# 1. Collaborative Award in Science - preliminary application

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| **Reference number** | UNS66940 |
| **Applicant name** | Prof Simon Baron-Cohen |
| **Title of application** | Common Variant Genetics of Autism and Autistic Traits (GWAS) Consortium |

# 2. Application summary

| **Application title** |
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| Common Variant Genetics of Autism and Autistic Traits (GWAS) Consortium |

| **Proposed duration of funding (months)** |
|---|
| 60 |

| **Proposed start date** | 15/12/2018 |
|---|---|

| **Name of administering organisation** |
|---|
| University of Cambridge |

| **Lead applicant's address at administering organisation** | |
|---|---|
| Department/Division | Psychiatry |
| Organisation | University of Cambridge |
| Street | Douglas House, 18b Trumpington Road |
| City/Town | Cambridge |
| Postcode/Zipcode | CB2 8AH |
| Country | United Kingdom |

| **Research funding area**<br>Indicate the relevant research funding area for the proposed project. |
|---|
| Genetics, Genomics and Population Research |

# 3. Lead applicant

| **Lead applicant details** | |
|---|---|
| **Full Name** | Prof Simon Baron-Cohen |
| **Department** | Department of Psychiatry |
| **Division** | |

| | |
|---|---|
| **Organisation** | University of Cambridge |
| **Address Line 1** | Autism Research Centre, Section of Developmental Psychiatry |
| **City/Town** | CAMBRIDGE |
| **Postcode** | CB2 8AH |
| **Country** | United Kingdom |
| **Telephone No.** | 01223 465215 |
| **Email Address** | sb205@cam.ac.uk |

**Career history (current/most recent first)**

| From | To | Position | Organisation |
|---|---|---|---|
| 01/2001 | 01/2025 | Professor in Developmental Psychopathology and Director of the Autism Research Centre | University of Cambridge |
| 01/1999 | 01/2001 | Reader in Developmental Psychopathology | University of Cambridge |
| 01/1994 | 01/1999 | Lecturer in Developmental Psychopathology | University of Cambridge |
| 01/1991 | 01/1994 | Senior Lecturer in Developmental Psychopathology | Institute of Psychiatry, London |
| 01/1988 | 01/1991 | New Blood Lecturer | Institute of Psychiatry, London |
| 01/1987 | 01/1988 | Lecturer | University College London |

**Education/training**

| From | To | Qualification | Subject | Organisation |
|---|---|---|---|---|
| 09/1985 | 09/1987 | Master of Philosophy (MPhil) | Clinical Psychology | Institute of Psychiatry, London |
| 09/1982 | 09/1985 | Doctor of Philosophy (PhD;DPhil) | Psychology | University College London |
| 09/1978 | 07/1981 | Bachelor of Arts (BA) | Human Sciences | University of Oxford |

**Source(s) of personal salary support**

University of Cambridge

**Experience relevant to this proposal**
Please summarise your key achievements and experience which are relevant to this proposal.

Simon Baron-Cohen is Professor of Developmental Psychopathology, University of Cambridge, Fellow at Trinity College, Cambridge and Director of the Autism Research Centre in Cambridge. He is author of *Mindblindness*, *The Essential Difference*, *Prenatal Testosterone in Mind*, and *Zero Degrees of Empathy*. He has edited scholarly anthologies including *Understanding Other Minds*. He has written books for parents and teachers including *Autism and Asperger Syndrome: The Facts*. He is author of the DVDs *Mind Reading* and *The Transporters*, to help children with autism learn emotion recognition, both nominated for BAFTA awards. He formulated the 'mindblindness' theory of autism (1985) and the 'prenatal sex steroid' theory of autism (1997). He has also made contributions to many fields of autism research, to typical cognitive sex differences, and synaesthesia research. He created the first UK clinic for adults with suspected Asperger Syndrome (1999) that has helped over 1,000 patients to have their disability recognized. He gave a keynote address to the United Nations in New York on Autism Awareness Day 2017 on the topic of *Autism and Human Rights.* He is a Fellow of the British Psychological Society, the British Academy, and the American Psychological Association. He is Vice-President of the National Autistic Society, and President of the International Society for Autism Research (INSAR). He was Chair of the NICE Guideline Development Group for Autism (Adults) and is Chair of the

Psychology Section of the British Academy. He is co-editor in chief of the journal *Molecular Autism* and is a National Institute of Health Research (NIHR) Senior Investigator. See www.autismresearchcentre.com. In the field of autism genetics, he has co-authored recent papers with Dr Varun Warrier using GWAS of relevant phenotypic traits such as the Reading the Mind in the Eyes (80,000 genotyped participants, via 23andMe) in Molecular Psychiatry and the Empathy Quotient (50,000 genotyped participants) in Translational Psychiatry. He also leads the Templeton World Charitable Foundation program on autism genetics studying rare variants in 20 highly multiplex families, which is moving into its final year of 3 years, which is a collaboration with Illumina Inc and is discovering novel rare genetic mutations in autism.

| **Career breaks**<br>Have you had any career breaks or periods of part-time work, for example parental or long-term sick leave? | No |
|---|---|

| Do you wish to undertake this award part time? | Yes |
|---|---|

**Career contributions**
What are your most important research-related contributions to your field to date? These may include contributions to health policy or practice, or to technology or product discovery and development.

(1) The **mindblindness theory** of autism (1985). To explain the social-communication deficits in autism, Baron-Cohen and colleagues formulated the 'theory of mind' (ToM) hypothesis and confirmed this using the False Belief test. He coined the term 'mindblindness' to describe autism. He showed that absence of the precursors to ToM predicts autism diagnosis as early as 18 months old, using the Checklist for Autism in Toddlers (CHAT). He outlined a model of ToM that has its roots in infant 'shared attention'. He conducted the first neuroimaging study of ToM and demonstrated lesions in prefrontal cortex and amygdala can impair ToM. He also conducted the first fMRI study to show atypical amygdala function in autism. Finally, he showed that children with autism can be taught to 'mindread' emotion recognition via specialist educational software.

(2) The **prenatal sex steroid theory**of autism (1997). To understand why autism is more common in males, he tested if prenatal sex steroid hormones play a role in the aetiology of autism, since animal research shows that prenatal sex steroids play a causal role in the sexual differentiation of the brain. He instigated a longitudinal study demonstrating for the first time in humans how normative variation in amniotic prenatal testosterone (pT) levels correlate with postnatal brain and behavioural development. This entailed studying children of women who had undergone amniocentesis in pregnancy. To date, these typically developing children have been tested postnatally at 6 time points. He discovered that in typical toddlers, amount of eye contact and vocabulary development are inversely correlated with pT levels, and in school age children, quality of social relationships, ToM performance, and scores on the EQ are also inversely correlated with pT levels. In contrast, he found that scores on the Embedded Figures Test (of attention to detail), on the Systemizing Quotient (SQ), and measures of narrow interests are positively correlated with pT levels. He conducted the first human neuroimaging studies of the correlates of pT. In 2015 he collaborated with the Danish Biobank to show that people with autism have elevated levels of pT and the Δ4 sex steroid precursors to pT.

**Research outputs**
List up to 20 of your most significant research outputs, ensuring that at least five of these are from the last five years. For 10 of these outputs, provide a statement describing their significance and your contribution (up to 50 words per output).

Research outputs may include (but are not limited to):

- Peer-reviewed publications and preprints
- Datasets, software and research materials
- Inventions, patents and commercial activity

For original research publications indicate those arising from Wellcome-funded grants in **bold**, and provide the PubMed Central ID (PMCID) reference for each of these. Please refer to guidance notes.

*Please give citation in full, including title of paper and all authors*. Citations to preprints should state "Preprint", the repository name and the articles persistent identifier (e.g DOI).*

*(*All authors, unless more than 10, in which case please use 'et al', ensuring that your position as author*

*remains clear.)*

**Top 20 Publications in chronological order, from Baron-Cohen***:*

1. Baron-Cohen, S, Leslie, A.M., & Frith, U, (1985) Does the autistic child have a "theory of mind?" Cognition, **21**, 37-46. [SBC collected the data as part of his PhD. This paper stimulated hundreds of subsequent studies into theory of mind in autism].
2. Baron-Cohen, S, (1995) *Mindblindness: an essay on autism and theory of mind*. MIT Press/Bradford Books. [SBC wrote this as a monograph summarising his PhD and postdoc research. This was the first time the theory of mind literature in autism had been integrated].
3. Stone, V, Baron-Cohen, S, & Knight, R, (1998) Frontal lobe contributions to theory of mind. Journal of Cognitive Neuroscience, **10**, 640-656. [SBC supervised the postdoc and co-designed the experiments. This paper identified both orbitofrontal cortex and amygdala lesions in theory of mind].
4. Baron-Cohen, S, Ring, H, Wheelwright, S, Bullmore, E, Brammer, M, Simmons, A, & Williams, S, (1999) Social intelligence in the normal and autistic brain: an fMRI study. European Journal of Neuroscience, **11**, 1891-1898. [SBC designed the experiment and wrote the paper. This paper was the first to report atypical amygdala function in autism].
5. Baron-Cohen, S, Ring, H, Bullmore, E, Wheelwright, S, Ashwin, C, & Williams, S, (2000) The amygdala theory of autism. Neuroscience and Behavioural Reviews, **24**, 355-364. [SBC was lead author and proposed the theory. This was the first paper to highlight the importance of the amygdala in autism].
6. Baron-Cohen, S, & Wheelwright, S, Skinner, R, Martin, J, & Clubley, E, (2001) The Autism-Spectrum Quotient: Evidence from Asperger Syndrome/high-functioning autism, males and females, scientists, and mathematicians. Journal of Autism and Developmental Disorders, **31**, 5-17. [SBC co-designed the experiment and wrote the paper. This was the first paper to provide evidence for the association between mathematical talent and autistic traits].
7. Baron-Cohen, S, Wheelwright, S, & Hill, J, (2001) The 'Reading the Mind in the Eyes' Test Revised Version: A study with normal adults, and adults with Asperger Syndrome or High-Functioning Autism. Journal of Child Psychiatry and Psychiatry,**42**, 241-252. [SBC designed the measure and wrote the paper. The measure has now been used in hundreds of other studies].
8. Baron-Cohen, S, (2002) The extreme male brain theory of autism. Trends in Cognitive Sciences, **6**, 248-254. [SBC wrote the paper and proposed the theory. This paper stimulated 15 years of research into prenatal sex steroid hormones in autism].
9. Nunn, J, Gregory, L, Morris, R, Brammer, M, Bullmore, E, Harrison, J, Williams, S, Baron-Cohen, S, and Gray, J, (2002) Functional magnetic resonance imaging of synaesthesia: activation of colour vision area V4/V8 by spoken words. Nature Neuroscience, **5,** 371-375. [SBC co-designed the study. This was the first demonstration using fMRI of the brain basis of synaesthesia].
10. Baron-Cohen, S, Knickmeyer, R, & Belmonte, M (2005) Sex differences in the brain: implications for explaining autism. Science, **310**, 819-823. [SBC wrote the paper. This review paper pulled together all the research relevant to the link between autism and gender].
11. Chakrabarti, B, Hill-Cawthorne, G, Dudridge, F, Kent, L, Wheelwright, S, Allison, C, Banerjee-Basu, S, & Baron-Cohen, S, (2009) Genes related to sex-steroids, neural growth and social-emotional behaviour are associated with autistic traits, empathy and Asperger Syndrome. Autism Research, **2,**157-177. [SBC co-designed the study. This was the first candidate gene study of Asperger Syndrome].
12. Baron-Cohen, S, Lombardo, M, Auyeung, B, Ashwin, E, Chakrabarti, B, & Knickmeyer, R, (2011) Why are Autism Spectrum Conditions more prevalent in males? PLOS Biology, **9**, 1-10. PMC3114757. [SBC co-authored the paper. This was a major overview of why being male is a risk factor for autism].
13. van Honk, J, Schuttera, D, Bosa, P, Kruijtc, A, Lentjes, E, & Baron-Cohen, S, (2011) Testosterone administration impairs cognitive empathy in women depending on second-to-fourth digit ratio. Proceedings of the National Academy of Sciences of the USA, **108**, 3448-52. PMC3044405 [SBC contributed to the design of the study. This was the first study to show that manipulation of testosterone changes social cognition].
14. Schwarz, E, Guest P, Rahmoune, H, Wang, L, Levin, Y, Ingudomnukul, E, Ruta, L, Kent, L, Spain, M, Baron-Cohen, S, & Bahn, S, (2011) Sex-specific serum biomarker patterns in adults with Asperger's Syndrome. Molecular Psychiatry,**16**, 1213-20. [SBC supervised the PhD student who collected the samples. This was the first biomarker study to show distinct profiles in autism as a function of sex].
15. **Lombardo, M, Ashwin, E, Auyeung, B, Chakrabarti, Taylor, K, Hackett, G, Bullmore, E, & Baron-Cohen, S, (2012) Fetal testosterone influences sexually dimorphic gray matter in the human brain. Journal of Neuroscience, 32, 674-80. PMC3306238.** [SBC co-authored the paper and co-designed the experiment. This Wellcome Trust funded study was the first human demonstration that fetal testosterone changes brain structure developmentally].
16. Lai, M-C, Lombardo, M, & Baron-Cohen, S, (2013) Autism. The Lancet,**383**(9920), 896-910. [SBC co-

authored the paper. This was a major update on what we know about autism].

17. **Lai, M-C, Lombardo, M, Suckling, J, Ruigrok, A, Chakrabarti, B, Ecker, C, Deoni, S, Craig, M, Murphy, D, Bullmore, E, MRC AIMS Consortium, & Baron-Cohen, S, (2013) Biological sex affects the neurobiology of autism. Brain, 136, 2799-2815. PMC3754459** [SBC co-supervised the PhD student, co-designed the study and co-authored the paper. This Wellcome Trust funded study showed how autistic women are masculinised in brain structure (both grey and white matter].
18. **Baron-Cohen, S, Auyeung, B, Nørgaard-Pedersen, B, Hougaard, D.M, Abdallah, M.W, Melgaard, L, Cohen, A.S, Chakrabarti, B, Ruta, L, Lombardo, M.V, (2014) Elevated fetal steroidogenic activity in autism. Molecular Psychiatry,1-8. PMC4184868** [SBC provided funding for the study (MRC program grant and Wellcome Trust project grant) and co-designed the experiment and co-authored the paper. It was the first demonstration of prenatal sex steroids being elevated in children who later show autism].
19. Cassidy, S, Bradley, P, Robinson, J, Allison, C, McHugh, M, & Baron-Cohen, S, (2014) Suicidal ideation and suicide plans or attempts in adults with Asperger's syndrome attending a specialist diagnostic clinic: a clinical cohort study. The Lancet Psychiatry, **1**, 142–147. [SBC provided access to the data in the NHS, and conceived of the study. This was the first major clinical study showing autistic adults have elevated rates of suicidal plans and attempts].
20. Warrier, V, Grasby, KL, Uzefovsky, F, Toro, R, Smith, P, Chakrabarti, B, Khadake, J, Mawbey-Adamson, E, Litteman, N, Hottenga, J-J, Lubke, G, Boomsma, DI, Martin, NG, Hatemi, PK, Medland, SE, Hinds, DA, Bourgeron, T, & Baron-Cohen, S, (2017) Genome-wide meta-analysis of cognitive empathy: heritability, and correlates with sex, neuropsychiatric conditions and cognition. Molecular Psychiatry, (DOI: 10.1038/mp.2017.122). PMC5656177. [SBC initiated the collaboration with 23andMe, suggested the measure, and co-wrote the paper. This was the first big data test (80,000 volunteers) for genes associated with cognitive empathy].

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| Total number of peer-reviewed publications which you have authored/co-authored. Please exclude abstracts and literature reviews. | 513 |

**Current and recent research funding (including Wellcome Trust grants)**
Please list all held in the last five years and any key prior grants (list the most recent first). State the name of the awarding body, name(s) of grantholder(s), title of project, amounts awarded, your role in the project, and start and end dates of support. For all active grants, indicate the number of hours per week that are spent on each project.

**1. Action autism innovative medicine studies – 2 – Trials (AIMS-2-TRIAL) (funded by Innovative Medicines Initiative)**

Professor Simon Baron-Cohen (Principal Investigator - 0.1fte)

Awarded €2,808,025

Dates of the grant – 01.05.2018 – 30.04.2023

**2. Investigating the role of NRXN1 in autism (funded by the Autism Research Trust)**

Professor Simon Baron-Cohen (Principal Investigator - 0.1fte)

Awarded £475,000

Dates of the grant - 01.01.2018 to 31.08.2020

**3. Autism and the criminal justice system (funded by the Autism Research Trust)**

Professor Simon Baron-Cohen (Principal Investigator - 0.1fte)

Awarded £164,896

Dates of the grant - 01.01.2018 to 31.12.2020

**4. Hormones and Biomarkers in Pregnancy (funded by the Autism Research Trust)**

Professor Simon Baron-Cohen (Principal Investigator - 0.1fte)

Awarded £40,000

Dates of the grant - 01.01.2017 to 30.09.2020

**5. Vulnerability in adults with autism spectrum conditions (funded by the Autism Research Trust and Autistica)**

Professor Simon Baron-Cohen (Principal Investigator - 0.1fte)

Awarded £80,000

Dates of the grant - 01.10.2016 to 31.05.2018

**6. NIHR Senior investigator award (funded by NIHR)**

Professor Simon Baron-Cohen (Award holder)

Awarded £45,000

Dates of the grant - 01.04.2016 to 31.03.2019

**7. Suicide, autism and autistic traits (funded by Collaboration for Leadership in Applied Health Research & Care (CLAHRC))**

Professor Simon Baron-Cohen (Principal Investigator)

Awarded £44,688

Dates of the grant - 01.04.2016 to 30.06.2017

**8. Investigating the link between mathematical ability and autism using genetics and epigenetics (IMAGE) (funded by the Templeton World Charity Foundation, Inc.)**

Professor Simon Baron-Cohen (Principal Investigator – 0.1 fte)

Awarded £1,805,657

Dates of the grant – 15.12.2015 to 14.12.2018

**9. Oxytocin inhalation (funded by the Autism Research Trust)**

Professor Simon Baron-Cohen (Principal Investigator – 0.1 fte)

Awarded £81,880

Dates of the grant – 23.01.2014 to 31.12.2018

**10. Hormones and biomarkers (funded by the Autism Research Trust)**

Professor Simon Baron-Cohen (Principal Investigator)

Awarded £32,000

Dates of the grant – 23.01.2014 to 31.12.2017

**11. Autism gene sequencing (funded by the Autism Research Trust)**

Professor Simon Baron-Cohen (Principal Investigator - 0.1fte)

Awarded £112,000

Dates of the grant – 06.07.2013 to 14.12.2018

**12. European Autism Interventions (EU-AIMS) (funded by Innovative Medicines Initiative)**

Professor Simon Baron-Cohen (Principal Investigator)

Awarded £528,572

Dates of the grant – 01.04.2012 to 31.03.2018

**13. Foetal testosterone effects on brain structure and function (funded by the Wellcome Trust)**

Professor Simon Baron-Cohen (Principal Investigator)

Awarded £289,602

Dates of the grant – 01.10.2010 to 30.09.2014

**14. Autistic traits, autism spectrum conditions, and foetal testosterone (funded by the Medical Research Council)**

Professor Simon Baron-Cohen (Principal Investigator)

Awarded £943,891

Dates of the grant - 01.01.2007 - 13.05.2012



## 4. Applicants

**1**

| **Applicant** | |
|---|---|
| **Full Name** | Prof David Rowitch |
| **Department** | Paediatrics |
| **Division** | School of Clinical Medicine |
| **Organisation** | University of Cambridge |
| **Address Line 1** | Hills Road |
| **City/Town** | Cambridge |
| **Postcode** | CB20QQ |
| **Country** | |
| **Telephone No.** | 01223 769386 |
| **Email Address** | dhr25@medschl.cam.ac.uk |

| Career history (current/most recent first) | | | |
|---|---|---|---|
| **From** | **To** | **Position** | **Organisation** |
| 03/2016 | 05/2026 | Professor and Head | University of Cambridge |
| 07/2006 | 02/2016 | Professor and Chief of Neonatology | University of California San Francisco |
| 07/1999 | 06/2006 | Assisitant, then Associate Professor | Harvard Medical School |
| 07/1996 | 06/1999 | Postdoctoral Fellow | Harvard University |

| Education/training | | | | |
|---|---|---|---|---|
| **From** | **To** | **Qualification** | **Subject** | **Organisation** |
| 07/1989 | 06/1996 | Intern, Resident and Neonatology Fellow | Paediatrics and Neonatology | Children's Hospital Boston |
| 07/1982 | 06/1989 | Doctor of Medicine (MD) | Medicine | University of California, Los Angeles |
| 07/1984 | 06/1987 | Doctor of Philosophy (PhD;DPhil) | Biochemistry | University of Cambridge |

| Source(s) of personal salary support |
|---|
| University of Cambridge |

**Experience relevant to this proposal**
Please summarise your key achievements and experience which are relevant to this proposal.

My laboratory program focuses on the developmental genetics of glial cells of the CNS called astrocytes and myelinating oligodendrocytes. As a neonatologist physician-scientist, I look for extensions of neuroscience that can impact our understanding of human neurological diseases, particularly cerebral palsy and neurogenetic diseases. I have worked productively with neurobiologists in mammalian and invertebrate systems as well as computer and imaging scientists. In my current capacity in Cambridge University, I am developing pediatric applications of genomic and stem cell medicine in the neonatal ICU and for childhood rare brain disorders.

On this collaborative grant my role is as Head of the Department of Paediatrics in Cambridge University and Head of the Paediatric Theme of the NIHR Biomedical Research Centre (BRC) in Cambridge where I have organised a network of Consultant Paediatricians across the East of England who can help us recruit autism cases to the UK Autism Biobank that is part of this grant. In addition, I have had 20 years of research experience in studying gene expression in the brain and how this affects risk of neurodevelopmental disorders, so can advise on the bioinformatics as autism gene discovery progresses.

| **Career breaks**<br>Have you had any career breaks or periods of part-time work, for example parental or long-term sick leave? | No |
|---|---|

| Do you wish to undertake this award part time? | No |
|---|---|

**Career contributions**
What are your most important research-related contributions to your field to date? These may include contributions to health policy or practice, or to technology or product discovery and development.

My laboratory was amongst the first to investigate the developmental genetics of glial lineages of the CNS. *Olig1/2* genes are master regulators of motor neuron and oligodendrocyte precursor (OPC) specification (Lu et al, 2002, *Cell*). More recently, we described a novel function for OPCs in regulating white matter angiogenesis through expression of Wnt ligands (Yuen et al, 2014, *Cell*). We have proposed that astrocytes comprise a functionally heterogeneous population and have shown that they are specified in the embryo according to a spatial template (Muroyama et al., 2005, *Nature*; Tsai et al., 2012, *Science*) and optimized to support local

neuronal circuits (Molofsky et al., 2014, *Nature*, Kelly et al., 2018, *Neuron)*. I have led or participated in studies showing Olig2 is a useful biomarker in human neonatal white matter lesions (Billards et al., 2008, *Brain Path*) and malignant gliomas (Ligon et al, 2004, *JNEN*, Ligon et al., 2007, *Neuron*, Griveau et al., 2018, *Cancer Cell*).

Clinical: I am PI of a first-in-man Phase I clinical study of oligodendrocyte progenitor transplant in boys with the rare leukodystrophy, Pelizeaus Mersbacher Disease (PMD), which reported safety and putative MRI myelin signals at 1-year post-transplant (Gupta et al., 2012, *Sci Trans Med*). I co-founded the Newborn Brain Research Institute with neurologist Donna Ferriero at UCSF in 2006. As Head of Neonatology (2006-2015), I began a neonatal brain bank to study human development and injuries leading to cerebral palsy. With colleagues, we have shown evidence for late migration of young neurons in term neonates (Sanai et al., 2011, *Nature*), which might comprise a target of injury in hypoxic-ischemic encephalopathy. Although I was recently been appointed as Professor of Paediatrics at Cambridge (2016) I have made a significant contribution to NIHR in a number of ways. I support the NHS England East of England Genomics Medicine Centre by promoting recruitment of paediatrics patients with rare diseases and their families. Overall recruitment for rare diseases within Cambridge, and the Centre as a whole, is ahead of trajectory.

Summary: My total publications number 176 with 29256 citations and H-index = 86.

**Research outputs**
List up to 20 of your most significant research outputs, ensuring that at least five of these are from the last five years. For 10 of these outputs, provide a statement describing their significance and your contribution (up to 50 words per output).

Research outputs may include (but are not limited to):

- Peer-reviewed publications and preprints
- Datasets, software and research materials
- Inventions, patents and commercial activity

For original research publications indicate those arising from Wellcome-funded grants in **bold**, and provide the PubMed Central ID (PMCID) reference for each of these. Please refer to guidance notes.

*Please give citation in full, including title of paper and all authors*. Citations to preprints should state "Preprint", the repository name and the articles persistent identifier (e.g DOI).*

*(*All authors, unless more than 10, in which case please use 'et al', ensuring that your position as author remains clear.)*

1. **Lu QR, Sun T, Zhu Z, Ma N, Garcia M, Stiles CD, Rowitch DH. Common developmental requirement for Olig function indicates a motor neuron/oligodendrocyte lineage connection. *Cell,* 2002; 109, 75-86.** In prior work (Lu et al., 2000, *Neuron*), we reported Olig transcription factors in the oligodendrocyte lineage. This paper established that Olig2 function regulates pattern formation and embryonic oligodendrocyte and motor neuron development. Olig2 was the first transcription factor described that was essential for glial development.
2. **Muroyama Y, Fujiwara Y, Orkin SH, Rowitch DH. Specification of astrocytes by bHLH protein SCL in a restricted region of the neural tube. *Nature.* 2005 Nov 17;438(7066):360-3**. Here we showed that bHLH protein SCL/TAL1 engaged in cross-antagonistic interactions with Olig2 to regulate astrocyte versus oligodendrocyte subtype specification. The paper showed a segmentally restricted mechanism for gliogenesis regulated by CNS pattern formation.
3. **Ligon KL, Huillard E, Mehta S, KesariS, Liu H, Alberta J, Bachoo RM, Kane M, Louis DN, DePinho RA, Anderson DJ, Stiles CD, Rowitch DH. Olig2-regulated lineage-restricted pathway controls replication competence in neural stem cells and malignant glioma. *Neuron.* 2007; 53:503-17.** As Olig2 is expressed--and has an essential role-- in high-grade glioma, this paper provided a demonstration that CNS developmental regulatory factors can also play important roles in brain cancer. PMCID: PMC1810344
4. **Sanai N, Nguyen T, Ihrie RA, Mirzadeh Z, Tsai HH, Wong M, Gupta N, Berger MS, Huang E, Garcia-Verdugo JM, Rowitch DH, Alvarez-Buylla A. Corridors of migrating neurons in the human brain and their decline during infancy. *Nature.* 2011 Sep 28;478(7369):382-6.** This paper reported a novel population of late migrating interneurons in the post-natal human forebrain, raising the possibility that this late developmental mechanism might be affected adversely by neonatal brain injury. PMCID: PMC3197903

5. **Fancy SPJ, Harrington EP, Yuen T, Silbereis JC, Zhao C, Baranzini SE, Bruce C, Otero JJ, Huang EJ, Nusse R, Franklin RJM and Rowitch DH. Axin2 as regulatory and therapeutic target in newborn brain injury and remyelination. *Nat. Neurosci.* 2011 Jun 26;14(8):1009-16.** We previously showed the Wnt pathway was an important modulator of oligodendrocyte maturation (Fancy et al., 2009, *Genes Dev*). Here, we reported Wnt pathway activation in human neonatal white matter injury. We found that the small molecule Wnt inhibitor XAV939 accelerated remyelination by stabilizing levels of Axin2. PMCID: PMC3145042
6. **Heine VM, Griveau A, Chapin C, Ballard PL, Chen JK, Rowitch DH. A small-molecule smoothened agonist prevents glucocorticoid-induced neonatal cerebellar injury. *Sci Transl Med*. 2011 Oct 19;3(105):105.** About 20% of extremely preterm infants will show cerebellar hypoplasia associated with severely impaired long-term neurodevelopmental outcomes. Here, we showed that a small molecule agonist of Sonic Hedgehog (SAG) can protect against glucocorticoid-induced cerebellar injury in mouse neonatal brain. PMCID: PMC3694585
7. **Tsai HH, Li H, Fuentealba LC, Molofsky AV, Taveira-Marques R, Zhuang H, Tenney A, Murnen AT, Fancy SP, Merkle F, Kessaris N, Alvarez-Buylla A, Richardson WD, Rowitch DH. Regional Astrocyte Allocation Regulates CNS Synaptogenesis and Repair. *Science.* 2012 337(6092):358-62.** This paper showed astrocytes are generated in multiple progenitor domains and are allocated according to a region-restricted template. It suggested that spatially diverse programmes of astrogenesis might confer long-term specialized functions. PMCID: PMC4059181
8. **Gupta N, Henry RG, Strober J, Kang SM, Lim DA, Bucci M, Caverzasi E, Gaetano L, Mandelli ML, Ryan T, Perry R, Farrell J, Jeremy RJ, Ulman M, Huhn SL, Barkovich AJ, Rowitch DH. Neural stem cell engraftment and myelination in the human brain. *Sci Transl Med*. 2012 4, 155.** In the fatal leukodystrophy Pelizaeus-Merzbacher disease (PMD), endogenous oligodendrocytes are unable to produce myelin due to mutation of PLP1. This first in man Phase I study of neural stem cells for treatment of white matter disorders has shown long-term safety promoting later Phase clinical investigation. *PMCID: PMC3893824*
9. **AV Molofsky, KW Kelley, H-HTsai, SA Redmond, SM Chang, L Madireddy, JR Chan, SE Baranzini, EM Ullian, and DH Rowitch. Astrocyte positional signals maintain sensorimotor circuit integrity. *Nature,* 2014 509:189-94.** This paper is the first to show that region-specific astrocyte-encoded function is required for neural circuit activity and integrity. This paradigm may extend to other aspects of the CNS in the regulation of normal neurological activity and in disease states. PMCID: PMC4057936
10. **TJ Yuen, JC Silbereis, A Griveau, SM Chang, R Daneman, SPJ Fancy, H Zahed, E Maltepe and DH Rowitch. Oligodendrocyte-encoded *HIF* function couples postnatal myelination and white matter angiogenesis, *Cell,* 2014 158:383-96.** In this paper, we show that oligodendrocyte precursors express angiogenic Wnts under control of the HIF pathway and that Wnt activity promotes white matter vascularization, coordinating this with the energy-expensive process of myelination PMCID: PMC4149873

| | |
|---|---|
| Total number of peer-reviewed publications which you have authored/co-authored. Please exclude abstracts and literature reviews. | 150 |

**Current and recent research funding (including Wellcome Trust grants)**
Please list all held in the last five years and any key prior grants (list the most recent first). State the name of the awarding body, name(s) of grantholder(s), title of project, amounts awarded, your role in the project, and start and end dates of support. For all active grants, indicate the number of hours per week that are spent on each project.

Completed/Significant:

Howard Hughes Medical Institute Investigator. **Pathogenesis and Rational Treatment of Cerebral Palsy** 04/01/2008-09/01/2015 **$5M**

Paul G. Allen Family Foundation-Allen Distinguished Investigators (ADI) Program (Ullian, Rowitch, co-PIs). **Matching Regional Diversity with Function: Unique Astrocyte Signals Mature Regionally Matched Neurons** 05/01/2015-4/30/2018 **$750K**

Active:

NIH/NINDS (P01NS083513; PI-Rowitch) **Regulation of Cellular Pathways in Human Brain Development** 07/01/14-06/30/19 **$5M**

Wellcome Trust Senior Investigator Award (PI-Rowitch) **Understanding Astrocyte Regional and Functional Diversity** 12/01/15-11/31/21 **£3M**

Action Medical Research (PI-Rowitch). **Personalised cell-based models of hypomyelinating leukodystrophy** 09/01/15-10/31/17 **£160K**

NIHR Cambridge Biomedical Research Centre (Theme co-lead Paediatrics-Rowitch) **Women's Health and Paediatrics Theme** 04/01/17-03/31/22 **£1.8M**

**2**

| **Applicant** | |
|---|---|
| **Full Name** | Dr Matthew Hurles |
| **Department** | |
| **Division** | |
| **Organisation** | Wellcome Trust Sanger Institute |
| **Address Line 1** | Wellcome Trust Genome Campus |
| **City/Town** | CAMBRIDGE |
| **Postcode** | CB10 1SA |
| **Country** | United Kingdom |
| **Telephone No.** | |
| **Email Address** | meh@sanger.ac.uk |

| **Career history (current/most recent first)** | | | |
|---|---|---|---|
| **From** | **To** | **Position** | **Organisation** |
| 09/2003 | 03/2023 | Senior Group Leader | Wellcome Trust Sanger Institute |

| **Education/training** | | | | |
|---|---|---|---|---|
| **From** | **To** | **Qualification** | **Subject** | **Organisation** |
| 09/1996 | 10/1999 | Doctor of Philosophy (PhD;DPhil) | Genetics | University of Leicester |

| **Source(s) of personal salary support** |
|---|
| Wellcome Sanger Institute |

**Experience relevant to this proposal**
Please summarise your key achievements and experience which are relevant to this proposal.

I am the head of the human genetics programme at the Wellcome Sanger Institute. My research has provided new insights into the contributions of structural variants including deletions and duplications to rare and common diseases, the factors infleuncing *de novo* mutation rates , and the delineation of the genetic causes of severe developmental disorders, including neurodevelopmental conditions and congenital heart defects.

In particular, I lead the Deciphering Developmental Disorders study, a UK-wide study on genetically undiagnosed developmental study. As a part of this we have brought together doctors in the 24 Regional Genetics Services, throughout the UK and Republic of Ireland to recruit participants into the study. Whole exome sequencing has been conducted in more than 13,600 probands from more than 13,500 families (total ~33,000 individuals including parents). Our research published in 2017 has identified 14 novel genes involved in developmental disorders providing genetic diagnosis for many participants in the DDD. We have since more

than doubled the cohort size identifying dozens of novel genes. Our research has also demonstrated a role for de novo variants in regulatory regions and splice sites in developmental disorders. Tied to this, we have also developed a website (DECIPHER) that allows for sharing of information in individuals with rare disorders, accelerating gene discovery.

I'm also collaborating on the PAGE study (Prenatal Assessment of Genomes and Exomes), which conducts whole exome sequence of foetuses with developmental abnormalities apparent through fetal ultrasound in 1000 fetuses across the UK. This additional information will help to acquire new knowledge about the genetic variation causing the observed abnormalities. The new insights gained by this study will be used to improve diagnostic methods, allowing better genetics-derived prognoses and more informed parental counselling as well as future management of pregnancy and childbirth.

I also co-founded Congenica Ltd,  to provide genetic analysis services to the NHS and other healthcare providers, which will also analyse patients' DNA sequenced in the UK 100,000 Genomes Project.

I will bring my knowledge from the DDD project to advise on autism gene discovery, and make the bioinformatics expertise of the Sanger Centre available.

| **Career breaks**<br>Have you had any career breaks or periods of part-time work, for example parental or long-term sick leave? | No |
|---|---|

| Do you wish to undertake this award part time? | No |
|---|---|

**Career contributions**
What are your most important research-related contributions to your field to date? These may include contributions to health policy or practice, or to technology or product discovery and development.

I am dedicated to applying new genetic technologies to improve the diagnosis of patients with rare genetic conditions. I lead the Deciphering Developmental Disorders (DDD) Study, a collaboration between 14,000 families with children with severe, undiagnosed developmental disorders, all 24 clinical genetic centres in the UK and Ireland, and the Wellcome Sanger Institute. Together we are understanding the diverse genetic landscape of these disorders, and applying this knowledge to achieve improved diagnostic testing. As a part of the DDD study, my lab has identified several novel genes associated with DDD, quantified recessive causes of DDD, demonstrated a role for de novo mutations in regulatory elements, and quantified the relative contribution of mutations at splice sites for DDD.

I also lead the Prenatal Assessment of Genomes and Exomes (PAGE) Study, a collaboration between pregnant mothers and their partners, a network of UK Fetal Medicine Centres caring for these pregnant women and the Wellcome Sanger Institute. Together we are investigating the genetic causes of developmental anomalies that are identified during prenatal ultrasound screening, with the aim of improving the prognostic information that can be provided to parents.

The work of my research group has been characterized by rapid adoption of new technologies for assaying genetic variation, development of novel analytical strategies for making sense from large datasets and thoughtful application of these tools for advancing our understanding of human genetic diseases. More recently, our highly collaborative research has had increasing translational impact, resulting in genetic diagnoses for over a thousand children with previously undiagnosed developmental disorders, and leading to the founding of a start-up company (Congenica Ltd) to provide sustainable genetic diagnostic services to the NHS and other healthcare providers.

I believe we have a moral imperative to give patients and their families the opportunity to share their genetic data anonymously, to enable them to benefit from having the greatest possible number of researchers and clinicians analysing their data. Together with Helen Firth, I lead the DECIPHER initiative that is enabling rare disease patients to share anonymised genetic and clinical data globally.

**Research outputs**

List up to 20 of your most significant research outputs, ensuring that at least five of these are from the last five years. For 10 of these outputs, provide a statement describing their significance and your contribution (up to 50 words per output).

Research outputs may include (but are not limited to):

- Peer-reviewed publications and preprints
- Datasets, software and research materials
- Inventions, patents and commercial activity

For original research publications indicate those arising from Wellcome-funded grants in **bold**, and provide the PubMed Central ID (PMCID) reference for each of these. Please refer to guidance notes.

*Please give citation in full, including title of paper and all authors*. Citations to preprints should state "Preprint", the repository name and the articles persistent identifier (e.g DOI).*

*(*All authors, unless more than 10, in which case please use 'et al', ensuring that your position as author remains clear.)*

De novo mutations in regulatory elements in neurodevelopmental disorders. Short PJ, McRae JF, Gallone G, Sifrim A, Won H, Geschwind DH, Wright CF, Firth HV, FitzPatrick DR, Barrett JC, **Hurles** ME.Nature. 2018 Mar 29;555(7698):611-616. doi: 10.1038/nature25983.

Distinct genetic architectures for syndromic and nonsyndromic congenital heart defects identified by exome sequencing. Sifrim A, Hitz MP, Wilsdon A, Breckpot J, Turki SH, Thienpont B, McRae J, Fitzgerald TW, Singh T, Swaminathan GJ, Prigmore E, Rajan D, Abdul-Khaliq H, Banka S, Bauer UM, Bentham J, Berger F, Bhattacharya S, Bu'Lock F, Canham N, Colgiu IG, Cosgrove C, Cox H, Daehnert I, Daly A, Danesh J, Fryer A, Gewillig M, Hobson E, Hoff K, Homfray T; INTERVAL Study, Kahlert AK, Ketley A, Kramer HH, Lachlan K, Lampe AK, Louw JJ, Manickara AK, Manase D, McCarthy KP, Metcalfe K, Moore C, Newbury-Ecob R, Omer SO, Ouwehand WH, Park SM, Parker MJ, Pickardt T, Pollard MO, Robert L, Roberts DJ, Sambrook J, Setchfield K, Stiller B, Thornborough C, Toka O, Watkins H, Williams D, Wright M, Mital S, Daubeney PE, Keavney B, Goodship J; UK10K Consortium, Abu-Sulaiman RM, Klaassen S, Wright CF, Firth HV, Barrett JC, Devriendt K, FitzPatrick DR, Brook JD; Deciphering Developmental Disorders Study, **Hurles** ME. Nat Genet. 2016 Sep;48(9):1060-5. doi: 10.1038/ng.3627. Epub 2016 Aug 1.

Discovery of four recessive developmental disorders using probabilistic genotype and phenotype matching among 4,125 families. Akawi N, McRae J, Ansari M, Balasubramanian M, Blyth M, Brady AF, Clayton S, Cole T, Deshpande C, Fitzgerald TW, Foulds N, Francis R, Gabriel G, Gerety SS, Goodship J, Hobson E, Jones WD, Joss S, King D, Klena N, Kumar A, Lees M, Lelliott C, Lord J, McMullan D, O'Regan M, Osio D, Piombo V, Prigmore E, Rajan D, Rosser E, Sifrim A, Smith A, Swaminathan GJ, Turnpenny P, Whitworth J, Wright CF, Firth HV, Barrett JC, Lo CW, FitzPatrick DR, **Hurles** ME; DDD study. Nat Genet. 2015 Nov;47(11):1363-9. doi: 10.1038/ng.3410. Epub 2015 Oct 5.

**Large-scale discovery** of **novel genetic causes** of **developmental disorders**. Deciphering **Developmental Disorders** Study. Nature. 2015 Mar 12;519(7542):223-8. doi: 10.1038/nature14135. Epub 2014 Dec 24.

**Variation** in **genome-wide mutation rates** within and between **human families**. Conrad DF, Keebler JE, DePristo MA, Lindsay SJ, Zhang Y, Casals F, Idaghdour Y, Hartl CL, Torroja C, Garimella KV, Zilversmit M, Cartwright R, Rouleau GA, Daly M, Stone EA, Hurles ME, Awadalla P; 1000 Genomes Project. Nat Genet. 2011 Jun 12;43(7):712-4. doi: 10.1038/ng.862.

A **map** of **human genome variation** from **population-scale sequencing.** 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. Nature. 2010 Oct 28;467(7319):1061-73. doi: 10.1038/nature09534.

Genome-wide association study of CNVs in 16,000 cases of eight common diseases and 3,000shared controls. Wellcome Trust Case Control Consortium, Craddock N, Hurles ME, Cardin N, Pearson RD, Plagnol V, Robson S, Vukcevic D, Barnes C, Conrad DF, Giannoulatou E, Holmes C, Marchini JL, Stirrups K, Tobin MD, Wain LV, Yau C, Aerts J, Ahmad T, Andrews TD, Arbury H, Attwood A, Auton A, Ball SG, Balmforth AJ, Barrett JC, Barroso I, Barton A, Bennett AJ, Bhaskar S, Blaszczyk K, Bowes J, Brand OJ, Braund PS, Bredin F, Breen G, Brown MJ, Bruce IN, Bull J, Burren OS, Burton J, Byrnes J, Caesar S, Clee CM, Coffey AJ, Connell JM, Cooper JD, Dominiczak AF, Downes K, Drummond HE, Dudakia D, Dunham A, Ebbs B, Eccles D, Edkins

S, Edwards C, Elliot A, Emery P, Evans DM, Evans G, Eyre S, Farmer A, Ferrier IN, Feuk L, Fitzgerald T, Flynn E, Forbes A, Forty L, Franklyn JA, Freathy RM, Gibbs P, Gilbert P, Gokumen O, Gordon-Smith K, Gray E, Green E, Groves CJ, Grozeva D, Gwilliam R, Hall A, Hammond N, Hardy M, Harrison P, Hassanali N, Hebaishi H, Hines S, Hinks A, Hitman GA, Hocking L, Howard E, Howard P, Howson JM, Hughes D, Hunt S, Isaacs JD, Jain M, Jewell DP, Johnson T, Jolley JD, Jones IR, Jones LA, Kirov G, Langford CF, Lango-Allen H, Lathrop GM, Lee J, Lee KL, Lees C, Lewis K, Lindgren CM, Maisuria-Armer M, Maller J, Mansfield J, Martin P, Massey DC, McArdle WL, McGuffin P, McLay KE, Mentzer A, Mimmack ML, Morgan AE, Morris AP, Mowat C, Myers S, Newman W, Nimmo ER, O'Donovan MC, Onipinla A, Onyiah I, Ovington NR, Owen MJ, Palin K, Parnell K, Pernet D, Perry JR, Phillips A, Pinto D, Prescott NJ, Prokopenko I, Quail MA, Rafelt S, Rayner NW, Redon R, Reid DM, Renwick, Ring SM, Robertson N, Russell E, St Clair D, Sambrook JG, Sanderson JD, Schuilenburg H, Scott CE, Scott R, Seal S, Shaw-Hawkins S, Shields BM, Simmonds MJ, Smyth DJ, Somaskantharajah E, Spanova K, Steer S, Stephens J, Stevens HE, Stone MA, Su Z, Symmons DP, Thompson JR, Thomson W, Travers ME, Turnbull C, Valsesia A, Walker M, Walker NM, Wallace C, Warren-Perry M, Watkins NA, Webster J, Weedon MN, Wilson AG, Woodburn M, Wordsworth BP, Young AH, Zeggini E, Carter NP, Frayling TM, Lee C, McVean G, Munroe PB, Palotie A, Sawcer SJ, Scherer SW, Strachan DP, Tyler-Smith C, Brown MA, Burton PR, Caulfield MJ, Compston A, Farrall M, Gough SC, Hall AS, Hattersley AT, Hill AV, Mathew CG, Pembrey M, Satsangi J, Stratton MR, Worthington J, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand W, Parkes M, Rahman N, Todd JA, Samani NJ, Donnelly P. Nature. 2010 Apr 1;464(7289):713-20. doi: 10.1038/nature08979.

**Origins** and **functional impact** of **copy number variation** in the **human genome**. Conrad DF, Pinto D, Redon R, Feuk L, Gokcumen O, Zhang Y, Aerts J, Andrews TD, Barnes C, Campbell P, Fitzgerald T, Hu M, Ihm CH, Kristiansson K, Macarthur DG, Macdonald JR, Onyiah I, Pang AW, Robson S, Stirrups K, Valsesia A, Walter K, Wei J; Wellcome Trust Case Control Consortium, Tyler-Smith C, Carter NP, Lee C, Scherer SW, Hurles ME. Nature. 2010 Apr 1;464(7289):704-12. doi: 10.1038/nature08516. Epub 2009 Oct 7.

Large, rare chromosomal deletions associated with severe early-onset obesity. Bochukova EG, Huang N, Keogh J, Henning E, Purmann C, Blaszczyk K, Saeed S, Hamilton-Shield J, Clayton-Smith J, O'Rahilly S, Hurles ME, Farooqi IS. Nature. 2010 Feb 4;463(7281):666-70. doi: 10.1038/nature08689. Epub 2009 Dec 6.

Global variation in copy number in the human genome. Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, Fiegler H, Shapero MH, Carson AR, Chen W, Cho EK, Dallaire S, Freeman JL, González JR, Gratacòs M, Huang J, Kalaitzopoulos D, Komura D, MacDonald JR, Marshall CR, Mei R, Montgomery L, Nishimura K, Okamura K, Shen F, Somerville MJ, Tchinda J, Valsesia A, Woodwark C, Yang F, Zhang J, Zerjal T, Zhang J, Armengol L, Conrad DF, Estivill X, Tyler-Smith C, Carter NP, Aburatani H, Lee C, Jones KW, Scherer SW, Hurles ME. Nature. 2006 Nov 23;444(7118):444-54.

| | |
|---|---|
| Total number of peer-reviewed publications which you have authored/co-authored. Please exclude abstracts and literature reviews. | 144 |

**Current and recent research funding (including Wellcome Trust grants)**
Please list all held in the last five years and any key prior grants (list the most recent first). State the name of the awarding body, name(s) of grantholder(s), title of project, amounts awarded, your role in the project, and start and end dates of support. For all active grants, indicate the number of hours per week that are spent on each project.

The Deciphering Developmental Disorder study - Health Innovation Challenge Fund [grant number HICF-1009-003]

The Deciphering Developmental Disorder Study - Wellcome and the Department of Health, and the Wellcome Sanger Institute [grant number WT098051].

**3**

| **Applicant** | |
|---|---|
| **Full Name** | Dr Varun Warrier |
| **Department** | Psychiatry |
| **Division** | |

| | |
|---|---|
| **Organisation** | University of Cambridge |
| **Address Line 1** | 18 b, Trumpington Road |
| **City/Town** | Cambridge |
| **Postcode** | CB2 1TP |
| **Country** | United Kingdom |
| **Telephone No.** | 07849467549 |
| **Email Address** | vw260@medschl.cam.ac.uk |

**Career history (current/most recent first)**

| From | To | Position | Organisation |
|---|---|---|---|
| 10/2012 | 10/2013 | Visiting Research Associate | University of Cambridge |
| 10/2012 | 06/2013 | Research Assistant | National Institute of Mental Health & Neuroscience, India |

**Education/training**

| From | To | Qualification | Subject | Organisation |
|---|---|---|---|---|
| 10/2014 | 03/2018 | Doctor of Philosophy (PhD;DPhil) | Psychiatry | University of Cambridge |
| 10/2013 | 09/2014 | Master of Philosophy (MPhil) | Medical Sciences (Psychiatry) | University of Cambridge |
| 10/2011 | 10/2012 | Master of Science (MSc) | Neuroscience | University College London |
| 07/2008 | 07/2011 | Bachelor of Science (BSc) | Zoology | University of Madras |

**Source(s) of personal salary support**

Templeton World Charity Foundation

**Experience relevant to this proposal**
Please summarise your key achievements and experience which are relevant to this proposal.

I have worked for the last five years on genome-wide association studies of traits related to autism. In particular, my work has focussed on the genetics of empathy, cognitive empathy, systemizing, aptitude in STEM (science, technology, engineering, and mathematics), and social relationship satisfaction. In parallel, I've analyzed data from methylation and neuroimaging datasets to integrate genetics with multimodal information with autism.

As a part of the GWAS studies and downstream analysis, I have designed the overall pipeline, conducted quality control and statistical analyses, and conducted downstream analysis. I've written the manuscripts and interpreted the results.

In parallel, I have also worked on and developed a study to conduct whole-genome sequencing of multiplex autism families. I have worked to design the study, the recruitment criteria and methods, phenotyping the participants, handling DNA samples and collaborating with companies to extract and sequence the samples. I am leading the bioinformatics analysis of the Templeton World Charity Foundation autism genetics grant at the Autism Research Centre, along with Dr Charles Bradshaw, Gurdon Institute, and with Dr David Bentley, Illumina Inc

| | |
|---|---|
| **Career breaks**<br>Have you had any career breaks or periods of part-time work, for example parental or long-term sick leave? | No |

| | |
|---|---|
| Do you wish to undertake this award part time? | Yes |

**Career contributions**
What are your most important research-related contributions to your field to date? These may include contributions to health policy or practice, or to technology or product discovery and development.

I have worked to dilineate the contribution of common genetic variation to traits related to autism. I conducted GWAS of social traits (empathy, cognitive empathy, theory of mind, and social relationship satisfaction) and non-social traits (systemizing, and aptitude in STEM subjects) in the general population (45,000 < N < 250,000) .

I identified genes and genetic loci associated with these phenotypes, highlighted enrichment in biological pathways, tissues and gene sets, and investigated sex differences in these traits. For example, one of the genes identified for social relationship satisfaction is NLGN1. NLGN1 is an important component of the synapse, and mutations in this gene increase the risk for autism, schizophrenia, and intellectual disability. Another locus in the HLA associated with social relationship satisfaction has been implicated in schizophrenia . I have also identified how these traits contribute to the risk for autism and other psychiatric conditions. Social traits – empathy and social relationship satisfaction – are negatively genetically correlated with autism, whereas non-social traits (STEM aptitude and systemizing) are positively genetically correlated with each other. However, social and non-social traits are not genetically correlated with each other. In other words, these studies reveal the presence of two independent sources of shared genetic risk for autism, one from the social domain, another from the non-social domain. Further, polygenic scores from systemizing predict other non-social behaviours in autism but not any social behaviour. This supports evidence from twin studies, and suggests that generating well-powered polygenic scores of these two orthogonal domains may help identify subgroups within the autism spectrum. I've also worked on the genetics of Asperger Syndrome and Mathematical aptitude using a pooled-DNA based GWAS approch.

In parallel, I've also worked on integrating genetic and neuroimaging data from multiple datasets in autism. I've identified gene sets that contribute to cortical morphology differences in autism. I've also worked on methylation datasets to identify methylation sites associated with autistic traits in the general population.

**Research outputs**
List up to 20 of your most significant research outputs, ensuring that at least five of these are from the last five years. For 10 of these outputs, provide a statement describing their significance and your contribution (up to 50 words per output).

Research outputs may include (but are not limited to):

- Peer-reviewed publications and preprints
- Datasets, software and research materials
- Inventions, patents and commercial activity

For original research publications indicate those arising from Wellcome-funded grants in **bold**, and provide the PubMed Central ID (PMCID) reference for each of these. Please refer to guidance notes.

*Please give citation in full, including title of paper and all authors*. Citations to preprints should state "Preprint", the repository name and the articles persistent identifier (e.g DOI).*

*(*All authors, unless more than 10, in which case please use 'et al', ensuring that your position as author remains clear.)*

Published (* indicates shared first authorship for equal contribution, # indicates corresponding author, articles in chronological order)

1.Warrier V# , Baron-Cohen S# . Genetic contribution to theory of mind in adolescence. Scientific Reports. 8(1):3465.

Significance: Deficits in theory of mind (the ability to attribute mental states to oneself and others) have been between psychiatric conditons and theory of mind, or other factors (such as the presence of a psychiatric conditions may interrupt normative development of theory of mind). This study validates some of the findings from a previous paper on cognitive empathy (Study 5), by using a theory of mind measure at a specific age (Age 13). We validate previous findings: shared genetics between theory of mind and measures of cognition, and lack of evidence for shared genetics between various psychiatric conditions and theory of mind.

Contribution: I was the analyst in this study. I designed the study, applied to gain access the data, conducted the genetic and statistical analysis, interpreted the results, and wrote the first draft of the manuscript.

2. Romero-Garcia R*, Warrier V*, Bullmore EB, Baron-Cohen S, Bethlehem RAI#. Synaptic and transcriptionally downregulated genes are associated with cortical thickness differences in children with autism. Molecular Psychiatry [Epub ahead of print]

Significance: Differences in cortical morphology—in particular, cortical volume, thickness and surface area—have been reported in individuals with autism compared to the general population. However, it is unclear if genes expressed in the brain are associated with these differences. To investigate this, we analysed MRI brain scans from more than 150 autistic children and compared them with MRI scans from similarly aged children without autism. We identified a set of genes associated with differences in the thickness of the cortex between autistic and non-autistic children. These genes were primarily involved in synaptic transmission, and enriched for genes dysregulated in the autism post-mortem cortex. This is the first study that links gene dysregulation with altered cortical thickness in autism.

Contribution: I co-designed the study with Romero-Garcia and Bethlehem. In particular, I designed and conducted the genetic analyses, and the interpretation of the results. I developed the methods and the mathematical reasoning behind the choice of parameters, and co-wrote the manuscript with Romero-Garcia and Bethlehem.

3. Warrier V#, Toro R, Chakrabarti B, Litterman N, Hinds D, Bourgeron T, Baron-Cohen S# . Genome-wide analyses of self-reported empathy: correlations with autism, schizophrenia, and anorexia nervosa. Translational Psychiatry. 8(1):35.

Significance: Difficulties in empathy have been identified in multiple different psychiatric conditions. However, these studies have typically been conducted in small sample sizes and may be confounded by other factors, limiting their interpration. To address this, we conducted a GWAS of empathy in a large sample (N ~ 50K), and investigated the shared genetics between empathy and psychiatric conditions. We identified a significant SNP heritability for empathy, suggesting that approximately a tenth of the variance can be attributed to all the SNPs en masse. We demonstrated a negative genetic correlation between empathy and autism, supporting the empathizing-systemizing theory of autism. We also identified a significant positive genetic correlation between empathy and anorexia nervosa, which validated our results from our work on cognitive empathy (Study 5). This is the first GWAS of empathy to date.

Contribution: I designed the study, conducted the analysis, interpreted the results, and wrote the first draft of the manuscript. I was the lead analyst of this study. 23andMe conducted the GWAS, and I conducted the subsequent analyses.

4. Warrier V# , Baron-Cohen S# (2017) The genetics of autism. eLS. John Wiley & Sons Ltd, Chichester [Review]

5. Warrier V# , Grasby K, Uzefovsky F, Toro R, Smith P, Chakrabarti B, Khadake J, Mawbey-Adamson E, Litterman N, Hottenga J, Lubke G, Boomsma D, Martin NG, Hatemi PK, Medland SE, Hinds DA, Bourgeron T, and Baron-Cohen S# (2017) A genome-wide meta-analysis of cognitive empathy: Heritability and correlates with psychiatric conditions, psychological traits and cognition. Molecular Psychiatry. [Epub ahead of Print] doi: 10.1038/s41380-018-0023-7

Significance: Difficulties in cognitive empathy, also sometimes defined as theory of mind, has been associated with multiple psychiatric conditions. In autism, several studies have demonstrated that autistic individuals, on average, have difficulties in cognitive empathy, and delayed development of theory of mind. Here, we conducted the largest GWAS of cognitive empathy (N ~ 90K). We identified one genome-wide significant locus associated with cognitive empathy in females. We demonstrate significant shared genetics with measures of cognition but did not identify shared genetics with autism. However, our study did identify a significant positive genetic correlation with anorexia nervosa, which has been later confirmed by our study on empathy (Study 3). Our results have been validated in another paper on theory of mind on which I was the lead analyst (Study 1).

Contribution: I was the lead analyst of this study. I designed the study, analysed the data, wrote the first draft of the manuscript and interpreted the results. 23andMe conducted the first GWAS, but I conducted all the subsequent analysis including the meta-analysis.

6. Warrier V#* , Bethlehem RAI*, Baron-Cohen S (2017) The Reading the Mind in the Eyes Test. Encyclopaedia of Personality and Individual Differences, edited by Virgil Zeigler-Hill and Todd K. Shackelford. 1:1-5. [Book Chapter]

7. Warrier V# , Baron-Cohen S# (2016) The genetics of mathematical aptitude. eLS. John Wiley & Sons Ltd, Chichester. [Review]

8. Warrier V* # , Chee V*, Smith PL, Chakrabarti B# , Baron-Cohen S (2015) A comprehensive meta-analysis of common genetic variants in Autism Spectrum Conditions. Mol Autism. 6:49

Significance: More than 500 genes have been associated with autism, largely through candidate gene association studies. However, these studies are typically underpowered, with limited correction for population stratification and other confounders. Further, as a group, these genes have been used to test for enrichment in multiple studies relating to autism. To investigates the reliability of the findings from candidate gene association studies, we conducted a comprehensive literature review and meta-analysis of SNPs in candidate genes associated with autism. Several findings emerged. First, less than 30 of these genes had been investigated in more than 3 independent studies. Second, none of the SNPs in these genes were replicably associated with autism in large GWAS studies. Third, effect sizes reported were considerably larger. This study provides a note of caution for results from candidate gene association studies in autism. This does not mean that these genes are not associated with autism, but just that there is insufficient evidence currently to link these genes with autism.

Contribution: I developed the idea and designed the study. I co-conducted the literature review and analysis with Chee, V. I wrote the first draft of the manuscript.

9. Warrier V* # , Chakrabarti B*, Laura Murphy, Chan A, Craig I, Mallya U, Lakatosova S, Rehnstrom K, Peltonen-Palotie L, Wheelwright S, Allison C, Fisher S and Baron-Cohen S# (2015) A pooled genome-wide association study identifies nominally significant loci for Asperger Syndrome. PLoS One. 10(7):e0131202

Significance: It is clear that autism is a heterogeneous condition. Here, we conducted the first GWAS of Asperger Syndrome, a subtype of autism that is associated with relatively preserved intelligence and verbal communication development. Unfortunately, this study was underpowered to identify significant variants associated with Asperger Syndrome.

Contribution: I conducted some of the analyses in this study (pooled-DNA GWAS analyses, and functional interpretation), and wrote the first draft of the manuscript.

10. Warrier V*, Di Napoli A# *, Murphy L, Baron-Cohen S, Chakrabarti B# (2015) Genetic variation rs17225178 in the ARNT2 gene is associated with Asperger Syndrome. Mol Autism. 6:9

11. Warrier V*, Di Napoli A# *, Baron-Cohen S, Chakrabarti B# (2014) Genetic variation in the oxytocin receptor (OXTR) gene is associated with Asperger Syndrome. Mol Autism. 5(1):48

12. Baron-Cohen S# , Murphy L, Chakrabarti B, Craig I, Mallya U, Lakatosova S, Rehnstrom K, Peltonen-Palotie L, Wheelwright S, Allison C, Fisher S and Warrier V# (2014) A genome wide association study of mathematical ability reveals an association at chromosome 3q29. PLOS One. 9(5):e96374

Significance: This is a pooled-DNA based genome-wide association study of mathematical ability, and one of the first studies to look into the genetics of mathematical ability. Unfortunately, this study was underpowered to detect any signifcant loci.

Contribution: I wrote edited a draft of the manuscript, contributed to the analyses, and conducted the revisions requested by the reviewers.

13. Durdiakova J # , Warrier V, Baron-Cohen S, Chakrabarti B# (2014) SLC25A12 is associated with Asperger Syndrome. Mol Autism. 5(1):25.

14. Durdiakova J # , Warrier V, Baron-Cohen S, Chakrabarti B# (2014) STX1A and Asperger Syndrome: a replication study. Mol Autism. 5(1):14.

15. Warrier V# , Baron-Cohen S, Chakrabarti B# (2013) Genetic variation in GABRB3 is associated with Asperger Syndrome and multiple endophenotypes relevant to autism. Mol Autism. 4(1):48

Significance: The GABA-ergic system has been implicated in autism in multiple different studies. We conducted a candidate gene analysis by investigating multiple SNPs in autism. We identified significant SNPs associated with autism. However, whilst this study (and a candidate gene approach in general) is underpowered, well powered studies have implicated GABRB3 in autism, and validated our findings.

Contribution: I conducted the analysis, and wrote the first draft of the manuscript. I was the lead analyst in this study.

16. Warrier V, Viera M, Mole SE# (2013) Genetic basis and phenotypic correlations of the neuronal ceroid lipofusinoses. Biochim Biophys Acta. (11):1827-30. [Review]

17. Guerreiro R, Bras JT, Vieira M, Warrier V, Agrawal S, Stewart H, Anderson G, Mole SE# (2013) CLN6 disease caused by the same mutation originating in Pakistan has varying pathology Eur J Paediatr Neurol. 17(6):657-60.

Preprints:

18. Warrier V#, Toro R, Chakrabarti B, iPSYCH-Broad autism consortium, the 23andMe Research Team, Grove J, Borglum A, Hinds DA, Bourgeron T, Baron-Cohen S#. Systemizing is genetically correlated with autism and genetically distinct from social autistic traits. BioRxiv. https://doi.org/10.1101/228254

Significance: Most studies to date have focussed on social difficulties in autism. However, there are considerable non-social difficulties and talent that is observed in autism. To this end, we focussed on the genetics of systemizing, which is an interest in systems, wherein autistic individuals are often perform better than the general population, on average. We identified three genome-wide significant loci, and identified a positive genetic correlation between autism and systemizing. Importantly, when considering social autistic traits, we did not identify significant genetic correlation for systemizing. In addition, polygenic scores for systemizing are significantly associated with other non-social traits (i.e. repetitive behaviour and stereotyped interests) but not social traits in a cohort of 2200 autistic individuals. These results provide the first molecular genetic evidence for the existence of distinct sets of shared genetic architecture in autism - one associated with social traits, and another associated with from non-social traits, underscoring what has been observed in twin studies.

Contribution: I designed the study, conducted the downstream analyses after obtaining GWAS results from 23andMe. I wrote the first draft of the manuscript.

19. Warrier V# , Bourgeron T, Baron-Cohen S# . Genome-wide association study of social relationship satisfaction: significant loci and correlations with psychiatric conditions. BioRxiv. https://doi.org/10.1101/196071

Significance: Poor quality and quantity of social relationships is one of the leading causes of mortality, comparable to smoking and alcohol. Yet, the genetic correlates of social relationship satisfaction, and by extension, dissatisfaction, is largely unknown. Here, we conducted a genome-wide association study of social relationship satisfaction in the UK Biobank. We identified two loci associated with family relationship satisfaction and friendship satisfaction, one of which has been previously implicated in schizophrenia. Social relationship dissatisfaction was positively genetically correlated with most psychiatric conditions tested, including schizophrenia and autism. We identified significant enrichment in genes expressed in the brain, in genes that are evolutionarily conserved, and genes that are intolerant to loss-of-function mutations. These results provide the first insights into the molecular genetics of social relationship satisfaction. I am collecting data from additional datasets to conduct a meta-analysis and use polygenic scores to predict social difficulties in childhood, adoloscence, and later adult life.

Contribution: I designed the study, conducted all the analyses, and wrote the first draft of the manuscript. I was the lead and only analyst in this study.

| | |
|---|---|
| Total number of peer-reviewed publications which you have authored/co-authored. Please exclude abstracts and literature reviews. | 15 |

**Current and recent research funding (including Wellcome Trust grants)**
Please list all held in the last five years and any key prior grants (list the most recent first). State the name of the awarding body, name(s) of grantholder(s), title of project, amounts awarded, your role in the project, and start and end dates of support. For all active grants, indicate the number of hours per week that are spent on each project.

2017 Marmaduke Shield Fund for imaging-genetics research (£13,000).

2017 Russel Sage Foundation Summer School in Social Science Genomics, Santa Barbara (Travel and workshop grant)

2016 World Congress of Psychiatric Genetics Early Career Investigator travel award

2016 Leena Peltonen School of Human Genetics, Wellcome Trust Sanger Institute

2016 IMFAR Diversity Student Award for IMFAR 2016 2015-18 Investigating Mathematical Talent and Autism using Genetics and Epigenetics (IMAGE) £1.8 million, Templeton World Charity Foundation, Inc.

2015 EU-AIMS National School of Advanced Study travel award

2015 British Psychological Society Travel Award for training at Institut Pasteur

2015 The Genetics Society Training Grant for training at Institut Pasteur

2015 EG Fearnside Fund for IMFAR 2015

2014 Guarantors of Brain Fund for IMFAR 2014

2014-17 St John's College Benefactors Scholarship and the Cambridge Trust Scholarship

2013-14 Cambridge Jawaharlal Nehru Memorial Trust and the Cambridge Trust Scholarship

2011-12 Commonwealth Scholarship



## 5. Details of proposal

**Project summary**
Please provide a summary of your proposed project.

Autism is a life-long developmental condition with a prevalence of approximately 1%, and heritability estimates of between 64-92%. It is polygenic, with variants across the frequency spectrum (from rare to common) contributing to risk. Considerable progress has been made in identifying rare variants in autism, but the largest genome-wide association study (GWAS) of autism (18K cases, 28K controls, in 2018, identified only five common variants associated with autism, compared to 179 in schizophrenia (40K cases, 65K controls). Polygenic scores account for only 2.45% of the variance in autism, despite between 30-50% of the variance in risk for autism being attributable to common variants, suggesting many more common variants remain to be found. In addition, autistic traits are normally distributed in the general population, but there is no well-powered GWAS of autistic traits. The proposed research aims to accelerate the discovery of common, low frequency, and copy number variants in autism and autistic traits. Specifically, we will: (1) Establish a UK-wide autism biobank (N = 10,000 cases), with links to electronic health records; (2) Conduct a GWAS of autism in 100K cases from around the world; and (3) Conduct a GWAS of autistic traits in the population in 250K individuals

**Aims and objectives**
Please describe the aims and objectives of your proposal and the approaches you will take to achieve these. Include milestones, if appropriate. (1,000 words maximum)

# Common Variant Genetics of Autism and Autistic Traits (GWAS) Consortium

**Principal Applicants:** Professors Simon Baron-Cohen (Autism Research Centre/ARC, Cambridge), Matthew Hurles (Wellcome Sanger Institute, Hinxton), David Rowitch (Pediatrics Department, Cambridge)**,** Daniel Geschwind (UCLA) and Dr Varun Warrier (ARC, Cambridge)

**Other Collaborators:** Professors Declan Murphy (KCL, London), Thomas Bourgeron (Pasteur Institut, Paris), Jakob Grove (Aarhus University, Denmark), Sarah Medland (QIMR - Berghofer), Nick Martin (QIMR - Berghofer), Dorret Boomsma (Vrije University, Amsterdam), John Perry (MRC Epidemiology Unit, University of Cambridge), Wendy Chung (Columbia University) for the SFARI SPARKS consortium, Anders Borglum (Aarhus University) and Mark-Daly (MIT-Harvard Broad Institute) for the PGC-iPSYCH consortium, Joseph Buxbaum (Mount Sinai Hospital, NY) for the Autism Sequencing Consortium, Declan Murphy (KCL, London) for the EU-AIMS consortium, Dr Carrie Allison (ARC, Cambridge).



**Aims and objectives**

Objective: To accelerate gene-discovery, genetic stratification, and biomarker identification of autism.
Aims:

1. To recruit 10K autistic individuals from the UK and where possible, their families;
2. To conduct genome-wide genotyping of all 10K individuals and use ancestry- and array-matched data from the UK Biobank as population controls for GWAS;
3. To conduct a GWAS and CNV meta-analysis of 100K autistic individuals with data collected from the UK (10K), the US (SPARKS, N = 50K), Australia (N = 10K), the iPSYCH and Psychiatric Genomics Consortium (N = 20K), the Autism Sequencing Consortium (5K) and other cohorts (5K) (Autism meta-analysis);
4. To conduct a multi-trait GWAS and CNV analysis of autism (100K) and autistic traits (250K, from the UK Biobank, and other sources);
5. To perform fine-mapping and identify functional genes by integrating gene expression (e.g., integration of human cell atlas and BRAIN initiative databases), meQTL, eQTL and chromatin interactions data from neural tissues;
6. To investigate how polygenic scores for autism alter normative developmental trajectories, and brain structure and function in adolescents and adults;
7. To develop polygenic scores for identifying subgroups based on deep phenotypic data and electronic medical health records, and use this for future recall-by-genotype studies; and
8. To identify modifiable genetic risk factors for autism using Mendelian randomization and related methods.

**Importance**

Autism is highly heritable, with twin and family-based heritability estimates between 64-92%[1–3]. Large-scale research efforts have advanced our understanding of autism genetics in three ways. First, it is clear that autism is highly polygenic, with recent estimates suggesting between 400-1000 genes may be involved[4–6]. Second, variation across the allele-frequency spectrum contributes to autism: rare genetic variants, including large copy number variations, are estimated to account for 10-30%[7–9] of the total risk, with large per-variant effect sizes, while common, inherited variation accounts for 15-50%[10–12] of the risk *en masse*, with each common variant contributing only modestly to the total risk[13]. Third, the phenotypic heterogeneity is tractable at a genetic level: Whole exome sequencing (WES) has identified specific clinical and behavioural phenotypes of autism attributable to variants in specific genes (e.g., *CHD8*[14], *ADNP*[15], and *PTEN*[16]), whereas emerging evidence from GWAS of autistic traits suggest at

least two distinct sources of shared risk with autism[17–19]. Currently 78 genes[a], 11 CNVs, and 5 SNPs[13] have been associated with high confidence with autism. Clearly, therefore, only a fraction of the total genetic risk for autism has been discovered. These genetic discoveries have provided insights into pharmacological targets with current clinical trials for mTOR inhibitors[20] for *PTEN*[b], *NF1, TSC1 and TSC2*, mGluR antagonists for *FMR1*[21], and rescue of autistic-like phenotypes in animal models for *SHANK3*[22,23] and *MECP2*[24].

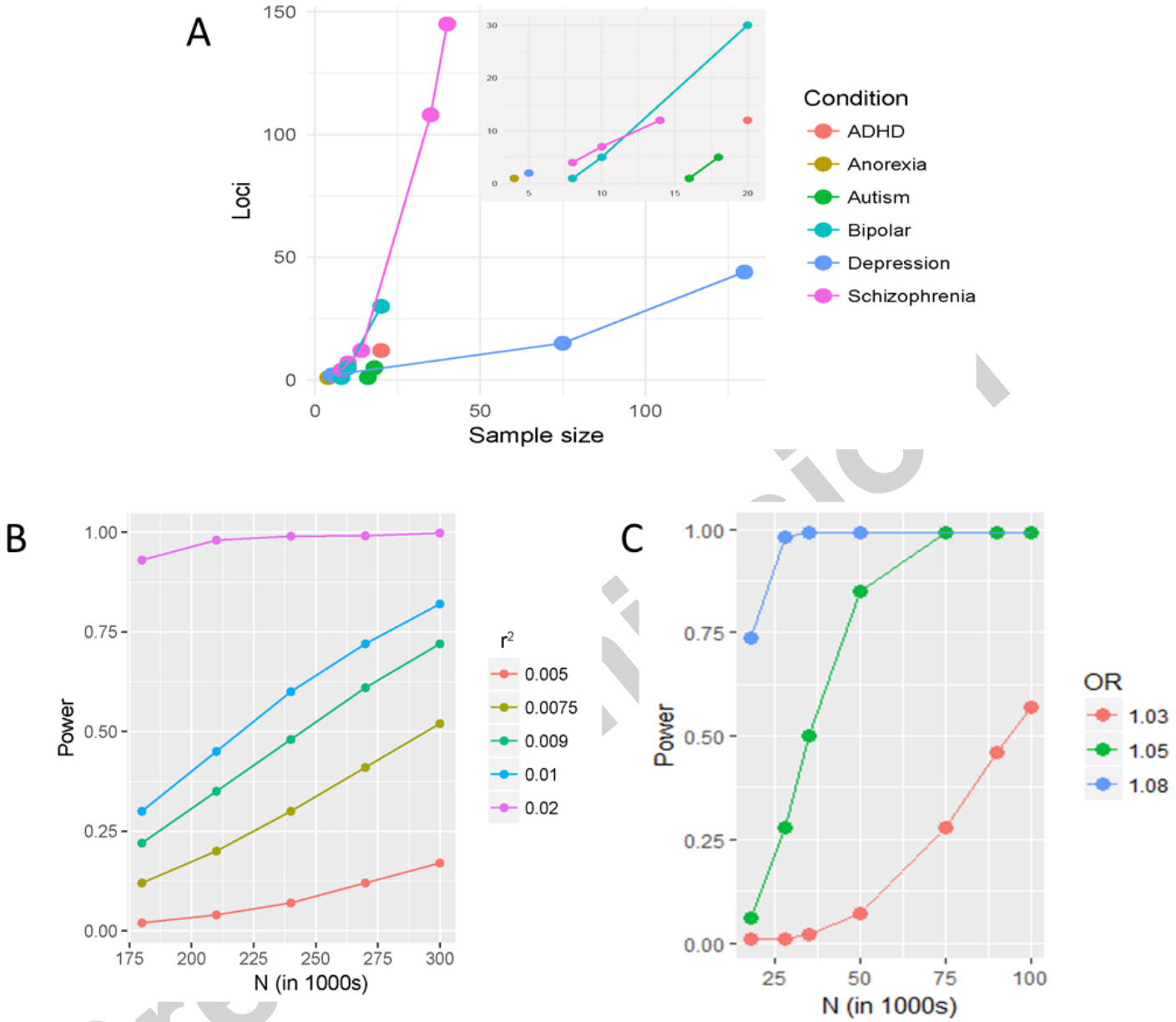
Despite these considerable advances in the genetics of autism, there are **6 outstanding challenges**: (a) We need larger sample sizes to robustly identify genetic variants associated with autism *(Figure 1A)* (Aims 1 – 3); (b) We need to systematically integrate functional information from developing and adult neural tissues and fine-map to identify casual variants and functional genes for further analysis (Aim 5); (c) We need well-powered polygenic scores to integrate genetic data into diagnosis and to better understand developmental, neural, and gene-environment effects in autism (Aim 6); (d) We need to disentangle the underlying genetic heterogeneity in autism (Aim 7); (e) We need to identify modifiable genetic risk factors for autism (Aim 8). These challenges can be addressed by conducting a well-powered GWAS and CNV analysis of autism. Our benchmark is the GWAS of schizophrenia on 40K cases, that identified novel 145 novel loci[25], whereas at present the largest GWAS of autism was only 18K cases. Finally, (f) many cases of idiopathic autism represent the extreme end of a continuum of autistic traits that are distributed across the population and there has not yet been a well-powered GWAS of autistic traits so this is needed (Aim 4). We expect our GWAS of 100K cases will identify at least 165 new common variants associated with autism. The relationship between sample size and variant discovery in psychiatric conditions is shown in *Figure 1*.

***Figure 1: The relationship between sample size and number of loci discovered in GWAS in psychiatry***



[a] http://spark-sf.s3.amazonaws.com/SPARK_gene_list.pdf

[b] https://www.ptenresearch.org/news/posts/2017/june/launch-of-clinical-trial-to-investigate-the-efficacy-on-neurocognition-and-behaviour-of-everolimus-in-children-and-adolescents-with-pten-mutations/




*A. Sample size to loci identified in psychiatric condition. Inset provides greater resolution for studies that have identified 20 or fewer loci. B. Statistical power of the autistic traits GWAS at various $r^2$ and sample sizes. C. Statistical power of the autism GWAS at various OR and sample sizes.*

**Methods**

*Sample collection*

We will collaborate with a team of international scientists to conduct the largest GWAS of autism, with 100K cases, of which 80K have already provided their DNA (*Figure 2a*). To achieve this goal, we will collect DNA from 10K autistic individuals and their immediate families from the UK, and genotype the probands. Participants will be recruited through the NIHR Clinical Research Network, Child Development Centres, autism research databases, and a media campaign. Similar methods have been used elsewhere to recruit autistic[26] and anorexic individuals[27]. Data from UK participants will be linked to electronic health and GP records, and will be phenotyped using additional measures where possible to provide deeper phenotypic and clinical information for stratification. The additional 10K in the UK will be useful because: 1. This will be the largest autism cohort with links to electronic records, enabling

investigation of deeper genotype-phenotype relationships, and investigation of the combined contribution of rare CNVs and polygenic risk to autism and co-morbidities. This high-level clinical phenotyping is absent in most existing large-scale cohorts of autism; 2. A substantial fraction of the cohort will be recruited from Child Development Centres, and longitudinal phenotypic data will be collected for these individuals, enabling deeper investigation into gene x environment effects; 3. Integrating parental phenotypic data, where available, alongside medical and genetic data from the probands will allow for future recall-by-genotype studies, genotyping of parents, and estimation of indirect genetic effects; 4. At larger sample sizes, variant discovery has a non-linear relationship to sample size, with greater returns. We estimate every 1000 cases above 70K will identify 4 additional loci. In sum, the extra 10K will add exponentially to gene discovery and polygenic prediction, and will enable deeper analysis of the genotype-phenotype effects and opportunity for recall-by-genotype; 5. This resource will be made available to other researchers who wish to use the anonymized phenotypic and genetic data or who want to recontact participants to conduct further downstream analysis including neuroimaging and cognitive testing, providing an excellent resource for multi-modal investigation of autism. We will, additionally, conduct a GWAS of autistic traits in 250K individuals from the general population using, primarily, the short version of the Autism Spectrum Quotient (AQ-10) that our lab developed[28] and which has been used widely internationally (*Figure 2c*). We will also integrate genetic data in cohorts that have been phenotyped using other measures of autistic traits as these are phenotypically correlated[29], and previous research on phenotypes such as subjective wellbeing and neuroticism has demonstrated the utility of combining multiple related traits for boosting statistical power (See Supplementary Note in reference[30]). This will identify variants associated with autistic traits (*Figure 2c*) and will inform variant discovery in the autism GWAS using multi-trait meta-analysis. The 250K individuals who have been genotyped will be drawn from the UK Biobank (200K) and other sources (see *Figure 2b*). This cohort is larger than the GWAS for autism as it is easier to recruit individuals from the general population through existing biobanks such as the UK Biobank. They will be invited to complete the AQ-10 if they have not already taken a related measure of autistic traits.

***Figure 2: How the samples will be assembled from existing cohorts and distribution of the AQ-10 scores in 700,000 individuals***

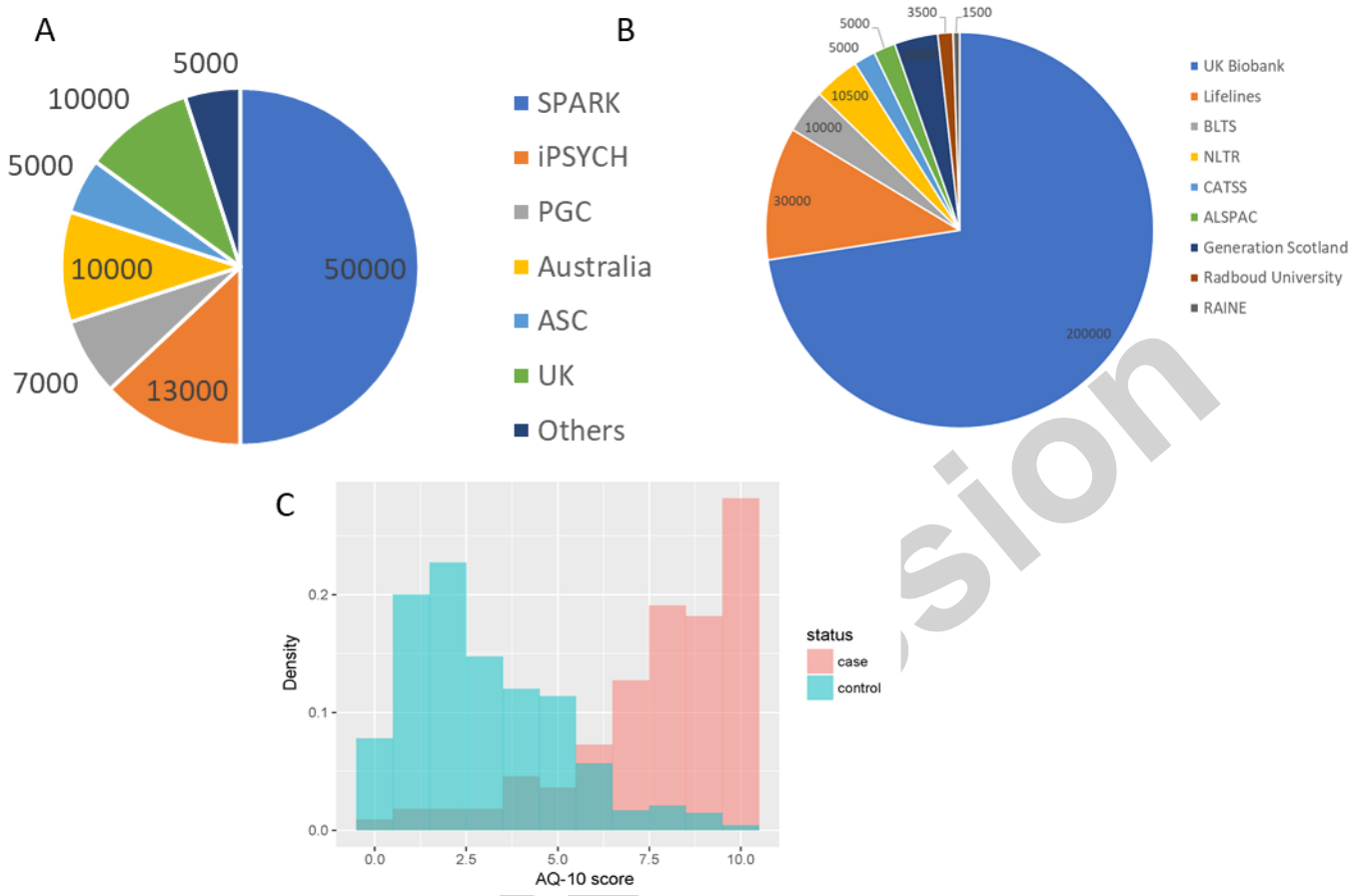



*Figure 2a provides the samples included in the case-control autism GWAS (cases only). Of these, samples from the Autism Sequencing Consortium (ASC), iPSYCH, and PGC have been collected and genotyped. Samples collection in SPARKS is in progress. New samples will include the UK 10K and the Australian 10K. The remaining 5K will be from other cohorts such as the EU-AIMS, DECODE, 23andMe, and Kaiser Permanente. Figure 2b provides the samples included in the autistic traits GWAS. Samples will primarily be from the UK Biobank. Figure 2c shows the distribution of AQ-10 scores in cases (pink) and controls (turquoise) in 700,000 individuals. The distribution histogram above shows the scores on the Autism Spectrum Quotient-10 (AQ-10) in autistic individuals and the general population in 700,000 individuals. An AQ-10 score greater than 6 is an excellent discriminator of case-control diagnosis (positive predictive power = 0.85).*

*Analytical plan*

All cases from the UK will be genotyped in the UK Biobank axiom array to enable the use of participants in the UK Biobank as population controls. We will integrate genetic data from case-control autism cohorts and from autistic traits from multiple different cohorts. We will then conduct GWAS and CNV analyses individually for both autism and autistic traits, and use methods to conduct multi-trait GWAS and CNV analyses. Integrating data from multiple different genomic functional categories, we will fine-map and prioritize causative variants and genes for downstream functional analysis. Following the primary analysis we will conduct the following analyses (*Figure 3*):

a. Fine-map to prioritize causal variants and integrate data from eQTL studies in the adult and foetal brain, chromatin interaction data, and methylation QTL to prioritize functional genes for downstream functional analysis.
b. Combine summary GWAS data from multiple related datasets, to investigate heterogeneity in effects and sex-specific effects in the UK autism GWAS.
c. Integrate polygenic scores for autism, related conditions, rare CNVs, electronic health records, and self-report measures to investigate genotype-phenotype correlations, heterogeneity, and additive contributions of common and rare variants in the UK cohort.
d. Investigate enrichment for specific tissue neural subtypes, cell populations, and gene sets, to further understand the biology of autism.
e. Conduct genetic causal investigation for autism and other related conditions using Mendelian randomization, latent causal modelling, and other methods. This will also help in identifying modifiable genetic risk factors for autism.
f. Investigate the contribution of polygenic scores in brain structure and function in adults (UK Biobank, max N = 100K) and adolescents (ABCD, N = 4.5K), and childhood developmental trajectories (ALSPAC and AddHealth, N = 10K).

This study will generate well-powered polygenic scores for autism and we will investigate the predictive power of the polygenic scores in independent samples. This can be used to inform diagnosis, particularly the impact on patient management in the UK cohort (specifically, using genetic scores to prioritize therapeutic strategies for autism and related co-morbidities), conduct recall-by-genotype studies, and investigate gene-by-environment effects. We will investigate the biological correlates of autism: which tissues, gene-sets, cell types, and developmental periods are enriched for common genetic risk for autism. We will further investigate heritability across subtypes, sex-specific effects, and heterogeneity using multiple sets of polygenic scores for related conditions and traits.

**Impact and Novelty:**
This will be the largest GWAS of autism and autistic traits to date, and will accelerate the identification of genetic loci and whole-genome genotyping of the entire cohort. We predict that this study will identify at least 165 new significant genetic loci and genes, assuming a similar slope of discovery to the current autism GWAS studies. We acknowledge that this is conservative as the relationship between sample size and locus discovery is not linear, and more likely to be a sigmoid function (*Figure 1a*). This will accelerate biomarker discovery and stratification using deep phenotyping, electronic health records, and polygenic scores, and will provide a central platform for autism research in the UK, accelerating discoveries by integrating data from genetics.

**Future studies:**
In addition to accelerating gene discovery in autism, this will create the largest autism biobank in the UK. All participants will be registered in a separate database and their biological material stored for future analysis. In addition, all participants will have the opportunity to sign up prospectively to the UK autism brain bank. DNA will be collected from immediate (1$^{st}$ degree) family members of autistic individuals. This will allow for recall-by-genotype for specific downstream studies (genetic sequencing, neuroimaging, and cognitive testing). It will further allow for combinatorial effects of common and rare variants, testing indirect effects, and investigating long-term longitudinal trajectories in autism. By integrating genetic scores and clinical information, this cohort will also allow for developing genetics-informed therapeutic strategies for autism and comorbidities in autistic individuals.

**Figure 3: Analytical plan**


Recruitment

- Rephenotype genotyped cohorts
- Meta-analyse with multiple measures of autistic traits

- UK recruitment via media campaign, coordination with autism researchers, child development centres, and letters via GP.
- Link to electronic health records, and additional questionnaire data collected.

## GWAMA

GWAMA conducted for autistic traits and autism separately. Data integration through multi-trait GWAS methods.

eQTL
meQTL
CCC

## Fine-mapping

Fine-mapping to prioritize variants and genes for functional analysis using multiple foetal and adult brain datasets

## Polygenic score prediction

Predictive power testing in hold-out samples, will be used for genotype-by-recall for future studies.

## Biological correlates

Enrichment in gene sets, tissue and cell types. Genetic correlation and heritability analysis. Mendelian randomization to test causality of variants.

## Stratification analyses

Sex-specific effects. Polygenic stratification using electronic health records, questionnaires, and polygenic scores for multiple related conditions.

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Queensland Institute of Medical Research

***Genetic Epidemiology Laboratory***
*Division of Genetics and Population Health*
*Professor Nick Martin*
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*Email: nick.martin@qimr.edu.au*

29 March 2018

Professor Simon Baron-Cohen, Dr Varun Warrier
Autism Research Centre
University of Cambridge

Dear Simon and Varun,

**Re: Wellcome Trust Grant on GWAS for Autism Spectrum traits**

Just a short note to say how strongly we support your application and how keen we are to collaborate with you on its aims. While there are some single major gene effects on autism, it is clear that much of the risk comes from polygenic inheritance which also affects endophenotypes which are normally distributed in the population. It follows that GWAS for those traits in large, unselected samples (much easier to collect than clinically defined case samples) can elucidate the genetics of autism, just as GWAS for blood pressure in the normal range has illuminated the genetics of hypertension. We in Australia have access to just such large unselected samples, already genotyped, and are already well embarked on collecting your AQ instrument for them, as well as the Eyes test and Social Reciprocity Scale on other subsets. We shall be delighted to contribute these data to your effort and look forward to collaborating.

We wish you success in your application.

Yours sincerely

Nick Martin

**Nicholas G. Martin, PhD, FAA**
**Professor and Senior Scientist**

SPARK
Igniting autism research
Improving lives

April 12th, 2018

Professor Simon Baron-Cohen, FBA
Fellow, Trinity College, Cambridge,
President, International Society for Autism Research,
Director, Autism Research Centre
Psychiatry Department
Cambridge University
Douglas House
18B Trumpington Road
Cambridge CB2 8AH UK
01223 746057
www.autismresearchcentre.com

Dear Simon,

I am pleased to write this letter of support for your Common Variant Genetics of Autism and Autistic Traits Consortium grant that aims to conduct a GWAS on 100,000 autistic individuals, and in parallel, a GWAS of autistic traits. This study will develop a resource of 10,000 autistic individuals and their families in the UK. This effort will complement the efforts of SPARK (https://sparkforautism.org/), which aims to recruit 50,000 autistic families in the United States.

Given the immense genetic heterogeneity in autism, a world-wide collaborative effort is needed to identify genetic variants that contribute to autism risk. In parallel, we need deeper phenotyping of autistic individuals to understand the source of the heterogeneity and link this to genetics. The autism common variant consortium aims to do precisely this by pooling together genetic data collected from 100,000 autistic individuals world-wide. This will be a significant and vital step towards using genetic scores for aiding diagnosis and informing therapeutics. As the principal investigator of SPARK, I will be delighted to collaborate on this study, and will be glad to share our genome wide genotyping and exome sequencing data and expertise for this study.

Best of luck with your application.

Sincerely,

Wendy Chung

Wendy Chung MD PhD
Director of Clinical Research, SFARI

DEPARTMENT OF BIOMEDICINE
THE FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

iPSYCH

To Whom It May Concern

**Letter of Support of the proposal "Common Variant Genetics of Autism and Autistic Traits Consortium"**

We are writing to express our full support of the proposal "Common Variant Genetics of Autism and Autistic Traits Consortium" and our enthusiasm for collaborating on this.

We are both part of iPSYCH (the Lundbeck Foundation Initiative for Integrative Psychiatric Research) as, respectively, PI (Anders Børglum) and lead analyst of the autism genetic investigations (Jakob Grove). In iPSYCH we are conducting genetic investigations of a Danish nation-wide birth cohort including 80,000 individuals of whom more than 50,000 suffer from psychiatric disorders, with a main focus on autism spectrum disorder (ASD) and other neurodevelopmental disorders.

Our recent GWAS paper (currently under review at Nature Genetics) which included data from iPSYCH and the PGC (Psychiatric Genomics Consortium) reported the first robustly identified common variants associated with ASD.

We have collaborated with Simon Baron-Cohen and Varun Warrier previously to conduct GWAS of traits related to autism. This includes a GWAS on empathy[1], social relationship satisfaction (under review), and on systemizing (under review).

In light of these recent successes, we are delighted to continue our fruitful collaboration on investigating the genetic basis of ASD.

With our warmest recommendations, sincerely,

Anders Børglum

Jakob Grove

**Department of Biomedicine**

**Centre for Integrative Sequencing, iSEQ**

**Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH**

**Anders D. Børglum**
MD, PhD
Professor
Centre Director

Dato: 10.04.2018

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Fax: +45 86123173
E-mail: anders@biomed.au.dk

Afs. CVR-nr.: 31119103





[1] V. Warrier et al., Transl. Psychiatry. 8 (2018), doi:10.1038/s41398-017-0082-6.

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MRC | Epidemiology Unit

***investigating the causes and prevention of diabetes and obesity***

**16th April 2018**

**Dear Professor Baron-Cohen**

**Re: Common Variant Genetics of Autism and Autistic Traits Consortium application**

I am writing in support of this highly collaborative grant that aims to conduct a Genome-Wide Association Study (GWAS) on autism and related quantitative traits at unprecedented scale. As you will be aware, only a tiny fraction of the heritable component of autism has been discovered to date, hugely limiting efforts to better understand the aetiology, disease sub-classification and prediction of this disorder. The proposed study will address this by collaboratively conducting the largest GWAS of autism to date, five times larger than the current GWAS of autism. In addition, there is a strong need to establish a UK-wide autism resource with deep-phenotyping and links to electronic health records, a resource which will enable future recall-by-genotype studies and the next generation of functional studies in this area.

I strongly support this endeavour and will be delighted to collaborate on this study.

John R.B Perry, Programme Leader (Growth and development)
MRC Epidemiology Unit, University of Cambridge.



MRC Epidemiology Unit
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Tel: +44 (0) 1223 769207 Fax: +44 (0) 1223 330316
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VU VRIJE UNIVERSITEIT AMSTERDAM

2500

Dr V. Warrier & prof S. Baron-Cohen

| DATE | OUR REFERENCE | YOUR LETTER DATED | YOUR REFERENCE |
|---|---|---|---|
| March 30, 2018 | | | |
| E-MAIL | TELEPHONE | ENCLOSURE(S) | |
| di.boomsma@vu.nl | +31 20 59 88787 | | |

Re: Application

Dear Prof Baron-Cohen,

It is my great pleasure to strongly support your application “Common Variant Genetics of Autism and Autistic Traits Consortium”.

Furthermore, as you know, the Netherlands Twin Register has collected information using a continuous scale to assess autism, in a general population sample and we will be delighted to contribute to analyses of phenotype-genotype associations using this resource.

I very much hope you may be successful with this application, which will greatly further our insights into the etiology of autism and autism spectrum disorder.

Yours sincerely,

Prof Dorret I. Boomsma, Ph.D.

Netherlands Twin Register, Dept Biological Psychology,
Vrije Universieit, Amsterdam
Van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands
Email: di.boomsma@vu.nl

**Institute of Psychiatry, Psychology & Neuroscience**
Department of Forensic & Neurodevelopmental Sciences (FANS)

**Prof Declan Murphy**
Head of Department

Box PO23
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Tel +44 (0)20 7848 0123
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KING'S College LONDON

Sackler INSTITUTE FOR TRANSLATIONAL NEURODEVELOPMENT
translating basic science into treatment advances

9 April 2018

**Letter of Support**

This is to confirm that I am happy to support **the Common Variant Genetics of Autism and Autistic Traits Consortium** collaborative grant proposal to the Wellcome Trust.

This highly collaborative initiative will help us identify many more common genetic variants and CNVs associated with autism. Polygenic scores developed from this study can be used to further investigate heterogeneity, gene-environment interactions and biological correlates.

The EU-AIMS and the IMI will be very happy to collaborate in this project where possible.

Sincerely,

Declan Murphy

Professor of Psychiatry and Brain Maturation.
Mortimer D Sackler Professor of Translational Neurodevelopment.
Director of the Sackler Institute of Translational Neurodevelopment, Institute of Psychiatry, King's College London.
Head of Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College London.

Icahn School of Medicine at Mount Sinai

**Joseph D. Buxbaum, Ph.D.**
*G. Harold and Leila Y. Mathers Professor*
*Director*, Seaver Autism Center for Research and Treatment
*Deputy Chair*, Department of Psychiatry
*Vice Chair for Mentoring*, Department of Psychiatry
*Chief*, Center of Excellence in Neurodevelopmental Disorders, Freidman Brain Institute

Departments of Psychiatry, Genetics and Genomic Sciences, and Neuroscience
Icahn School of Medicine at Mount Sinai
Mount Sinai Health System
One Gustave L. Levy Place, Box 1230
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Tel: (212) 241-0200
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April 16th, 2018

Prof. Simon Baron-Cohen
Dr. Varun Warrier
Autism Research Centre
Cambridge University
Cambridge, UK

Dear Simon and Varun,

This is to confirm that I am happy to support the **Common Variant Genetics of Autism and Autistic Traits Consortium** collaborative grant proposal to the Wellcome Trust.

As my group has shown, it is clear that, by far, the largest fraction of the genetic risk for autism can be attributed to polygenic inheritance (Gaugler et al, Nat Genet 2014, 46(8):881-5, "Most genetic risk for autism resides with common variation"). The current proposal to conduct a GWAS of autism in 100,000 individuals with autism, followed by a GWAS of autistic traits, will provide considerable insights into the biology of autism. Collecting deeper phenotypic measures, including links to medical records will certainly help in studying the underlying heterogeneity in autism.

As you know, I am the founder and communicating PI for the Autism Sequencing Consortium (ASC) which currently has whole exome data on close to 40,000 autism-related samples (quads, trios, and cases with ancestry matched controls). About 14,000 of these WES samples were completed by the ASC since our 2015 publication, and, through our collaboration with iPSYCH and Broad (Borglum, Daly, Grove, also collaborators on your proposal), we are incorporating about 10,000 WES samples from the Danish blood spot program, so much of the data is at yet unpublished. In the remaining 4 years of the grant we anticipate having at least 60,000 samples analysed by WES or WGS. For many of the samples in the ASC there is genotype data available through the ASC or other databases, however, for over half the recent samples that genotyping is in process. In short, we expect to be able to add GWAS data for ~5,000 samples in the next year and additional GWAS data for another ~10,000 samples within four years. All data will be available to you. We have additional phenotypic data (beyond a categorical autism diagnosis) for most ASC samples.

Furthermore, we have, as one of our three current ASC aims, the plan to: "Use results from common and rare variant studies to describe the interplay of such variation in ASD risk." In this Aim, we will integrate WES variants with data from WGS and GWAS to produce a complete picture of the genetic architecture of ASD, to improve gene discovery, and to refine clinical interpretation. This is an area where we would be happy to collaborate further with you. For many of the samples in existing cohorts, we have already organized the WES and GWAS data. In addition, going forward, we will run the Global Screening Array (GSA) for all ASC sample that are to be run with WES, and we even have some capacity to run WES on additional samples.

I look forward to a strong collaboration and to being part of your very exciting and critical study. I will be available for regular calls and annual meetings. In short, I strongly support this endeavour and will be delighted to collaborate on this study.

Sincerely,

Joseph Buxbaum, PhD

*Edward Bullmore PhD FRCP FRCPsych FMedSci*
*Professor of Psychiatry*
*Head of Department*

**Department of Psychiatry**

6th April 2018

**To Whom It May Concern**



**Letter of support**

This is to confirm that I am happy to support **the Common Variant Genetics of Autism and Autistic Traits Consortium** collaborative grant proposal to the Wellcome Trust.

Twin and familial studies have clearly demonstrated that autism is heritable. While studies have identified rare genetic variants associated with autism, only a handful of common genetic variants have been associated with autism. This is a critical gap in our understanding of the biology of autism. To address this, Simon Baron-Cohen and colleagues have developed an ambitious proposal to conduct a genome-wide meta-analysis using data from multiple autism cohorts world-over and, in parallel, cohorts with information on autistic traits. This will considerably advance our understanding of the biology of autism and autistic traits.

Power calculations have suggested that the study will identify more than 160 genetic loci associated with autism, providing a significant increase in the statistical power of polygenic scores. In addition, the development of a UK-wide genotyped autism cohort with links to electronic medical health records will be of great significance to the scientific and autistic community. This will allow for recall by genotype approaches in a number of downstream studies such as exome or whole-genome sequencing, neuroimaging, or cognitive testing. It will also enable deeper interrogating of genotype-phenotype correlations by integrating data from a number of questionnaires measuring traits related to autism, electronic medical health records, and genotypes.

The Autism Research Centre has a long-standing interest in investigating the dimensional nature of autism. Over the last few years, it has been active in investigating the genetic correlates of autism and autistic traits, and has developed close collaborations with leading researchers in the field of psychiatric genetics both in the UK and abroad. The ARC also closely works with industry experts in the field – Illumina, Inc., and 23andMe, Inc. The Department of Psychiatry has been rated one of the UK's nationally leading research groups in the three most recent Research

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Assessment Exercises, and it plays a leading role in the internationally excellent Cambridge Neuroscience community of researchers in neuroscience and mental health.

Yours sincerely

Ed Bullmore
Head of Department



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Institut Pasteur

*Paris, le 24/04/18*

Thomas Bourgeron
Institut Pasteur
25, Rue du Docteur Roux
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Tel : 33 1 40 61 32 16
Fax: (33) 1 40 61 39 53
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To whom it may concern,

I am writing in my capacity as the Director of the Human Genetics and Cognitive Functions Unit from the Neuroscience Department of the Institut Pasteur. My group gathers psychiatrists, neurobiologists and geneticists to better understand the social brain and the conditions that affect it such as autism.

It is my great pleasure to support the grant application for the Wellcome Trust proposed by Prof. Simon Baron-Cohen and Varun Warrier. I think that this project is crucial if we want to accelerate the research on the genetic architecture of autism and autistic traits. The establishment of a UK-wide autism biobank that's linked to electronic medical health records is mandatory if we want to tackle the genetic and phenotypic heterogeneity of autism. This project will also foster the collaboration with other autism researchers worldwide.

Their proposal includes a large-genome wide meta-analysis association (GWAMA) study of autism in 100K individuals, and recruit 10K new cases of autism from the UK into this; they will also conduct a GWAMA of autistic traits in the general population in 250K individuals. Following these two GWAMAs, they will identify causal variants for functional analysis using fine mapping. Their analysis pipeline will investigate enrichment in tissues, cell types, and neural networks as well as a deep investigation of the clinical heterogeneity within the autism cohort, in particular, mechanisms that contribute to sex differences and large variances in cognitive ability within the autism spectrum.

My group is already collaborating with Prof. Simon Baron-Cohen and Varun Warrier on different projects and this new application will clearly addresses key questions that are still not understood. For example, we have, still very few information on the combination of *de novo*, rare and common variants that will impact on the severity of the clinical symptoms. It has now been repeatedly observed that the same genes can be risk factors for different neuropsychiatric conditions. What we do not understand, however, is how the same genetic 'risk' can have such divergent outcomes.

As the PI of the genetics Work Package of the EU-AIMS funded by the European Union, I consider this application as an remarkable opportunity to have a complementary approach to this complex field of research.

Sincerely yours,

Prof. Thomas Bourgeron

Member of the French Academy of Sciences

Professor at the University Paris Diderot

Director of the Unit "Human Genetics and Cognitive Functions "

*Institut Pasteur*
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*75724 Paris Cedex 15*

Mark J. Daly, Ph.D.
*Chief*
Analytic and Translational Genetics Unit
Massachusetts General Hospital

*Associate Professor of Medicine*
Harvard Medical School
Massachusetts General Hospital

*Institute Member*
*Co-Director, Program in Medical and Population Genetics*
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April 10, 2018

Dear Review Committee:

This letter is written to confirm my strong support for **the Common Variant Genetics of Autism and Autistic Traits Consortium** collaborative grant proposal to the Wellcome Trust.

I am very enthusiastic to collaborate on this study as it is important and complementary to existing efforts and will move the field ahead. As you know, the Psychiatric Genomics Consortium has been actively involved in delineating the polygenic risk for autism. However, we simply do not have the existing collections nor convenient strategies from biobanks to advance the autism effort forward in the way it needs to be. To this end, this is a timely and significant proposal that will advance our understanding of autism biology. Further, as the Director at the Institute for Molecular Medicine Finland (FIMM) I plan to initiate activities in Finland that can make meaningful contributions to this effort as well.

I strongly support this important proposal and look forward to contributing in whatever way possible.

Sincerely,

Mark Daly, PhD

*Supporting autism research at Cambridge*
www.autismresearchtrust.org

**The Autism Research Trust**
19-21 Cookridge Street
Leeds LS2 3AG
www.autismresearchtrust.org
info@autismresearchtrust.org

Wellcome Trust
Gibbs Building
215 Euston Road
London NW1 2BE

17 April 2018

To whom it may concern,

**The Common Variant Genetics of Autism and Autistic Traits Consortium**

I am writing on behalf of the Autism Research Trust in support of the Common Variant Genetics of Autism and Autistic Traits Consortium. The study aims to conduct a GWAS on 100,000 autistic individuals and a GWAS on autistic traits.

We believe this is a very important project which will significantly advance our understanding of the genetics of autism, and therefore the Autism Research Trust would look to support the project by funding the data collection and acquisition for the GWAS of autistic traits (£50,000), should this application be funded by the Wellcome Trust.

Yours faithfully,

Charlotte Anderson
Chief Executive

**Collaborative approach**
Briefly outline why a collaborative approach is required to deliver the project, and describe the roles of all applicants.

The data and analytical methods required to identify common genetic variants associated with autism are immense. The data cannot be generated by a single lab and concerted efforts are required on a global scale to recruit, phenotype, and genotype participants. This series of studies could not be achieved without the Cambridge ARC collaborating with the Sanger Centre. The ARC will have the responsibility of cohort recruitment, and the Sanger will have the responsibility of the genotyping.

Genetic and statistical analysis for the UK wing of the study will be conducted by **Hurles and Perry**, along with **Warrier**. They will engage with multiple child development centres and other autism research labs to accelerate recruitment. **Baron-Cohen** is a world-leading autism researcher, the Director of the Autism Research Centre, and has funds to recruit 1K autistic individuals already from the Templeton World Charity Foundation and the Autism Research Trust. **Hurles** leads the DDD study, a UK-wide collaborative genetic study on undiagnosed developmental disorders. He is also the head of Human Genetics at the Wellcome Sanger Institute, who will contribute free data storage and super computing facilities. **Perry** is the co-leader of the growth and development programme at the MRC Epidemiology Unit and has experience leading large-scale population genetics studies so will add his statistical expertise. **Rowitch** is Head of the Department of Pediatrics in Cambridge University and Director of the Pediatric theme in the NIHR Biomedical Research Centre in Cambridge, and has established a network among all Consultant paediatricians in the East of England, which will (i) accelerate the collection of 10K cases of autism in the UK and (ii) provide linkage to NHS medical records. **Warrier** will coordinate with existing genotyped cohorts to re-phenotype participants using measures of autistic traits. **Geschwind** heads the UCLA Centre for Autism Research and Treatment, and oversees the Autism Genetic Research Exchange. He has worked extensively on transcriptional data and CCC data that will be used to inform fine-mapping. We will also have a team of advisors or those who can bring cohorts: **Murphy**, **Bourgeron, Daly**, **Buxbaum, Grove**, **Borglum**, **Medland, Martin**, **Boomsma** and **Chung.**

**Additional information**
Please provide any other relevant information in support of your application.

Informed consent will be obtained from participants or guardians to enable access to anonymized information to researchers. Researchers will need to provide ethical approval for the study, and the study will be internally reviewed by the UK Autism Biobank PIs. Once approved, data will be provided at a nominal cost that will cover costs associated with data transfer and database management. All data will be stripped of identifiable information, and participants will be identified by unique IDs. Anonymized data will be stored on the University of Cambridge servers. Identifiable data will be stored in the Secure Data Hosting Service in the University of Cambridge. Biological samples will be stored at the UK Biocentre, and funds have been requested for storage for 10 years. Due to the limited quantity of DNA that will be collected, biomaterials will not be made available to researchers outside the consortium. Funds to phenotype genotyped individuals and obtain data for the GWAS on autistic traits have been requested from the Autism Research Trusts. These funds will be made available to the researchers should this proposal be awarded. Simon Baron-Cohen and Varun Warrier have received in principle approval to include a measure of autistic traits in the UK Biobank. The full proposal will be presented to the Enhancement Committee in September. The researchers are also in talks with 23andMe to include a measure of autistic traits. In principle approval for data access for other cohorts in which autistic traits has been measured has been obtained from the relevant PIs already.

## 6. Approximate costs

**Currency requested**
Please select the currency requested for award

GBP - Pound Sterling

| | |
|---|---|
| Salaries | 1,142,678 |
| Materials and consumables | 1,842,508 |
| Equipment | 0 |

| | |
|---|---|
| Other significant costs | 42,500 |
| **Total** (£) | 3,027,686.00 |