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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the same neurobiological process. Recent examples of the success of a cytogenetic approach to studying mood disorders include the identification of an interstitial duplication of chromosome 15q associated with panic and phobic disorders in a family (Gratacos et al. 2001 *Cell;106:367*) and the analysis of a balanced reciprocal translocation in a large Scottish family that has identified two genes implicated in major psychiatric disorder, directly disrupted at the breakpoint on chromosome 1 (Millar et al. 2000 *Hum Mol Genet;9:1415*). This chromosome translocation segregates in a single large family with a phenotype that includes unipolar and bipolar affective disorder and schizophrenia (Blackwood et al.2001. *Am J Hum Genet 69:428*). Analyses of families with chromosome rearrangements segregating with major mental illness are likely to implicate further genes whose disruption leads to mood disorders and the phenotypes associated with these rearrangements may help to clarify or redefine diagnostic categories.

S18. Gene–environment interplay

Chairs: P. McGuffin (GB), H. Ewald (DK)

S18.1

Genes and environment in ADHD

A. Thapar*. *Child & Adolescent Psychiatry Section, Department of Psychological Medicine, University of Wales College of Medicine, UK*

There is now considerable evidence that Attention deficit hyperactivity disorder (ADHD) is strongly influenced by genetic factors. There have been a wealth of family, twin and adoption studies and now there is considerable international effort directed towards identifying susceptibility genes for ADHD. Early results look promising. Nevertheless the role of environmental factors and the question of how ADHD is best defined remain important issues. There is also increasing interest in the application of genetic findings in clinical settings with pharmacogenetic research aimed at examining what genetic factors influence treatment response. Recent and emerging research on the genetics of ADHD will be reviewed.

S18.2

The role of personality in influencing genetic and environmental risk factors for major depression

A. Farmer*. *SGDPRC Institute of Psychiatry, Denmark Hill, Camberwell, London, UK*

Personality factors such as extraversion or neuroticism could influence the way individuals respond to environmental adversity that could lead, in turn, to the development of an episode of depression. For example, subjects with high rates of neuroticism, may view the world as particularly threatening and hostile, and consequently may be unable to satisfactorily resolve the problems caused by an adverse life event. Alternatively, an extravert individual may indulge in risky activities, which have an attendant high risk of excess adverse events occurring, and who could be considered as leading "hazard-prone" life styles.

The role of personality will be considered in relation to the genetic vulnerability to depression in a sib-pair design. Depressed probands, their nearest aged siblings, healthy control probands and their nearest aged siblings were compared for the rates of depression in the 2 groups of siblings, and the number of different types of life events experienced in a 12 month period by all four groups of subjects. In addition, the relationship between various measures of current mood, personality and life events will be discussed.

S18.3

Genetic influences on autism

M. Rutter. *Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London, UK*

Twin and family studies over the last quarter of a century have consistently pointed to a strong genetic influence on the liability to autism – a liability that extends beyond the traditional diagnosis of a seriously handicapping disorder, and which probably involves a relatively small number of susceptibility genes. During the last decade, several large-scale collaborative molecular genetic studies of autism have been established, with some partially replicated findings of gene loci. The paper will provide an update on the state of genetic knowledge and will consider the implications for our understanding of this multifactorial psychiatric disorder.

S18.4

What do comorbidity studies with somatic disorders tell us about the etiology of schizophrenia?

O. Mors*. *Institute for Basic Psychiatric Research, Risskov, Denmark*

It has proven very difficult to progress from evidence confirming a genetic contribution to the etiology of schizophrenia to evidence implicating the specific genes in the disease. At the same time the environmental risk factors have eluded us their discovery. The study of possible associations between somatic disorders and schizophrenia may generate hypotheses about the role of both genetic and non-genetic factors in etiology of schizophrenia: candidate chromosomal regions for schizophrenia may be identified, gene-environment interactions suggested and sources of natural selection in man illustrated. Comorbidity studies have usually been register based, since large data sets is needed to generate sufficient power to demonstrate significant, moderate increased or decreased relative risks. Results from on ongoing study in Denmark of associations between schizophrenia and other complex disorders such as autoimmune diseases (e.g. rheumatoid arthritis and type I diabetes) and also appendicitis will be presented. Methodological pitfalls such as selection bias will be discussed.

S18.5

Genetic and non-genetic factors in bipolar affective disorder

H. Ewald. *Institute for Basic Psychiatric Research, Risskov, Denmark*

Developments in diagnostic instruments and criteria, molecular genetics, computer programs and statistics have helped to identify more than 10 candidate chromosome regions potentially containing genes which increase susceptibility to bipolar affective disorder. A number of research groups are now attempting to identify the specific risk genes in the most promising chromosome regions including chromosome 4p, 12q, 18 and 21. Increased knowledge of the neurobiology of the brain has also resulted in new candidate genes. Though no DNA sequence variation of relevance has yet been reported the draft sequence of the human genome and recent developments for high-throughput genotypings and other molecular genetic methods will facilitate this. Genetic mapping studies