

Association of the Muscarinic Cholinergic 2 Receptor (*CHRM2*) Gene With Major Depression in Women

David E. Comings,^{1*} Sujihan Wu,¹ M. Rostamkhani,¹ Matt McGue,² William G. Iacono,² and James P. MacMurray³

¹Department of Medical Genetics, City of Hope Medical Center, Duarte, California

²Department of Psychology, University of Minnesota, St. Paul, Minnesota

³Department of Psychiatry, Loma Linda University, Loma Linda, California

Cholinergic neurons have been implicated in depression and in the disorders of REM sleep in depression. We examined a common A->T 1890 polymorphism in the 3' UTR of the cholinergic muscarinic receptor 2 (*CHRM2*) gene. There was a significant increase in the frequency of 11 homozygotes in 126 women with major depression (43.7%) compared to 304 women without major depression (25.7%), $P = .001$. There was no increase in the frequency of 11 homozygotes in 52 men with depression (26.9%) compared to 278 men without depression (27.7%). Regression analysis, scoring subjects with the 11 genotype as 1, and those with other genotypes as 0, showed that in women $r^2 = .030$, $F = 13.37$, $P = .0003$. By contrast, in men $r^2 = .00001$, $F = 0.002$, $P = .96$. These results are consistent with a gender-specific role of the *CHRM2* gene in depression in women.

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INTRODUCTION

The lifetime frequency of major depression is twice as high in women as in men [Weisman, 1991]. Twin studies have shown a significant genetic contribution to major depression (MD) in women with heritabilities ranging from .33 to .45 and higher [Kendler et al.,

1993a,b; Bierut et al., 1999; Kendler & Prescott, 1999], and an important role of stress [Kendler et al., 1995, 2000]. Some twin studies have suggested a comparable heritability for men and women [Kendler & Prescott, 1999], while others have suggested a greater heritability for women [Bierut et al., 1999]. The muscarinic cholinergic receptors belong to a larger family of G protein-coupled receptors. The binding of acetylcholine to these receptors leads to further intracellular and intranuclear events in the signal transduction pathway. The cholinergic muscarinic₂ receptor is present throughout the central nervous system. In 1972, 1981, and again in 1994, Janowsky reviewed the evidence for a role of cholinergic hypersensitivity in depression [Janowsky et al., 1972, 1994; Risch et al., 1981]. Both REM and non-REM sleep is regulated by cholinergic, serotonergic, and noradrenergic neurons in the brain stem [Riemann et al., 1994]. The early onset of REM sleep, increased REM density, and exaggerated REM response to cholinergic stimulation, are consistent with CNS cholinergic overactivity or muscarinic supersensitivity in depression [Riemann et al., 1994]. Cholinergic mechanisms have also been implicated in stress. While the HPA axis has been emphasized in the response to stress, recent studies of Kaufer et al. [1998] have identified an important alternative cholinergic pathway. They showed that acute stress resulted in an immediate increase in synaptosomal acetylcholine with neuronal excitability, with a delayed phase response of increased expression of acetylcholinesterase, decreased choline acetyl transferase and vesicular acetylcholine transporter (CHAT) activity, and a resulting decrease in neuronal excitability [Kaufer et al., 1998; Sapolsky, 1998]. Others have also emphasized the important role of stress in activating muscarinic systems [Dilsaver, 1988].

We have recently identified a common single A->T nucleotide polymorphism in the cholinergic muscarinic receptor 2 (*CHRM2*) gene. The above literature on the potential role of defects in muscarinic cholinergic

was no increase in frequency for the 11 genotype for those with MD (26.9%, $\chi^2 = 1.48$, d.f. = 1., $P = .47$). The *CHRM2* alleles were in Hardy-Weinberg equilibrium for those without MD. Regression analysis showed that in women, the fraction of the variance of major depression explained by the *CHRM2* gene, r^2 , was .030, $F = 13.37$, $P = .0003$. By contrast, in men $r^2 = .00001$, $F = 0.002$, $P = .96$.

DISCUSSION

While requiring replication in independent samples, these results suggest that *CHRM2* may be a gene associated with MD in women but not in men. This association with MD is consistent with the postulated role of enhanced or hypersensitive cholinergic systems in depression [Janowsky et al., 1972, 1994]. The association of cholinergic systems with REM sleep [Gillin et al., 1979; Riemann et al., 1994], and the disturbance of REM sleep in individuals with depression are consistent with the presence of genetic defects in the cholinergic system in MD.

In women, the *CHRM2* gene accounted for 3% of the variance of MD while in men it accounted for virtually none of the variance. The increased frequency of MD in females and some twin studies [Bierut et al., 1999], suggesting a greater heritability of MD in women, raises the possibility that the *CHRM2* is a gender-specific gene for MD. While the mechanism by which a non-X-linked gene would have this effect is not known, there are several possibilities. These include hormone responsive promoters or enhancers, affecting either *CHRM2* or other genes that interact with *CHRM2*. A second possibility is that if women are more sensitive to stress expressed through the cholinergic stress pathway [Dilsaver, 1988; Kaufert et al., 1998; Sapolsky, 1998], they would also be more likely to show an association between the *CHRM2* gene and depression.

Since the A/T polymorphism was in the 3' region of the *CHRM2* gene we assume it was in linkage disequilibrium with alleles affecting gene function, possibly microsatellites [Comings, 1998]. Although the *CHRM2* gene accounted for only 3% of the variance of MD in women, this association was significant. This is an expected and characteristic aspect of a complex polygenic disorder where multiple genes are involved and each gene accounts for only a small percent of the total variance. In our experience, 3% is a higher than the average r^2 for most gene-phenotype associations for behavioral disorders [Comings et al., 2000a,b,c; Comings et al., 2001].

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