Abstract

On the influence of serotonin- and sex steroid-related genetic variation on mood, anxiety, personality, autism and transsexualism

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Background: The neurotransmitter serotonin has been related to mood and anxiety, and variation in genes that encode important members of the serotonergic system may hence affect mood- and anxiety-related traits. Sex steroids influence brain development, and variation in genes encoding androgen and estrogen receptors, or enzymes needed for sex steroid synthesis, may be of importance for both personality traits and risk for psychiatric disorders. The specific aims of this thesis were: (i) to investigate the possible influence of serotonin-related genetic variation on the neural correlates of anxiety, and on mood- and anxiety-related phenotypes, including premenstrual dysphoric disorder (PMDD), depression and anxiety-related personality traits, (ii) to investigate the possible influence of sex steroid-related genetic variation on personality, autism spectrum disorder and transsexualism, and (iii) to try to ameliorate the chance of detecting effects of combinations of genetic variations by restricting the statistical analysis to particular patterns.

Results: (i) The serotonin transporter (5-HTT) linked polymorphic region (5-HTTLPR) and a polymorphism in an important enzyme for serotonin synthesis (tryptophan hydroxylase 2; TPH2) were associated with amygdala response during presentation of angry faces in subjects with social phobia and controls. (ii) The same polymorphisms were associated with response to placebo and also with placebo-induced changes in amygdala activity during public speaking in subjects with social phobia. (iii) In men, genetic variation in the neurotrophic factor BDNF, which is closely related to the serotonergic system, was associated with the amount of serotonin transporter in the brain. (iv) Polymorphisms in genes that encode proteins important for the development of the serotonergic system (GATA2), for serotonin synthesis (TPH2) and for serotonergic transmission (5-HT3B) were associated with PMDD. (v) The 5-HTTLPR was shown to influence reports of controllable stressful life events in combination with the BDNF Val66Met polymorphism or anxiety-related personality traits in non-depressed men. (vi) Variants that may increase the function of the androgen receptor were associated with extraversion and spiritual acceptance in men. (vii) A variant that is associated with increased androgen receptor function was more common in women with autism spectrum disorder than in controls. (viii) The same androgen receptor polymorphism was associated with transsexualism in combination with polymorphisms in the genes encoding the estrogen receptor β or the testosterone-converting aromatase enzyme. (ix) A method that restricts the search for genetic combinations to monotone effect patterns was shown to increase the probability of finding gene-gene effects.

Conclusions: The results support the notion that variation in genes that encode serotonin-related and sex steroid-related proteins are of importance for the psychiatric traits studied in this thesis.


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Akademisk avhandling
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Fakultetsopponent: Associate professor Turhan Canli, Ph.D.
Department of Psychology, Stony Brook University, USA

The thesis is based on the following papers:


III. Susanne Henningsson, Jacqueline Borg, Johan Lundberg, Jessica Bah, Mats Lindström, Erik Ryding, Hristina Jovanovic, Ingmar Rosén, Lil Träskman-Bendz, Lars Farde, Elias Eriksson. Genetic variation in BDNF is associated with serotonin transporter but not 5-HT1A receptor availability in humans. Submitted manuscript.

IV. Jessica Bah, PhD, Susanne Henningsson, Petra Suchankova, Agneta Ekman, Olle Eriksson, Göran Holm, Mikael Landén, Lars-Göran Nilsson, Staffan Nilsson, Hans Nissbrandt, Lars Westberg, Jonas Melke, Elias Eriksson. A study of 22 serotonin-related genes reveals association between premenstrual dysphoria and genes encoding the GATA2 transcription factor, the 5-HT3B receptor subunit and tryptophan hydroxylase 2. Submitted manuscript.

V. Susanne Henningsson, Jody M. Ganiban, Jenae M Neiderhiser, David Reiss, Erica L. Spotts, Nancy L. Pedersen, Paul Lichtenstein, Elias Eriksson. Possible effects of interactions between the serotonin transporter polymorphism 5-HTTLPR, the BDNF Val66Met polymorphism and anxiety-related personality traits on controllable stressful life events. Preliminary manuscript.


VII. Susanne Henningsson, Lina Jonsson, Elin Ljunggren, Lars Westberg, Carina Gillberg, Maria Råstam, Henrik Anckarsäter, Gudrun Nygren, Mikael Landén, Kent Thuresson, Catalina Betancur, Marion Leboyer, Christopher Gillberg, Elias Eriksson, Jonas Melke. Possible association between the androgen receptor gene and autism spectrum disorder. Submitted manuscript.
