ABSTRACT

Autism spectrum disorders (ASD) are neuropsychiatric disorders characterized by restricted repetitive behavior and abnormalities in communication and social interaction. Although the heritability of the trait has been estimated to be relatively high, the model of inheritance of ASD seems to be very complex and probably involves multiple interacting genes. Also, environmental factors together with genetic risk factors may increase the risk for autism.

The purpose of this study was to detect genetic variants predisposing to ASD. We initiated the study with fine mapping of chromosomal region Xq11.1-q21.33 in 99 Finnish ASD families where linkage has been observed in earlier studies. The highest multipoint LOD score was obtained with the marker DXS1225 at Xq21.1 (NPL_all=3.43). However, Sanger sequencing of five candidate genes in the linkage region did not reveal any disruptive mutations. Despite that, in Study IV we detected significant association in a family-based genome-wide association (GWA) scan at Xq21 in the PCDH11X gene. There are several candidate genes in the linkage region and exome sequencing of the X chromosome might reveal disruptive mutations in ASD.

Aberrant glutamate metabolism has been observed in both ASD and obsessive compulsive disorder (OCD). In Study II we analyzed if single nucleotide polymorphisms (SNPs) previously associated in OCD in the glutamate transporter gene SLC1A1 at 9p24 are also associated in ASD. We further analyzed whether the SNPs reported earlier in the largest linkage study of ASD by the Autism Genome Project (2007) at chromosomal areas 9p24 (rs1340513 and rs722628) and 11p12-13 (rs1358054 and rs1039205) are associated with ASD in a sample of 175 Finnish ASD cases and 216 controls. SNP rs1340513, in JMJD2C, the neighboring gene of SLC1A1, showed significant association with ASD in this study. In this thesis, the GWA scan (Study IV) and copy number variants (CNVs) with a different sample set also supported the association at locus 9p24 with SLC1A1, JMJD2C and PTPRD.

Synaptic defects have been suggested to be the mechanism underlying autism. Disruptive mutations in synaptic genes NRXN1, NLGN3/4X and SHANK2/3 have been detected in ASD patients. In Study III we continued the mutation screen of the SHANK2 gene in 455
European ASD families. Several harmful mutations were detected and in functional analyses we observed that they reduced synaptic density in vitro. We also detected deletions in the SHANK2 gene in ASD samples. We noticed that patients who had a SHANK2 deletion carried additional CNVs on chromosomal region 15q11-q13, which has previously been associated to ASD and several other neuropsychiatric disorders. This supports a multiple hit model for ASD. Additional studies are warranted to analyze how many mutations are sufficient to contribute to ASD and what kind of combination of genetic defects will be detected in individual ASD families.

In this thesis, we performed a genome-wide scan with a novel sample set of 83 Finnish ASD families and 750 controls (a cohort of Health 2000 study). We detected the strongest association at chromosome 16p13.2 with the RBFOX1 gene, which regulates tissue-specific splicing of several autism related genes. Preliminary evidence of epistatic interactions was obtained between SNPs in NRXN1 and UBA52, as well as RBFOX1 and SCN1A, and DLG2 and RBFOX3. In addition, we performed promoter analyses for ASD candidate genes and discovered a possible transcriptional regulatory site in the promoter area of AVPR1A, which might partly explain the associations with autism observed with the promoter polymorphisms of this gene. Furthermore, a transcription factor (TF) binding site for early growth response (EGR) was enriched in autism candidate genes. Finally, we performed CNV analyses and detected large (>400 kb) CNVs in chromosomal regions 15q13.3, 16p11.2, 17q12 and 22q11. CNVs in the same regions have been detected in ASD and other neuropsychiatric disorders such as ADHD, epilepsy, schizophrenia and intellectual disability in earlier studies. We also observed CNVs in known ASD candidate genes for example DISC1, FOXG1, ASMT, PCDH11X, and PRODH.

In conclusion, the results obtained in this thesis show that several genetic risk variants predispose to ASD and epistasis between ASD candidate genes play an important role in these disorders. More studies are warranted to explore the combination and interaction of genetic risk variants and their pathways and environmental triggers which all together could contribute to ASD.