Summary IMpACT Brainstorm session, May 8 2017

Present: Barbara, Andreas, Alejandro, Klaus-Peter, Jan B., Claiton, Eugenio, Bru, Marta, Jonna, Stefan, Tetyana, Toni, Henrik, Angelien, Nina, Janita, Oliver, Sarah, Emma, Martine, Thomas, Cristina, Noelia, Paula, Joanna, Giorgia, Nicoletta

Agenda:

1. Epigenetics (Tetyana)
2. GWAS IMpACT (Marta)
3. Pharmacogenetics (Claiton)
4. sMIPs to follow-up rare variant findings (Barbara)
5. Imaging results from ENIGMA ADHD looking for interpretation (Thomas)
6. Open discussion of new plans

1. <u>Epigenetics</u>

Tetyana showed us an idea for an epigenetics study in IMpACT. These ideas are written up for a grant application in Norway, and have been submitted in April. They hope to hear within 5 months if the proposal will be granted.

The idea is to investigate epigenetics in psychiatry, by looking at methylation patterns. Tetyana e-mailed many of you to ask if you would be interested in participating. She would like to investigate the clinical comorbidities and the environmental factors. Samples are useful if the DNA is extracted from blood, they are genotyped, and information on environmental factors is available (like smoking, drug use, alcohol use). Longitudinal data will be helpful, as they will focus on periods of the lifespan. They would also like to focus on minorities, and on interests of patient groups. Their aim is to collect 6000 samples, for which they will obtain high density methylation typing with the EPIC chip (on samples that already have genotype data and environmental data available). The collection should have been done with blood (not saliva). Spain has data on the methylome from PBM cells.

The differentially methylated regions (DMRs) will be investigated within disorder and between disorders and combined with genetics and environmental data. Polygenic risk scores from cases and controls will be matched to create individuals with a similar genetic load. If the interest is to create individuals that are genetically similar, Alejandro suggests that their new gene-score method might be able to help. Another option suggested by Emma is to not match, but use the genetic background as a covariate in the analysis (this could lead to larger sample sizes compared to a matching approach).

There are no age restrictions, as they are interested in including across the lifespan. As environmental factors, they might investigate diet or vitamin D, if enough data will allow them to do this. Childhood trauma can also be very interesting to study.

Finally they will annotate their findings to potentially find applications, like drugable targets, or disease prediction options.

The grant will provide funding for the methylation measurements, as well as a person that can be hired to do this. Processing capacity is available in Norway, and they are collaborating with Jonathan Mill, who has great experience with epigenetics.

A discussion point that came up is whether the preprocessing should be the same as for DNA. They are asking for extracted DNA, however, it might be of influence if the blood was frozen (and how long it was frozen) before extraction. For now, the only requirement is that the DNA is of good quality (not degraded). In Spain, the DNA is extracted within an hour, in Nijmegen, the material is not frozen either, but kept at RT longer (for other sites this might be different). All IMpACT groups that have DNA indicate interest in participating.

2. **GWAS IMpACT**

GWAs has been run, not yet significant single variants. The question is whether we want to include 23&me data in the analysis, the general trend is to say that it would not help. Next step is to run a combined meta-analysis with the childhood samples from PGC and iPSYCH.
Many people are interested in using the adult ADHD GWAS summary stats for additional analyses. Marta will collect all the ideas to get a more clear overview about the plans of all IMpACT members with the data.
The PGC-iPSYCH data are still under embargo; this paper needs to be published before we can publish our data. It is not clear, whether we can use the data for presentations at a congress or for a poster presentation. Marta will enquire.

3. **Pharmacogenetics**

Claiton Bau asks which sites have these data:
1. self-ratings ASRS/SNAP-IV
2. CGI
3. other relevant measures

Additional optional measures; BDI, Sheehan disability, Beck, K-SADS, insomnia index.

This is what is available in IMPACT:

- Tetyana (Norway): response to medication (better/worse/no change) and CGI.
- NeuroIMAGE (Netherlands): no medication response information available, there is data on duration of medication treatment (could be used for replication of SYT1 project).
- Toni (Spain): they have 500 subjects genotyped for SNARE complex. And they have 2 point of follow up after treatment start and ASRS. They have data in adults but not in children (Eva Caldo).
- Andreas (Germany): there is short follow-up, but not as long as Claiton would like to have. More follow-up is difficult in (their) clinic as patients are referred to others and they lose contact with those patients.
- Henrik (Sweden) suggests to use the registry data for studying medication effects. Registry database can be used to assess medication use in siblings/ family members although without genetic data, but heritability of medication use can be studied.

4. **sMiPs to follow-up rare variants findings**

The idea is to take genes observed in rare variant studies of ADHD as well as the new GWAS results and investigate whether (more) mutations can be found in those genes. This will be done so using a targeted next generation sequencing approach with sMIPs. Nijmegen group is seeking samples from different IMpACT sites.

- Samples needed: Adult cases and controls
- Participation: all IMpACT sites are willing to provide DNA for the study
- Suggestion was to also include linkage regions, but those would likely be too big
- Marieke will make a list with all candidate genes and people who are interested can add genes.
- Marieke will circulate the slides with a brief summary of the project idea, so that the IMpACT sites interested in collaborating can join.
- Stefan asked what the costs per sample are. This depends on the number/size of genes to be included. Costs are covered by a grant from Barbara. They are looking for at least 1000 samples.

5. **Imaging results from ENIGMA ADHD looking for interpretation**

Christina Isakoglou and Thomas Wolfers have developed a pattern recognition approach for meta-analyses. This approach can be applied ENIGMA-wide for different disorders and allows for the creation of novel brain X behaviour predictive phenotypes, that may be used in GWAS studies. During the meeting Thomas presented the initial results, showing that females with ADHD have an extremely gender-typical brain, even more so than healthy controls. The results are preliminary and require further scrutiny, however, the finding could be reproduced across almost all studies contributing data to ENIGMA ADHD. Emma and others provide some suggestions on how the data might be interpreted.

6. **Open discussion of new plans**

CDH13, Alejandro

- Gene-wide analysis was performed a long time ago, we wanted to look into this again, now that the new data is available.
- Alejandro will take the lead and continue this project.

Andreas

- Further look into the data for NEO-neuroticism genes, they found some hotspots
- The question Andreas would like to answer is: is there genetic variation with NEO-neuroticism that affects ADHD.
- Brazil has collected the list with personality data from all of the IMpACT samples, which can be used for this project. Nina will send the list with personality data to Andreas. Andreas adapt the list for the needs of the project and send it around.
- UK Biobank also has neuroticism (from Eysenck) but not ADHD information.

Barbara: how can we measure ADHD in a better way?

- Validity of interviews/questionnaires limited for real life. Accelerometers in conjunction with experience sampling would be good. Problem is how to capture impairment sufficiently well. Conclusion: measure as broad as possible. CoCA could provide proof of concept, as accelerometers will be used there, as is experience sampling.