Association of Diras2 with attention-deficit / hyperactivity disorder

L. Weißflog1,5, H. Haavik1, T.T. Nguyen1, C.P. Jacob1, M. Romans1, T. Renner1, C. Freitag1, J. Meyer1, J. A. Ramos-Quiroga2, B. Cormand3, B. Franke4, K.P. Lesch7, A. Reif6

1 Department of Psychiatry, Psychoneurotics and Psychotherapy, University of Würzburg; 2 Department of Child and Adolescent Psychiatry, University of Würzburg, Germany; 3 Institute of Medical Biometry and Epidemiology, Philipps-University of Marburg, Germany; 4 Department of Genetics, Euskal Deiturikuntza, University of Barakaldo, Spain; 5 Department of Psychiatry, Haukeland University Hospital, Bergen, Norway; 6 Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; 7 Department of Child and Adolescent Psychiatry, University of Frankfurt, Germany.

Scientific Background

Attention-deficit/hyperactivity disorder (ADHD)
- Genetically complex
- Neurodevelopmental disorder
- Heritability of ADHD ~70-80%
- High persistence into adulthood
- Linkage studies and genome-wide association studies ➔ susceptibility loci

Results: Expression studies

Diras2 Expression during Development

Fig. 1: MOD scores achieved in a linkage study. MOD global is shown in red, MOD single in blue. The MOD global on Chr. 9q22 is 3.30. (Romans et al., 2008)

Fig. 2: Genome-wide association study in adult ADHD. (Lesch et al., 2008)

Methods

Finemapping of 11 potential candidate genes
- iPLEX™: Mass array based SNP genotyping
- Case-control association studies
  - >1600 adult ADHD patients and >1800 controls from Germany, the Netherlands, Norway and Spain (IMpACT Consortium)
  - Two independent family-based childhood ADHD samples (234 trios, 71 quartets, 15 multi-sibling families)

Immunocytochemistry: Fluorescence double stainings
- Mouse hippocampal primary cell culture
- Primary antibodies against Diras2 and cell markers
- Fluorescence labeled secondary antibodies

Expression analysis during development
- Total RNA from mouse brains at different embryonic and postnatal developmental stages
- Quantitative real-time PCR
- Calculation of PCR efficiencies using LinRegPCR
- Determination of normalized expression levels by the CFX Manager™ software (Biorad)

Association of Diras2 with ADHD

aADHD: 6 SNPs (p=0.0098-0.04), 2 haplotypes, replication in IMpACT sample, pooled analysis p=0.0552 (corrected)

Fig. 3: LD blot of the Diras2 gene. Locations of associated SNPs are marked with boxes. Red: German aADHD sample; Green: German family sample from Homburg; Pink: Dutch aADHD sample; Light blue: Norwegian aADHD sample; Blue: association with personality traits in the German aADHD sample; Magenta frame: pooled analyses of the IMpACT sample

Advantages of iPLEX™

- High density SNP arrays: novel loci at 5q13.1 and 14q12.1

References