IMpACT Meeting, Frankfurt, 29-07-2014

Present: Jan H, Bru C, Toni RQ, Andreas R, Marta R, Cristina SM, Olga R, Tetyana Z, Alejandro AV, Barbara F

1. **Presentation by Tetyana on exome chip results**: Conclusion: there are some promising findings for both the common and rare variants, both point to cell growth as a process of importance in ADHD. We think that the work will make a nice publication, although the challenge will be to present it as a well-coherent story. Publication should be done soon, as the PsychChip genotyping for the new ADHD samples at Broad seems already to be finished.

2. **Presentation by Olga on Cdh13 k.o. mouse; comment by Alejandro on CDH13 human association**: Conclusion: Cdh13 in the mouse is expressed in subpopulation of inhibitory neurons. The mouse has a alterations in the expression of GABA-based signaling molecules. At the level of behavior, alterations are observed in activity, possibly consistent with hyperactivity, and a reduction in learning. The human association studies have not provided a clear picture. The analysis of the tagging analysis performed several years back gave borderline significant findings in gene-wide analysis. We are still waiting for the gene-wide analyses of exome chip including common and rare variants (57 common, 24 rare variants), which will be carried out by Alejandro remotely on the Norwegian server. Given the findings in mice, one should try association with hyperactivity, specifically.

3. **IMpACT SWOT analysis (see slides for full content):**

Multiple Strengths identified by the group:

- Great collaboration
- High quality sample
- Training and development of student and junior participants

And multiple Weaknesses also:

- Not being able to use the strengths properly
- Patchy data
- Loss of coherence of the group
- Not dedicated funding – not dedicated people => IMpACT receives less priority
- Output has decreased dramatically

As opportunities:

- There is funding through AGGRESSOTYPE as means to fund IMpACT
- Use existing funding to help IMpACT
- Consolidation of the database

Threats:

- Research in genetics of ADHD is becoming still (in general)
- Lack of fixed economic support
- Competition among IMpACT members

4. **Where to go from here, what to do?**
   - Definitely go on with IMpACT and keep the collaboration.
   - Define a goal for IMpACT and a strategy for the next 5 years.

- Keep a small coherent group (which limits the size of the collaboration) and go for mechanistic research by profiling the systems involved in ADHD, prioritize this and downplay the association analyses (which are underpowered if we go beyond candidate genes).
- To do the above, the selection of candidate genes is still difficult and extremely complex, as one will put much money and effort in single genes (example CDH13). A potential source could be results of the PGC cross-disorder analysis (4-5 loci identified). *Tetyana will check those SNPs in the exome chip data for evidence of involvement in adult ADHD.*
- The use of clinical data/symptoms should be prioritized over the more statistical approaches.
- We should make a better use of the clinical and behavioral/neuropsychological data that is available, and run cross-site analyses.
- The commitment to the IMpACT project has to be real, if this is not happening, people are free to leave the consortium. But is also important to realize that IMpACT started without any economic result and thanks to the collaboration served as the base to obtain the AGGRESSOTYPE project.
- We discuss that groups could try to commit funding for a common position that helps (i.e.) a person that manages the database and helps organizing the data in order to write other big sized projects. More feasible seems to be commit a person per site for a limited number of hours per week to work with IMpACT to give projects more priority.
- We discuss extending the focus of IMpACT beyond the adult phenotype to work on ADHD across the lifespan.
- The IMpACT goal as we define it: Understand ADHD across the lifespan from phenotype to genotype and translate knowledge into improving patient care.
- Should this goal be also translated into treatment efforts? It could if we split the clinical studies across groups, but the costs are very high (depend on the size of the study but, in general, are very expensive).
- More feasible could be to explore the prospects of using genetics or biomarkers for diagnosis, prediction of persistence and/or comorbidity.
- Treatment studies are also difficult because methylphenidate works in 80% of the cases so what can get new? A more feasible approach would be to work with non-responders of the pharmacological approach, or genetically informed subgroups and design treatment studies for those patients.
- Other options include the treatment with non-pharmacological approaches (light, circadian rhythm) in order to provide the patient with alternatives to improve their QoL.
- These two approaches can be complemented (and should) with the investigation of biomarkers (i.e.) in serum (metabolome). An idea could be to measure multiple levels of data in as many samples as possible (ideally) and then use these data for a prediction model (for the individual patient) of multiple risks, comorbidities, persistence in multiple (clinical phenotypes). Part of this work (e.g. method development) already started in several consortia that IMpACT members are involved in (Aggressotype, IMAGEMEND, Bipolar disorder consortium).
- The inclusion of Sweden was good but up to now has not lead to specific studies/proposals. The epidemiological data sets are important and more active inclusion of the group would be welcomed. A potential way to do so is to combine registry-based research with IMpACT's patient database. Also, Henrik will get genotyping for large samples of phenotyped individuals, which might provide opportunities in the future.
- Should we go ahead working on gene-finding? We have multiple sources of data genotyped but nothing has yet been found consistently. It has been suggested that NGSing these samples could be an option. Part of IMpACT is being sequenced already, and there are still funding to do this for large pedigrees in the Netherlands. However, there might also still be opportunities with the GWAS data that will become available for virtually all IMpACT

samples. In general, we should contribute to gene-finding in the large consortia, but also try to do something in our own data.

- From the side of the collection, we should apply a consensus protocol for all newly included IMpACT cases/controls and/or approach existing patients and invite them to participate in a web-based data collection system (i.e. self-assessment questionnaires, cognitive tests)
- In order to boost paper production each group can pledge that one paper for each student (PhD project) can be an IMpACT project => paper. MSc students can also be a sources of papers. Each group should, however, produce at least one IMpACT paper per year.
- We should make IMpACT more visible by marking our papers (preferably also those from single sites) as IMpACT papers. This could be done by describing the sample used as part of IMpACT (see e.g. papers from Dutch group), and/or by adding an acknowledgement to IMpACT (see below – point 6 - for a suggested text).
- We should have two dedicated IMpACT meeting per year – one for the PIs only (e.g. attached to Aggressotype meeting), one for all participants.
- Small points:
  a. Add info on availability of biomaterials other than DNA in database (e.g. there seems to be quite some PACS RNA across sites)
  b. Add environmental and perinatal data to database
  c. Add info on BMI, weight, height, etc.
  d. Include life events questionnaires in the online phenotyping tool
  e. Add questions about parental age to online phenotyping tool
  f. Put project proposals for use of IMpACT database on intranet for prioritization

➔ Based on the discussion, we redefine the goal of IMpACT and formulate 5-year strategies and instruments. In addition, we define priorities for the coming year. See the slides.

5. Definition of specific projects based on the IMpACT database:

- Personality analysis
  - Personality in ADHD
  - Relationship between personality and comorbidity across sites

- Latent class analysis (or comparable, like community detection analysis) to subgroup ADHD. Can be based on:
  - Rating scales
  - Comorbidity
  - Personality
  - Genetic load

- Link of CDH13 to variables related to ADHD:
  - Rating scales (look at domains of hyperactivity and inattention separately)
  - Comorbidity (especially SUDs)

- Exome chip analysis:
  - Use alternative phenotypes for this analysis

- Seasonality of ADHD and its comorbidities: are people born in a certain season more prone to ADHD and/or specific comorbidities? → combination with research in the Swedish registries

- Parental age and genetic load: is the load lower in affected children of fathers at higher age?

- Is ADHD (or its comorbidities) related to ancestral alleles of SNPs or more to the novel alleles?
    - Use SNP linked to pubertal age as a proxy for age at start of puberty
- Does smoking in mothers/parents increase ADHD risk and/or affect the phenotype of patients?
    - Replication of Spanish work

- microRNA genes and adult ADHD phenotypes
    - use data from GWAS and/or exome chip
    - perform transcription analysis of selected miRNA targets in the RNA collected across sites

- Migraine and ADHD
    - Combination of research in registries and the database

- Immunological data (e.g. asthma) and ADHD – are they comorbid?
    - Combination of research in registries and the database

- Comorbidity of Tourette's syndrome and ADHD
    - Combination of research in registries and the database

6. **Suggested byline for acknowledgement of studies at different sites participating in IMpACT:**
   The sample used in this study is part of the international multicentre persistent ADHD collaboration (IMpACT). IMpACT unites major research centres working on the genetics of ADHD persistence across the lifespan and has participants in the Netherlands, Germany, Spain, Norway, the United Kingdom, the United States, Brazil and Sweden. Principal investigators of IMpACT are: Barbara Franke (chair), Andreas Reif, Stephen V. Faraone, Jan Haavik, Bru Cormand, Antoni Ramos Quiroga, Philip Asherson, Klaus-Peter Lesch, Jonna Kuntsi, Claiton Bau, Jan Buitelaar, Stefan Johansson, Henrik Larsson, Alysa Doyle, and Eugenio Grevet.