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# Genetic variants in Nogo receptor signaling pathways may be associated with early life adversity in schizophrenia susceptibility

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ABSTRACT

*Background:* Schizophrenia is a severe neuropsychiatric disorder thought to result from abnormal brain development. Nogo, an oligodendrocyte bound molecule, signals by binding to the Nogo receptor (NgR) located on axonal membranes. The NgR co-receptors include p75 neurotrophin receptor or TNF receptor orphan Y (TROY). Nogo signaling is responsible for central nervous system myelin regulation and neurite outgrowth during neurodevelopment, and plasticity in the mature brain.
*Methods:* We examined single nucleotide polymorphisms (SNPs) in *NgR*, *p75*, and *TROY* receptor genes and downstream signaling partner *With No Lysine (K) (WNK1)* and *Myelin transcription factor 1-like (Myt1l)* genes in an Australian case–control schizophrenia cohort ($n = 268$/group). High-throughput SNP genotyping was performed using the MassARRAY® genotyping assay.
*Results:* Analysis revealed a significant association between the *Myt1l* SNP rs2304008 and female schizophrenia subjects. The *WNK1* SNP rs1468326 and the *Myt1l* SNP rs3748988 showed significant associations with schizophrenia in subjects with a maternal mental history and in subjects who experienced childhood trauma respectively. Following Bonferroni correction, all significance was lost.
*Conclusions:* Despite the lack of positive findings in our population after correction for multiple testing, previous gene expression and association studies in schizophrenia suggest the implication of *NgR* signaling pathway genes in the etiology of schizophrenia remains topical and timely.
*General significance:* Further investigations will be necessary to fully assess the role of these genes in the pathophysiology of schizophrenia. However these genes may prove useful in further understanding the mechanism by which negative experiences early in life can affect myelin-related processes in the context of schizophrenia.


## 1. Introduction

Schizophrenia is a severe neuropsychiatric disorder with an elusive etiology, thought to result from abnormal brain development. Receptor/ligand interactions on oligodendrocytes are critically involved in axonal outgrowth processes which are key to normal brain development [1]. Inappropriate outgrowth and myelination of axons could subsequently result in axonal miswiring which has been previously reported in schizophrenia and in children who have experienced stress and trauma early in life [2,3]. In normal brain development, oligodendrocytes are responsible for regulating axonal growth via the Nogo protein and its receptor, Nogo receptor (NgR). Nogo binds to the leucine-rich repeat (LRR) domains of NgR and facilitates the inhibition of axon growth [4]. There are a number of co-receptors that signal with NgR on the axonal membrane including Lingo-1 as a co-factor [5–7]. Since NgR itself does not contain a transmembrane domain, it requires a transmembrane co-receptor in order to elicit intracellular signals. NgR contains a glycosylphosphatidylinositol-anchored-ligand-binding subunit which binds with either the p75 neurotrophin receptor or Tumor necrosis factor Receptor Orphan Y (TROY). The resulting trimolecular NgR receptor complex activates RhoA a small GTP-binding protein, subsequently setting off a cascade of intracellular molecular events resulting in the collapse of growth cones, thus preventing further growth by the axon, and the inhibition of myelination [4,8].

Many genes have been tested for their implication in the genetic susceptibility for schizophrenia over the last 2 decades; however no studies have found a single gene unambiguously linked to dysfunction leading to schizophrenia. Genotyping of single nucleotide

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polymorphisms (SNPs) is the most common technique used to measure genetic variation between members of a species. SNPs are defined as the change in a single base pair, or a point mutation within a DNA strand, occurring in both coding and non-coding regions of the genome; they are the most frequently occurring type of genetic variation, accounting for 90–95% of DNA sequence variation within a population.

Numerous human genetic linkage studies, examining the tendency of certain genes (or loci, the location of the genes on the chromosome) to be inherited together in patient families, and association studies which measure the concurrence of genetic markers (e.g. insertions/deletions, microsatellites, and SNPs) with a particular phenotype, suggest a link between Nogo signaling and schizophrenia [6,9,10]. Functional genetic polymorphisms in the *NgR* gene previously associated with schizophrenia have been reported to directly affect the interactions between NgR and its co-receptors p75 and TROY in *in vitro* neuronal culture [6,9]. Patients with 22q11 deletion syndrome (including the *NgR* gene locus) showed schizophrenia related endophenotypes including impaired working memory, impaired prepulse inhibition and other cognitive dysfunctions [11–13]. An increase in the levels of the Nogo ligand mRNA has also been reported in schizophrenia patients, supporting the hypothesis that the stimulation of NgR may be altered in schizophrenia [14]. However, little is known regarding the genetic implication of *NgR* co-receptors *p75* and *TROY* in the genetic susceptibility of schizophrenia.

Interestingly, downstream signaling partners of NgR pathways, With No Lysine (K) (WNK1) and Myelin transcription factor 1-like (Myt1l) have also been found to be altered in schizophrenia patients compared to controls at the genetic level. *WNK1* gene expression has been consistently reported to be upregulated in the prefrontal cortex of schizophrenia sufferers in genome wide association studies [13,15], suggesting that it plays a significant role in this disorder. In addition, a copy number variation meta-analysis study revealed that microduplications disrupting the *Myt1l* gene are associated with schizophrenia, in particular childhood-onset schizophrenia, a rare and more severe form of this devastating disorder [16]. Furthermore, significant genetic associations have also been reported between polymorphisms in the *Myt1l* gene and schizophrenia in a Chinese population [17], confirming the potential of *Myt1l* to be involved in the genetic susceptibility of schizophrenia. However to date, no case–control genetic association for either *Myt1l* or *WNK1* genes has been tested in a Caucasian schizophrenia population.

Early life neglect has been shown to disrupt the translation of myelin-related genes in a mouse model of childhood neglect [18]. Additionally, early traumatic experiences including neglect, physical abuse, sexual abuse, post-traumatic stress disorder, and psychiatric illness, have been shown to be significantly associated with a decrease in the size of the highly myelinated corpus callosum [19]. Considering the role of NgR signaling in myelin-related processes it could be speculated that these pathways may also be playing a role in the neurobiological processes occurring during childhood, the critical period of brain development. Furthermore due to adolescence also being a critical period for the development of schizophrenia and the known implications of NgR signaling in schizophrenia, we hypothesized that NgR signaling may play an underlying role in the implication of childhood maltreatment with incidence of psychiatric disorders including schizophrenia.

Due to the implication of the NgR complex in neurite outgrowth and myelination processes throughout neurodevelopment, as well as the genetic implication of *NgR, WNK1 and Myt1l* in schizophrenia susceptibility, we sought to examine several SNPs of interest within *NgR* signaling pathways in a selected case–control schizophrenia population, factoring in early life stresses such as having a parental history of mental illness or other traumatic events, to assess if genetic abnormalities within these genes may have an association with early life adversity and schizophrenia.

## 2. Materials and methods

### 2.1. DNA samples

DNA samples were obtained from the Australian Schizophrenia Research Bank (ASRB). Subjects with schizophrenia were identified using the *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria. In addition, all participants were subjected to thorough psychometric testing to assess the extent of psychiatric illness in our schizophrenia population, in addition to excluding the presence of mental disorders in our control group. The battery of psychometric testing included: the Psychosis Screener (from the Western Australian Family Study of Schizophrenia), the Diagnostic Interview for Psychosis (ASRB modification [20]), the Scale for the Assessment of Negative Symptoms (SANS), the General Assessment of Functioning Scale (GAF), the International Personality Disorder Examination Screening Questionnaire (ICD-10 Module), the Childhood Adversity Questionnaire, and the Schizotypal Personality Questionnaire (SPQ). Subjects were matched for gender and age and all samples were from Caucasian volunteers. The ethnic origin of the Caucasian volunteers was determined by the participant's response to questions regarding their birth place, in addition to the birth place of their family members 2 generations before them on both maternal and paternal sides of the family. Of the 536 subjects in this study 458 (85.4%) were born in Australia or New Zealand, 43 (8.0%) were born in the United Kingdom, and 12 (2.2%) were born in the United States or Canada; the remaining 23 (4.4%) were born in Europe. All subjects were of (self-reported) European descent. The complete sample consisted of 268 schizophrenia cases, composed of 186 males and 82 females, with an average age of 38.86 years (males: 38.14 years, females: 40.48 years); and 268 matched controls, composed of 169 males and 99 females, with an average age of 38.56 years (males: 42.22 years, females: 32.19 years), with no prior history of mental disorders (Table 1). While the sample size of this cohort may seem somewhat limited for a case–control study, it must be noted that this population was very carefully selected for its homogeneity, only schizophrenia patients were included in the cohort, no schizoaffective subjects were included. Additionally, extensive subject demographics and medical histories were collected for all patients, supporting the validity of this case–control cohort for this study. After complete description of the study to the subjects, written informed consent was obtained. This study was approved by and conducted according to the guidelines of the University of Wollongong Human Research Ethics Committee (HE 10/161).

### 2.2. SNP genotyping

SNPs within the *NgR* (rs701427, rs701428 and rs696880), *p75* (rs1061622), *TROY* (rs9317882), *WNK1* (rs1012729, rs12828016 and rs1468326), and *Myt1l* genes (rs2304008, rs3748988, rs4073540 and rs7592630) were tested in the Caucasian case–control schizophrenia

**Table 1**
Subject Demographics for Control ($n = 268$) and Schizophrenia Subjects ($n = 268$).

| | Control subjects *n* (%) | Schizophrenia subjects *n* (%) |
|---|---|---|
| *Gender* | | |
| Female | 99 (37%) | 82 (30.6%) |
| Male | 169 (63%) | 186 (69.4%) |
| *Age at assessment (years)* | | |
| Female | 32.19 | 40.48 |
| Male | 42.22 | 38.14 |
| *Family history of mental disorders* | | |
| Mother | 41 (15.3%) | 95 (35.5%) |
| Father | 49 (18.3%) | 106 (39.6%) |
| Traumatic childhood experience | 60 (22.4%) | 110 (41.0%) |

population. The selection of these SNPs was based on their previous associations with schizophrenia and/or other disorders, and on their Minor Allele Frequencies (MAF) reported in Caucasian populations (MAF > 10%). High-throughput SNP genotyping was performed using the MassARRAY® genotyping assay (Sequenom, Inc., San Diego, CA), with the analysis performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). PCR and extension primer design, selection and multiplexing were performed using MassARRAY® Designer Software (Sequenom, Inc., San Diego, CA). Control samples were run in parallel with the case–control population, allowing for accurate evaluation and quality control checks of each of the steps involved (PCR amplification, Shrimp Alkaline Phosphatase (SAP) treatment, extension PCR, nano-dropping to check product concentrations, nano-dispensing of samples onto the chip, and instrument performance). Additionally, only samples which had a call rate of ≥80% were included in the analysis for this study. Any samples yielding less than 80% were omitted from the analysis steps.

### 2.3. Statistical analysis

The distribution of all of the tested SNPs did not deviate significantly from the Hardy–Weinberg Equilibrium (HWE) ($p > 0.05$) except for *NgR* rs701428, ($p = 2.34 \times 10^{-13}$) which was then excluded from further analysis. To detect associations between each SNP and schizophrenia, chi-square ($\chi^2$) analysis was performed to test for significant differences in allele and genotype frequencies between the case and control groups. The significance for all statistical tests was set to $p < 0.05$. Data are expressed as specific counts for alleles and genotypes. Bonferroni correction was utilized to adjust for multiple comparisons in the SNP analysis resulting in a corrected significance level of $p < 0.004$ to give a 95% probability of correctly concluding not to reject the null hypothesis in the $\chi^2$ test.

## 3. Results

Two SNPs within *NgR*, one SNP within *p75* and *TROY*, three SNPs within *WNK1* and four SNPs within the *Myt1l* genes were analyzed for association with schizophrenia in a large Caucasian population (268 schizophrenia patients *versus* 268 matched controls with no prior history of psychiatric disorders).

Analysis revealed that there were no significant associations between any of the allelic frequencies of any of the tested SNPs (*NgR* rs701427 and rs696880, *p75* rs1061622, *TROY* rs9317882, *WNK1* rs1012729, rs12828016 and rs1468326, and *Myt1l* rs2304008, rs3748988, rs4073540 and rs7592630) and schizophrenia ($0.10 \leq p \leq 0.95$; Tables 2, 3, 4 and 5). Additionally, none of the tested SNPs showed any significant genotypic associations with schizophrenia ($0.10 \leq p \leq 0.99$; Tables 2, 3, 4 and 5).

Further, analysis of each of the genetic markers by gender revealed that the rs2304008 SNP within the *Myt1l* gene had a significant genotypic but not allelic association when comparing the female schizophrenia subjects to the female control subjects only ($p = 0.04$; Table 5). None of the remaining genetic markers showed any significant allelic or genotypic associations with gender ($0.08 \leq p \leq 0.98$; Tables 2, 3, 4 and 5). However after Bonferroni correction the significance of the *Myt1l* genotypic association in female schizophrenia subjects was lost.

It was interesting to note that our tested population demographics revealed that a large percentage of our schizophrenia subjects, twice as many as the control group, had a family history of mental disorders (either mother, father or both parents), or experienced some sort of trauma or adversity during their childhood (Table 1). $\chi^2$ analysis revealed that the *WNK1* rs1468326 SNP had a significant allelic and genotypic association with schizophrenia in those subjects who had a mother with a history of mental disorders ($5.82 \geq \chi^2 \geq 6.38$, $0.01 \geq p \geq 0.04$; Table 6). In subjects who experienced some sort of adversity during childhood, there was a significant genotypic but not allelic association with schizophrenia for the *Myt1l* SNP rs3748988 ($\chi^2 = 7.72$, $p = 0.02$; Table 6). None of the other tested SNPs in any of the genes displayed any significance when analyzed according to a family history of mental disorders or traumatic childhood ($p > 0.05$). Again, following Bonferroni correction for multiple testing, significance for the allelic and genotypic *WNK1* associations in schizophrenia subjects with a maternal history of mental disorders, and the genotypic *Myt1l* association with schizophrenia in subjects who experienced childhood trauma was lost.

## 4. Discussion

The present study examined the implication of genetic variants in the *NgR* gene and its signaling co-factors (*p75* and *TROY*) and genes

**Table 2**
Distribution of *NgR* genetic markers in schizophrenia subjects ($n = 268$) and controls ($n = 268$).

| NgR SNP | Group Numbers | *N* (alleles) rs696880 | Alleles A | Alleles G | Genotypes AA | Genotypes AG | Genotypes GG |
|---|---|---|---|---|---|---|---|
| Schizophrenia | 161 | 322 | 162 (50.3%) | 160 (49.7%) | 38 (23.6%) | 86 (53.4%) | 37 (23%) |
| Male | 119 | 238 | 115 (48.3%) | 123 (51.7%) | 27 (22.7%) | 61 (51.3%) | 31 (26%) |
| Female | 42 | 84 | 47 (56%) | 37 (44%) | 11 (26.2%) | 25 (59.5%) | 6 (14.3%) |
| Control | 215 | 430 | 231 (53.7%) | 199 (46.3%) | 68 (31.6%) | 95 (44.2%) | 52 (24.2%) |
| Male | 141 | 282 | 145 (51.4%) | 137 (48.6%) | 41 (29.1%) | 63 (44.7%) | 37 (26.2%) |
| Female | 74 | 148 | 86 (58.1%) | 62 (41.9%) | 27 (36.5%) | 32 (43.2%) | 15 (20.3%) |
| Total case vs. control | | | $\chi^2 = 0.86$ | $p = 0.35$ | | $\chi^2 = 3.79$ | $p = 0.15$ |
| Male case vs. control | | | $\chi^2 = 0.50$ | $p = 0.48$ | | $\chi^2 = 1.59$ | $p = 0.45$ |
| Female case vs. control | | | $\chi^2 = 0.10$ | $p = 0.74$ | | $\chi^2 = 2.84$ | $p = 0.24$ |
| NgR SNP | Group Numbers | *N* (alleles) rs701427 | Alleles C | Alleles A | Genotypes CC | Genotypes CA | Genotypes AA |
| Schizophrenia | 169 | 338 | 258 (76.3%) | 80 (23.6%) | 99 (58.6%) | 60 (35.5%) | 10 (5.9%) |
| Male | 123 | 246 | 185 (75.2%) | 61 (24.8%) | 69 (56.1%) | 47 (38.2%) | 7 (5.7%) |
| Female | 46 | 92 | 73 (79.3%) | 19 (20.7%) | 30 (65.2%) | 13 (28.3%) | 3 (6.5%) |
| Control | 207 | 414 | 295 (71.3%) | 119 (28.7%) | 105 (50.7%) | 85 (41.1%) | 17 (8.2%) |
| Male | 133 | 266 | 187 (70.3%) | 79 (29.7%) | 67 (50.4%) | 53 (39.8%) | 13 (9.8%) |
| Female | 74 | 148 | 108 (73%) | 40 (27%) | 38 (51.4%) | 32 (43.2%) | 4 (5.4%) |
| Total case vs. control | | | $\chi^2 = 2.46$ | $p = 0.11$ | | $\chi^2 = 2.49$ | $p = 0.28$ |
| Male case vs. control | | | $\chi^2 = 1.55$ | $p = 0.21$ | | $\chi^2 = 1.80$ | $p = 0.41$ |
| Female case vs. control | | | $\chi^2 = 1.24$ | $p = 0.26$ | | $\chi^2 = 2.72$ | $p = 0.25$ |

**Table 3**
Distribution of the *p75* and *TROY* genetic markers in schizophrenia subjects ($n = 268$) and controls ($n = 268$).

| *p75* SNP | Group Numbers | *N* (alleles) rs1061622 | Alleles | | Genotypes | | |
|---|---|---|---|---|---|---|---|
| | | | T | G | TT | TG | GG |
| Schizophrenia | 142 | 284 | 202 (71.1%) | 82 (28.9%) | 68 (47.9%) | 66 (46.5%) | 8 (5.6%) |
| Male | 100 | 200 | 149 (74.5%) | 51 (25.5%) | 52 (52%) | 45 (45%) | 3 (3%) |
| Female | 42 | 84 | 53 (63.1%) | 31 (36.9%) | 16 (38.1%) | 21 (50%) | 5 (11.9%) |
| Control | 195 | 390 | 298 (76.4%) | 92 (23.6%) | 111 (56.9%) | 76 (39%) | 8 (4.1%) |
| Male | 124 | 248 | 194 (78.2%) | 54 (21.8%) | 75 (60.5%) | 44 (35.5%) | 5 (4%) |
| Female | 71 | 142 | 104 (73.2%) | 38 (26.8%) | 36 (50.7%) | 32 (45.1%) | 3 (4.2%) |
| Total case vs. control | | | $\chi^2 = 2.40$ | $p = 0.12$ | | $\chi^2 = 2.77$ | $p = 0.25$ |
| Male case vs. control | | | $\chi^2 = 0.86$ | $p = 0.35$ | | $\chi^2 = 2.13$ | $p = 0.34$ |
| Female case vs. control | | | $\chi^2 = 2.56$ | $p = 0.10$ | | $\chi^2 = 3.25$ | $p = 0.19$ |
| *TROY* SNP | Group Numbers | *N* (alleles) rs9317882 | Alleles | | Genotypes | | |
| | | | T | C | TT | TC | CC |
| Schizophrenia | 186 | 372 | 256 (68.8%) | 116(31.2%) | 92 (49.5%) | 72 (38.7%) | 22 (11.8%) |
| Male | 132 | 264 | 179 (67.8%) | 85 (32.2%) | 63(47.7%) | 53 (40.2%) | 16 (12.1%) |
| Female | 54 | 108 | 77 (71.3%) | 31 (28.7%) | 29 (53.7%) | 19 (35.2%) | 6 (11.1%) |
| Control | 171 | 342 | 253 (74.0%) | 89 (26.0%) | 97 (56.8%) | 59 (34.5%) | 15 (8.7%) |
| Male | 113 | 226 | 169 (74.8%) | 57 (25.2%) | 65 (57.5%) | 39 (34.5%) | 9 (8.0%) |
| Female | 58 | 116 | 84 (72.4%) | 32 (27.6%) | 32 (55.2%) | 20 (34.5%) | 6 (10.3%) |
| Total case vs. control | | | $\chi^2 = 2.32$ | $p = 0.12$ | | $\chi^2 = 2.12$ | $p = 0.34$ |
| Male case vs. control | | | $\chi^2 = 2.88$ | $p = 0.08$ | | $\chi^2 = 2.66$ | $p = 0.26$ |
| Female case vs. control | | | $\chi^2 = 0.03$ | $p = 0.85$ | | $\chi^2 = 0.03$ | $p = 0.98$ |

**Table 4**
Distribution of *WNK1* genetic markers in schizophrenia subjects ($n = 268$) and controls ($n = 268$).

| *WNK1* SNP | Group Numbers | *N* (alleles) rs1012729 | Alleles | | Genotypes | | |
|---|---|---|---|---|---|---|---|
| | | | A | G | AA | AG | GG |
| Schizophrenia | 224 | 448 | 338 (75.4%) | 110 (24.6%) | 130 (58%) | 78 (34.8%) | 16 (7.1%) |
| Male | 155 | 310 | 239 (77%) | 71 (23%) | 93 (60%) | 53 (34.1%) | 9 (5.8%) |
| Female | 69 | 138 | 99 (71.7%) | 392 (28.3%) | 37 (53.6%) | 25 (36.2%) | 7 (10.1%) |
| Control | 234 | 468 | 352 (75.2%) | 116 (24.8%) | 133 (56.8%) | 86 (36.7%) | 15 (6.4%) |
| Male | 154 | 308 | 234 (76%) | 74 (24%) | 91 (59.2%) | 52 (33.7%) | 11 (7.1%) |
| Female | 80 | 160 | 118 (73.8%) | 42 (26.2%) | 42 (52.5%) | 34 (42.5%) | 4 (5.0%) |
| Total case vs. control | | | $\chi^2 = 0.01$ | $p = 0.93$ | | $\chi^2 = 0.24$ | $p = 0.88$ |
| Male case vs. control | | | $\chi^2 = 0.11$ | $p = 0.74$ | | $\chi^2 = 0.23$ | $p = 0.89$ |
| Female case vs. control | | | $\chi^2 = 0.15$ | $p = 0.69$ | | $\chi^2 = 1.70$ | $p = 0.42$ |
| *WNK1* SNP | Group Numbers | *N* (alleles) rs12828016 | Alleles | | Genotypes | | |
| | | | G | T | GG | GT | TT |
| Schizophrenia | 220 | 440 | 266 (60.5%) | 174 (39.5%) | 84 (38.1%) | 98 (44.5%) | 38 (17.2%) |
| Male | 154 | 308 | 192 (62.3%) | 116 (37.7%) | 63 (40.9%) | 66 (42.8%) | 25 (16.2%) |
| Female | 66 | 132 | 74 (56.1%) | 58 (43.9%) | 21 (31.8%) | 32 (48.4%) | 13 (19.6%) |
| Control | 235 | 470 | 285 (60.6%) | 185 (39.4%) | 90 (382%) | 105 (44.6%) | 40 (17%) |
| Male | 154 | 308 | 188 (61%) | 120 (39%) | 58 (37.6%) | 72 (46.7%) | 24 (15.5%) |
| Female | 81 | 162 | 97 (60%) | 65 (40%) | 32 (39.5%) | 33 (40.7%) | 16 (19.7%) |
| Total case vs. control | | | $\chi^2 = 0.00$ | $p = 0.95$ | | $\chi^2 = 0.01$ | $p = 0.99$ |
| Male case vs. control | | | $\chi^2 = 0.11$ | $p = 0.74$ | | $\chi^2 = 0.49$ | $p = 0.78$ |
| Female case vs. control | | | $\chi^2 = 0.44$ | $p = 0.50$ | | $\chi^2 = 1.09$ | $p = 0.57$ |
| *WNK1* SNP | Group Numbers | *N* (alleles) rs1468326 | Alleles | | Genotypes | | |
| | | | C | A | CC | CA | AA |
| Schizophrenia | 183 | 366 | 314 (85.7%) | 52 (14.3%) | 134 (73.2%) | 46 (25.1%) | 3 (1.6%) |
| Male | 129 | 258 | 223 (86.4%) | 35 (13.6%) | 96 (74.4%) | 31 (24%) | 2 (1.5%) |
| Female | 54 | 108 | 91 (84.3%) | 17 (15.7%) | 38 (70.3%) | 15 (27.7%) | 1 (1.8%) |
| Control | 213 | 426 | 376 (88.3%) | 50 (11.7%) | 169 (79.3%) | 38 (17.8%) | 6 (2.8%) |
| Male | 142 | 284 | 256 (90.1%) | 28 (9.9%) | 116 (81.6%) | 24 (16.9%) | 2 (1.4%) |
| Female | 71 | 142 | 120 (84.5%) | 22 (15.5%) | 53 (74.6%) | 14 (19.7%) | 4 (5.6%) |
| Total case vs. control | | | $\chi^2 = 1.07$ | $p = 0.30$ | | $\chi^2 = 3.55$ | $p = 0.16$ |
| Male case vs. control | | | $\chi^2 = 1.81$ | $p = 0.17$ | | $\chi^2 = 2.16$ | $p = 0.33$ |
| Female case vs. control | | | $\chi^2 = 0.00$ | $p = 0.95$ | | $\chi^2 = 2.03$ | $p = 0.36$ |

**Table 5**
Distribution of *Myt1l* genetic markers in schizophrenia subjects ($n = 268$) and controls ($n = 268$).

| *Myt1l* SNP | Group Numbers | *N* (alleles) rs2304008 | Alleles A | Alleles C | Genotypes AA | Genotypes AC | Genotypes CC |
|---|---|---|---|---|---|---|---|
| Schizophrenia | 193 | 386 | 261 (67.6%) | 125 (32.3%) | 93 (48.1%) | 75 (39.1%) | 25 (12.9%) |
| Male | 134 | 268 | 180 (67.2%) | 88 (32.8%) | 61 (45.5%) | 58 (43.2%) | 15 (11.1%) |
| Female | 59 | 118 | 81 (68.6%) | 37 (31.4%) | 32 (54.2%) | 17 (28.8%) | 10 (16.9%) |
| Control | 222 | 444 | 323 (72.7%) | 121 (273%) | 116 (52.2%) | 91 (40.9%) | 15 (6.7%) |
| Male | 147 | 294 | 213 (72.4%) | 81 (27.6%) | 77 (52.3%) | 59 (40.1%) | 11 (7.4%) |
| Female | 75 | 150 | 110 (73.3%) | 40 (26.7%) | 39 (52%) | 32 (42.6%) | 4 (5.3%) |
| Total case vs. control | | | $\chi^2 = 2.61$ | $p = 0.10$ | | $\chi^2 = 4.57$ | $p = 0.10$ |
| Male case vs. control | | | $\chi^2 = 1.86$ | $p = 0.17$ | | $\chi^2 = 1.58$ | $p = 0.39$ |
| Female case vs. control | | | $\chi^2 = 0.71$ | $p = 0.39$ | | **$\chi^2 = 6.03$** | **$p = 0.04$** |

| *Myt1l* SNP | Group Numbers | *N* (alleles) rs3748988 | Alleles A | Alleles G | Genotypes AA | Genotypes AG | Genotypes GG |
|---|---|---|---|---|---|---|---|
| Schizophrenia | 225 | 450 | 298 (66.2%) | 152 (33.7%) | 105 (46.6%) | 88 (39.1%) | 32 (14.2%) |
| Male | 156 | 312 | 214 (68.6%) | 98 (31.4%) | 77 (49.3%) | 60 (38.4%) | 19 (12.1%) |
| Female | 69 | 138 | 84 (60.8%) | 54 (39.2%) | 28 (40.5%) | 28 (40.5%) | 13 (18.8%) |
| Control | 235 | 470 | 299 (63.6%) | 171 (36.4%) | 93 (39.5%) | 113 (48%) | 29 (12.3%) |
| Male | 154 | 308 | 198 (64.3%) | 110 (35.7%) | 65 (42.2%) | 68 (44.1%) | 21 (13.6%) |
| Female | 81 | 162 | 101 (62.3%) | 61 (37.7%) | 28 (34.5%) | 45 (55.5%) | 8 (9.8%) |
| Total case vs. control | | | $\chi^2 = 0.68$ | $p = 0.40$ | | $\chi^2 = 3.77$ | $p = 0.15$ |
| Male case vs. control | | | $\chi^2 = 1.29$ | $p = 0.25$ | | $\chi^2 = 1.60$ | $p = 0.44$ |
| Female case vs. control | | | $\chi^2 = 0.07$ | $p = 0.79$ | | $\chi^2 = 4.22$ | $p = 0.12$ |

| *Myt1l* SNP | Group Numbers | *N* (alleles) rs4073540 | Alleles A | Alleles C | Genotypes AA | Genotypes AC | Genotypes CC |
|---|---|---|---|---|---|---|---|
| Schizophrenia | 234 | 468 | 280 (60%) | 188 (40%) | 80 (34.1%) | 120 (51.2%) | 34 (14.5%) |
| Male | 160 | 320 | 193 (60.3%) | 127 (39.7%) | 54 (33.7%) | 85 (53.1%) | 21 (13.1%) |
| Female | 74 | 148 | 87 (58.8%) | 61 (41.2%) | 26 (35.1%) | 35 (47.2%) | 13 (17.5%) |
| Control | 238 | 476 | 292 (61.3%) | 184 (38.7%) | 83 (34.8%) | 126 (52.9%) | 29 (12.1%) |
| Male | 156 | 312 | 189 (60.3%) | 123 (39.4%) | 52 (33.3%) | 85 (54.4%) | 19 (12.1%) |
| Female | 82 | 164 | 103 (62.8%) | 61 (37.2%) | 31 (37.8%) | 41 (50%) | 10 (12.1%) |
| Total case vs. control | | | $\chi^2 = 0.23$ | $p = 0.63$ | | $\chi^2 = 0.56$ | $p = 0.75$ |
| Male case vs. control | | | $\chi^2 = 0.00$ | $p = 0.94$ | | $\chi^2 = 0.09$ | $p = 0.95$ |
| Female case vs. control | | | $\chi^2 = 0.53$ | $p = 0.46$ | | $\chi^2 = 0.90$ | $p = 0.63$ |

| *Myt1l* SNP | Group Numbers | *N* (alleles) rs7592630 | Alleles T | Alleles C | Genotypes TT | Genotypes TC | Genotypes CC |
|---|---|---|---|---|---|---|---|
| Schizophrenia | 226 | 452 | 293 (64.8%) | 159 (35.2%) | 95 (42%) | 103 (45.5%) | 28 (12.3%) |
| Male | 157 | 314 | 213 (67.3%) | 101 (32.2%) | 72 (45.8%) | 69 (43.9%) | 16 (10.1%) |
| Female | 69 | 138 | 80 (58.9%) | 58 (42%) | 23 (33.3%) | 34 (49.2%) | 12 (17.3%) |
| Control | 236 | 472 | 294 (62.3%) | 178 (37.7%) | 90 (38.1%) | 114 (48.3%) | 32 (13.5%) |
| Male | 155 | 310 | 194 (62.6%) | 116 (37.4%) | 61 (39.4%) | 72 (46.4%) | 22 (14.2%) |
| Female | 81 | 162 | 100 (61.7%) | 62 (38.3%) | 29 (35.8%) | 42 (51.8%) | 10 (12.3%) |
| Total case vs. control | | | $\chi^2 = 0.64$ | $p = 0.42$ | | $\chi^2 = 0.74$ | $p = 0.68$ |
| Male case vs. control | | | $\chi^2 = 1.90$ | $p = 0.16$ | | $\chi^2 = 1.91$ | $p = 0.38$ |
| Female case vs. control | | | $\chi^2 = 0.44$ | $p = 0.50$ | | $\chi^2 = 0.76$ | $p = 0.68$ |

Significant associations are shown in bold.

encoding for its downstream signaling molecules (*WNK1* and *Myt1l*), in an Australian Caucasian schizophrenia case–control population, taking early life adversities into consideration.

*NgR* mutations are present within 1–2% of the schizophrenia population [6,9,21]. It has been reported that deletion mutations within the chromosomic region 22q11 (including the *NgR* locus), have an association with a risk of schizophrenia 25 times greater than the general population [22,23]. This makes the 22q11 deletion mutation one of the strongest known genetic risk factors for schizophrenia [24,25]. The *NgR* SNP rs701428 was found in the present study to lie outside HWE, meaning it could not be included in our analysis. However, rs701428 is located near the 3′ end of the gene, and Liu et al. have provided evidence to suggest that common *NgR* variants located at the 3′ end of *NgR* gene are associated with schizophrenia in North American populations [23] which supports our hypothesis for including this marker in our study, despite our lack of association found. Association of SNPs in the *NgR* gene with schizophrenia has previously been found in various Caucasian populations [9,23], but not in Chinese [26] and Japanese populations [27], with only a weak association found in Afrikaners [28]. While the present study did not find any significant associations with schizophrenia and either of our investigated intronic *NgR* SNPs, rs701427 and rs696880 which have been examined in other schizophrenia populations [9], several rare coding variants of *NgR* (R119W, R196H, L18L, R377W, R227C and R399W) have been previously found in patients with schizophrenia [6,9]. Subjects expressing R377Q, R377W, R119W and R196H were shown to have an inhibition of signal transduction of NgR by its oligodendrocyte-bound ligands in coimmunoprecipitation and ligand binding experiments [6,9]. Genetic mutations in the *NgR* gene could therefore be involved in the stabilization of neuronal wiring in the development of the schizophrenia brain. Interestingly, R119W and R196H were found in patients who displayed predominantly negative symptoms which were strongly resistant to

**Table 6**
Allelic and genotypic distributions for *WNK1* and *Myt1l* genetic markers in schizophrenia subjects and controls with respect to parental history of mental health issues and traumatic childhood experiences.

| *WNK1* | | Alleles | | Genotypes | | |
|---|---|---|---|---|---|---|
| rs1468326 | Group Numbers | C | A | CC | CA | AA |
| Schizophrenia | 183 | 314 (85.8%) | 52 (14.2%) | 134(73.2%) | 46(25.1%) | 3(1.6%) |
| Mother mental history | 65 | 106 (81.5%) | 24 (18.5%) | 42 (64.6%) | 22 (33.8%) | 1 (1.5%) |
| Father mental history | 75 | 130 (86.7%) | 20 (13.3%) | 56 (74.7%) | 18 (24.0%) | 1 (1.3%) |
| Traumatic childhood | 76 | 131 (86.2%) | 21 (13.8%) | 55 (72.4%) | 21 (27.6%) | 0 (0.0%) |
| Control | 213 | 376 (88.3%) | 50 (11.7%) | 169(79.3%) | 38(17.8%) | 6(2.8%) |
| Mother mental history | 34 | 64 (94.1%) | 4 (5.9%) | 30 (88.2%) | 4 (11.8%) | 0 (0.0%) |
| Father mental history | 39 | 71 (91.0%) | 7 (9.0%) | 33 (84.6%) | 5 (12.8%) | 1 (2.6%) |
| Traumatic childhood | 43 | 74 (86.0%) | 12 (14.0%) | 33(76.7%) | 8 (18.6%) | 2 (4.7%) |
| Mother mental case vs. control | | **$\chi^2 = 5.82$** | **$p = 0.01$** | | **$\chi^2 = 6.38$** | **$p = 0.04$** |
| Father mental case vs. control | | $\chi^2 = 0.93$ | $p = 0.34$ | | $\chi^2 = 2.13$ | $p = 0.34$ |
| Traumatic childhood case vs. control | | $\chi^2 = 0.00$ | $p = 0.97$ | | $\chi^2 = 4.52$ | $p = 0.10$ |
| *Myt1l* | | Alleles | | Genotypes | | |
| rs3748988 | Group Numbers | C | A | AA | AG | GG |
| Schizophrenia | 225 | 298 (66.2%) | 152 (33.8%) | 105(46.6%) | 88(39.1%) | 32(14.2%) |
| Mother mental history | 76 | 92 (60.5%) | 60 (39.5%) | 28 (36.8%) | 36 (47.4%) | 12 (15.8%) |
| Father mental history | 87 | 103 (59.2%) | 71 (40.8%) | 33 (37.9%) | 37 (42.5%) | 17 (19.5%) |
| Traumatic childhood | 91 | 113 (62.1%) | 69 (37.9%) | 39 (42.9%) | 35 (38.5%) | 17 (18.7%) |
| Control | 235 | 299 (63.6%) | 171 (36.4%) | 93(39.5%) | 113(48%) | 29(12.3%) |
| Mother mental history | 40 | 47 (58.8%) | 33 (41.3%) | 12 (30.0%) | 23 (57.5%) | 5 (12.5%) |
| Father mental history | 43 | 54 (62.8%) | 32 (37.2%) | 15 (34.9%) | 24 (55.8%) | 4 (9.3%) |
| Traumatic childhood | 52 | 67 (64.4%) | 37 (35.6%) | 18 (34.6%) | 31 (59.6%) | 3 (5.8%) |
| Mother mental case vs. control | | $\chi^2 = 0.07$ | $p = 0.79$ | | $\chi^2\chi^2 = 1.08$ | $p = 0.58$ |
| Father mental case vs. control | | $\chi^2 = 0.31$ | $p = 0.58$ | | $\chi^2 = 3.02$ | $p = 0.22$ |
| Traumatic childhood case vs. control | | $\chi^2 = 0.15$ | $p = 0.69$ | | **$\chi^2 = 7.72$** | **$p = 0.02$** |

Significant associations are shown in bold.

conventional and novel drug treatments [6]. This result suggests that both R119W and R196H may play a role in affecting the binding interactions between NgR protein and its ligands or with its co-receptors.

Analysis of genetic polymorphisms in both co-receptor and cofactor *p75* and *TROY* genes, did not display any significant difference within the tested SNPs of their respective genes in the schizophrenia sufferers compared to their controls ($p > 0.05$). To our knowledge, no previous reports have investigated the role of genetic polymorphisms in the *p75* and *TROY* genes in the susceptibility for schizophrenia however, our tested SNP in the *TROY* gene has been previously implicated in the genetic vulnerability of another neurological disorder (vascular dementia [29]). Changes in protein levels of both p75 and TROY have been previously reported in postmortem hippocampal regions from schizophrenia sufferers compared to controls in two independent brain cohorts (Stanley consortium brain cohort [30] and the New South Wales Brain Bank Network schizophrenia case–control cohort [31] respectively), supporting a role of these two proteins in the pathophysiology of schizophrenia and their potential as candidate genes in the susceptibility of schizophrenia.

Regarding the downstream partners of NgR, our tested SNPs in the *WNK1* and *Myt1l* genes were not associated with schizophrenia in our population $p > 0.05$. We studied two intronic SNPs (rs4073540 and rs7592630) located within the exon rich region located at the distal part of the *Myt1l* gene, as well as two SNPs in exon 7 (rs2304008) and exon 9 (rs3748988) within the *Myt1l* gene. None of these SNPs were associated with schizophrenia in our Caucasian population. However, polymorphisms in the *Myt1l* gene have recently been reported to be associated with schizophrenia in a Chinese Han population, with one SNP having an association with a family history of schizophrenia in females [17]. Despite our results not having an overall significant association with schizophrenia, before Bonferroni correction our *Myt1l* SNP rs2304008 had a significant association in female schizophrenia subjects compared to female controls. Our findings, in concert with those found by Li *et al.*, suggest that SNPs within the homologous *Myt1* and *Myt1l* genes may increase the susceptibility for schizophrenia in females. Interestingly, the *Myt1* gene has been shown to regulate the expression of the *Neuregulin-1* (*NRG1*) gene, an extensively studied schizophrenia candidate gene involved in myelination processes [32], in schizophrenia patients [33] confirming the potential for the susceptibility of this gene in schizophrenia.

The expression of the *WNK1* gene has been previously reported to be upregulated in the postmortem prefrontal cortex from schizophrenia sufferers [13,15], in addition to a recent report of an upregulation of WNK1 protein expression in the hippocampus of schizophrenia sufferers [31], thus triggering our initial interest to involve the gene of this kinase in our study. Despite the consistently reported upregulation of *WNK1* in the prefrontal cortex of schizophrenia sufferers, no SNPs were found to be significantly associated with schizophrenia in the same studies [13,15,34] thus supporting the lack of significant findings within the *WNK1* gene in the present study.

The suppression of *WNK1* expression by RNA interference has been shown to promote neurite extension and eliminate the inhibitory response to Nogo signaling in cortical cultured neurons [35]. In addition, the overexpression of WNK1 (123-510) reduces Nogo-induced inhibition of neurite extension rather than strengthening it, and inhibits the activation of RhoA [35]. Previous studies have shown that WNK1 is a negative regulator of cell growth via phosphorylation by the PI3-K/Akt signaling pathway [36], which is largely implicated in the schizophrenia pathophysiology. Furthermore, disruption of the *WNK1* gene in mice leads to death of the embryo at day 13 [23–25], suggesting an essential role of *WNK1* in embryonic and neural development, which is a critical period implicated in schizophrenia.

When we factored a family history of psychiatric illness or traumatic childhood experiences into our analysis; we found that *WNK1* and *Myt1l* SNPs had significant associations with schizophrenia in subjects with a maternal mental history and childhood trauma respectively. These results suggest that the genes for the downstream signaling partners of NgR may play a role in the inheritance of psychiatric disorders. Furthermore, alterations in brain volumes [19,37,38] and abnormal axonal connectivity, in particular within the corpus callosum (the highest myelinated fiber tract in the brain), have been observed in children with a history of abuse or neglect [3,39–42]. The large majority of nerve fiber connections passing through the corpus callosum are established before

birth, and the experience-dependent pruning and elimination of fibers through this region continue into adolescence [43], which is a critical period for the development of schizophrenia. Considering the role that NgR and its co-factor signaling partners have in myelin-related processes, and that a number of studies have shown strong associations between negative childhood experiences and adult psychiatric illnesses in addition to alterations in myelinated regions of the brain [19,44–46]; it seems reasonable to speculate that these genes may prove useful in understanding the mechanism by which negative experiences early in life can affect myelin-related processes in the context of schizophrenia.

## 5. Conclusions

Despite the fact that our study reported no significant associations after Bonferroni correction between any of the tested genetic markers in any of our studied genes within *NgR* signaling pathways, there is ample literature to support the hypothesis that NgR signaling is altered in schizophrenia as highlighted by the involvement of these pathways in neuronal growth, myelination and memory processes. Previous studies have found alterations in these genes through gene expression and genetic association studies in schizophrenia patients; and evidence suggests a role for these genes in myelin-related processes in psychiatric disease. The characterization of the complete pathway involved in this model remains to be a warranted avenue of research yet to be fully investigated in the pathogenesis of schizophrenia.

## Competing interests

There are no competing interests in relation to the work described here.

## Author contributions

Jessica L. Andrews performed the experiments and data analysis, wrote the first draft and made changes to the final version of the manuscript. Francesca Fernandez-Enright designed the study and supervised the experiments and helped draft and make final changes to the manuscript. Both authors have approved the final version of the manuscript.

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