

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*
Author's Email: j.tielbeek@amsterdamumc.nl
P.I. Sponsor: Terrie Moffit (if the proposing author is a student or colleague of an original PI)
Today's Date: 6/15/2020

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 $r^2 = 0.2$, 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. Conduct disorder symptoms at age 12 and age 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)

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, adolescence-limited, childhood-limited, and low involvement in offending)
3. Continuous score on ASB/CD in several developmental stages (i.e. childhood, early/mid/late adolescence, adulthood) to establish the continuity of predictive strength of PRS at age 9, 13, 15, 18, 26, 45.
4. Antisocial behaviours in the workplace of employment

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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Proposing Author: Jorim Tielbeek*
Today's Date: 6/15/2020

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

<input checked="" type="checkbox"/>	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
<input checked="" type="checkbox"/>	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
<input checked="" type="checkbox"/>	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.
<input checked="" type="checkbox"/>	I will not "sync" the data to a mobile device.
<input checked="" type="checkbox"/>	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
<input checked="" type="checkbox"/>	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
<input checked="" type="checkbox"/>	I will not post data online or submit the data file to a journal for them to post. <i>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>
<input checked="" type="checkbox"/>	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

CONCEPT PAPER RESPONSE FORM

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Provisional Paper Title	Tackling the genetic etiology of antisocial behavior through genome-wide association meta-analysis and polygenic risk scoring.
Proposing Author	Jorim Tielbeek*
Other Contributors	Collaborators within the Broad Antisocial Behavior Consortium (BroadABC) From Dunedin: Terrie Moffitt, Richie Poulton, Karen Sugden, From E-risk: Avshalom Caspi, Ben Williams, JC Barnes
Potential Journals	Nature Human Behavior, Lancet Psychiatry
Today's Date: 6/24/2020	
Intended Submission Date: 6/25/2020	

Please keep one copy for your records and return one to the proposing author

B. To be completed by potential co-authors:

<input type="checkbox"/>	Approved
<input type="checkbox"/>	Not Approved
<input type="checkbox"/>	Let's discuss, I have concerns

Comments: [Click here to enter text](#)

Please check your contribution(s) for authorship:

<input type="checkbox"/>	Conceptualizing and designing the longitudinal cohort study
<input type="checkbox"/>	Conceptualizing data collection protocols and creating variables
<input type="checkbox"/>	Data collection
<input type="checkbox"/>	Conceptualizing and designing this specific paper project
<input type="checkbox"/>	Statistical analyses and interpretation (or reproducibility check)
<input type="checkbox"/>	Writing
<input type="checkbox"/>	Reviewing manuscript drafts
<input type="checkbox"/>	Final approval before submission for publication
<input type="checkbox"/>	Agreement to be accountable for the work
<input type="checkbox"/>	Acknowledgment only, I will not be a co-author

Signature: Click here to enter text