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The role of gender in the effect of folate pathway-related MTHFD1L gene on ruminative response style

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Our previous results recently demonstrated that the rs11754661 polymorphism A allele, situated in the folate-related *MTHFD1L* gene, increases the risk of ruminative response style (depressive rumination, or shortly rumination) in a European white population, and this association completely explains the risk that the A allele confers to depression [1]. Although it has been shown that gender differences in rumination play a considerable part in explaining the gender differences in depressive symptoms [2], data on gender differences in the effect of the *MTHFD1L* gene on neuropsychiatric [3] or neural [4] outcomes are lacking. Our present aim was to explore the role of gender in the association between rs11754661 and rumination.

N=2120 white European adults (aged 18–60 years) from Budapest and Manchester filled out the 10-item Ruminative Responses Scale and were genotyped for *MTHFD1L* rs11754661. We built linear regression models separately in women and men, with population and age as covariates, to test the effect of the A allele of rs11754661 on rumination score. We also ran a

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linear regression model on rumination in the total sample, with population, age, rs11754661 A allele, gender, and the interaction term of rs11754661 A allele and gender as predictors. The Bonferroni-corrected threshold of significance for these three tests was p = 0.0167.

Our results show that the presence of the A allele of rs11754661 increases rumination in both genders but this effect was only significant in females but not in males (see Table 1).

Table 1. Effect of the rs11754661 A allele on rumination score, in a linear regression model, with population and age as covariates, separately in females and males.

	n	β	t	p
Females	1485	0.153	3.414	0.0007
Males	635	0.048	0.672	0.502

To follow up the results of separate analyses in females and males, an analysis was run in the total sample (as mentioned above) which showed that the interaction effect of the rs11754661 A allele and gender proved to be nonsignificant (β = 0.117; t = 1.388; p = 0.165) suggesting that despite the observed difference in effect strength of the A risk allele between females and males it could not cause significant interaction in this model.

Our findings suggest that gender does not modify the direction in which the rs11754661 A allele exerts its effect on rumination, even though this effect was stronger and only significant in females. It should be further investigated if the lack of significance in males can be attributable to decreased power in statistical testing or to real underlying biological differences. If real biological differences exist between women and men in the effect of the *MTHFD1L* gene on rumination, this may have numerous consequences regarding the possibilities of folate supplementation in the prevention of mental disorders having been linked to rumination, e.g. depression, anxiety, substance abuse and eating disorders [5].

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