

Brain DNA methylation signatures of major depressive disorder

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Research question and background

Major depressive disorder (MDD) is a leading cause of the global disease burden with a life time prevalence of almost 15%. Genetic approaches that have worked for other psychiatric disorders have largely been unsuccessful for MDD. DNA methylation studies are a particularly promising complementary way forward as they may have better predictive power, can account for a wide range of clinical MDD features (e.g. individual differences in course and episodicity), and have profound translational potential.

The concrete goal of this project is two-fold. First, we aim to identify methylation signatures in brain associated with MDD. To improve statistical power the data generated in the Netherlands Brain Bank (NBB) samples will be combined with data generated in samples from the Victorian Brain Bank Network (VBBN, 34 MDD cases and 34 matched controls) and the Stanley Medical Research Institute (SMRI, 15 MDD cases and 15 controls). Second, in a collaborative project (NIH grant R01MH099110) between the VU University Amsterdam (PI Brenda Penninx) and Virginia Commonwealth University (PI Edwin van den Oord, biosketch attached) we are currently studying 1,500 DNA samples from the Netherlands Study of Depression and Anxiety (NESDA) to find methylation sites in whole blood associated with MDD and its stability over a 6-year period. The ability to examine whether results found in blood replicate in post-mortem brain, where MDD pathogenic processes are likely to occur, will be critical to improve inferences about possible etiological processes.

Methylation of human (non-stem cell) DNA occurs commonly at CpG sites. As the knowledge needed to identify good candidate sites is lacking, we will assay all ~27 million CpGs in the human genome for their association with MDD using state-of-the-art next-generation sequencing technology. To mimic the NESDA design we will also generate whole genome transcript and SNP data to enable in-depth analyses of the underlying disease processes. We request tissue from Brodmann Areas BA10 that has been implicated in MDD and will allow us to combine NBB data with VBBN and SMRI data for which we have the same region. On 10/8/2013 the proposed study qualified for exemption according to 45 CFR 46.101(b), category 4 (IRB ruling attached). The initial application involved only samples from the Victorian Brain Bank Network. Once we know where possible additional samples will come from, we will file an amendment. DNA will be extracted and assays will be performed in our labs

(<http://www.pharmacy.vcu.edu/biomarker/labs.aspx>) that is approved to with and store post-mortem tissue samples (MUA attached).

Methods and tissues used

We received 24 samples from either GFS1 or GFSM1. DNA was extracted and we then used the Covaris™ S2 System to shear genomic DNA into ~150 bp fragments through ultrasonication followed by enrichment with MethylMiner™, which applies a methyl-CpG-binding (MBD) protein in combination with streptavidin Dynabeads® to capture the methylated fraction of the genome. For each captured methylome, we will insert a unique barcode to allow multiplexing. The sequencing-fragment libraries of each sample will be pooled in equal molarities prior to sequencing by ligation using the novel SOLiD5500-xl WildFire upgrade. With this latest upgrade, nucleic acid samples are adaptor-tagged and placed directly into the flow-chip without the need for prior ePCR or

bead enrichment. A single in-situ (in-flow-cell) isothermal step generates a “self-assembled-sequencing-array” with all the amplification required for NGS.

Results and conclusion

Data have been generated but not analyzed as we are awaiting the finish samples from other brain banks so that all data can be analyzed together to maximize power.