Disease-oriented Genome Networks

Network: Systematic Gene Identification and Functional Analyses in Common CNS Disorders

Project: Animal Models for the Analysis of Candidate Genes in Affective Disorder

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Introduction:
Bipolar affective disorder is a severe mood disorder that afflict approximately 1% of the population worldwide. Twin and adoption studies have indicated that genetic factors contribute to the complex disorder. While many chromosomal regions have been implicated, no susceptibility genes have been identified. The strongest support for specific susceptibility genes common to bipolar disorder comes from the G72/G30 locus in the 13q candidate region (Hattori, Liu et al. 2003; Addington, Gormick et al. 2004; Chen, Akula et al. 2004; Korostishevsky, Kaganovich et al. 2004; Wang, Chen et al. 2004). This gene locus is curious, because it constitutes more or less a “gene desert”, but there are two overlapping genes, G30 and G72, which are transcribed form opposite strands. The whole locus is only conserved in higher primates. In some populations the at-risk haplotypes are shared between schizophrenia and bipolar disorder (Schumacher, Jamra et al. 2004). The pathogenic mutations have not yet been identified but might be located between schizophrenia and bipolar disorder.

Genetic variants of the DAAO gene were also found to be associated with bipolar disorder and schizophrenia (Schumacher, Jamra et al. 2004). DAOA is of particular interest as it degrades D-serine, which acts, similar to glycine, as a coactivator on the “glycine binding site” of the glutamatergic NMDA receptor. D-serine is produced form L-serine in cerebral astrocytes by the serine racemase and degraded by DAAO (Chumakov, Blumenfeld et al. 2002). Interestingly Hashimoto et al. (2005) recently showed that the percentage of D-serine in the total serine in the cerebrospinal fluid of drug naïve schizophrenia patients was significantly lower than that of the controls (Hashimoto, Engberg et al. 2005). A role of NMDA receptors in the pathogenesis of schizophrenia was suggested, because the NMDA receptor (Steinpreis, 1996) agonists induce schizophrenia-like symptoms both in humans and animals. It is also known that the NMDA receptor is differentially expressed in patients with schizophrenia and bipolar disorder (Law and Deakin 2001). Taken together these data suggests that synthetic or metabolic pathways of D-serine may be abnormal in the brain of drug naïve schizophrenic patients, supporting the glutamate hypothesis of schizophrenia (Fig 1).

We are currently generating mouse strains with decreased brain D-serine levels. Alterations of the D-serine concentrations in the brain should affect the activity of the NMDA receptor, which may result in a behavioral phenotype. Since the G72/G30 gene locus is not conserved in mice, we are introducing the human gene locus into the mouse genome via the BAC (Bacterial Artificial Chromosome) technology. Murine expression of DAAO overexpressing mice: For expression of DAAO under the human GFAP promoter a ca. 1.6 kb EcoRI/NotI fragment, containing the whole DAAO-ORF from vector IRAKp961M024Q2 (RZPD-clone) was cloned into the EcoRI/NotI cut hGFAP pGEM T-easy vector (Barton, Dunlop et al. 2002) containing a ca. 2.2 kb fragment of the human GFAP promoter. The resulting vector was cut with Eagl and Asel to release the GFAP promoter DAAO fragment. The fragment was injected in FVB/N oocytes. Currently offspring are analyzed for genomic fragment integration.

Outlook:
The aim of this project is the generation and analysis of transgenic mouse models with a human G72 gene locus and glial overexpression of the DAAO protein. These models will be used to study the expression of transcripts...
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from this gene locus and to address its potential function in the modulation of neuronal signalling. The activity of NMDA receptors in the brain of transgenic animals will be investigated. Moreover both animal models are going to be analyzed in behavior tests related to depression, schizophrenia and anxiety.