Update of genetics of dementia diseases*

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John Hardy, the keynote speaker in the session "Update of genetics of dementia diseases", emphasised how genetic variability at pathogenic loci contributes to the risk of sporadic neurodegenerative disease. He started the presentation by pointing out how recently identified duplications around the amyloid precursor protein (APP) gene locus in Alzheimer's disease (AD) patients further support the amyloid cascade hypothesis in AD pathogenesis. This means that similarly to altered processing of APP seen in presenilin (PSEN) and APP gene mutations, the increase in APP protein dose is the initiating event in pathogenesis leading to aggregation of Aβ peptide, tangle formation, inflammation, synaptic dysfunction, and eventually manifestation of dementia. Dose-dependent gene effect is also evident in the rare cases of Parkinson's disease (PD), where the triplication of α-synuclein gene locus has been recently identified as cause of PD. Although these rare examples indicate how the increased quantities of APP and α-synuclein proteins are actually causing AD and PD, it is anticipated that altered expression of certain susceptibility genes due to the genetic variability may also lead to increased risk in more complex disease cases. In the complex diseases, however, it is likely that the changes in the expression levels of risk genes are more subtle owing to functional alterations in the susceptibility genes. As an example of this, John Hardy referred to AD-associated H1c haplotype in MAPT gene, which has been shown to cause 9% increase in total tau expression. John Hardy also introduced the recent genome-wide association (GWA) analysis in which 502,627 single-nucleotide polymorphisms (SNPs) from ~1200 AD cases and ~900 healthy controls were genotyped. Interestingly, this GWA survey showed that APOE was the only gene locus, which survived after the multiple testing and no other loci were even close to the magnitude of APOE association. Nevertheless, this study revealed some putative AD risk gene loci, which were replicated, but which obviously do not possess major risk gene effect comparable to APOE (Reiman [2007]). GWA-based assessment of 16 genes, which are among those genes currently been listed to the "Alzgene top list" (see below), revealed that only the positive association of ACE gene was replicated. Finally, John Hardy emphasized the importance of keeping the genetic identification of putative risk genes straightforward and simple in conjunction with expressional analyses rather than resorting to underpowered interaction and stratification analyses.

In his response to John Hardy, Lars Bertram addressed that the past decade has witnessed hundreds of reports declaring or refuting genetic association with putative AD susceptibility genes. This wealth of information has become increasingly difficult to follow and much less interpreted. Recently, Lars Bertram together with other members of the Genetics and Aging Research Unit directed by Rudolph E. Tanzi has created a publicly available and continuously updated database that comprehensively catalogs all genetic association studies in the field of AD (http://www.alzgene.org; Bertram [2007]). After performing systematic meta-analyses for each polymorphism with available genotype data in at least three case-control samples, they were able to pinpoint a total of thirteen potential AD susceptibility genes with statistically significant allelic summary odds ratios (ranging from 1.1 to 1.5), in an initial freeze of the database on 1 December 2005. Since most of these genes were tested in case-control designs only, they set out to assess these associations in a large collection of four independent family-based AD samples. In these samples, two of the original AlzGene hits showed significant evidence for association of the same alleles and AD risk (TF and CHRNB2), while two other genes showed marginal evidence for association (ACE and PSEN1), suggesting that these variants represent particularly compelling AD candidate genes. In the nearly two years since the original freeze of the database, over 250 new studies have been added to AlzGene, and nearly 20 additional genes have now emerged to show nominally significant risk effects across all published papers. During the same time Lars Bertram

and his group have developed a methodology allowing to include and systematically meta-analyse genotype data published from GWA analyses, that is expected to change the landscape of AD and many other genetically complex diseases over the years to come. As a matter of fact, several of the currently most promising (by meta-analysis) AD candidate genes emerged from such studies (e.g. PGBD1, LMNA, or PCK1). Finally, Lars Bertram informed that his group has created similar databases for both PD (www.pdgene.org) and schizophrenia (www.szgene.org). In the case of PD and AD, this allows a direct comparison of the emerging genetic effects across both disorders, e.g. for those of MAPT or APOE. For instance, the same MAPT haplotype H1 that shows significant association with PD, is also associated with risk for AD. However, the underlying haplotype clade responsible for the AD association (H1c) currently fails to show significant association with PD, either suggesting that different variants are responsible for the disease-modifying effects across both diseases, or that the true predisposing clade/polymorphism has yet to be identified.

Mikko Hiltunen highlighted in his presentation the important aspects related to the proper study design of genetic studies in complex diseases. Issues related to homogeneity of study population, size and statistical aspects were discussed. It is evident that larger study populations for case-control studies are needed to overcome the problems-related underpowered genetic studies which simply lack the statistical power to detect risk gene effects. Despite the growing number of risk genes identified in dementia diseases, only few of these studies have employed functional approaches to determine the underlying biological consequences of the genetic alterations. In complex diseases, such as in AD, alterations modulating the risk (functional SNPs) are likely located to promoter or regulatory regions of the gene and thus affecting the expression, stability or splicing status of the risk gene. Thus, in vitro and in vivo modified candidate protein effects on certain key events such as altered Aβ production and degradation cannot be avoided, and therefore initial functional assessments are reasonable to focus on factors involved in these events such as α-, β-, and γ-secretases or Aβ degrading enzymes. Only after these factors linked to APP processing and Aβ degradation have been fully assessed and possibly excluded, subsequent functional studies can be redirected to determine candidate gene effects on other biological processes.

In conclusion, all three speakers in the "Update of genetics of dementia diseases" session agreed that risk gene effects predisposing to dementia diseases are likely very low. Thus, it is anticipated that as yet unidentified susceptibility genes in dementia diseases will not reach the genetic effect size or level of statistical significance seen with APOE. These conclusions reinforce the urgent need to significantly increase population sizes in genetic studies conducted with dementia diseases as well as the need to integrate efficiently the genetic data with the functional approaches in the process of identifying the predisposing genetic determinants.

** This session is held at the occasion of the ECNP Targeted Expert Meeting 2007 Dementia, 12-13 October 2007, Vienna, Austria. For further details see the ECNP website www.ecnp.eu*

References

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