

## 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  $\beta$  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.

Key words: serotonin – 5-HTTLPR – TPH2 – 5-HT3 – sex steroids – androgen receptor – estrogen receptor – genetics – gene-gene interaction – social phobia – anxiety – premenstrual dysphoric disorder – depression – personality – autism – transsexualism – amygdala – emotional perception – life events

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The thesis is based on the following papers:

**I.** Tomas Furmark, Susanne Henningsson, Lieuwe Appel, Fredrik Åhs, Clas Linnman, Anna Pissioti, Vanda Faria, Emilio Merlo Pich, Lars Orelund, Elias Eriksson, Mats Fredrikson. Genotype over diagnosis in amygdala responsiveness: Affective processing in social anxiety disorder. *The Journal of Psychiatry and Neuroscience*. In press.

**II.** Tomas Furmark, Lieuwe Appel, Susanne Henningsson, Fredrik Åhs, Vanda Faria, Clas Linnman, Anna Pissioti, Örjan Frans, Massimo Bani, Paolo Bettica, Emilio Merlo Pich, Eva Jacobsson, Kurt Wahlstedt, Lars Orelund, Bengt Långström, Elias Eriksson, Mats Fredrikson. A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety. *The Journal of Neuroscience*. Preliminary accepted.

**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-HT<sub>1A</sub> 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-HT<sub>3B</sub> 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.

**VI.** Lars Westberg, Susanne Henningsson, Mikael Landén, Kristina Annerbrink, Jonas Melke, Staffan Nilsson, Roland Rosmond, Göran Holm, Henrik Anckarsäter, Elias Eriksson. Influence of androgen receptor repeat polymorphisms on personality traits in men. *The Journal of Psychiatry and Neuroscience*. In press.

**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.

**VIII.** Susanne Henningsson, Lars Westberg, Staffan Nilsson, Bengt Lundström, Lisa Ekselius, Ove Bodlund, Eva Lindström, Monika Hellstrand, Roland Rosmond, Elias Eriksson, Mikael Landén. Sex steroid-related genes and male-to-female transsexualism. *Psychoneuroendocrinology* (2005) 30, 657–664.

**IX.** Susanne Henningsson and Staffan Nilsson. Detecting two-locus gene-gene effects using a monotone penetrance matrix. *Statistical Applications in Genetics and Molecular Biology* (2008) 7, 1, 17.