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Research Report

Genes for Psychosis and Creativity

A Promoter Polymorphism of the *Neuregulin 1* Gene Is Related to Creativity in People With High Intellectual Achievement

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ABSTRACT—***Why are genetic polymorphisms related to severe mental disorders retained in the gene pool of a population? A possible answer is that these genetic variations may have a positive impact on psychological functions. Here, I show that a biologically relevant polymorphism of the promoter region of the* neuregulin 1 *gene (SNP8NRG243177/rs6994992) is associated with creativity in people with high intellectual and academic performance. Intriguingly, the highest creative achievements and creative-thinking scores were found in people who carried the T/T genotype, which was previously shown to be related to psychosis risk and altered prefrontal activation.***

Mad or genius? This enigma plays a central role in the history of human culture and evolution (Runco & Richards, 1998). It has been suggested that there is an association between psychotic features and creativity, which may explain the retention of genes related to psychosis in the gene pool of a population (Brod, 1997; Chadwick, 1997). However, no studies have been conducted to directly investigate the relationship between psychosis genes and creativity in the general population.

One of the most widely investigated candidate genes for psychosis is *neuregulin 1*, which affects neuronal development, synaptic plasticity, glutamatergic neurotransmission, and glial functioning (Harrison & Law, 2006). A functional promoter polymorphism of the *neuregulin 1* gene (SNP8NRG243177/rs6994992; C vs. T) may have a special relevance. The T/T genotype is associated with an increased risk of psychosis (Hall et al., 2006; Kéri, Kiss, & Kelemen, 2009), lower premorbid IQ (Hall et al., 2006; Kéri, Kiss, & Kelemen, 2009), lower working memory capacity (Stefanis et al., 2007), higher sensitivity for harsh criticism during interpersonal interactions (Kéri, Kiss, Seres, & Kelemen, 2009), decreased activation of frontal and temporal cortex during cognitive tasks (Hall et al., 2006), and reduced white-matter density (McIntosh et al., 2008). This single-nucleotide polymorphism has a unique biological relevance and is related to increased expression of the type IV transcript of *neuregulin 1* in postmortem tissue (Law et al., 2006; Tan et al., 2007). Is there any advantage of this genetic variation? To answer this question, we studied the relationship between the *neuregulin 1* promoter polymorphism and creativity in 200 healthy participants with high intellectual and academic performance.

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METHOD

Participants were recruited via newspaper advertisements and university e-mail and personal networks. The advertisement stated that people who felt that they were particularly creative or had achieved significant scientific or artistic results in their lives were wanted for investigations. All participants were Hungarian with Central European ancestry and were free from psychiatric and neurological disorders, as evaluated by the Structured Clinical Interview for DSM Disorders, Clinician Version (First, Spitzer, Gibbon, & Williams, 1996). We assessed IQ (Wechsler, 1981), socioeconomic status (Hollingshead Four-Factor Index; Cirino et al., 2002), and schizotypal traits (Schizotypal Personality Questionnaire; Raine, 1991), and administered the Creative Achievement Questionnaire (Carson, Peterson, & Higgins, 2005), and the "Just Suppose" subtest of

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the Torrance Test of Creative Thinking (Torrance, 1974; Table 1). In addition to data from the investigated groups of high achievers, population means, which were obtained from a group of volunteers during the validation of the Hungarian version of the creativity tests, are also reported for the creativity scales. This group consisted of 128 participants who were age- and gender-matched to the sample of the high achievers (mean IQ = 102.3, *SD* = 10.2; mean socioeconomic status = 30.5, *SD* = 9.3).

The Creative Achievement Questionnaire is a self-report measure for real-life creative achievements in the field of arts and sciences. It has a good test-retest reliability, internal consistency, and convergent validity with other measures of creativity, such as divergent thinking, creative personality traits, and intellect (Carson et al., 2005). The population mean for this questionnaire is 4.6 (*SD* = 2.4). The Torrance Test of Creative Thinking is a classic laboratory measure. In the "Just Suppose" subtest, participants are asked: "Just suppose clouds had strings attached to them which hang down to earth. What would happen? List your ideas and guesses." Responses are scored for originality, flexibility, and fluency. The originality score reflects the rarity of the response, which is based on the statistical infrequency of each individual response within the current sample (population mean = 4.7, *SD* = 3.4). The flexibility score is defined as a change in focus during the responses (population mean = 4.3, *SD* = 3.6). If the attitude is similar in each response, the flexibility score is zero. Each shift in attitude or focus (change in concept of written response) is awarded 1 point. The fluency score reflects the number of different possibilities produced (population mean = 5.1, *SD* = 2.9; Torrance, 1974). The Creative Achievement Questionnaire correlated with fluency ($r = .34$), originality ($r = .47$), and flexibility ($r = .37$). All tests were administered by two trained and independent investigators who were blind to the genetic and demographic data (Cronbach's $\alpha > .8$; interrater correlation: Pearson's $r > .8$).

Genomic DNA was extracted from venous blood samples. Genotyping was performed using TaqMan Bioassay (Applied Biosystems, Foster City, CA) for SNP8NRG243177/rs6994992 and two other control single-nucleotide polymorphisms of the *neuregulin 1* gene (rs10954867 and rs7005288; duplicate run, error rate < 0.2%), which are not related to psychosis and do not affect gene expression (for details regarding these control polymorphisms, see Law et al., 2006).

The association between genotypes and creativity scores was determined with analyses of variance (ANOVAs) and hierarchical regression analyses. The level of significance was set to $\alpha < .05$. The study was done in accordance with the Declaration of Helsinki and was approved by the ethics board. All participants gave written informed consent.

RESULTS AND DISCUSSION

The results are summarized in Table 1. The linear-trend ANOVA, including the *neuregulin 1* promoter genotypes, revealed significant main effects for each creativity measure—Creative Achievement Questionnaire: $F(1, 197) = 14.79$, $p = .0002$; originality: $F(1, 197) = 8.08$, $p = .005$; flexibility: $F(1, 197) = 7.71$, $p = .006$; fluency: $F(1, 197) = 6.02$, $p = .02$. Analyses for quadratic trends revealed no significant main effects for any measures of creativity ($p > .1$). These results consistently indicated the highest creativity scores in the T/T group, the lowest creativity scores in the C/C group, and

TABLE 1
Characteristics of Participants With Different* neuregulin 1 *Genotypes

	Neuregulin 1 genotype		
Variable	T/T ($n = 25$)	C/T ($n = 94$)	C/C ($n = 81$)
Mean age (years)	35.6 (6.2)	36.4 (7.4)	34.4 (7.2)
Gender			
Males	16	50	35
Females	9	44	46
Mean education (years)	17.4 (3.2)	17.8 (4.2)	17.6 (3.8)
Mean socioeconomic status	39.6 (10.3)	38.4 (10.2)	39.8 (10.1)
Mean IQ	124.3 (9.4)	124.6 (9.8)	125.2 (9.3)
Number employed	25	90	76
Number married	14	56	63
Mean Schizotypal Personality Questionnaire score	20.3 (9.5)	20.7 (9.8)	20.4 (9.1)
Creativity measure			
Mean Creative Achievement Questionnaire score*	10.0 (4.6)	8.0 (6.0)	5.5 (4.2)
Mean originality score*	8.4 (3.8)	6.3 (4.2)	5.7 (4.1)
Mean flexibility score*	7.1 (4.1)	5.6 (3.6)	4.8 (3.3)
Mean fluency score*	8.3 (3.3)	6.6 (4.4)	6.0 (3.9)

Note. Standard deviations are given in parentheses. The possible range for socioeconomic status is 8 to 66 (Cirino et al., 2002). Creativity measures that showed a significant linear effect of genotype are marked with an asterisk ($p < .05$; for detailed analysis, see the text).

the middle-ranking scores in the C/T group (Table 1); mean effect size values (Cohen's *d*): $d_{T/T>C/T} = 0.43$, $d_{T/T>C/C} = 0.67$, $d_{C/T>C/C} = 0.24$.

We also conducted hierarchical regression analyses to explore how the *neuregulin 1* promoter genotype contributed to each creativity measure. We used two contrast codes for the linear and quadratic aspects, which together fully represent the differences among the three genotypes. The first step of the analysis was designed to investigate the effect of genotypes; the coefficients for the individual contrast codes indicated the size and significance of the linear and quadratic trends. At the second step of the analysis, the potential mediating variables were entered into the analysis (gender, IQ, socioeconomic status, schizotypal traits), and the coefficients were evaluated again. The first step of the analysis revealed that linear or quadratic aspects alone did not reach the level of statistical significance ($p > .1$). However, the whole model, including both contrast codes, was significant for each creativity measure—Creative Achievement Questionnaire: $F(2, 197) = 9.10, p < .001, R = .29, R^2 = .09$; originality: $F(2, 197) = 4.06, p < .05, R = .20, R^2 = .04$; flexibility: $F(2, 197) = 3.92, p < .05, R = .20, R^2 = .04$; fluency: $F(2, 197) = 3.22, p < .05, R = .17, R^2 = .03$. Next, we included gender, IQ, schizotypal traits, and socioeconomic status in the regression analysis in order to examine the remaining effect after controlling for these variables. None of these variables contributed significantly to creativity measures ($p > .1$), and the models remained significant—Creative Achievement Questionnaire: $F(9, 190) = 3.85, p < .001, R = .28, R^2 = .08$; originality: $F(9, 190) = 2.06, p < .05, R = .17, R^2 = .03$; flexibility: $F(9, 190) = 2.12, p < .05, R = .19, R^2 = .04$; fluency: $F(9, 190) = 2.10, p < .05, R = .16, R^2 = .03$.

We also calculated the semi-partials (i.e., R^2 changes when the genotype was added to the potential mediators). These analyses revealed significant changes for all creativity measures—Creative Achievement Questionnaire: R^2 change = .07, $F(1, 194) = 17.04, p < .01$; originality: R^2 change = .03, $F(1, 194) = 4.90, p < .05$; flexibility: R^2 change = .03, $F(1, 194) = 5.61, p < .05$; fluency: R^2 change = .02, $F(1, 194) = 4.35, p < .05$.

ANOVAs and regression analyses did not indicate similar associations in the case of the two control polymorphisms (rs10954867 and rs7005288; $p > .1$). In addition, we observed no effect of any genotype on IQ, Schizotypal Personality Questionnaire scores, and demographic measures ($p > .1$; Table 1). There were no significant differences between male and female participants ($p > .1$).

In summary, the biologically relevant promoter polymorphism of the *neuregulin 1* gene has a significant impact on creativity: The T/T genotype, which has previously been shown to be related to psychosis risk and altered brain structure and function (Hall et al., 2006; Kéri, Kiss, & Kelemen, 2009; McIntosh et al., 2008), was associated with the highest creativity scores when lifetime achievement or laboratory scores of creative thinking were taken into consideration. This relationship was not mediated by intellectual differences or by schizotypal features, and these measures were not affected by the genotype. It is important to note that the relationship with creativity was found in a relatively homogeneous sample with high intellectual and academic performance, as reflected by the IQ scores, years of education, and socioeconomic status. It is possible that, in an intellectually less-prominent sample, no such relationship could be found because of the lower range of creativity scores and because of the possible subtle but negative impact of the *neuregulin 1* promoter polymorphism on cognition (Stefanis et al., 2007), which might have been compensated for by other factors in our participants. It is also noteworthy, however, that in the general population, the *neuregulin 1* promoter polymorphism is not related to schizotypal traits and is only weakly related to spatial, but not verbal, working memory (Stefanis et al., 2007).

To my knowledge, this is the first study to show that a genetic polymorphism related to severe mental disorders may have a positive impact on psychological functions. However, the question is still open: How does this polymorphism lead to higher creativity? A possible link may be reduced cognitive inhibition, which is related to schizotypal features (Braunstein-Bercovitz & Lubow, 1998) and increased creativity in people with high intelligence (Carson, Peterson, & Higgins, 2003). The prefrontal cortex is important in cognitive inhibition and creativity (Dietrich, 2004), and there is evidence that the promoter polymorphism of the *neuregulin 1* gene affects the functioning of this brain region (Hall et al., 2006; Stefanis et al., 2007). Indeed, it has been reported that the reduction of prefrontal functions may lead to creative peaks in highly functioning people, even if they are in the presymptomatic stage of severe neurodegenerative illnesses (Seeley et al., 2008). Future studies should focus on this hypothesis and extend the findings of the present study.

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