BIOGRAPHICAL SKETCH

NAME: Voloudakis, Georgios

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

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
University of Crete, Heraklion	BS	07/2005	Biology
University of Crete, Heraklion	MS	12/2007	Cellular and Genetic Etiology, Diagnosis and Treatment of Human Diseases
University of Crete, Heraklion	MD	11/2011	Medicine
University of Crete, Heraklion	PHD	11/2015	Mechanisms of brain neuronal cell death in Alzheimer's disease
Icahn School of Medicine at Mount Sinai, New York, NY	Postdoctoral Fellow	06/2016	Molecular pathophysiology of Alzheimer's disease
Icahn School of Medicine at Mount Sinai, New York, NY	Resident	06/2020	Psychiatry Residency (Physician-Scientist Track)

A. Personal Statement

I am an Assistant Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai (ISMMS) where my research is focused on the identification of molecular pathways through which non-coding genetic variants confer susceptibility to neuropsychiatric disorders. My long-term research goal is to increase our understanding of the genetic component of these disorders and to identify biological targets and devise approaches for reversing genetically driven disease-associated perturbations. As genotyping and deep phenotyping approaches become more ubiquitous, I plan to work on the integration of multiple modalities to translate neuroscience in to precision psychiatry applications.

Towards furthering my long-term research plan, I have spent 11 years in research (contributing in the publication of 15 peer-reviewed studies that have been collectively cited > 650 times/ h-index: 10), obtaining the knowledge and skills that can support a genetically-informed drug discovery pipeline for neuropsychiatric disorders: (1) Identification of molecular targets with computational genomics approaches. Working under the mentorship of Dr. Roussos during my psychiatry residency, I have gained valuable experience in analyzing human genetic and multi-omics datasets. I am developing and applying mathematical models to identify causal variations, biological pathways and putative therapeutic targets in neuropsychiatric diseases. Specifically, we recently developed a novel machine-learning approach[1] for transcriptomic imputation that outperforms existing methods by integrating epigenetic information. My lab is now employing these models in the VA's Million Veteran Program (MVP) cohort and is leading the PsyheMERGE working group: "Towards a Precision Medicine Approach in Psychiatry based on Individual Imputation of Genomic Features" where we work with the other leading US biobanks to establish this field. (2) *In vitro* and *in vivo* preclinical validations. I have extensive experience in dissecting biological pathways and testing ways to reverse phenotype-associated molecular signatures *in vitro* (cell lines and primary cultures) and in animal models[2]. This experience will help me in the future to conceive and design *in vitro* and *in vivo* validation experiments for interesting findings from the above computational analyses. (3) Human clinical trials and cohort phenotyping. I have participated as a study physician in three clinical trials on schizophrenia spectrum disorders led by Dr. Perez to gain a deeper understanding of human studies and to help inform research ideas. Finally, I am part of the Phenomics working group of the VA's MVP to help improve the accuracy of the assignment of neuropsychiatric disorders to individuals in the cohort.

1. Zhang W‡, **Voloudakis G‡**, Rajagopal VM, Reahead B, Dudley JT, Schadt EE, […], Roussos P. 2019. Integrative Transcriptome Imputation Reveals Tissue-Specific and Shared Biological Mechanisms

Mediating Susceptibility to Complex Traits. Nat Commun. 2019 Aug 23;10(1):3834. PubMed PMID: 31444360; PubMed Central PMCID: PMC6707297.

2. Yoon YJ‡, **Voloudakis G‡**, Doran N, Zhang E, Dimovasili C, Chen L, […], Georgakopoulos A. PS1 FAD mutants decrease ephrinB2-regulated angiogenic functions, ischemia-induced brain neovascularization and neuronal survival. Mol Psychiatry. 2020 Jun 15. PubMed PMID: 32541930.

‡ Authors contributed equally to this work

B. Positions and Honors

Positions and Employment

2003 - 2005	BS thesis student, Dr. Despina Alexandraki's Lab (Yeast molecular genetics), Institute of Molecular Biology and Biotechnology (IMBB), Foundation for Research and Technology - Hellas (FORTH), Heraklion, Greece
2006 - 2006	Training MS student, Dr. Dimitrios Boumpas' Lab (Genetics of autoimmune and autoinflammatory diseases), Medical School, University of Crete, Heraklion, Greece
2006 - 2007	MS thesis student, Dr. Dimitrios Georgopoulos' Lab (ICU lab: lung mechanics and inflammation), Medical School, University of Crete, Heraklion, Greece
2007 - 2007	Visiting Scholar, Dr. John Lygeros' Lab (Automatic Control Laboratory: mathematical modeling and automatic control systems), Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
2007 - 2011	Medical Student, Medical School, University of Crete, Heraklion, Greece
2011 - 2015	Associate Researcher, Dr. Nikolaos Robakis' Lab (Molecular Biology and Genetics of Neurodegeneration), Icahn School of Medicine at Mount Sinai, Department of Psychiatry, PI: Nikolaos Robakis, PhD, New York, NY, USA
2015 - 2016	Postdoctoral Fellow, Dr. Nikolaos Robakis' Lab (Molecular Biology and Genetics of Neurodegeneration), Icahn School of Medicine at Mount Sinai, Department of Psychiatry, PI: Nikolaos Robakis, PhD, New York, NY, USA
2016 - 2020	Psychiatry Resident (Physician-Scientist Track), Icahn School of Medicine at Mount Sinai, New York, NY, USA
2019 - 2020	Chief Resident for Research, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
2020 - present	Assistant Professor (investigator-track), Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Other Experience and Professional Memberships

2004 - 2007	Teaching Assistant: "Applications of computers in Biology", Biology Department, University of Crete, Greece
2006 - 2008 2010 - 2011	Teaching assistant: "Interdisciplinary approach to the molecular and genetic etiology, diagnostics and therapeutics of the hereditary and acquired diseases of the human", Graduate Program: "Cellular and Genetic Etiology, Diagnosis and Treatment of Human Diseases", Medical School, University of Crete, Greece
2018 - 2020	Course Lecturer (2018-2020) & Course Director (2019-2020): "Evidence-Based Psychiatry & Psychopharmacology", Psychiatry Residency program, Icahn School of Medicine at Mount Sinai
2018 - 2020	Study physician on Clinical Trials – Site: Icahn School of Medicine at Mount Sinai - PI: Mercedes Perez, MD, PhD: ● "A Phase 4, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Persistence of Effect and Safety of Valbenazine for the Treatment of Tardive Dyskinesia", Neurocrine Biosciences. (2018-2019) ● "Visual Attention to Social Cues as a Target for Social Cognitive Enhancement with Oxytocin in the Schizophrenia Spectrum", AiCure (2018-2020) ● "A Pilot Study of Digital Health Technology Assessments in Schizophrenia", Takeda Pharmaceutical Company (2018-2020)

2018 - present	Ad hoc reviewer for Biological Psychiatry (2×), PeerJ (2×; Bioinformatics and Genomics section) and Frontiers in Molecular Biosciences (1×; RNA section)

Honors

2005	BS Biology awarded with Honors (ranked 2nd; Salutatorian), Biology Department, University of Crete, Greece
2005 - 2006	Masters Fellowship (1-year; academic merit-based: top 3 students; graduate program-specific), Graduate Program: "Cellular and Genetic Etiology, Diagnosis and Treatment of Human Diseases", Medical School, University of Crete, Greece
2006	3rd Place for the abstract: “Effect of Ventilatory Rate on the Development of Ventilator Induced Lung Injury in a Mouse Model.”, 10th State-of-the-Art Interdisciplinary Review Course on Pulmonary Diseases, Critical Care, Emergency Medicine & Nursing Care, Athens, Greece
2007	MS awarded with High Honors, Medical School, University of Crete, Greece
2010	Erasmus mobility grant to be an exchange medical student at Karolinska Institutet, Sweden, European Commission
2011	MD awarded with Honors, Medical School, University of Crete, Greece
2012 - 2014	2 × “Maria Michail Manasaki” award scholarship for excellence in graduate studies (1-year; academic merit-based: top 1.5%; university-specific), University of Crete, Greece
2018 - 2020	Leon Levy Fellowship in Neuroscience (2-year; academic merit-based; selection from top Neuroscience institutes in New York), Icahn School of Medicine at Mount Sinai
2019 - 2020	Chief Resident for Research, Department of Psychiatry, Icahn School of Medicine at Mount Sinai
2020	Career Development Institute (CDI) for Psychiatry Awardee, University of Pittsburgh & Stanford University, NIMH (R25MH090947)
2020	Mentored Clinical Scientist Career Development Award, NIMH (K08MH122911)
2020	BBRF (NARSAD) Young Investigator Grant
2020	Million Veteran Program (MVP) Early Stage Investigator (ESI) Award

C. Contribution to Science

1. **Identified roles for noncoding variation in Neuropsychiatric disorders.** Despite advancements in identifying genetic loci that increase susceptibility to common psychiatric disorders like schizophrenia (SCZ), our understanding of how these variants confer liability remains poor. Most identified risk variants reside within non-coding regions of the genome, or in intergenic regions, and as such, the formulation of testable hypotheses to elucidate their potential function is challenging. Towards identifying a functional role for these variants, we are a) analyzing large-scale genomics and transcriptomics data to generate reference datasets[a], b) applying integrative analyses to model the effect of common disease-associated noncoding variants on gene expression and epigenome regulation[b] and c) validating these findings in cell systems[c]. We were the first to identify and validate variants that lie within brain-specific *cis* regulatory regions affecting the expression levels of proteins implicated in SCZ[c]. Our studies have been highly cited and have highlighted the need for annotating the brain epigenome and quantifying the effect of regulatory element variants on gene expression.

    a. Hoffman GE, Bendl J, **Voloudakis G**, Montgomery KS, Sloofman L, Wang YC, […], Roussos P. CommonMind Consortium provides transcriptomic and epigenomic data for Schizophrenia and Bipolar Disorder. Sci Data. 2019 Sep 24;6(1):180. PubMed PMID: 31551426.

    b. Zhang W‡, **Voloudakis G‡**, Rajagopal VM, Reahead B, Dudley JT, Schadt EE, […], Roussos P. 2019. Integrative Transcriptome Imputation Reveals Tissue-Specific and Shared Biological Mechanisms Mediating Susceptibility to Complex Traits. Nat Commun. 2019 Aug 23;10(1):3834. PubMed PMID: 31444360; PubMed Central PMCID: PMC6707297.

    c. Roussos P, Mitchell AC, **Voloudakis G**, Fullard JF, Pothula VM, Tsang J, […], Sklar P. A role for noncoding variation in schizophrenia. Cell Rep. 2014 Nov 20;9(4):1417-29. PubMed PMID: 25453756; PubMed Central PMCID: PMC4255904.

    ‡ Authors contributed equally to this work

2. **Novel role of Presenilin 1 (PS1) in neuroprotection and endothelial cell function.** There is a small proportion of Alzheimer's disease (AD) patients (~5%) that develop Familial AD (FAD) due to the presence of highly-penetrant mutations. More than 150 distinct mutations in PS1 cause FAD (18-50% of all FAD cases) but the mechanisms by which this happens are poorly understood and the amyloid cascade hypothesis can explain how this would happen in a small subset of the cases. Thus, we decided to study a) what is the physiological role of PS1 and b) how do PS1 FAD mutation cause AD. We have demonstrated that PS1 is required for growth factor mediated neuroprotection against toxic stimuli (like glutamate excitotoxicity or oxygen and glucose deprivation). Specifically, absence of PS1 leads to neuron-specific gene expression dysregulation (including miRNAs[c]) that impairs the neuronal ability to respond to glucose deprivation or use epidermal growth factor receptor ligands to prevent neuronal cell death from glutamate excitotoxicity[d]. Moreover, we have demonstrated that PS1 is required for primary endothelial cell function. We have shown that PS1 acting as the catalytic domain of the γ-secretase complex cleaves Ephrin B2 and that the CTF fragment then leads to endothelial cell sprouting and tube formation[b]. Towards a more translational approach we demonstrated that presence of PS1 FAD mutations also impairs these PS1 functions both *in vitro* and *in vivo*. Interestingly, in our middle cerebral artery occlusion model, mice carrying PS1 FAD mutations exhibit impaired revascularization after stroke that leads to extended brain damage and prolonged brain edema[a]. These studies carry a substantial potential in changing the way we perceive FAD, if not AD in general, as they suggest that a) the inability of neuronal cells to recover from toxic stimuli and b) the impairment or the revascularization process in the brain after mini-strokes may play an important role in the development of the disease.

   a. Yoon YJ‡, **Voloudakis G‡**, Doran N, Zhang E, Dimovasili C, Chen L, […], Georgakopoulos A. PS1 FAD mutants decrease ephrinB2-regulated angiogenic functions, ischemia-induced brain neovascularization and neuronal survival. Mol Psychiatry. 2020 Jun 15. PubMed PMID: 32541930.
   b. Warren NA, **Voloudakis G**, Yoon Y, Robakis NK, Georgakopoulos A. The product of the γ-secretase processing of ephrinB2 regulates VE-cadherin complexes and angiogenesis. Cell Mol Life Sci. 2018 Aug;75(15):2813-2826. PubMed PMID: 29428965; PubMed Central PMCID: PMC6023733.
   c. Huang Q, **Voloudakis G**, Ren Y, Yoon Y, Zhang E, Kajiwara Y, […], Robakis NK. Presenilin1/γ-secretase protects neurons from glucose deprivation-induced death by regulating miR-212 and PEA15. FASEB J. 2018 Jan;32(1):243-253. PubMed PMID: 28855274; PubMed Central PMCID: PMC5731132.
   d. Bruban J‡, **Voloudakis G‡**, Huang Q, Kajiwara Y, Al Rahim M, Yoon Y, […], Robakis NK. Presenilin 1 is necessary for neuronal, but not glial, EGFR expression and neuroprotection via γ-secretase-independent transcriptional mechanisms. FASEB J. 2015 Sep;29(9):3702-12. PubMed PMID: 25985800; PubMed Central PMCID: PMC4550373.

   ‡ Authors contributed equally to this work

3. **First animal model study to identify the harmful effects of increasing the respiratory rate in mechanical ventilation under normal tidal volume conditions - a common practice in a subset of patients at that time.** When critically ill patients with compromised pulmonary function (ARDS) are mechanically ventilated it is difficult to keep gas exchange in the lungs at adequate levels. It had already been shown in the literature that increasing the tidal volume, thus stretching the lungs, can lead to ventilator-induced lung injury and inflammation, thus, clinical guidelines suggested to increase the number of breaths (respiratory rate; RR) to deliver more air. However, the safety of a high RR had not been supported by experimental data. We were the first group to show in a clinically relevant constant P_aCO_2 mouse model that increasing the respiratory rate even when keeping the tidal volume at normal levels leads to ventilator-induced lung injury (confirmed by inflammatory markers and histology) even without alteration of pulmonary mechanics (what would be frequently tested in the clinic). This was a very highly cited study in the field that provided evidence for changing mechanical ventilation guidelines after the findings were verified in patients.

   a. Vaporidi K, **Voloudakis G**, Priniannakis G, Kondili E, Koutsopoulos A, Tsatsanis C, Georgopoulos D. Effects of respiratory rate on ventilator-induced lung injury at a constant PaCO2 in a mouse model of normal lung. Crit Care Med. 2008 Apr;36(4):1277-83. PubMed PMID: 18379255.

4. **Characterization of the genetic basis of autoimmune and autoinflammatory conditions.** The aberrant responses of the innate and adaptive immune systems are poorly understood. I have participated in studies that have associated functional polymorphisms of the *PTPN22* gene – a T and B cell receptor modulator -

with increased risk of developing systemic lupus erythematosus and other autoimmune disorders[b]. In a different line of research, we elucidated why humans are generally more sensitive to endotoxins (bacterial components) when compared with experimental animals such as mice. By expressing human caspase-4 in mice we were able to mimic the human responses to endotoxins in mice; this overzealous innate immune system response is considered to be the culprit that drives septic/ toxic shock and multiple organ dysfunction syndromes[a]. This study could now provide a novel therapeutic target for systemic inflammatory response syndrome, sepsis, septic shock, and related disorders.

a. Kajiwara Y, Schiff T, **Voloudakis G**, Gama Sosa MA, Elder G, Bozdagi O, Buxbaum JD. A critical role for human caspase-4 in endotoxin sensitivity. J Immunol. 2014 Jul 1;193(1):335-43. PubMed PMID: 24879791; PubMed Central PMCID: PMC4066208.
b. Eliopoulos E, Zervou MI, Andreou A, Dimopoulou K, Cosmidis N, **Voloudakis G**, […], Goulielmos GN. Association of the PTPN22 R620W polymorphism with increased risk for SLE in the genetically homogeneous population of Crete. Lupus. 2011 Apr;20(5):501-6. PubMed PMID: 21543514; PubMed Central PMCID: PMC3312778.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/georgios.voloudakis.1/bibliography/public/

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

Ongoing Research Support

1K08MH122911-01, NIMH Voloudakis, G (PI) role: PI 07/01/20-06/30/24
Characterizing and targeting subphenotypes of schizophrenia and bipolar disorder via individually imputed tissue and cell-type specific transcriptomes. This project will use tissue and cell-type specific imputed transcriptomes for individuals with SCZ or BD to identify, characterize and target subphenotypes of those disorders. We will use the Million Veteran Program and Cooperative Studies Program 572 ("The Genetics of Functional Disability in Schizophrenia and Bipolar Illness") as the discovery cohorts and will validate our findings in the PsycheMERGE and BioMe cohorts.

Completed Research Support

1P30AG066514 Sub# 7747, NIA Robakis, N (PI) role: Co-I (scholar) 05/01/20-06/30/20
Mount Sinai ADRC Years 36-40 - Research Educational Component (REC). The Mount Sinai ADRC Research Education Component will provide a formalized training program to prepare the next generation of researchers for careers in Alzheimer's disease. I had to withdraw from this grant after I received my K08 award (as above).

3R01MH109677-03S2, NIMH Roussos, P (PI) role: Co-I 09/01/18-05/31/20
NIMH Administrative Supplement Program to Enable Continuity of Research Experiences of MD/PhDs during Clinical Training. The purpose of this NIMH Administrative Supplement Program is to support advanced research opportunities for exceptional individuals holding the MD/PhD degree who are early in their research careers and thereby help these individuals transition efficiently and effectively from the period of clinical training to the next stage of their research careers.

5P50AG005138-35, NIA Sano, M (PI) role: Pilot Project PI 07/15/19-03/31/20
Alzheimer's Disease Research Center [PILOT 35-3: Identifying genetically-driven microglial gene expression changes in AD]. First, we will generate and make publicly available brain tissue and microglia-specific transcriptomic imputation changes. Second, we will identify genetically-driven brain and microglial gene expression changes in AD. Third, we will identify drug repurposing candidates that would reverse these changes. We expect this analysis to increase our mechanistic understanding of AD pathogenesis and prioritize drug repurposing candidates for preclinical studies of AD by targeting AD-specific microglial dysfunction.