Newsletter
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Society News

The 9th Annual Meeting of the DGNG (10th Workshop Neurogenetics in Germany) will be held in Tübingen from September 21 – 23, 2003. The conference will be organized by Professors O. Rieß, T. Gasser, and J. B. Schulz. Details and registration forms are on the web (http://www.uni-tuebingen.de/Klinische_Genetik/Jahres treffen.htm). Deadline for abstracts is Sunday 06/30/2003.

Research News

Promoter polymorphism results in reduced expression of presenilin 1 and increases the risk of Alzheimer disease (AD). Many common neurological disorders have a multifactorial etiology, i.e. the interplay of both environmental and genetic factors causes disease. Alzheimer disease (AD) is a prominent example. In order to identify and eventually characterize the genetic component in multifactorial disorders, association studies are being performed with polymorphisms in genes that potentially contribute to disease. Numerous polymorphisms in many genes have been described to be associated with common AD both of early (EOAD) and late onset (LOAD). An association between AD and allele e4 of Apolipoprotein E is best established. The e4 allele might promote plaque formation in patients´ brains by increased binding affinity to amyloid beta polypeptide. ApoE e4 is thought to account for up to 50% of the genetic component in some forms of AD. In most cases the effect of a polymorphism in a given gene is rather small and might be due to alterations in expression levels. Several years ago, two groups of investigators found an association between a polymorphism (-22C? T) in the promoter region of the presenilin 1 gene (*PSEN1*) and EOAD and LOAD (van Duijn et al., 1999; Lambert et al., 2001). Theuns et al. (2003) have now studied a potential effect of the -22C? T polymorphism on the level of *PSEN1* transcription. The authors first characterized the *PSEN1* promoter by deletion mapping. Subsequently, they transiently expressed relevant constructs containing either the T or C polymorphism in human neuroblastoma (N2a) and in human embryonic kidney cells (HEK293). While no difference in transcription was observed between a T or C containing construct in HEK293, a 2-fold decrease of PSEN1 expression was found for the –22C allele in N2a cells. The authors mapped a 13 bp region spanning the -22C? T polymorphism that is a binding site for a negative regulatory element. It appears that this regulatory element has a higher binding affinity for the –22C allele. Furthermore, the difference between expression levels found in HEK293 and N2a cells suggests neuron-specificity of this factor. The findings indicate that homozygosity for –22C results in significant reduction in expression of *PSEN1* in patients. Reduced expression in turn might increase the level of highly amyloidogenic Aß42. This hypothesis is supported by anti-sense induced reduction

of *PSEN1* transcripts and the observation of an increase in Aß42 production in a cell system (Refolo et al., 1999).

Lambert JC, Mann DM, Harris JM, Chartier-Harlin MC, Cumming A, Coates J, Lemmon H, StClair D, Iwatsubo T, Lendon C (2001) The -48 C/T polymorphism in the presenilin 1 promoter is associated with an increased risk of developing Alzheimer's disease and an increased Abeta load in brain. J Med Genet 38:353-355

Refolo LM, Eckman C, Prada CM, Yager D, Sambamurti K, Mehta N, Hardy J, Younkin SG (1999) Antisense-induced reduction of presenilin 1 expression selectively increases the production of amyloid beta42 in transfected cells. J Neurochem 73:2383-2388.

Theuns J, Remacle J, Killick R, Corsmit E, Vennekens K, Huylebroeck D, Cruts M, Van Broeckhoven C (2003). Alzheimer-associated C allele of the promoter polymorphism –22C>T causes a critical neuron-specific decrease of presenilin 1 expression. Hum Mol Genet 12: 869-877.

van Duijn CM, Cruts M, Theuns J, Van Gassen G, Backhovens H, van den Broeck M, Wehnert A, Serneels S, Hofman A, Van Broeckhoven C (1999) Genetic association of the presenilin-1 regulatory region with early-onset Alzheimer's disease in a population-based sample. Eur J Hum Genet 7:801-806.

More genes identified in monogenic forms of Parkinson disease / parkinsonism. Mutations in the gene NR4A2 have been identified in familial Parkinson disease and alterations in DJ-1 were found to be associated with PARK7 autosomal recessive parkinsonism.

NR4A codes for a member of a nuclear receptor superfamily and plays an important role in the differentiation of dopaminergic neurons. It also regulates expression of the gene coding for tyrosine hydroxylase. Le et al. (2003) have identified two heterozygous mutations in the first, untranslated exon of NR4A, a one base deletion (-291Tdel) and a transversion (–245T-G) in patients with familial (putatively autosomal dominant) Parkinson disease. Clinically, the disease was not different from sporadic PD. The age of onset in mutation carriers was 54±7 years. Haplotype analysis was performed in four of the ten families in whom a mutation was found. The authors detected a common haplotype in affecteds of three families indicating that the mutation in these families was introduced by a common founder. Since these families shared German ancestry, the founder might have originated in this country. Performing transfection assays the authors demonstrated that both mutations drastically reduce expression of NR4A in HEK293 and SHSY-5Y cell lines. Furthermore, in SHSY-5Y cells, they found drastic reduction in the expression of the gene coding for tyrosine hydroxylase. They also measured the expression level of NR4A in lymphocytes from two mutation carriers. They observed a >50% reduction in NR4A transcripts indicating a dominant / negative effect of the mutated allele. Absence of NR4A2 mutations in sporadic PD and the finding of a founder effect in ¾ families tested indicate that mutations in NR4A are rare in PD.

DJ-1 codes for a ubiquitous, highly conserved polypeptide of unknown function. Homozygosity mapping in one Dutch and one Italian consanguineous family had assigned a gene for autosomal recessive, early-onset parkinsonism, PARK7, to a 20 cM interval on chromosome 1p36 (van Duijn et al., 2001; Bonifati et al, 2002). Fine mapping reduced this interval to a region of 5.6 Mb containing about 90 genes (Bonifati et al., 2003). Sequencing of candidate genes in the region in patients from the two families failed to detect a mutation. Therefore, Bonifati et al. performed systematic RT-PCR analysis of transcripts from lymphoblastoid cell lines from one patient of each family. They

found that the entire open reading frame (ORF) of DJ-1 could not be amplified in the Dutch patient. Analysis of genomic DNA from the same patient showed a homozygous deletion of exons 1 A/B to 5 of the gene. Only the centromeric exons 6 and 7 were present. DJ-1 was the only homozygously deleted gene in the region. Genes flanking DJ-1 were present in patients. Sequencing of DJ-1 in the Italian patient revealed a T-C transition at position 497 from the ORF start codon. This results in the exchange of a highly conserved leucine at position 166 with a proline (Leu166Pro). The mutation cosegregated with the disease allele in the family and was not present in 320 chromosomes from the Italian population. Bonifati et al. transfected COS and PC12 cells with wild-type and mutant DJ-1. While diffuse cytoplasmic and nuclear DJ-1 immunoreactivity was found in wild-type transfectants, the cytoplasmic staining of mut DJ-1 transfectants localized to the mitochondria. This indicates that the cytoplasmic activity of DJ-1 is vital for its function. Although this function is not yet known, it may be related to oxidative stress response.

Bonifati V, Breedveld GJ, Squitieri F, Vanacore N, Brustenghi P, Harhangi BS, Montagna P, Cannella M, Fabbrini G, Rizzu P, van Duijn CM, Oostra BA, Meco G, Heutink P (2002) Localization of autosomal recessive early-onset parkinsonism to chromosome 1p36 (PARK7) in an independent dataset. Ann Neurol 51:253-256.

Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, Dekker MCJ, Squitieri F, Ibanez P, Joosse M, van Dongen JW, Vanacore N, van Swieten JC, Brice A, Meco G, van Duijn CM, Oostra BA, Heutink P (2003) Mutations in the *DJ*-1 gene associated with autosomal recessive early-onset parkinsonim. Science 299: 256-259.

Le W-d, Xu P, Jankovic J, Jiang H, Appel SH, Smith RG, Vassilatis DK (2003) Mutations in NR4A2 associated with familial Parkinson disease. Nat Genet 33: 85-89.

van Duijn CM, Dekker MC, Bonifati V, Galjaard RJ, Houwing-Duistermaat JJ, Snijders PJ, Testers L, Breedveld GJ, Horstink M, Sandkuijl LA, van Swieten JC, Oostra BA, Heutink P (2001) Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am J Hum Genet 69:629-634.

Looking forward to seeing you in Tübingen.

Sincerely yours,

Ulrich Müller
Olaf Riess
G. B. Landwehrmeyer