sun YH, Ren C, Chen J, Wu XQ, Jiang YH, Lv XL. Association of HTR2A T102C and A-1438G polymorphisms with susceptibility to major depressive disorder: a meta-analysis. Neurological Science. 2014; 35(12):1857–1866.

Zouk H, McGirr A, Lebel V, Benkelfat C, Rouleau G, Turecki G. The effect of genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. American Journal of Medical Genetics Part B Neuropsychiatric Genetics. 2007; 144B:996–1002.

Table 1

Genotype frequencies of selected SNPs at high and low familial risk for major depressive disorder

	Total	Rs2254298				
		AA (%) −1	AG (%) 0	GG(%) 1	Unknown(%)missing	Chi-square test
High Risk	225	2 (0.89)	53 (23.56)	158(70.22)	12 (5.33)	$\chi^2 = 0.09$
Low Risk	109	1 (0.92)	24 (22.02)	78 (71.56)	6 (5.50)	*p* =f954
	Total	**Rs6298**				
		AA (%) −1	AG (%) 0	GG(%) 1	Unknown(%)missing	Chi-square test
High Risk	225	12 (5.33)	75 (33.33)	137 (60.89)	1 (0.44)	$\chi^2 = 0.93$
Low Risk	109	4 (3.67)	41 (37.61)	63 (57.80)	1 (0.92)	*p* = .629
	Total	**Rs130058**				
		AA (%) −1	AT(%) 0	TT(%) 1	Unknown(%)missing	Chi-square test
High Risk	225	21 (9.33)	98 (43.56)	101(44.89)	5 (2.22)	$\chi^2 = 1.44$
Low Risk	109	8 (7.34)	42 (38.53)	56 (51.38)	3 (2.75)	*p* = .488
	Total	**Rs11568817**				
		CC (%) −1	CA (%) 0	AA (%) 1	Unknown(%)missing	Chi-square test
High Risk	225	49 (21.78)	115 (51.11)	56 (24.89)	5 (2.22)	$\chi^2 = 2.09$
Low Risk	109	31 (28.44)	54 (49.54)	22 (20.18)	2 (1.83)	*p* = .352
	Total	**Rs1390938**				

		AA (%)	AG (%)	GG (%)	Unknown(%)missing	Chi-square test
		−1	0	1		
High Risk	225	8 (3.56)	94 (41.78)	110(48.89)	13 (5.78)	$\chi^2 = 1.67$
Low Risk	109	5 (4.59)	53 (48.62)	46 (42.20)	5 (4.59)	$p = .434$
Rs1800497						
	Total	AA (%)	AG (%)	GG (%)	Unknown(%)missing	Chi-square test
		−1	0	1		
High Risk	225	11 (4.89)	64 (28.44)	145 (64.44)	5 (2.22)	$\chi^2 = 5.84$
Low Risk	109	7 (6.42)	43 (39.45)	54 (49.54)	5 (4.59)	$p = .054$
Rs6311						
	Total	CC (%)	CT (%)	TT (%)	Unknown(%)missing	Chi-square test
		−1	0	1		
High Risk	225	69 (30.67)	114 (50.67)	37 (16.44)	5 (2.22)	$\chi^2 = 2.80$
Low Risk	109	33 (30.28)	48 (44.04)	26 (23.85)	2 (1.83)	$p = .247$

Table 2

The association between importance of S/R and SNP

N=291				
SNP	**Low-risk (N=96)**		**High-risk (N=96)**	
	Estimate (95% CI)	***p***	**Estimate (95% CI)**	***p***
rs2254298	0.527 (0.069, 0.985)	**.024**	0.056 (−0.220, 0.331)	.693
rs6298	0.093 (−0.311, 0.498)	.652	0.113 (−0.139, 0.365)	.380
rs130058	−0.493 (−0.781, −0.206)	**.001**	0.061 (−0.229, 0.351)	.680
rs11568817	0.258 (0.026, 0.491)	**.029**	0.066 (−0.191, 0.323)	.614
rs1390938	0.268 (0.022, 0.515)	**.033**	−0.145 (−0.408, 0.118)	.281
rs1800497	0.433 (0.051, 0.816)	**.026**	0.194 (−0.128, 0.515)	.238
rs6311	−0.231 (−0.479, 0.018)	.069	0.058 (−0.174, 0.290)	.626

Table 3

The association between lifetime MDD and SNP

N=334				
SNP	**Low-risk (N=96)**		**High-risk (N=96)**	
	Estimate (95% CI)	***p***	**Estimate (95% CI)**	***p***
rs2254298	1.034 (−0.776, 2.844)	.263	0.831 (0.003, 1.658)	**.049**
rs6298	−0.221 (−0.834, 0.393)	.480	−0.106 (−0.903, 0.691)	.795
rs130058	−0.005 (−0.575, 0.564)	.985	0.103 (−0.347, 0.553)	.654
rs11568817	0.037 (−0.567, 0.641)	.905	−0.076 (−0.601, 0.450)	.778
rs1390938	−0.203 (−0.898, 0.492)	.567	0.217 (−0.502, 0.936)	.554
rs1800497	−1.022 (−1.818, −0.226)	**.012**	0.055 (−0.589, 0.700)	.867
rs6311	−0.121 (−0.744, 0.503)	.704	−0.058 (−0.568, 0.452)	.823

Table 4

Mean, standard deviation & analysis of variance of importance of S/R by genotype and risk group

	Total	**Rs2254298** *M*(*SD*) of importance				
		AA −1	AG 0	GG 1	Unknown missing	ANOVA
High Risk	195	3.00 (.)	3.31 (0.94)	3.26 (1.06)	3.38 (1.19)	$F = 0.81$
Low Risk	96	4.00 (.)	3.62 (1.02)	3.07 (0.98)	3.33 (1.21)	$p = .584$
	Total	**Rs6298** *M*(*SD*) of importance				
		AA −1	AG 0	GG 1	Unknown missing	ANOVA
High Risk	195	3.67 (0.89)	3.32 (1.01)	3.23 (1.05)	2.00 (.)	$F = 0.58$
Low Risk	96	3.25 (0.50)	3.28 (1.16)	3.18 (0.96)	3.00 (.)	$p = .769$
	Total	**Rs130058** *M*(*SD*) of importance				
		AA −1	AT 0	TT 1	Unknown missing	ANOVA
High Risk	195	3.05 (0.97)	3.45 (1.01)	3.16 (1.03)	3.00 (1.41)	$F = 2.40$
Low Risk	96	2.86 (1.07)	2.92 (0.81)	3.54 (1.07)	2.33 (0.58)	$\mathbf{p = .021}$
	Total	**Rs11568817** *M*(*SD*) of importance				
		CC −1	CA 0	AA 1	Unknown missing	ANOVA
High Risk	195	3.32 (1.06)	3.27 (1.04)	3.25 (0.98)	3.25 (1.50)	$F = 0.38$
Low Risk	96	3.40 (1.10)	3.22 (1.00)	2.95 (0.97)	3.00 (0)	$p = .916$
	Total	**Rs1390938** *M*(*SD*) of importance				

		AA	AG	GG	Unknown missing	ANOVA
		−1	0	1		
High Risk	195	3.38 (1.19)	3.17 (1.03)	3.35 (1.02)	3.40 (1.07)	$F = 0.85$
Low Risk	96	4.00 (1.00)	3.13 (1.06)	3.17 (1.00)	3.60 (0.55)	$p = .549$

Rs1800497 *M*(*SD*) of importance

	Total	AA	AG	GG	Unknown missing	ANOVA
		−1	0	1		
High Risk	195	4.00 (0.94)	3.32 (1.01)	3.21 (1.03)	2.50 (0.71)	$F = 2.45$
Low Risk	96	4.14 (0.69)	3.35 (1.03)	2.96 (0.98)	3.40 (0.89)	$\mathbf{p = .019}$

Rs6311 *M*(*SD*) of importance

	Total	CC	CT	TT	Unknown missing	ANOVA
		−1	0	1		
High Risk	195	3.25 (1.02)	3.31 (1.11)	3.24 (0.83)	3.25 (0.50)	$F = 0.58$
Low Risk	96	3.00 (0.95)	3.18 (1.05)	3.52 (1.05)	3.50 (0.71)	$p = .770$

Table 5

Frequency and rate of MDD by genotype and risk group.

		Rs2254298				
		AA	AG	GG	Unknown missing	Chi-square test
Total		−1	0	1		
High Risk	225	2 (100.00)	18 (33.96)	78 (49.37)	2 (16.67)	$\chi^2 = 2.71$
Low Risk	109	0 (0.00)	4 (16.67)	20 (25.64)	2 (33.33)	$p = .439$
		Rs6298				
		AA	AG0	GG	Unknown missing	Chi-square test
Total		−1		1		
High Risk	225	3 (25.00)	36 (48.00)	60 (43.80)	1 (100.00)	$\chi^2 = 2.44$
Low Risk	109	0 (0.00)	13 (31.71)	13 (20.63)	0 (0.00)	$p = .487$
		Rs130058				
		AA	AT	TT	Unknown missing	Chi-square test
Total		−1	0	1		
High Risk	225	7 (33.33)	44 (44.90)	46 (45.54)	3 (60.00)	$\chi^2 = 1.38$
Low Risk	109	1 (12.50)	11 (26.19)	14 (25.00)	0 (0.00)	$p = .708$
		Rs11568817				
		CC	CA	AA	Unknown missing	Chi-square test
Total		−1	0	1		
High Risk	225	23 (46.94)	57 (49.57)	17 (30.36)	3 (60.00)	$\chi^2 = 1.41$
Low Risk	109	6 (19.35)	17 (31.48)	3 (13.64)	0 (0.00)	$p = .702$
		Rs1390938				
Total						

		AA	AG	GG	Unknown missing	Chi-Square test
		−1	0	1		
High Risk	225	1 (12.50)	49 (52.13)	47 (42.73)	3 (23.08)	$\chi^2 = 2.12$
Low Risk	109	1 (20.00)	15 (28.30)	9 (19.57)	1 (20.00)	$p = .548$
Rs1800497						
		AA	AG	GG	Unknown missing	Chi-square test
Total		−1	0	1		
High Risk	225	4 (36.36)	28 (43.75)	66 (45.52)	2 (40.00)	$\chi^2 = 12.75$
Low Risk	109	2 (28.57)	13 (30.23)	8 (14.81)	3 (60.00)	$\mathbf{p = .005}$
Rs6311						
		CC	CT	TT	Unknown missing	Chi-square test
Total		−1	0	1		
High Risk	225	32 (46.38)	46 (40.35)	20 (54.05)	2 (40.00)	$\chi^2 = 0.72$
Low Risk	109	9 (27.27)	11 (22.92)	6 (23.08)	0 (0.00)	$p = .868$