BIOGRAPHICAL SKETCH

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NAME: Lea Karatheodoris Davis

eRA COMMONS USER NAME (credential, e.g., agency login): LEADAVIS2

POSITION TITLE: Assistant Professor of Medicine, Vanderbilt University Medical Center

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
University of Alabama	BS	1999-2003	Psychology/Biology
University of Iowa	PhD	2004-2009	Genetics
University of Illinois	Postdoctoral	2009-2011	Psychiatric Genetics
University of Chicago	Postdoctoral	2010-2013	Statistical Genetics

A. Personal Statement

Like many of my colleagues, I was initially drawn to psychiatric genetics for personal reasons. My stepson, Dylan, who is now 25 years old, is autistic, non-verbal, and has intellectual disability. For years we struggled to find a medication that could help with mood stability, irritability, and impulsivity, without causing sedation. He tried one medication after another with little improvement (sometimes worsening) until we finally tried Risperdal in 2003. It completely changed our quality of life. All of a sudden he was able to access the world in a way he never had before. He went to his first movie, he engaged in group activities, he participated in our wedding. Risperdal allowed us to take care of him at home for far longer than we otherwise would have been able to. But, there was a down side. Almost immediately he became hyperphagic. He would cry pitifully if he wasn't allowed to over-eat, and for a family struggling with so many issues, providing an extra helping to assuage tears at the dinner table seemed relatively harmless. But over time, the harm became apparent. During the first year that he was on Risperdal, Dylan gained ~30 pounds and struggled to keep up with us during active play outside. In retrospect, I realize that we needed both nutritional and emotional support intervention. It took several years and a lot of trial and error to get Dylan's weight back under control. Our family would have been helped tremendously by knowing early on that he was at risk for significant weight gain and having an intervention plan at the very beginning of his treatment. I believe in the goals of this study because I have lived the consequences of these problems.

Over the past twenty years, I have conducted research on complex traits and earned degrees in both psychology (BS) and human genetics (PhD). My graduate research on the role of copy number variation in diverse phenotypes including autism spectrum disorders (ASD), age-related macular degeneration (AMD), and primary open angel glaucoma (POAG) impacted the field by establishing a role for the *TBK1* gene in normal tension glaucoma, and syntaxin binding proteins in ASDs. Both findings have since been replicated. As a postdoctoral fellow, I worked with Dr. Nancy Cox at the University of Chicago and was trained in statistical and computational approaches to genomic data. Funded by a CTSA-KL2 career development award, I organized and lead multi-center analytic efforts on behalf of three neuropsychiatric disease consortia including the Tourette Syndrome (TS) Association International Consortium for Genetics, the International Obsessive Compulsive Disorder (OCD) Foundation Genomic Consortium, and the University of Illinois Autism Center of Excellence. My work in these consortia established the genetic architecture of TS and OCD as highly polygenic and genetically correlated traits, and showed that early GWAS for ASDs, while underpowered to identify

genome-wide significant associations, contained biologically informative associations distributed among sub-threshold results. During my time at the University of Chicago, I also expanded my publication track record to include the methods development papers published in top tier journals including *Bioinformatics* and *American Journal of Human Genetics*.

My sponsored research now focuses on psychiatric genomics in the electronic health record (EHR). We are currently working on phenotype development and genomic studies of autism, Tourette Syndrome, Obsessive Compulsive disorder, Major Depression, Schizophrenia and Anxiety. Additionally, because we have access to the entire medical phenome for patients in our biobank, we are working to understand the genetic and phenotypic correlations between psychiatric disorders and common somatic comorbitidies. I have collaborated with group leaders in the Psychiatric Genomics Consortium (PGC) and eMERGE to develop EHR-based algorithms (deposited in collaborator space in PheKB) allowing us to identify and genotype cases and controls for ASD, TS, OCD, and eating disorders. I am leading a polygenic analysis using biobank data to discover and validate novel biomarkers among routinely collected labs, for neuropsychiatric disorders. Finally, though early in my independent career, I have earned leadership positions within established consortia and have developed a strong track record of successful mentoring. I currently mentor six PhD students in my lab, one postdoctoral fellow, and one faculty fellow. I am enthusiastic about mentoring and teaching, as evidenced by my recent Vanderbilt 'Excellence in Mentoring' and 'Excellence in Teaching' awards (May, 2019). I am looking forward to providing support and direction to trainees on this training grant. To date, I have mentored nearly a dozen trainees including undergraduates, graduate students, postdocs, and faculty fellows. Trainee authors on publications are <u>underlined</u> in the selected publications below.

B. Positions and Honors

Academic Positions:

1999-2003: Undergraduate Research Assistant, Autism Spectrum Disorders Clinic, University of Alabama
2003-2004: Research Assistant, Biological Sciences Department, University of Alabama
2004-2009: Graduate Research Assistant, Interdisciplinary Genetics Program, University of Iowa
2009-2011: Postdoctoral Fellowship, Department of Psychiatry, University of Illinois (Chicago)
2010-2013: Postdoctoral Fellowship, Department of Medicine, University of Chicago
2013-2015: Research Associate (Assistant Professor), Department of Medicine, University of Chicago
2015 – present: Assistant Professor, Department of Medicine, Division of Genetic Medicine, Vanderbilt University Medical Center

Academic Honors and Awards:

2003 Outstanding Research Award, Psychology Department, University of Alabama
2003 Elected member of Phi Beta Kappa, University of Alabama
2008 Scholarship Travel Award, Complex Human Genetics Workshop, Cold Spring Harbor Laboratory
2009 NIH Predoctoral T32 Training Grant Recipient, University of Iowa
2013 Early Career Investigator Program Travel Award, International Society of Psychiatric Genetics
2013 Young Investigator Travel Award, Molecular Psychiatry Association
2013 Outstanding Oral Presentation Award, International Society of Psychiatric Genetics
2014 KL2 Clinical and Translational Science Career Development Award, University of Chicago
2019 Vanderbilt Genetics Institute Excellence in Mentoring Award, Vanderbilt University Medical Center
2019 Vanderbilt Genetics Institute Excellence in Teaching Award, Vanderbilt University Medical Center

C. Contributions to Science

1. Genetic architecture and genome-wide association studies of common neuropsychiatric phenotypes. I have worked on genome wide association studies (GWAS) across multiple phenotypes as described in Stewart et al., (2012), Scharf et al., (2012), Gao et al., (2016), and Sanchez-Roige et al. (2018). My role in these studies has varied and included hands-on analysis and supervision of student and postdocs performing analysis, development of rigorous quality control pipelines, principal components analysis, GWAS, SNP-based heritability, and interpretation of results. I have also worked to creatively integrate results from functional genomic analysis into my work. For example, in Davis et al., (2012), we integrated eQTL annotations to demonstrate that loci nominally associated with autism were enriched for regulatory variants in the brain, a finding that helped to establish the now widely-recognized observation that subthreshold associations remain biologically meaningful.

A. **Davis LK**, Gamazon ER, Kistner-Griffin E, Liu C, Badner JA, Cook Jr EH, Sutcliffe JS and Cox NJ. (2012) Loci nominally associated with autism from genome-wide analysis show enrichment of brain expressed quantitative trait loci (eQTL) but not lymphoblastoid cell line eQTLs. *Molecular Autism*. May 16;3(1):3. (PMCID: PMC3484025)
B. Jianjun Gao, **Lea K. Davis**, Amy B. Hart, Sandra Sanchez-Roige, Lide Han, John T. Cacioppo, Abraham A. Palmer (2016) Genome-wide Association Study of Loneliness Demonstrates a Role for Common Variation. *Neuropsychopharmacology*.
C. International Obsessive Compulsive Disorder Foundation Genetics Consortium (IOCDFGC) and OCD Collaborative Genetics Association Studies (OCDGAS). (2017) Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. *Molecular Psychiatry*. (PMID:28873088) **Author contributions cited in manuscript: data analysis, interpretation, and manuscript writing

2. Polygenic characterization of neuropsychiatric disorders. Prior to 2013, the genetic architecture of TS and OCD were unknown. Two GWAS were published in 2012 and neither identified genome-wide significant associations, leading some to suggest that perhaps TS and OCD were primarily due to rare variants. My 2013 *PLoS Genetics* paper used SNP-based heritability methods to establish the polygenic architecture of both TS and OCD and has been cited >160 times to date. Additionally, we demonstrated that TS and OCD are genetically correlated ($r2 = 0.4$) and that SNPs modestly associated with TS, and OCD ($p< 0.001$) are enriched for variants associated with gene expression in the frontal cortex. I then went on to conducted the polygenic analyses described in Yu et al (2014) and in Darrow et al (2016) demonstrating that while TS and OCD are genetically related, they also have separate genetic contributions that appear to correlate with symptom domains. Finally, I directed the SNP-based heritability and polygenic analyses described in the most recent (2017) and largest published OCD meta-analysis. This study replicated our earlier result from Davis et al., (2013) and confirmed that the majority of heritability for OCD is accounted for by variants with high minor allele frequency (MAF>30%). These findings are informing subsequent polygenic analyses, pathway analyses, and rare variant analyses and have significantly impacted the field.

A. **Davis LK**, Yu D, Keenan C, Konkashbaev A, Gamazon ER, Derks ES, Neal BM, Evans P, et al. (2013) Partitioning heritability of Tourette Syndrome and obsessive-compulsive disorder reveals differences in genetic architectures. *PLoS Genetics.* (PMCID: PMC3812053)
B. D. Yu, C.A. Mathews, J. Scharf, B.M. Neale, **L.K. Davis**, E.R. Gamazon, et al. (2014) Genome-Wide Association and Polygenic Score Analyses Suggest Separate Genetic Contributions to Tourette Syndrome and Obsessive-Compulsive Disorder. *American Journal of Psychiatry*.
C. Ekaterina A Khramtsova, Raphael Heldman, Eske M Derks, Dongmei Yu, TS/OCD Psychiatric Genomics Disorders Workgroup, ***Lea K Davis** and *Barbara E Stranger (2018) Sex differences in the genetic architecture of obsessive-compulsive disorder. *American Journal of Medical Genetics: Neuropsychiatric Genetics*.
D. Yu D, Sul JH, Tsetsos F, Nawaz MS, Huang AY, **Davis LK**, Paschou P, Coppola G, Mathews CA, Scharf JM; Tourette Association of America International Consortium for Genetics, the Gilles de la Tourette GWAS Replication Initiative, the Tourette International Collaborative Genetics Study, and the Psychiatric Genomics Consortium Tourette Syndrome Working Group. (*2019*) Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. *Am J Psychiatry*. Mar 1;176(3):217-227. (PMID:30818990)

3. Electronic Health Record-based phenotyping and genomic analysis of biobank samples. I am the co-PI (along with Jordan Smoller at MGH and Harvard) of the PsycheMERGE consortium which is focused on psychiatric genomics research in the electronic health record (EHR). We are deeply engaged in EHR research nationally and internationally. As the VUMC PI of psycheMERGE, I collaborate with clinical faculty at Vanderbilt and across the world (through the Psychiatric Genomics Consortium (PGC) and eMERGE network) to develop EHR-based algorithms for the identification of cases and controls for ASD, TS, OCD, and eating disorders and to perform genomic studies of these conditions and their comorbidities. Our early successes in this field have distinguished us as world leaders in EHR-based psychiatric genomics.

A. Salem JE, Shoemaker MB, Bastarache L, Shaffer CM, Glazer AM, Kroncke B, Wells QS, Shi M, Straub P, Jarvik GP, Larson EB, Velez Edwards DR, Edwards TL, **Davis LK**, Hakonarson H, Weng C, Fasel D, Knollmann BC, Wang TJ, Denny JC, Ellinor PT, Roden DM, Mosley JD. (2019) Association of

Thyroid Function Genetic Predictors With Atrial Fibrillation: A Phenome-Wide Association Study and Inverse-Variance Weighted Average Meta-analysis. *JAMA Cardiol*.

B. Mosley JD, Feng Q, Wells QS, Van Driest SL, Shaffer CM, Edwards TL, Bastarache L, Wei WQ, **Davis LK**, McCarty CA, Thompson W, Chute CG, Jarvik GP, Gordon AS, Palmer MR, Crosslin DR, Larson EB, Carrell DS, Kullo IJ, Pacheco JA, Peissig PL, Brilliant MH, Linneman JG, Namjou B, Williams MS, Ritchie MD, Borthwick KM, Verma SS, Karnes JH, Weiss ST, Wang TJ, Stein CM, Denny JC, Roden DM. (2018) A study paradigm integrating prospective epidemiologic cohorts and electronic health records to identify disease biomarkers. *Nat Commun*. Aug 30;9(1):3522.

C. Amanda B Zheutlin, Jessica Dennis, Richard-Karlsson Linnér, Arden Moscati, Nicole Restrepo, Peter Straub, Douglas Ruderfer, Victor M Castro, Chia-Yen Chen, Tian Ge, Laura M Huckins, Alexander Charney, H Lester Kirchner, Eli A Stahl, Christopher F Chabris, **Lea K Davis***, Jordan W Smoller*. (2019) Penetrance and pleiotropy of polygenic risk scores for schizophrenia in 106,160 patients across four healthcare systems. *Am J Psychiatry*.

D. Jessica Dennis, Julia Sealock, Rebecca T Levinson, Eric Farber-Eger, Jacob Franco, Sarah Fong, Peter Straub, Donald Hucks, MacRae F Linton, Wen-Liang Song, Pierre Fontanillas, Sarah L Elson, Douglas Ruderfer, Abdel Abdellaoui, Sandra Sanchez-Roige, Abraham A Palmer, Dorret I Boomsma, Nancy J Cox, Guanhua Chen, Jonathan D Mosley, Quinn S Wells, **Lea K. Davis** (*in press*) Genetic risk for major depressive disorder and loneliness in sex-specific associations with coronary artery disease. *Mol Psychiatry*.

4. Copy number variant (CNV) analysis of complex traits. My work has been instrumental in understanding the role of CNVs in autism spectrum disorders (ASDs), Tourette Syndrome (TS), OCD, age related macular degeneration, and glaucoma. The genetic architecture of autism includes a significant polygenic component and a substantial contribution from rare CNVs (~10% of cases). During my PhD work, I conducted studies demonstrating that dysmorphologies can be used as "phenotypic markers" to enrich samples for CNVs. We identified a burden of rare variants in genes such as *PAX6*, *STXBP5*, *LRNN1*, and *A2BP1 (*Davis et al*., 2012)*, which have been subsequently replicated in independent samples. Importantly, the Human Genetics paper on *PAX6* in autism led to the clinical appreciation of the increased risk of ASDs among children with Aniridia (*PAX6* deletion) and has been cited 83 times to date (Davis et al., *Human Genetics,* 2008). In addition, I have been an integral part of large-scale genome-wide CNV and association studies in idiopathic ASDs, TS, and OCD. This work has demonstrated that deletions of *NRXN1* are more common among individuals with TS than controls. In contrast, we have shown that rare CNVs are not enriched in OCD, a finding consistent with our previous results demonstrating that the majority of heritability for OCD is accounted for by common variants with MAF > 30%. I also performed the first genome-wide analyses of CNVs in age related macular degeneration (AMD) and primary open angle glaucoma (POAG). Importantly, my studies of CNV in POAG discovered that haploinsufficency of the *TBK1* gene results in a rare form of normal tension glaucoma. Others have also now replicated this finding, confirming the role of *TBK1* in normal tension glaucoma. The identification of a normal tension glaucoma gene has significantly impacted the field and investigation into the disease-causing mechanism is now underway.

A. **LK Davis***; KJ Meyer*, EI Schindler, JS Beck, DS Rudd, AJ Grundstad, TE Scheetz, TA Braun, JH Fingert, WL Alward, Y Kwon, JC Folk, SR Russell, TH Wassink, VC Sheffield, EM Stone. (2011) Copy Number Variations (CNVs) and Primary Open Angle Glaucoma (POAG). *Investigations in Ophthalmology and Visual Sciences*. Sep 9;52(10):7122-33. (PMCID: PMC3207715)

B. KJ Meyer*; **LK Davis***, EI Schindler, JS Beck, DS Rudd, AJ Grundstad, TE Scheetz, TA Braun, JH Fingert, WL Alward, Y Kwon, JC Folk, SR Russell, TH Wassink, EM Stone, VC Sheffield. (2011) Copy Number Variations (CNVs) and Age-Related Macular Degeneration (AMD). *Human Genetics*. Jan;129(1):91-100. (PMCID: PMC3613489)

C. L.M. McGrath, D. Yu, C. Marshall, **L.K. Davis**, et al., on behalf of the TS GWAS Consortium and the IOCDFGC. (*2014*) A cross-disorder, genome-wide analysis of copy number variation in Tourette Syndrome and Obsessive-Compulsive Disorder. *Journal of the American Association of Child and Adolescent Psychiatry.* (PMID: 25062598)

D. Alden Y Huang, Dongmei Yu, **Lea K Davis**, Jae-Hoon Sul, Fotis Tsetsos et al., on behalf of the TSAICG/GGRI (2017) De Novo Coding Variants Are Strongly Associated with Tourette Disorder. *Neuron*. E-pub.

URL with all references: https://www.ncbi.nlm.nih.gov/sites/myncbi/1xalt-IKFNiAv/bibliography/40995234/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

5U54MD010722-04 (Wilkins) 05/19/2016 - 03/31/2021
NIMHD $1,865,373
Center of Excellence in Precision Medicine and Population Health
Our Center is designed to fill an important gap in disparities science by developing robust methods to enable examination of multilevel determinants that drive disparity broadly and not for a specific disease phenotype.

U01HG009086 w/VU (Cox) 05/01/2016 – 04/30/2020
NHGRI $279,225
Analysis, Validation and Resource Creation for Genome Sequencing of Complex Diseases
We aim to develop a suite of statistical and computational methods to identify genes and variants associated with complex disease.

5RM1HG009034-04 (Malin) 05/16/2016 – 04/30/2020
NHGRI $637,668
Genetic Privacy and Identity in Community Settings-GetPreCiSe
The Genetic Privacy and Identity in Community Settings – GetPreCiSe Center will use broadly interdisciplinary approaches to develop a more complete understanding of community concerns about genetic privacy.

5R01MH113362-03 (Knapik) 08/01/2017 - 04/30/2022
Discovering Biology for Neuropsychiatric Diseases Through Omics Studies on Comorbidities
Co-morbid phenotypes that cut across neuropsychiatric disorders can be used to identify more homogeneous genetic risk factors that will also be cross-cutting for neuropsychiatric diseases.

1DP2HD098859-01 (Gordon) 09/30/2018 - 06/30/2023
NICHD $24,629
Biomarkers of Rhythmic Communication Integrating Foundational and Translational Approaches
This New Innovator award proposes to characterize biomarkers of human rhythm skills.

NS102371-01A1 w/Mass Gen (Davis) 04/01/2018 – 03/31/2023
NINDS $16,391
Integrating Common and Rare Variation to Discover Genes for Tourette Syndrome
The overarching goal of this study is to identify genes associated with Tourette Syndrome.

1R01DC016977-01A1 (Gordon) 02/01/2019 - 01/31/2024
NIDCD $441,653
Neurobiological Markers of Rhythm: Risk and Resilience for Language Acquisition
This project explores rhythm as a potential factor contributing to specific language impairment (SLI).

R01MH118233-01 w/ Mass Gen (Davis) 02/15/2019-11/30/2022
NIMH $180,000
PsycheMERGE: Leveraging electronic health records and genomics for mental health research
This project enables clinical and genetic research in the context of the electronic health record that will improve the knowledge of psychiatric disorders and their life-threatening comorbidities.

R01NS105746-01A1 w/ Mass Gen (Davis) 04/01/2019 - 03/31/2024
NINDS $28,110
Large-scale collaborative genetic and epigenetic studies of Tourette Syndrome
The goal of this collaborative effort is to illuminate the developmental and neurobiological pathways underlying Tourette Syndrome and Tic disorders through integrative genetic and epigenetic analysis.

***1R56MH120736-01** (Davis) 07/01/2019 - 06/30/2021
NIMH $597,185
Mental health and chronic disease: A psycheMERGE investigation into the shared biology underlying psychiatric disorders and their physical comorbidities
This project focuses on the genetic and clinical relationships between mental and physical health phenotypes.