BIOGRAPHICAL SKETCH

NAME: Geschwind, Daniel H.

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Distinguished Professor in Residence

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Dartmouth College, Hanover, NH	A.B.	06/1982	Chemistry & Psychology
Yale Univ. School of Medicine, New Haven, CT	M.D., Ph.D.	05/1991	Medicine, Neurobiology
UCLA School of Medicine, Los Angeles, CA	Internship	06/1992	Internal Medicine
UCLA School of Medicine, Los Angeles, CA	Residency	06/1995	Neurology
UCLA School of Medicine, Los Angeles, CA	Fellowship	06/1997	Neurogenetics

A. Personal Statement

Following medical school, formal training as a PhD in neurobiology, post-graduate training in genetics, and clinical neurology residency, I founded the neurogenetics program at UCLA in 1997. Since then, my laboratory has focused on integrating genetics and genomics with basic neurobiology to develop a more systematic understanding of neurodevelopmental and neurodegenerative disorders. This includes identifying genes causing autism spectrum disorder (ASD) and developing a systems biology framework for integrating genetic and genomics findings to understand disease mechanisms. More broadly, we have worked to apply a range of functional genomics techniques to elucidate the mechanisms of complex CNS disease, as well as the development and application of new analytic methods that define the underlying network organization in multi-dimensional data, permitting integration of genomic and genetic data with phenotype data on a large scale. I have also worked to develop internationally recognized shared scientific resources for neuropsychiatric disease research, as well as inclusion of under-represented groups in genetics research, playing a leading scientific role in the development of the Autism Genetic Resource Exchange (www.AGRE.org). I am the chair of the NIH funded PsychENCODE consortium, which is producing a public resource of multi-dimensional genomic data for understanding gene regulation and disease risk for a range of brain disorders. In my role as Director of the UCLA Institute for Precision Health (IPH), I have led institutional efforts to organize and implement large-scale DNA biobanking and genotyping, and mobilization of the EHR for genomic medicine across diverse ethnicities. The IPH articulates strongly with multiple CTSI-supported efforts, especially in mobilizing informatics, community outreach and diversity efforts.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019-present Honorary Affiliate Professor, Faculty of Health and Medical Sciences, University of Copenhagen
2017-present Director, Institute for Precision Health at UCLA
2016-present Senior Associate Dean & Associate Vice Chancellor, Precision Medicine, UCLA
2016-present Clinical and Translational Science Institute (CTSI) Associate Director, Precision Health, UCLA
2016-2017 Visiting Professor, Institute of Biological Psychiatry, Sct. Hans; iPSYCH; Center for Basic and Translational Neuroscience, University Copenhagen
2012 Wiersma Visiting Professor, California Institute of Technology, Pasadena, CA
2009-2010 Visiting Professor, Institute of Psychiatry, Kings College, London, UK
2009-2010 Visiting Scientist, Wellcome Trust Sanger Institute, Hinxton-Cambridge, UK
2007 Kavli Distinguished Visiting Professor, University of California, San Diego
2005-present Professor, Departments of Neurology and Psychiatry & Biobehavioral Sciences
2005-present Gordon and Virginia MacDonald Distinguished Professor, Departments of Neurology,

Psychiatry, Biobehavioral Sciences and Human Genetics
2003-2005 Associate Professor-in-Residence, Department of Neurology, David Geffen School of Medicine at UCLA
2003-present Director, UCLA Center for Autism Research and Treatment
2003-present Co-Director, Center for Neurobehavioral Genetics, UCLA Neuropsychiatric Institute
1997-2003 Assistant Professor-in-Residence, Department of Neurology, David Geffen School of Medicine at UCLA
1997-present Director, Neurogenetics Program, Department of Neurology, David Geffen School of Medicine at UCLA
1995-1997 Clinical Instructor in Neurology (Neurogenetics), David Geffen School of Medicine at UCLA
1982-1984 Research Associate, The Boston Consulting Group, Boston, MA, Management Consulting and Corporate Strategy

MEDICAL LICENSURE

1992-present California Medical Board

BOARD CERTIFICATION

1996-2006 Adult Neurology, The American Board of Psychiatry and Neurology
2006-present Adult Neurology, The American Board of Psychiatry and Neurology

Other Experience and Professional Memberships (subset)

1996-present, Board Certification in Adult Neurology; 1998 Oral Board Examiner, The American Board of Neurology and Psychiatry; 1999-2004, Chair, Steering Committee, Autism Genetic Resource Exchange; 2002-2005 Editorial Board, *Lancet Neurology*; 2003-2006; Chair, Education Committee, Program Committee Member, Society for Neuroscience; 2016, 2005-2009 Councilor, Chair, Neurogenetics Section, American Academy of Neurology; 2006-present, Deputy Editor, *Biological Psychiatry*; 2007- present, Editorial Board, *Neuron*; 2007- 2011 NIMH National Advisory Mental Health Council; 2009-2012, NIH Council of Councils; 2011 Institute of Medicine, National Academy of Science, 2013- present, Board of Reviewing Editors, *Science*; 2014-present, Editorial Board, *Cell;* 2016-present Co-Head of Faculty, Genomics and Genetics Section, Faculty of 1000 Medicine; Chair, Program Committee, World Congress of Psychiatric Genetics 2019; 2019-present, Allen Institute, Scientific Advisory Board.

Honors/Awards

1982 *Magna Cum Laude* with Distinction in Chemistry, Dartmouth College 1990; John F. Enders Research Award, Yale University; 1991 Alpha Phi Omega Medical Honor Society, Yale University; 1999-2001 NARSAD Young Investigator Award; 2004 Derek Denny-Brown Neurological Scholar Award, American Neurological Association (ANA); 2006 Harold Brenner Pepinsky Award in Behavioral Neuroscience (Ohio State University); 2006-2015 MERIT (Method to Extend Research in Time) Award, NIMH; 2007 KAVLI Distinguished Visiting Professor, University of California, San Diego; 2008 Autism Speaks Scientific Service Award; 2011 Member, National Academies, Institute of Medicine; 2012 Wiersma (Endowed) Visiting Professor, California Institute of Technology; 2012 Ruane Prize for Research in Child and Adolescent Psychiatry, Brain and Behavior Research Foundation; 2013 Taking on Tomorrow Award (Research/Scientific Breakthrough in Autism), Children's Hospital, Boston; 2014, American Academy of Physicians, full member; 2015 Paul G Allen Distinguished Investigator Award; 2016 Raymond Adams Award/ Lecture, ANA; World's most highly cited/influential researchers 2017-present; 2019, Amgen, Early Innovator Award. 2021, International Society for Autism Research (INSAR), Fellow; Society for Biological Psychiatry, Gold Medal.

C. Contribution to Science (Complete List of Published Work (H-index 162, citations >105,000): http://www.ncbi.nlm.nih.gov/sites/myncbi/daniel.geschwind.1/bibliography/40487828/public/?sort=date&direction=descending)

1) Elucidating the genetic basis of brain disorders. In the late 1990s, little was known about the genetic architecture of autism. Starting in 1998, I began leading large-scale collaborative studies of ASD genetics and in collaboration with the Cure Autism Now foundation, developed AGRE, a public shared family resource for the

study of autism genetics (*Neuron* 68:187-91). My group played a leading role in the first major whole exome sequencing studies performed in ASD, was the first to apply transcriptional profiling to determine the functional impact of genome-wide structural chromosomal variation in ASD, and recently, to contrast the contribution of *de novo* and inherited CNV to ASD in multiplex and simplex families, as well as whole genome sequencing in multiplex families to identify rare inherited mutations.

1. Ruzzo E, Perez-Cano L, Jung J-Y, Wang L-K, Kashef-Haghighi D, Hartl C, Hoekstra J, Leventhal O, Gandal MJ, Paskov K, Stockham N, Polioudakis D, Lowe JK, **Geschwind DH***, Wall DP* (2019). Whole genome sequencing in multiplex families reveals novel inherited and de nove genetic risk in autism. *Cell* * co-senior, supervised the study.
2. Leppa VM, Kravitz SN, Martin CL, Andrieux J, Le Caignec C, Martin-Coignard D, DyBuncio C, Sanders SJ, Lowe JK, Cantor RM, **Geschwind DH** (2016). Rare inherited and de novo CNVs reveal complex contributions to ASD risk in multiplex families. *Am J Hum Genet*. 99(3): 540-54. PMCID: PMC5011063.
3. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, Ercan-Sencicek AG, DiLullo NM, Parikshak NN, Stein JL, Walker MF, Ober GT, Teran NA, Song Y, El-Fishawy P, Murtha RC, Choi M, Overton JD, Bjornson RD, Carriero NJ, Meyer KA, Bilguvar K, Mane SM, Sestan N, Lifton RP, Günel M, Roeder K, **Geschwind DH***, Devlin B*, State MW* (2012). De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature*. 485(7397): 237-41. (*Co-senior authors). PMCID: PMC3667984.
4. Luo R, Sanders SJ, Tian Y, Voineagu I, Huang N, Chu SH, Klei L, Cai C, Ou J, Lowe JK, Hurles ME, Devlin B, State MW, **Geschwind DH** (2012). Genome-wide transcriptome profiling reveals the functional impact of rare de novo and recurrent CNVs in Autism Spectrum Disorder. *Am J Hum Genet*. 91(1): 38-55. PMCID: PMC3397271.

2) Developed and applied integrative genomic methods to identify convergent pathways in a major neurodevelopmental condition, autism spectrum disorder (ASD). My laboratory identified the first genome wide evidence for convergent biology in ASD via transcriptomic studies of both lymphoblasts and post mortem brain, validated this in independent samples using RNA sequencing and used co-expression network analysis to demonstrate circuit and pathway convergence in ASD. In parallel, we have performed studies of epigenetic regulation in brain, identifying genome-wide patterns of dysregulation that parallel transcriptomic changes, and integrated multiple forms of epigenetic data with miRNA and mRNA networks to characterize convergent pathways in ASD.

1. Ramaswami G, Won H, Gandal M, Haney J, Wang JC, Wong CC, Sun W, Prbahakar S, Mill J, **Geschwind DH** (2020). Integrative genomics identifies a convergent molecular subtype that links epigenomic with transcriptomic differences in autism. *Nature Communications.* 11:4873. PMCID: PMC7519165.
2. Parikshak NN, Swarup V, Belgard TG, Irimia M, Ramaswami G, Gandal MJ, Hartl C, Leppa V, de la Torre Ubieta L, Huang J, Lowe JK, Blencowe BJ, Horvath S, **Geschwind DH** (2016). Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. *Nature*. 540(7633): 423-7. PMCID: PMC29995847.
3. Sun W, Poschmann J, Cruz-Herrera Del Rosario R, Parikshak NN, Hajan HS, Kumar V, Ramasamy R, Belgard TG, Elanggovan B, Wong CC, Mill J, **Geschwind DH***, Prabhakar S* (2016) Histone acetylome-wide association study of Autism Spectrum Disorder. *Cell*. 167(5): 1385-1397. (*senior authors, co-supervised this study). PMID: 27863250.
4. Parikshak NN, Luo, R, Zhang A, Won H, Lowe JK, Chandran V, Horvath SH, **Geschwind DH** (2013). Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. *Cell*. 155(5): 1008-21. PMC3934107.

3) Analysis of gene expression and its regulation in the brain. My laboratory has performed pioneering work in neurogenetics via the application of genome wide transcriptomics in normal brain and the development of systems biology methods for analysis and data integration. We performed the first genome-wide analysis of human cortical patterning and demonstrated that the brain transcriptome has a reproducible structure that can be used to identify drivers of human brain evolution and disease. We have extended our analysis of transcriptomic networks to understand the epigenetic mechanisms of gene regulation via integrative analysis of 3-dimensional chromatin structure and enhancer marks. This work identified novel mechanisms, and unexpected overlap between neuropsychiatric disorders, such as schizophrenia and ASD.

1. Walker RL, Ramaswami G, Hartl C, Mancuso N, Gandal MJ, de la Torre-Ubieta L, Pasaniuc B, Stein JL, **Geschwind DH** (2019). Genetic Control of Expression and Splicing in Developing Human Brain Informs Disease Mechanisms. *Cell*. 179(3):750-771. PMID: 31626773
2. De la Torre-Ubieta L, Stein JL, Won H, Opland CK, Liang D, Lu D, **Geschwind DH** (2018). The dynamic landscape of open chromatin during human cortical neurogenesis. *Cell*. 172(1-2): 289-304. PMCID: PMC5924568.
3. Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, Won H, van Bakel H, Varghese M, Wang Y, Shieh AW, Haney J, Parhami S, Belmont J, Kim M, Moran Losada P, Khan Z, Mleczko J, Xia Y, Dai R, Wang D, Yang YT, Xu M, Fish K, Hof PR, Warrell J, Fitzgerald D, White K, Jaffe AE; PsychENCODE Consortium, Peters MA, Gerstein M, Liu C, Iakoucheva LM, Pinto D, **Geschwind DH** (2018). Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science*. 362(6420): eaat8127. PMCID: PMC6443102.
4. Wang D, Liu S, Warrell J, Won H, Shi X, Navarro FCP, Clarke D, Gu M, Emani P, Yang YT, Xu M, Gandal MJ, Lou S, Zhang J, Park JJ, Yan C, Rhie SK, Manakongtreecheep K, Zhou H, Nathan A, Peters M, Mattei E, Fitzgerald D, Brunetti T, Moore J, Jiang Y, Girdhar K, Hoffman GE, Kalayci S, Gümüş ZH, Crawford GE; PsychENCODE Consortium, Roussos P, Akbarian S, Jaffe AE, White KP, Weng Z, Sestan N, **Geschwind DH***, Knowles JA, Gerstein MB* (2018). Comprehensive functional genomic resource and integrative model for the human brain. *Science*. 362(640): eaat8464. (*Co-senior authors). PMCID: PMC6413328.
5. Won H, de la Torre-Ubieta L, Stein JL, Parikshak NN, Huang J, Opland CK, Gandal M, Sutton G, Hormozdiari F, Lu D, Lee CH, Eskin E, Voineagu I, Ernst J, **Geschwind DH** (2016). Chromosome conformation elucidates regulatory relationships in developing human brain. *Nature.* 538(7626): 523-7. PMCID: PMC5358922.
6. Oldham MC, Konopka G, Iwamoto K, Langfelder P, Kato T, Horvath S, **Geschwind DH** (2008). Functional organization of the transcriptome in human brain. *Nature Neuroscience*. 11(11): 1271-82. PMCID: PMC2756411.

4) Develop and validate *in vitro* and *in vivo* models of brain disorders. A major challenge in human genetics is to develop an understanding of the functional consequences of genetic variation on relevant phenotypes, so as to build a mechanistic framework on which to develop therapies. My laboratory has developed human neural progenitors for use in studying neurodevelopmental and neurodegenerative diseases, implemented 3D organoids protocols developed by the Pasca lab at Stanford, and spent considerable effort validating that these systems are reliable and recapitulate in vivo biology using functional genomics.

1. Gordon A, Yoon SJ, Tran SS, Makinson CD, Park JY, Andersen J, Valencia AM, Horvath S, Xiao X, Huguenard JR, Pașca SP, **Geschwind DH** (2021). Long-term maturation of human cortical organoids matches key early postnatal transitions. *Nat Neurosci.* 24(3):331-342. PMID: 33619405.
2. Stein JL, de la Torre-Ubieta L, Tian Y, Parikshak NN, Hernandez IA, Marchetto MC, Baker DK, Lu D, Lowe JK, Wexler EM, Muotri AR, Gage FH, Kosik KS, **Geschwind DH** (2014). A quantitative framework to evaluate modeling of cortical development by neural stem cells. *Neuron*. 83(1): 68-86. PMCID: PMC4277209.
3. Rosen E, Wexler EM, Versano R, Coppola G, Gao F, Winden K, Oldham M, Martens LH, Zhou P, Farese RV, **Geschwind DH** (2011). Functional genomic analyses identify pathways dysregulated by progranulin deficiency implicating Wnt signaling. *Neuron*. 71,1030-1042. PMCID: PMC3633414.
4. Konopka G, Bomar JM, Winden K, Coppola G, Jonsson ZO, Gao F, Peng S, Preuss TM, Wohlschlegel JA, **Geschwind DH** (2009). Human-specific transcriptional regulation of CNS development by FOXP2. *Nature*. 462(7270): 213-7. Highlighted in *Nature News and Views:* Dominguez MH and Rakic P (Nov 12, 2009) 462:169-70*.* PMCID: PMC2778075.

5) Analysis of endophenotypes in neuropsychiatric disorders. As early as 2001, we hypothesized that a portion of risk for ASD was on a continuum with common genetic risk for quantitative component phenotypes seen in the general population, and that are intermediate between genes and the disease, called endophenotypes (e.g. see Geschwind *Cell,* 2008). We have tested this model with varying degrees of success, identifying loci for quantitative impairment in social responsiveness/communication, non-verbal communication, and language, loci related to male or female genetic risk, and quantitative functional imaging or transcriptional endophenotypes, so as to connect genetic risk to brain circuits and molecular networks.

1. Alarcón M, Abrahams BS, Stone JL, Duvall JA, Perederiy JV, Bomar JM, Sebat J, Wigler M, Martin CL, Ledbetter DH, Nelson SF, Cantor RM, **Geschwind** DH. Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. Am J Hum Genet. 2008 Jan;82(1):150-9. doi:

10.1016/j.ajhg.2007.09.005. PubMed PMID: 18179893; PubMed Central PMCID: PMC2253955.
2. Scott-Van Zeeland AA, Abrahams BS, Alvarez-Retuerto AI, Sonnenblick LI, Rudie JD, Ghahremani D, Mumford J, Poldrack RA, Dapretto M, **Geschwind DH***, Bookheimer SY* (2010). Altered functional connectivity in frontal lobe circuits is associated with variation in the autism risk gene CNTNAP2. *Sci Transl Med.* 2(56): 56ra80. (*Co-senior authors). PMC3065863.
3. Lowe JK, Werling DM, Constantino JN, Cantor RM, **Geschwind DH** (2015). Social responsiveness, an autism endophenotype: genomewide significant linkage to two regions on chromosome 8. *Am J Psychiatry*. 172(3): 266-75. PMC4523091.
4. Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, Schork AJ, Appadurai V, Buil A, Werge TM, Liu C, White KP, CommonMind Consortium, PsychENCODE Consortium, iPSYCH-BROAD Working Group, Horvath S, **Geschwind DH** (2018). Shared Molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science*. 359(6376): 693-7. PMCID: PMC5898828.

Subset of ASD-related Research Support

NIH/NIMH 5 R01 MH109912-05 Geschwind, PI
07/01/16-03/31/22 1/3 Building Integrative CNS Networks for Genomic Analysis of Autism

NIH/NIMH 5 U01 MH115746-04 Geschwind, PI 09/21/17-07/31/22
½ Cross Modal Integration of Molecular and Physiological Networks in ASD

NIH/NIMH 5 U01 MH116489-04 Geschwind, PI 05/01/18-04/30/23
2/2 Discovery and Validation of Neuronal Enhancers Associated with the Development of Psychiatric Disorders

NIH/NIMH 5 R01 MH100027-14 Geschwind, PI 07/01/18-03/31/23
Autism Genetics, Phase II Increasing representation of human diversity

NIH/NICHD 5 P50 HD055784-14 Bookheimer, PI; Geschwind, Core PI 09/07/17-07/31/22
Heterogeneity in Autism Spectrum disorders: Biological Mechanisms, Trajectories, and Treatment Response

NIH/NIMH 5 R01 MH100028-10 Pelphrey, PI, Geschwind, Site PI01/31/19-07/31/22
Multimodal Developmental Neurogenetics of Females With ASD

NIH/NIDCD 1 P50 DC018006-02 Helen Tager-Flusberg, PI; Geschwind, Site PI09/01/19-08/31/24
Genetic Investigation of Minimally Verbal Children with ASD

NIH/ NIMH 1 R01 MH121601 Prober, PI; Geschwind, Site PI 09/01/20-08/31/25
High-Throughput Modeling of Autism Risk Genes Using Zebrafish