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Nathan Gerald Skene

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Current appointment

UK Dementia Research Institute, Imperial College, London **Feb 2019--current**

Edmond and Lily Safra – UK DRI Fellow developing my own research programme

Previous appointment

Karolinska Institute, Stockholm **2016--2019**

Supervisor: Dr Jens Hjerling-Leffler

- Development of methods for inferring the cellular basis underlying complex genetic traits. Found strong relationships between cell type transcript specificity and trait association for numerous conditions. Key result shows that Schizophrenia is independently caused by three cell types: Pyramidal neurons, Medium Spiny Neurons and Reln+ Cortical Interneurons. Five papers applying this to Schizophrenia, Intelligence, Alzheimer's, Insomnia and Neuroticism published in Nature Genetics.

- Single cell transcriptome analysis of interneurons found in CA1 region of hippocampus & dorsal striatum. Developed new protocol for capturing healthy cells from adult animals. Applied novel statistical approaches for analysing variability within cell types. Published in Plos Biology and Cell Reports.

- Spatial transcriptomics. Development of analysis methods for highly multiplexed in situ RNA "sequencing" using padlock probes. Preprint on bioRxiv, under review at science. Further publication in preparation applying the method to three CNV models of disease.

- Initiated a collaboration with 23andMe and the Michael J Fox foundation through writing a competitively evaluated project proposal which gained us access to their data on Parkinsons. Resulting analysis is under review at Nature.

University of Edinburgh, Centre for Clinical Brain Sciences **2014-2016**

Supervisor: Prof Seth Grant

- Developed a new analytical method for analysis of time series gene expression data which indicated a transcriptional basis for adult onset of psychiatric disorders. Published in eLife.

- Developed an algorithm for testing whether genetic/transcriptomic gene sets are enriched in specificity for particular cell types (utilising data from single cell RNA sequencing). Demonstrated that this enables significant advances in understanding of disease associated genomic data. Published in Frontiers in Neuroscience. Code was released via Bioconductor coincident with publication.

- Utilized JAGS to develop a Bayesian approach to the analysis of high throughput imaging data wherein it was necessary to control for differences in age, as well as variation between individuals and brain regions. Code was incorporated into the lab's analytical pipeline and results were published in Neuron.

Education

University of Cambridge/Wellcome Trust Sanger Institute **2009-2014**
PhD in Molecular Biology, supervised by Professor Seth Grant

- Developed novel statistical approaches to analysis of a transcriptome datasets involving microarray and miRNA-Seq analysis of hippocampal RNA from 35 mutant lines. Investigated the expected frequency with which gene sets should be detected as differentially expressed across multiple cohorts, if each cohort is assumed to be independent. Used this technique to test whether there is differential expression resulting from synaptic dysfunction.

- Demonstrated that Support Vector Machines trained on gene expression data from the brains of mice and humans are able to accurately predict biological age. Extended this to show that predictors trained on sedentary cohorts, predict athletic individuals to be younger.

University of Cambridge (MPhil in Computational Biology) **2008-2009**

University of Reading (BSc AI and Cybernetics --- First class) **2005-2008**

Honours and Awards

UCL Early Career Neuroscience (Advanced) award 2019;
Edmond and Lily Safra – UK DRI Fellowship, 2019;
Wellcome Trust 4 Year PhD Studentship, 2009;
Fulbright International Science & Technology Award [Offered, 2009]: 10,000 applicants for 40 awards, with selections on the basis of scientific credentials and ambassadorial qualities;
EPSRC Postgraduate Scholarship, 2008; **Nuffield Foundation, Summer Research Grant**, 2007

Technical & Biological Skills

- Analysis of complex genetic traits using LD Score Regression and MAGMA
- Statistical modelling with both frequentist and bayesian approaches within the R environment
- Application of machine learning and data visualisation techniques, i.e. SVM, tSNE
- Programming in interpreted, object-oriented languages and event-driven languages. In recent years I have most often used R and Matlab, but also have worked with C++/C#, Python, VB, Perl and PhP.
- Automated image segmentation and analysis using the MATLAB Image Processing Toolbox
- Parallelisation of computationally complex task using computing clusters
- Single cell RNA sequencing & tissue disassociation; RNA sequencing; In Situ RNA sequencing using padlock probes; mouse handling and colony management; Western blotting; qRT-PCR; immunohistochemistry; multi-fluorescent in situ hybridisation; stereotaxic injections

First Author Publications:

- "Genetic identification of brain cell types underlying schizophrenia", ***Nathan G. Skene****, Julien Bryois, Trygve E. Bakken, Gerome Breen, James J. Crowley, Helena Gaspar, Paola Giusti-Rodriguez, Rebecca D. Hodge, Jeremy A. Miller, Ana Munoz-Manchado, Michael C. O'Donovan, Michael J. Owen, Antonio F. Pardinas, Jesper Ryge, James T. R. Walters, Sten Linnarsson, Ed S. Lein, Patrick F. Sullivan, Jens Hjerling-Leffler*, Nature Genetics, June 2018

- "Genetic Identification of Cell Types Underlying Brain Complex Traits Yields Novel Insights Into the Etiology of Parkinson's Disease", *Julien Bryois*, **Nathan G. Skene***, Thomas Folkmann Hansen, Lisette J.A. Kogelman, Hunna J. Watson, Eating Disorders Working Group of the Psychiatric Genomics Consortium, International Headache Genetics Consortium, The 23andMe Research Team, Leo Brueggeman, Gerome Breen, Cynthia M. Bulik, Ernest Arenas, Jens Hjerling-Leffler, Patrick F. Sullivan*, [* = co-first], Jan 2019, bioRxiv (out for review at Nature)

- "A genomic lifespan program that reorganises the young adult brain is targeted in schizophrenia", ***N. Skene**, M. Roy, T. le Bihan, S. Grant*, Sept 2017, eLife

- "Identification of Vulnerable Cell Types in Major Brain Disorders Using Single Cell Transcriptomes and Expression Weighted Cell Type Enrichment", ***N. Skene** & S. Grant, January 2016,* Frontiers in Neuro. - Highest altmetric score of any article of this age from this journal

Contributing Author Publications:

- "Biological annotation of genetic loci associated with intelligence in a meta-analysis of 87,740 individuals", *J. Coleman, J. Bryois, H. Gaspar, P. Jansen, J. Savage, **N. Skene**, R. Plomin, A. Muñoz-Manchado, S. Linnarsson, G. Crawford, J. Hjerling-Leffler, P. Sullivan, D. Posthuma, Gerome Breen*, Molecular Psychiatry, Jan 2018

- "Classes and continua of hippocampal CA1 inhibitory neurons revealed by single-cell transcriptomics", *K Harris, C Gonzales, H Hochgerner, **N Skene**, L Magno, L Katona, P Somogyi, N Kessaris, S Linnarsson, J Hjerling-Leffler*, Plos Biology, June 2018

- "Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence", *J Savage, P Jansen, S Stringer, K Watanabe, J Bryois, C Leeuw, M Nagel, S Awasthi, P Barr, J Coleman, K Grasby, S Hägg, A Hammerschlag, J Kaminski, I Karlsson, R Karlsson, E Krapohl, M Lam, S Linnarsson, A Muñoz-Manchado, M Nygaard, E Quinlan, C Reynolds, **N Skene**, B Webb, T White, H Young, D Zabaneh, G Abecasis, O Andreassen, G Breen, L Christiansen, B Debrabant, D Dick, J Eriksson, A Heinz, J Hjerling-Leffler, A Ikram, K Kendler, J Lahti, T Lencz, N Martin, S Medland, W Ollier, A Palotie, A Payton, N Pedersen, N Pendleton, R Plomin, T Polderman, S Ripke, G Schumann, S Sluis, O Smeland, P Sullivan, H Tiemeier, S Vrieze, M Wright, D Posthuma,* Nature Genetics, June 2018

- "Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways", *M Nagel, P Jansen, S Stringer, K Watanabe, C Leeuw, J Bryois, J Savage, A Hammerschlag, **N Skene**, A Muñoz-Manchado, S Linnarsson, J Hjerling-Leffler, T White, H Tiemeier, T Polderman, P Sullivan, S Sluis, D Posthuma,* Nature Genetics, June 2018

- "Architecture of the Mouse Brain Synaptome", *F Zhu, M Cizeron, Z Qiu, R Benavides-Piccione, M Kopanitsa, **N Skene**, J DeFelipe, E Fransén, N Komiyama, S Grant, Neuron, August 2018*

- "Postsynaptic proteome composition localizes functions within the human neocortex", *M Roy, O Sorokina, **N Skene**, C Simonnet, F Mazzo, R Zwart, E Sher, C Smith, J Armstrong and S Grant*, Nature Neuroscience, Dec 2017

- "Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways", *P. Jansen, K. Watanabe, S. Stringer, **N. Skene**, J. Bryois, A. Hammerschlag, C. de Leeuw, J. Benjamins, A. Muñoz-Manchado, M. Nagel, J. Savage, H. Tiemeier, T. White, 23andMe, J. Tung, D. Hinds, V. Vacic, P. Sullivan, S. Sluis, T. Polderman, A. Smit, J. Hjerling-Leffler, E. Someren, D. Posthuma, [Accepted by Nature Genetics, pre-print available on BioRxiv]*

- "Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk", *I Jansen, J Savage, K Watanabe, J Bryois, D Williams, S Steinberg, J Sealock, I Karlsson, S Hagg, L Athanasiu, N Voyle, P Proitsi, A Witoelar, S Stringer, D Aarsland, I Almdahl, F Andersen, S Bergh, F Bettella, S Bjornsson, A Braekhus, G Brathen, C Leeuw, R Desikan, S Djurovic, L Dumitrescu, T Fladby, T Homan, P Jonsson, A Rongve, I Saltvedt, S Sando, G Selbak, N Skene, J Snaedal, E Stordal, I Ulstein, Y Wang, L White, J Hjerling-Leffler, P Sullivan, W van der Flier, R Dobson, L Davis, H Stefansson, K Stefansson, N Pedersen, S Ripke, O Andreassen, D Posthuma, Nature Genetics, Jan 2019*

- "A spatial atlas of inhibitory cell types in mouse hippocampus", *Xiaoyan Qian, Kenneth D Harris, Thomas Hauling, Dimitris Nicoloutsopoulos, Ana Munoz Manchado,* ***Nathan Skene****, Jens Hjerling-Leffler, Mats Nilsson, [Submitted to Science, pre-print available on bioRxiv, doi.org/10.1101/431957]*

- "Stress-Induced Lipocalin-2 Controls Dendritic Spine Formation and Neuronal Activity in the Amygdala", *Skrzypiec AE, Shah RS, Schiavon E, Baker E,* ***Skene N****, Pawlak R, Mucha M, April 2013,* PloS One

- "TNiK Is Required for Postsynaptic and Nuclear Signaling Pathways and Cognitive Function", *Coba MP, Komiyama NH, Nithianantharajah J, Kopanitsa MV, Indersmitten T,* ***Skene NG****, Tuck EJ, Fricker DG, Elsegood KA, Stanford LE, Afinowi NO, Saksida LI, Bussey TJ, O'Dell TJ and Grant SGN, August 2012,* The Journal of Neuroscience

- "Diversity of Interneurons in the Dorsal Striatum Revealed by Single-Cell RNA Sequencing and PatchSeq", *A Muñoz-Manchado, C Gonzales, A Zeisel, H Munguba, B Bekkouche,* ***N Skene****, P Lönnerberg, J Ryge, K Harris, S Linnarsson, J Hjerling-Leffler, Cell Reports, August 2018*

- "Molecular architecture of the mouse nervous system", *Amit Zeisel, Hannah Hochgerner, Peter Lonnerberg, Anna Johnsson, Fatima Memic, Job van der Zwan, Martin Haring, Emelie Braun, Lars Borm, Gioele La Manno, Simone Codeluppi, Alessandro Furlan,* ***Nathan Skene****, Kenneth D Harris, Jens Hjerling Leffler, Ernest Arenas, Patrik Ernfors, Ulrika Marklund, Sten Linnarsson, Cell, August 2018*

- "Synaptic combinatorial molecular mechanisms generate repertoires of innate and learned behavior", *Noboru H Komiyama, Louie Van De Lagemaat, Lianne E Stanford, Charles M Pettit, Douglas H Strathdee, Karen E Strathdee, David Fricker, Eleanor J Tuck, Kathryn A Elsegood, Tomas J Ryan, Jess Nithianantharajah,* ***Nathan G Skene****, Mike DR Croning, Seth GN Grant, bioRxiv, Dec 2018*

Patents: UK Patent no. GB1517219.0 filed October 2015

Software: *Expression Weighted Cell-type Enrichment R package: (github.com/NathanSkene/EWCE)*
MAGMA Celltyping R package: (github.com/NathanSkene/MAGMA_Celltyping)

Reviewer for journals: Molecular Psychiatry; Nature Communications; Nature Neuroscience; Genes, Brains and Behaviour; Biological Psychiatry