SES05.3
Gender, marital status and quality of life in schizophrenia

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Objectives: The association of gender and marital status with Quality of Life (QoL) was studied in long-term schizophrenia patients.

Methods: The study sample consists of 3256 schizophrenia patients. Data were collected from case records and the patients were interviewed three years after the index discharge.

Results: Female patients were more often married and lived alone or with their spouse more often than men. Women and married men had migrated more often than single men, who had often remained living in a remote rural area. The QoL of single men was poorer than others in almost all the areas in which it was measured.

Conclusions: Single male patients with schizophrenia seem to have dropped out of the development of society. Single women migrate more consistently into urban areas, which may be favourable for their QoL. Married patients with schizophrenia, possibly partly helped by their spouse, can best follow changes in the society.

SES05.4
Gender differences in anxiety disorders

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No abstract was available at the time of printing.

SES05.5
Women and dementia

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There are a number of epidemiological and clinical differences between man and women regarding dementia: (1) The prevalence of DAT is higher in women. However, it is not entirely clear whether this is an age or a gender effect. (2) The genetic risk factor ApoE4 appears to be more relevant in women. (3) In the clinical appearance there are no marked gender-specific differences, but there is an greater impairment of speech in women and more aggressive behavior in men.

A meta-analysis of prospective observational studies and case control studies shows that the risk of DAT among postmenopausal women taking ERT was reduced 30 % compared to women never exposed to estrogens. This may also be explained by confounding factors in case control studies, because women on ERT may be better educated, have higher socioeconomic status, have better access to medical care and may be more concerned about their health.

The results of prospective randomized clinical trials shows that estrogens have no beneficial effect in DAT patients. The effects of estrogens may depend on the point at which intervention occurs: Estrogens may be effective in delaying the onset of DAT and have some cognitive benefits in women who are free of dementia. Furthermore, estrogens may result in enhanced mood and secondarily enhanced memory effects.

S17. Genetic basis for affective disorders

Chairs: M. Schalling (S), J.R. Kelsoe (USA)

S17.1
Polysomnographic, neuroendocrine and psychometric risk factors for depression

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Affective disorders are familial conditions and present a considerable risk factor for an individual carrying a high genetic load. We have investigated 83 healthy subjects who had at least 2 close relatives with an affective disorder. These "high-risk probands" (HRPs) were examined with polysomnography and a neuroendocrine challenge test (DEX/CRH test), since both areas show abnormalities in depression. Moreover psychometric measurements were included. The HRPs exhibited a depression-like sleep-EEG profile and DEX/CRH test results. The psychometric profile revealed elevated scores for "rigidity" and "autonomic lability". In a follow-up study these results showed a high stability over time. In the meantime we were able to identify 20 HRPs who have developed a psychiatric disorder. Premorbidly these HRPs show an increased REM density and elevated scores for "vegatative lability" and "stress coping". This indicates that these polysomnographic and psychometric parameters could serve as vulnerability markers for the onset of a psychiatric disease.

S17.2
Data from the biomed european consortium for affective disorders*

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Background: Linkage analyses and association studies are the two common types of strategies used in genetic studies. Linkage analyses aim at detecting a cosegregation of a specific variant (allele) of a genetic marker with a particular disorder in families. Association studies aim at demonstrating a significantly different distribution of gene variants (alleles) in control and affected populations. Evidence supporting the possible role of neurotransmitter changes in the pathogenesis of some psychiatric disorders has led to a candidate gene strategy in association studies.

Objectives and Methods: The European Collaborative Project on Affective Disorders (ECPAD) «Interactions between genetic and psychosocial vulnerability factors», involving 15 european centers apply a multicenter-based methodology to examine the possible role of candidate genes in affective disorders. Special attention is given to statistical analysis, the statistical power of the samples and the interaction with psychosocial variables. More than 3000 subjects have been recruited for case-control association studies with candidate genes. This material provides a powerful tool in the search for susceptibility genes in affective disorders and also takes into account non-genetic aetiological factors. Phenotypic heterogeneity has been considered and subgroups analyses have been conducted with relevant variables: age at onset, family history and diagnostic stability.

Results: In a sample of 401 BPAD patients and 401 normal controls with genotyped for a tetranucleotide polymorphism of Tyrosine Hydroxylase (TH) gene, no association has been found between BPAD phenotype and TH alleles frequency, genotypes

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counts and homo-heterozygote distribution. No linkage disequilibrium between alleles of this marker and BPAD disorder has been observed in the total sample. In addition, we didn't find any association in the subgroups stratified according age at onset, family history and diagnostic stability.

The Tryptophan Hydroxylase (TPH) A218C polymorphism was not associated with BPAD or UPAD in our large European sample. The large sample size provided by the multicenter approach in the study (527 BPAD, 400 UPAD and their matched controls) allows reaching a high statistical power. We also investigated the possible role of TPH polymorphism in suicidal behaviour in mood disordered patients. An association was found with TPH only for UPAD patients with prior personal history of suicidal attempt. The frequency of the genotype C-C, indicating homozygosity for the short allele, was lower in UPAD than in controls. No difference was found for BPAD patients nor for patients with violent suicidal behaviour. However, for this last subgroup results should be interpreted with caution since BPAD and UPAD patients were analysed together to reach a reasonable sample size.

We tested the possible genetic contribution of the polymorphic DNA variation T102C in exon 1 of HTR2A gene. Allele and genotype frequencies, as well as homo-heterozygote distributions were compared between the two groups of 309 BPAD patients and 309 matched controls. No significant differences were observed in the allelic and genotypic (also for homo-heterozygote) distribution, between BPAD and controls.

In a sample of 358 BPAD and 133 UPAD, evidence of significant association between BPAD and DRD2 emerged, with an over-representation of genotype 5–5 and allele 5 in BPAD compared to controls. No association was found for UPAD. No association was found for DRD3, neither for BPAD, nor for UPAD.

Conclusion: In summary, in the European sample, association was found between BPAD and DRD2. The results are negative for TH, TPH, HTR2A, DRD3 when considering the phenotypes BPAD and UPAD. For TPH, association was observed in a subsample of UPAD patients with prior history of suicidal attempt. Considering the sample sizes available in these studies, the negative findings obtained can be interpreted as true negatives, excluding the implication of the polymorphisms investigated in BPAD and UPAD phenotypes. However, we cannot exclude association with different polymorphisms in the regions investigated.

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S17.3

Identifying genes for bipolar disorder on chromosome 22 using a convergent functional genomics approach

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Several studies of both bipolar disorder and schizophrenia have reported evidence for susceptibility genes on chromosome 22. Chromosome 22 was first investigated because a microdeletion in a centromeric region caused a dysmorphism syndrome, velo-cardio-facial syndrome, which is associated with both mood cycling and psychosis. Linkage studies of schizophrenia, however, implicated a more distal region at 22q13. We have recently completed a genome scan of 20 families with bipolar disorder that identifed two different regions on 22q as possible containing a susceptibility gene. In order to identify candidate genes within these regions, we employed an animal model in which rats were treated with methamphetamine as a model of mania. RNA expression profiles in the prefrontal cortex and amygdala of these animals was examined using Affymetrix microarray technology. Out of 8,000 genes examined, the gene with the greatest increase in expression was G protein receptor kinase 3 (GRK3) which mapped precisely to one of the linkage peaks on 22q11. GRK3 mediates the homeostatic downregulation of the D1 dopamine receptor and other G protein coupled receptors by phosphorylation. We have subsequently identified six sequence variants in the promoter of this gene that are associated with illness in two independent samples. These data argue that a defect in transcriptional regulation of the GRK3 gene results in an impaired desensitization to dopamine, and hence an effective supersensitivity. Together this suggests that GRK3 may be one of possibly three genes for bipolar disorder on chromosome 22.

S17.4

Identification of a bipolar disorder susceptibility gene locus on chromosome 12

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The Saguenay-Lac-St-Jean population of Eastern Quebec stems from the migration of families into this region in the middle of the 19th century and, because of a possible founder effect combined with a prevalence of very large families, is ideal for genetic studies. Results of genome-wide scans in very large pedigrees derived from this homogeneous population suggested a region of interest on the long arm of chromosome 12 that saturation analysis with additional markers and further families supported. Highly significant LOD scores for several markers in the 12q24.1–24.3 region were corroborated by significant SimIBD and Sib-pair p-values and delimited a region of about 2.5 cM containing around 30 known or putative genes that we have analyzed by sequence determination. Polymorphisms in linkage disequilibrium and significant allelic association point to one gene or gene cluster as probable candidate. Identification of this susceptibility locus permits classification of the spectrum of bipolar disorders and brings closer the possibility of finding novel therapy based on genetic.

S17.5

Chromosomal abnormalities and depression

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The analysis of chromosome abnormalities in patients with a mood disorder is a powerful positional cloning strategy to find genes contributing to these complex psychiatric disorders. Balanced reciprocal translocations, insertions, deletions and duplications, when fully characterised, can offer a direct signpost to genes directly disrupted by chromosomal rearrangements or whose expression is altered by a positional affect e.g when a chromosomal rearrangement disrupts a regulatory region at a distance from the gene itself. Typically the region identified by chromosomal rearrangements is very much narrower than regions identified in family linkage studies. A cytogenetic approach is likely to be particularly productive in diseases (probably including some types of depression) with marked locus and allelic heterogeneity. A possible criticism of the approach is that it may identify only rare types of illness in cases that are not typical of the disease in general. However identifying a rare gene may lead to other candidates taking part in

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