IMPACT minutes, Barcelona meeting September 1st 2008

Present: Bru Cormand, Toni Ramos, Marta Ribases, Monica Bayes, Jan Haavik, Stefan Johansson, Andreas Reif, Barbara Franke (minutes)

Bru:

- In Spain, numbers of adult patient now >350, controls (ADHD-excluded) 2200 (including 100 super controls)
- Kiddie sample genotyping for DRD1 in progress; replication of LPHN3 in Spanish sample
- Projects on DRD4, BDNF, laterality genes: replication of one laterality gene in German sample
- DRD4 meta-analysis data exon 3 VNTR, promoter 120 bp repeat) from most sites already present in Spain, German samples are currently being genotyped in Spain for the 120 bp repeat. Dutch data on exon 3 VNTR have been reanalyzed in The Netherlands and will be sent to Spain, shortly.

Marta:

- BDNF: Meta-analysis with 1345 patients and 2278 controls from all 4 countries. No apparent association with ADHD or subtypes. → please try stratification according to gender and performing the analysis with only those patients that show mood disorders as ADHD-comorbidity. BDNF meta-analysis first draft will be ready before meeting in Florida.
- Laterality genes, 30 SNPs in 6 (BAIAP2, DAPPER, LMO4, NEUROD6, ID2, ATP2B3) genes are being investigated (1200 cases : 1200 CTR). Association of SNPs in BAIAP2 (involved in insulin receptor signaling) with adult ADHD (only combined subtype is investigated). Also association found in German sample, but with different haplotype yet higher significance levels. No association in Norwegian sample. → please repeat analysis in entire sample before making subdivision according to subtype. Possible explanations for differences include differences in LD structure between countries and/or differences in clinical evaluation and instruments. No evidence for genetic stratification in Spain / Germany, Norway not tested.

Barbara:

- Meta-analysis is nearly ready, association of 9-6 haplotype and 9/9 genotype with aADHD. → re-structure Materials and Methods to focus on the similarities between samples rather than differences. Provide table. On this paper we will include all clinical participants on the study as co-authors, in future publications we will restrict the number of authors to 3 per centre (+ additional optional co-authors). The DAT1 paper is to be sent to Mol. Psychiatry.

Stefan:

- TPH1 and TPH2: No association findings for TPH2. Findings in Norwegian sample for TPH1, replicates in German sample, but not in other two samples. → try meta-analysis. TPH1 and TPH2 are going to be published together. Tph1 2 SNPs $p < .05$, haplo $p = .004$ with impact on disease severity
- HTTLPR: Sample not yet complete. Currently no association in meta-analysis. → try inclusion of mood disorder info. Gender stratification?
- CIGENE project: performance of Spanish samples was extraordinary good, Dutch samples also did well, with some minor contamination in blancs, Norwegian samples from amplified DNA showed consistent trend for under-representation of heterozygotes in all SNPs. Genotyping of the Norwegian sample is currently repeated on non-amplified DNA. Sequenom in Germany is currently broken, possibly back in operation during coming week. Otherwise samples will be measured elsewhere.

- In Norwegian sample rating scales have been used for determining subtype of ADHD, as these data were not available to the researchers. Although all patients were diagnosed with ADHD before, on the rating scale a relatively large number scored subthreshold, as under medication. Jan and Stefan have decided to change the threshold for subtype determination from 21 to 17, so some analyses, like the DAT1 and BDNF have to be done again with the new phenotyping file. For DAT1 this has already been incorporated in the data shown here today.

Andreas:

- Integration of data from pooled GWAS, linkage study and CNV analysis.
- NPY-duplication in obese ADHD-affected individuals in large pedigree. No association found in adult or kiddy ADHD sample and also not in related (NPY receptor) genes.
- Glut3-deletion. SNPs show association with German kiddy sample and adult sample. Replication in Spanish sample, but not Norwegian sample ??? → Dutch samples will be checked
- Glut6 (from GWAS), association with German adult sample. No replication in other samples. → Dutch samples will be checked
- CNV analysis, which was done by arrayCGH in 100 cases and 100 controls will be published as soon as possible.
- NOS1 shows association with ADHD, will be analysed as meta-analysis in all samples of IMPACT.

Future meetings:

- We have put in proposals for symposia to the Biological Psychiatry meeting in Paris in June 2009 and the ECNP in Istanbul 2009. Furthermore, there will be an International ADHD meeting in Vienna next year that we try to get in. Also, we will try to have a symposium or session at the WCPG 2009. Therefore, we will not apply for a symposium at the APA next year, it will become too much.
- We will meet at the meeting of the ADHD Molecular Genetics Network. We will have a 'private' meeting there with all the IMPACT members. In addition, we will propose a workshop on adult ADHD, with the goal of getting to a common (consensus) protocol for future adult ADHD genetics research. We will propose a protocol as a basis for discussion (see below).
- We will have to think about starting a new study in which we assess all participants with a common protocol, to get beyond being a replication group. An important question with regard to adult ADHD is what determines persistence of ADHD going from childhood to adulthood. To investigate this, we might think about collecting an entire new child sample, that we follow into adulthood. This will take very long, though. We might also identify individuals with a childhood diagnosis of ADHD and recruit them back for adult evaluation.

Funding opportunities:

- We are planning to submit a EU proposal on ADHD + SUD, that we would probably also have the opportunity to include IMPACT (and IMAGE). This is a proposal on genetic variation in Europe, including GWAs and CNV analysis and probably next generation sequencing.
- Barbara has put in a proposal for funding for a workshop to come to a project proposal in the Dutch Brain and Cognition Program. If funded, this workshop would be held in April 2009.

Adult ADHD protocol for genetics research for ADHD Molecular Genetics Network:

- Minimal requirements for a good protocol would be the following:

- Clinical interview, e.g. the CAADID
- ADHD-rating scale to assess severity of symptoms, e.g. ADHD-RS or CAARS
- Interview to assess comorbidity, the SCID-I and –II
- A personality questionnaire, e.g. the NEO-P or the Zuckerman personality questionnaire

Points to do:

Barbara:	send Dutch DRD4 exon 3 data to Spain
Barbara:	genotype HTTLPR in Dutch controls and send to Norway
Barbara:	ask Phil and Steve about plans with regard to contribution of samples to IMPACT
Barbara:	send samples to Germany
Barbara:	plan date for possible 2-day workshop in April 2009 in The Netherlands
All:	send data on mood-disorder comorbidity to Spain for BDNF analysis
All:	send names + order co-authors for DAT1 meta-analysis to Barbara
All:	Think about IMPACT logo
Stefan:	send new phenotyping file to Spain and Germany
Andreas:	send paper on European genetic variability to all IMPACT members
Andreas:	send more DRD4 control subjects to Bru