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HUMAN DEVELOPMENT, BIRTH TO DEATH

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Concept Paper Form

Provisional Paper Title: Tackling the genetic etiology of antisocial behavior through genome-wide association meta-analysis and polygenic risk scoring.
Proposing Author: Jorim Tielbeek*
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P.I. Sponsor: Terrie Moffitt (if the proposing author is a student or colleague of an original PI)
Today's Date: 7/12/2020

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

The BroadABC represents a combined research initiative to conduct genetic analyses at a larger scale on antisocial behaviour and that aims to increase the probability of detecting genetic variants associated with antisocial behavior (for more information on the Consortium's efforts, see Tielbeek et al. 2017). BroadABC focuses on the broad spectrum of antisocial behaviour and has currently access to genotypic and phenotypic data from >80.000 individuals across twenty unique samples.

Within this larger study, one of our aims is to perform a polygenic risk score (PRS) analysis in the E-risk and Dunedin cohort to test whether a genetic risk for ASB could significantly predict antisocial outcomes, such as criminal conviction records, lifetime diagnoses of CD and antisocial trajectories. If the predictive value is high, future research may also explore how these polygenic scores relate to outcomes beyond antisocial measures (i.e. cortical and subcortical brain structure and connectivity, mental disorders, credit scores, social welfare records, histories of mental disorder, physical health, suicide attempts, etc.)

Data analysis methods:

To achieve this, we created a polygenic score for broad antisocial behavior using all available SNPs of the discovery dataset (Altshuler et al. 2010) after adjustment for linkage disequilibrium (GE et al. 2019). All long-range LD blocks were removed prior to the analysis.

We will only compute polygenic scores in individuals of European ancestry. Polygenic scores will be computed as the weighted sum of the effect-coded alleles per individual. We

will calculate the polygenic scores for subjects from two datasets, selected for their detailed phenotypes related to antisocial outcomes: (1) the Dunedin Study; (2) the E-risk study.

To maintain uniformity across target cohorts we adhere to the following parameters:

Clumping will be performed by removing markers in linkage disequilibrium, utilizing the following thresholds: maximum r2 = 0.2, window size = 500 kb. Example format in PLINK: --clump-kb 500, --clump-p1 1, --clump-p2 1, --clump-r2 0.2.We have already excluded variants within regions of long-range LD (including the MHC, see attachment for exact regions).

PRS will be constructed for each individual for each of the outcome measures at the following 10 P-value thresholds (P T)
(P T < .5; P T < .4; P T < .3; P T < .2; P T < .1; P T < .05; P T < .01; P T < .001),
$p < 1 \times 10^{-4}$, $p < 1 \times 10^{-6}$)

We recommend additional filtering of low MAF/INFO variants in all target samples. Also, it is preferred to remove ambiguous SNPs with a high MAF (i.e. C/T or G/C variants with MAF > .4 or so) since it's almost impossible to detect strand flips, especially in the presence of samples with different reference panels.

Variables needed at which ages:

E-risk

1. Antisocial behaviours/conduct disorder symptoms at ages 5, 7, 10, 12, and 18
2. Criminal conviction records (up to age 19)
3. E-risk fathers' and mothers' history of antisocial behaviours (check if the twin children's polygenic score is elevated when parents were more antisocial)
4. Externalising factor at age 18

The Dunedin Study

1. Criminal court conviction data up to age 45.
2. Compare the strength of polygenic score across different trajectory groups of antisocial behavior, as determined by longitudinal reports (life-course persistent, adolesence-limited, childhood-limited, and low involvement in offending)
3. Antisocial behavior at ages 5-11 and ages 13-15
4. Dunedin father's and mother's history of antisocial behavior (check if the Study member's polygenic score is elevated when parents were more antisocial)
5. Antisocial behaviours in the workplace of employment
6. Intimate partner violence, as assessed by the CTS.
7. Externalising factor at ages 18-45

Significance of the Study (for theory, research methods or clinical practice):

Antisocial behaviour has been recognized internationally as a mental health priority. Further research into the mechanisms underlying pathogenesis and persistence of antisocial

behaviour is warranted to inform and improve current treatment strategies. A key aspect of the proposed study is the interdisciplinary collaboration between psychologists, criminologists, psychiatrists, statistical geneticists and epidemiologists to collectively tackle antisocial behaviour from an integrated imaging genomics perspective. The identification of functional gene-sets or pathways involved in antisocial brain endophenotypes could reveal biological pathways that play a role in antisocial behaviour, thereby facilitating the search for potential treatment targets. Moreover, longitudinal research relating neurobiological markers to the persistence of antisocial behaviour could provide clues to prevent antisocial development.

References cited:

Tielbeek JJ, Johansson A, Polderman TJC, et al. Genome-Wide Association Studies of a Broad Spectrum of Antisocial Behavior. JAMA Psychiatry. 2017;74(12):1242–1250. doi:10.1001/jamapsychiatry.2017.3069

D. M. Altshuler, R. A. Gibbs, L. Peltonen, Integrating common and rare genetic variation in diverse human populations. Nature. 467, 52–58 (2010).

T. Ge, C.-Y. Chen, Y. Ni, Y.-C. A. Feng, J. W. Smoller, Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat. Commun. 10, 1776 (2019).

Data Security Agreement

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*Please note that I (Jorim Tielbeek) do not have access to any data.

☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: Jorim Tielbeek and JC Barnes