

# Genetic Studies of Autism and Autistic-Like Traits

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

- I. **Lina Jonsson**, Elin Ljunggren, Anna Bremer, Christin Pedersen, Mikael Landén, Kent Thuresson, MaiBritt Giacobini and Jonas Melke. 2010. Mutation screening of melatonin-related genes in patients with autism spectrum disorders. *BMC Med. Genomics* 3, 10.
- II. **Lina Jonsson**, Henrik Anckarsäter, Anna Zettergren, Lars Westberg, Hasse Walum, Sebastian Lundström, Henrik Larsson, Paul Lichtenstein, Jonas Melke. 2014. Association between ASMT and autistic-like traits in children from a Swedish nationwide cohort. *Psychiatr. Genet.* 24(1):21-7
- III. **Lina Jonsson**, Anna Zettergren, Erik Pettersson, Daniel Hovey, Henrik Anckarsäter, Lars Westberg, Paul Lichtenstein, Sebastian Lundström and Jonas Melke. 2014. Association study between autistic-like traits and polymorphisms in the autism candidate regions *RELN*, *CNTNAP2*, *SHANK3*, and *CDH9/10*. *Molecular Autism* 5:55.
- IV. **Lina Jonsson**, Carmela Miniscalco, Mats Johnson, Christopher Gillberg, Tommy Martinsson, Jonas Melke. Screening for rare inherited variation in a multiplex family with autism and language disorders. *Manuscript*.

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# Genetic Studies of Autism and Autistic-Like Traits

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## ABSTRACT

Autism spectrum disorder (ASD) is characterized by impairment in social interaction, language impairment and repetitive behavior with varying degrees of severity. ASD represents the lower end on a continuously distributed measure of autistic-like traits (ALTs). Although a strong genetic component has repeatedly been identified in ASD, the genetic cause of ASD is still unknown for the majority of ASD cases.

One of the main interests in this thesis is the neurobiology of melatonin, this interest is based on findings indicating lower levels of melatonin in children with ASD. In our investigations of rare mutations in melatonin related genes in subjects with ASD, we identified a previously reported mutation that has been shown to decrease the activity of one of the enzymes involved in the melatonin synthesis: the acetylserotonin O-methyltransferase (ASMT) (paper I). In the analysis of five common variations in the ASMT gene in relation to ALTs in the general population we found association between a single nucleotide polymorphism and social interaction impairment in girls (paper II).

To broaden the analysis of genetic influences on ALTs, we have performed association analyses between ALTs in the general population and common variation in genes previously found to be associated with ASD (*RELN*, *CNTNAP2*, *SHANK3* and *CDH9/10* region) (paper III). Although these regions have previously been suggested to be strong ASD candidate regions, our results do not suggest a major influence of the investigated common variations on ALTs.

In the final paper, rare inherited genetic variations were investigated in a large family with autism and language disorders. In this study, we used several techniques, including whole exome sequencing and copy number variation analysis (paper IV). In the family, several rare genetic variations which may partly explain the genetic etiology for autism in this family were identified. We performed functional analyses for a mutation identified in the *CYP11A1* gene, indicating a gain of function mutation. The *CYP11A1* gene encodes the first enzyme in the steroid hormone biosynthesis, thus our results may be in line with previous findings that have shown an elevated prenatal steroidogenic activity in ASD.

In conclusion, we have identified both common and rare genetic variation that may increase the genetic susceptibility for ASD. Our analyses have highlighted the importance of taking both rare and common genetic susceptibility factors, as well as different symptoms of the disorders, into account when elucidating the complex inheritance of ASDs.

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