BIOGRAPHICAL SKETCH

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NAME: Deborah L. Levy

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

POSITION TITLE: Director, Psychology Research Laboratory, McLean Hospital

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 Chicago, Chicago, IL	B.A.	06/72	Political Science
University of Chicago, Chicago, IL	Ph.D.	08/76	Psychology
NY Hospital-Cornell Medical Center, White Plains, NY	Internship	06/77	Clinical Psychology
Menninger Foundation, Topeka, KS	Post-doc	08/79	Clinical Psychology

A. Personal Statement

Deborah Levy is Associate Professor in the Department of Psychiatry at Harvard Medical School. Her research focuses on characterizing pleiotropic effects of schizophrenia risk genes and identifying risk genes. Dr. Levy's group was among the first to recognize the value of studying well relatives of schizophrenia patients, which led to conceptualizing the importance of endophenotypes in genetic studies. This group was the first to identify eye-tracking dysfunction in the pathophysiology of schizophrenia and to delineate the specific thought disorder profiles associated with schizophrenia and bipolar disorder. Other endophenotypes, such as craniofacial dysmorphology and evoked response potentials, have added to the impact of this work (see section C below). We have already developed a quantitative and qualitative phenotype for schizophrenia-related thought disorder that shows excellent sensitivity and specificity. Our preliminary thought disorder data on bipolar probands and their relatives are quite promising in discriminating these probands and relatives from controls, schizophrenia probands and their relatives. A publication based on these findings was recently published in *Schizophrenia Bulletin* (2017; 43:523-535). The primary goals of the proposed project are: 1) to determine whether particular features of the thought disorder found in patients with bipolar disorder with psychotic features meet the co-familiality criterion for an endophenotype for bipolar disorder, and 2) to develop a composite serious mental illness thought disorder phenotype that maximizes the discrimination between all probands with psychotic disorders (independent of specific diagnoses) and their first-degree biological relatives from controls and relatives of controls. These goals will set the stage for using this cognitive phenotype, in combination with polygenic risk scores, to improve the power of genetic analyses to identify non-penetrant gene carriers. I am very well qualified to direct this study, having had more than 30 years of experience carrying out family studies of schizophrenia endophenotypes. An established infrastructure and lab personnel are in place to accommodate the recruitment, subject flow and data processing needs of this project, which are very labor-intensive. We have access to large numbers of patients and families through the Psychotic Disorders Division at McLean Hospital, NAMI, the Depressive and Manic-Depressive Association, and other local resources. Based on our prior experience, data acquisition for the proposed sample size is quite feasible.

B. Positions and Honors

Positions and Employment

1980-1987 Assistant Professor, Department of Psychiatry, University of Chicago
1987-1991 Director, Psychophysiology Laboratory, Hillside Hospital, Long Island Medical Center
1991-2004 Assistant Professor of Psychology, Department of Psychiatry, Harvard Medical School

1991-2004 Co-Director, Psychology Research Laboratory, McLean Hospital
1994-present Associate Professor of Psychology, Department of Psychiatry, Harvard Medical School
2004-present Director, Psychology Research Laboratory, McLean Hospital

Other Experience and Professional Memberships

1976-present Member, American Psychological Association
1976-present Member, American Association for the Advancement of Science
1977-present Member, New York Academy of Sciences
1980-present Member, Rapaport-Klein Study Group
1983-2005 Member, American Psychopathological Association
1986-present Member, Society for Research in Psychopathology (SRP)
1988-present Member, Society for Neuroscience
1988-2002 Member, Association for Research in Vision and Ophthalmology
1990 Member, Program Committee, SRP
1993-present Member, International Society of Psychiatric Genetics
1993-1997 Editorial Board, *Biological Psychiatry*
1998 Chair, Program Committee, SRP
2002-2004 Executive Board, SRP
2006-present Member, Schizophrenia International Research Society
2006-present Fellow, American Psychopathological Association
2008-2012 Member, Initial review Group (NPAS), National Institute of Mental Health
2012 *Ad hoc* reviewer, NIMH Special Emphasis Panel
2013-present Editorial Board, *Schizophrenia Bulletin*
2013-present Editorial Board, *Journal of Bioequivalence and Bioavailability*
2015-present Scientific Advisory Board, INSERM, Center for Psychiatry & Neurosciences, University of Paris Descartes

Honors

1979 Prize-winning Research Paper, Alumni Association, Menninger School of Psychiatry
1991 Valerie Schoenfeld Award, Mental Health Association of Suffolk County, New York
2004-2008 Philip S. Holzman Memorial Investigator, National Alliance for Research on Schizophrenia and Depression (NARSAD)
2007-2010 Sidney R. Baer, Jr. Foundation Investigator, NARSAD

C. Contributions to Science

1. Endophenotypes as pleiotropic effects of schizophrenia-related genes; The Levy laboratory's contributions have significantly advanced our understanding of the genetic complexity of psychotic disorders, especially schizophrenia. Her group was the first to show that certain traits associated with schizophrenia have a much higher recurrence in relatives than does schizophrenia. These include eye-tracking dysfunction, thought disorder, craniofacial dysmorphology, and evoked potential responses. Her laboratory proposed and advanced the concept that such traits are pleiotropic expressions of schizophrenia risk genes that are more penetrant than the clinical disorder. She and her collaborators have also documented the enhanced power of using a disease-related endophenotype in genetic studies.

a. **Levy DL**, Bowman E, Abel LA, Krastoshevsky O, Krause V, Mendell NR (2008). Does performance on the standard antisaccade task meet the co-familiality criterion for an endophenotype? *Brain & Cognition*, 68: 462–475. PMCID: PMC2587517.
b. **Levy DL**, Coleman MJ, Sung H, Ji F, Mendell NR, Titone D (2010). The genetic basis of thought disorder and language and communication disturbances in schizophrenia. *Journal of Neurolinguistics*, 23:176–192. PMCID: PMC2821112.
c. Deutsch CK, **Levy DL**, Price SF, Bodkin JA, Boling L, Coleman MJ, Johnson F, Lerbinger J, Matthysse S, Holzman PS (2015). Quantitative measures of craniofacial dysmorphology in a family study of schizophrenia and bipolar illness. *Schizophrenia Bulletin*, 41:1309-1316. PMCID: PMC4601702.

d. Morgan CJ, Coleman MJ, Ulgen A Boling L Cole JO Johnson FV, Lerbinger J, Bodkin, JA, Holzman PS, **Levy DL** (2017). Thought disorder in schizophrenia and bipolar disorder probands, their relatives, and non-psychiatric controls. *Schizophrenia Bulletin*, 43:523-535. PMID: 28338967

2. Rare and *de novo* structural variants as risk factors in neurodevelopmental disorders; Our studies have documented the increased mutational burden for rare structural variants in schizophrenia. Some of these, the so-called "hot spots," are recurrent, but many more are "warm spots" or even private mutations. Although most are inherited, many are *de novo* events. These studies have also shown that some of the same genomic regions implicated in schizophrenia are also associated with risk for autism, with reciprocal events involving the same region carrying differential risk for each disorder.

a. Sebat J, **Levy DL**, McCarthy S. (2009). Rare structural variants in schizophrenia. *Trends in Genetics*, 25:528-535. PMCID: PMC3351381.
b. Vacic V, McCarthy S, Malhotra D, Murray F, Cho H-H, Peoples A, Makarov V, Yoon S, Bhandari A, Corominas R, Iakoucheva L, Krastoshevsky O, Krause V, Larach-Walters V, Welsh DK, Craig D, Kelsoe JR, Gershon ES, Leal SM, Dell Aquila M, Morris DW, Gill M, Corvin A, Insel PA, McClellan J, King M-C, Karayiorgou M, **Levy DL**, DeLisi L, Sebat J. (2011). Duplications of the neuropeptide receptor *VIPR2* confer significant risk for schizophrenia. *Nature*, 471:499-503. PMCID: PMC21346763.
c. Malhotra D, McCarthy S, Michaelson JJ, Vacic V, Burdick KE, Yoon S, Cichon S, Corvin A, Gary S, Gershon ES, Gill M, Karayiorgou M, Kelsoe JR, Krastoshevsky O, Krause V, Leibenluft E, **Levy DL**, Makarov V, Bhandari A, Malhotra AK, McMahon FJ, Nothen MM, Potash JB, Rietschel M, Schulze TG, Sebat, J. (2011). High frequencies of *de novo* CNVs in bipolar disorder and schizophrenia. *Neuron*, 72:951-963. PMCID: PMC22196331.
d. Need AC, McEvoy JP, Gennarelli M, Heinzen EL, Ge D, Maia JM, Shianna KV, He M, Cirulli ET, Gumbs CE, Zhao Q, Campbell CR, Hong L, Rosenquist P, Putkonen A, Hallikainen T, Repo-Tiihonen E, Tiihonen J, **Levy DL**, Meltzer HY, Goldstein DB (2012). Exome sequencing followed by large-scale genotyping suggests a limited role for moderately rare risk factors of strong effect in schizophrenia. *Am J Hum Genet*, 91:303-312. PMCID: PMC 22863191.

3. Other Genetic Studies; The Levy laboratory participated in an international consortium to identify genetic risk factors for the development of clozapine-induced agranulocytosis (CIA). Risk for CIA is the chief factor limiting the more widespread use of this 'gold standard' among antipsychotic drugs. As part of the Levy laboratory's collaboration with Dr. Brennand, we recently characterized *CNTNAP2* expression patterns in hiPSC neural progenitor cells, hiPSC-derived neurons, and hiPSC-derived oligodendrocyte precursor cells in individuals with a heterozygous deletion of *CNTNAP2* and discordant clinical phenotypes. We showed that differences in exon- and allele-specific expression may play a critical role in the variable expressivity of schizophrenia-associated loci.

a. Goldstein JI, Jarskog LF, Hilliard C, Duncan L, Huang H, Lehner T, Lek M, Neale BM, Ripke S, Shianna K, Szatkiewicz JP, van den Oord EJCG, Cascorbi I, Dettling M, Gazit E, Goff DC, Holden AL, Kelly DL, Malhotra AK, Nielsen J, Pirmohamed M, Rujescu D, Werge T, **Levy DL**, Josiassen RC, Kennedy JL, Lieberman JA, Daly MJ, Sullivan PF (2014). Clozapine-induced agranulocytosis is associated with rare HLA-DQB1 and HLA-B alleles. *Nature Communications*, 5:4757. PMCID: PMC4155508.
b. Lee I, Carvalho Fonseca CMB, Douvaras P, Ho S-M, Hartley BJ, Zuccherato LW, Ladran IG, Siegel AJ, McCarthy S, Malhotra D, Sebat J, Rapoport J, Fossati V, Lupski JR, **Levy DL**, Brennand KJ (2015). Characterization of molecular and cellular phenotypes associated with a heterozygous *CNTNAP2* deletion using patient-derived hiPSC neural cells. *Npj Schizophrenia*, 1:Article number: 15019. PMCID: PMC4789165.
c. Legge SE, Hamshere ML, Ripke S, Pardinas AF, Goldstein JI, Rees E, Richards AL, Leonenko G, Jorskog LF, **Clozapine-Induced Agranulocytosis Consortium**, Chambert KD, Collier DA, Genovese G, Giegling I, Holmans P, Jonasdottir A, Kirov G, McCarroll SA, MacCabe JH, Mantripragada K, Moran JL, Neale BM, Stefansson H, Rujescu D, Daly MJ, Sullivan PF, Owen MJ, O'Donovan MC, Walters JTR (2016). Genome-wide common and rare variant analysis provides novel insights into clozapine-associated neutropenia. *Molecular Psychiatry* Jul 12. doi: 10.1038/mp.2016.97. [Epub ahead of print] PubMed PMID: 27400856.
d. Julia TCW, Carvalho CMB, Yuan B, Gu S, McCarthy S, Malhotra D, Sebat J, Siegel AJ, Rudolph

U, Lupski JR, **Levy DL**, Brennand KJ. Divergent levels of marker chromosomes in an hiPSC-based model of psychosis. *Stem Cell Reports*, 2017; 8:519-528. PMCID: PMC5355568.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40439359/?sort=date&direction=ascending

D. Research Support

Ongoing

R21MH105732 (Levy) 09/05/2014-08/31/2017
NIH/NIMH
Targeting a Genetic Mutation in Glycine Metabolism with D-Cycloserine
The goals of this study are to characterize the neurobiology of a triplication of the glycine decarboxylase gene and to determine the efficacy of augmentation with d-cycloserine.
Role: Principal Investigator

U01MH105670 (Goldstein) 01/01/2015-07/31/2018
NIH/NIMH/Subaward to Columbia University
1/3-Identifying regulatory mutations that influence neuropsychiatric disease
The goal is to identify mutations in regulatory regions of the genome that influence neuropsychiatric risk.
Role: McLean Hospital Corporation Subaward Site Principal Investigator

Ellison Foundation (Levy) 01/01/2012-12/31/2017
The Dissection of Genetic Mutations in Schizophrenia and Autism
The goals are to characterize the molecular and cellular mechanisms underlying specific mutations associated with neuropsychiatric disease and their differential expression across disorders and to identify the genetic and neuroprotective factors that modify the phenotypic consequences of targeted genetic mutations.
Role: Principal Investigator

Anonymous Foundation (Levy) 09/01/2007-No End Date
Identifying Schizophrenia Genes Using Copy Number Variants And Endophenotypes
The goals are to identify mutations in genes of schizophrenic individuals, to determine if they were inherited or arose *de novo*, and to determine whether any of these mutations is associated with schizophrenia itself and/or with an endophenotype.
Role: Principal Investigator

Carmela and Menachem Abraham Fund (Levy) 01/01/2011-No End Date
Genetic Studies of Autism and Schizophrenia Specified
Limited private funding to support the operations of the Psychology Research Laboratory.
Role: Principal Investigator

Team Daniel Fund (Levy) 06/01/2011-No End Date
Family Studies of Schizophrenia Specified
Limited private funding to support the operations of the Psychology Research Laboratory.
Role: Principal Investigator

Completed

R21MH097470 (Levy) 09/01/2012-11/30/2015*
R21MH097470 Supplement (Levy) 05/22/2014-11/30/2015
NIH/NIMH * 18-month NCE
Neurobiology of a Mutation in Glycine Metabolism in Psychotic Disorders
The goals are to characterize the neurobiology of a mutation in glycine metabolism and to carry out a double blind placebo-controlled glycine augmentation trial in mutation carriers with psychotic disorders.
Role: Principal Investigator

Fuller Foundation (Levy) 07/01/2013-06/30/2014
Targeted Treatment of a Genetic Mutation in Psychiatry

The goal was to help support the pharmacy costs associated with treating a rare mutation.
Role: Principal Investigator

Johnson Family Foundation (Levy) 12/01/2013-11/30/2014
Toward Personalized Medicine: New Frontiers in Psychiatric Genetics.
The goal was to help support the pharmacy costs associated with treating a rare mutation.
Role: Principal Investigator