

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 identified 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 19<sup>th</sup> 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