BIOGRAPHICAL SKETCH

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NAME: Gilad D. Evrony

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

POSITION TITLE: Assistant Professor, New York University, Center for Human Genetics and Genomics, Depts. of Pediatrics and Neuroscience & Physiology

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
Massachusetts Institute of Technology	B.S.	05/2007	Brain and Cognitive Sciences
Harvard University	Ph.D.	05/2013	Neuroscience; Genetics
Harvard Medical School	M.D.	05/2015	Medicine
Mount Sinai Hospital / Icahn School of Medicine		06/2018	Pediatrics residency

A. Personal Statement

My research is focused on the development of foundational new technologies for neuroscience and genomics with both basic science and clinical impact. As a graduate student in the laboratory of Christopher Walsh, I led the development of the first single-cell genomics methods applied to the brain. I was motivated to develop technologies to sequence single brain cells because of the knowledge that this would be the only way to fully reveal the scope of somatic mutation in the human brain, as well as the possible role of somatic mutations in neuropsychiatric disease. Through extensive technology development, these studies were the first to achieve genome-wide sequencing of single normal human cells and the first to perform single-cell genome sequencing in the brain. Using these methods, we found that diverse somatic mutations are prevalent in every cell of the normal brain, we performed lineage tracing in human brain, and we identified pathogenic brain-specific somatic mutations causing focal dysplasias— the first brain-specific somatic mutation disease whose genetic etiology was determined.

In addition to broad training in bioengineering (laboratory of Dr. Robert Langer; MIT), developmental neuroscience, molecular biology, and bioinformatics, I have extensive experience in human genetics. In the laboratory of Dr. Walsh, I developed transcriptome (RNA)-sequencing as a systematic approach to functionally profile and discover pathogenic non-coding mutations in Mendelian diseases for which DNA-sequencing alone failed to identify any causative coding mutations. This led to the discovery of a novel human disease gene (*DONSON*) encoding a previously unknown and essential component of the DNA replication machinery. During my pediatrics residency, I also co-founded, together with Dr. Bruce Gelb, an Undiagnosed Diseases Program at the Mount Sinai Kravis Children's Hospital, which employs precision genomics and functional studies to find genetic diagnoses for children with rare and atypical diseases for whom standard genetic and medical evaluations (sometimes spanning many years) have been unfruitful. In its first year, the program profiled 25 cases and identified the causes of ~30% of these, finding both novel mutations in known ultra-rare disease genes and discovering a novel disease gene causing multi-systemic autoimmune disease for which there is an FDA-approved small-molecule drug specific to the mutant protein (treatment of the patient is ongoing; unpublished).

Overall, my research focused on technology development for neuroscience, development, and genomics, has been motivated by the belief that new technologies are essential for progress in understanding the brain, how it forms, and neuropsychiatric diseases. As a physician-scientist, I am also deeply motivated to

understand and research diseases whose causes are unknown to help alleviate the burden of these diseases. I have had significant leadership experience (including as a team leader in the Israel Defense Forces Intelligence Division) and have worked closely with collaborators from diverse scientific and personal backgrounds (for example, launching a comparative medicine initiative at Harvard Medical School with zoological veterinarians). I value the excitement of team-building, shared creation, and discovery in an interdisciplinary environment, and I plan to apply these skills and collaborative approach in my laboratory.

B. Positions and Honors

Professional Experience

2018- Assistant Professor, Center for Human Genetics and Genomics, Depts. of Pediatrics and Neuroscience & Physiology

2016-18 Pediatric Precision Medicine Program, Co-founder with Dr. Bruce Gelb, Mount Sinai Hospital
Developed a precision medicine program applying advanced genomics technologies for patients with rare and undiagnosed diseases at Mount Sinai Kravis Children's Hospital.

2015-18 Pediatrics Resident, Mount Sinai Hospital / Icahn School of Medicine

2007-15 Medical Scientist (MD-PhD) Training Program, Harvard Medical School

2005-07 Research assistant, Laboratories of Professors Robert Langer and Robert H. Brown, Jr, MIT and Massachusetts General Hospital
Developed a nanoparticle-based noninvasive diagnostic and drug delivery system targeted to neurons for treating amyotrophic lateral sclerosis (ALS).

2002-05 Technology R&D (Rank: Staff Sgt.), Intelligence Division, Israel Defense Forces
Directed a team of researchers in strategic, long-term projects pioneering new intelligence gathering technologies.

Awards and Recognitions

2018 Kurt Hirschhorn Clinician-Scientist Award
Awarded to the best research by a pediatrics resident at Mount Sinai Hospital.

2016 Eppendorf & *Science* Prize for Neurobiology
Awarded annually by the AAAS and *Science* magazine for the most outstanding neurobiological research by a young scientist.

2015 MIT Technology Review TR35 Young Innovator Award
Recognizes the top young innovators in the world under age 35.

2015 Sirgay Sanger Award, Harvard Medical School
Recognizing a graduating student’s excellence in psychiatry or applied neuroscience research.

2013 Cajal Club Foundation Krieg Cortical Scholar Prize

2013-15 Louis Lange III, MD, PhD Scholar in Translational Research at Harvard Medical School
Awarded to one MD-PhD student every two years at Harvard Medical School.

2007 Hans-Lukas Teuber Award for Outstanding Academics, MIT Dept. of Brain and Cognitive Sciences

2007 MIT Biomedical Engineering Society - Excellence in Biomedical Engineering Research Prize

2005 Personal Achievement Award for “Exceptional Achievements and Contributions to the Security of the State of Israel”, Israel Defense Forces

Clinical Licensure

New York State Medical License
American Board of Pediatrics, Board Eligible

Invited Talks (Selected)

2017, “What gorillas, tapirs, and meerkats can teach us: The One Health approach to medicine”. Dept. of Medicine Grand Rounds, New York Medical College, NY

2017, “One Brain, Many Genomes”. Allen Institute for Brain Science, Seattle, WA.

2015, “Single-neuron Sequencing Studies of Somatic Mutation in the Human Brain”. Dept. of Psychiatry, Mount Sinai Hospital, NY.

2013, “Single-neuron Sequencing Analysis of L1 Insertions in Human Brain”. Mobile Genetic Elements conference, Cold Spring Harbor Laboratory, NY.

2013, “Tracing Cell Lineages in the Human Brain by Somatic Mutation Analysis”. Broad Institute, MA.

C. Contributions to Science

1. Single-neuron genomics studies of somatic mutation in the human brain: In my doctoral research with Dr. Christopher A. Walsh, I led the development of methods to sequence the genomes of single cells from the human brain, with the goal of systematically characterizing the prevalence and patterns of somatic mutation. The degree to which somatic mutations occur in normal tissues during development and aging is largely unknown and is a blindspot in understanding the origins of genetic disease. At the same time, the role of somatic mutations in diverse neurologic diseases is becoming increasingly appreciated. This work was the first set of single-cell studies systematically measuring the prevalence and patterns of somatic mutation in the brain (and indeed in any normal non-cancer tissue), and together with single-cell studies of sperm and breast cancer heralded the emergence of the field of single-cell genomics. The identification of somatic mutations using this technology also enabled us to perform the first spatial tracing of cell lineages in the human brain to study its development and progenitor migration patterns, something previously possible only using invasive markers (GFP, retroviruses, etc.) in animal models. We further applied these methods to surgically-resected brains from patients with hemimegalencephaly in whom one malformed brain hemisphere leads to intractable seizures necessitating hemispherectomy. Single-cell genomics traced the origin of the inciting somatic mutations to neuroglial progenitors of the cortex, providing insight into the origins of focal neurologic diseases. As a result of these studies, the NIH has assembled a consortium (Brain Somatic Mosaicism Network) to use these technologies to further characterize to what extent somatic mutations are involved in other neuropsychiatric diseases. This work has led to my receiving several awards, including the Eppendorf & *Science* magazine Prize for Neurobiology and the *MIT Technology Review* World’s Top 35 Innovators Under Age 35 award.

Evrony GD. One brain, many genomes. **Science**. 354(6312):557-558. 2016. PMCID: 6141038

Evrony GD*, Lee E*, Mehta BK, Benjamini Y, Johnson RM, Cai X, Yang L, Haseley P, Lehmann HS, Park PJ, Walsh CA. Cell Lineage Analysis in Human Brain Using Endogenous Retroelements, **Neuron**. 85(1): 49-59. 2015. (* co-first authors) PMCID: 4299461

Evrony GD*, Cai X*, Lee E, Hills LB, Elhosary PC, Lehmann HS, Parker JJ, Atabay KD, Gilmore EC, Poduri A, Park PJ, Walsh CA. Single-neuron sequencing analysis of L1 retrotransposition and somatic mutation in the human brain, **Cell**. 151(3): 483-496 (Front cover). 2012. (* co-first authors) PMCID: 3567441

Poduri A, Evrony GD, Cai X, Elhosary PC, Beroukhim R, Lehtinen MK, Hills LB, Heinzen EL, Hill A, Hill RS, Barry BJ, Bourgeois BF, Riviello JJ, Barkovich AJ, Black PM, Ligon KL, Walsh CA. Somatic activation of AKT3 causes hemispheric developmental brain malformations, **Neuron**. 74(1):41-8. 2012. PMCID: 3460551

2. Development of transcriptomic methods for gene discovery in Mendelian disease: Despite significant progress in identifying disease-causing mutations by next-generation sequencing, there remain many families with rare genetic diseases in whom coding (exonic) mutations are not found, suggesting that the responsible mutation is non-coding. It remains a significant challenge to identify the responsible mutation(s) in these individuals out of the haystack of thousands of non-coding variants, as it relies fundamentally on the ability to predict the effects of non-coding genetic variants, which can be difficult. I hypothesized that transcriptome (RNA)-sequencing of tissues from these families, in conjunction with DNA-sequencing, could reveal pathogenic non-coding mutations by identifying their effects on the transcriptome (expression levels and splicing). Using this approach, I first corroborated a splicing mutation our lab had already identified in *ZNF335* causing microcephaly (**Cell** 151(5): 1097-1112), and additional RNA-seq of embryonic human brains also helped characterize a non-coding element involved in cerebral cortical patterning (**Science** 343(6172):764-8). Next, I led a project applying this transcriptomic approach to an unsolved and unique syndrome, microcephaly-micromelia, that had been studied by our lab with every DNA sequencing modality without success for nearly a

decade. This identified a pathogenic intronic mutation in a novel human disease gene (*DONSON*) encoding a previously unknown and essential component of the DNA replication machinery (**Genome Research** 27(8): 1323-35), providing a proof of principle that transcriptome sequencing can identify novel disease genes in syndromes refractory to DNA-only sequencing.

Evrony GD*, Cordero DR*, Shen J*, Partlow JN, Yu TW, Walsh CA, et al. Integrated genome and transcriptome sequencing identifies a noncoding mutation in the genome replication factor DONSON as the cause of microcephaly-micromelia syndrome, **Genome Research**. 27(8):1323-1335. 2017. (* co-first authors) PMCID: 5538549

Bae BI*, Tietjen I*, Atabay KD, Evrony GD, Johnson MB, Asare E, Wang PP, Murayama AY, Im K, Lisgo SN, Overman L, Sestan N, Chang BS, Barkovich AJ, Grant PE, Topcu M, Politsky J, Okano H, Piao X, Walsh CA. Evolutionarily Dynamic Alternative Splicing of *GPR56* Regulates Regional Cerebral Cortical Patterning, **Science**. 343(6172):764-768. 2014. (* co-first authors) PMCID: 4480613

Yang YJ, Baltus AE, Matthew RS, Murphy EA, Evrony GD, Gonzalez DM, Wang EP, Marshall-Walker CA, Barry BJ, Jernej M, Tatarakis A, Mahajan MA, Samuels HH, Shi Y, Golden JA, Mahajnah M, Shenhav R, Walsh CA. Microcephaly gene links trithorax and REST/NRSF to control neural stem cell proliferation and differentiation, **Cell**. 151(5): 1097-1112. 2012. PMCID: 3567437

3. Co-founded a Pediatric Undiagnosed Diseases Program. In every pediatric population there are children with conditions that remain undiagnosed despite extensive evaluation and testing by multiple medical specialties. There are also children who present for the first time in the hospital, prior to any evaluations, with rare syndromes that do not fit any particular disease category or known diagnosis. These "medical mysteries" often have either already undergone or will lead to lengthy diagnostic odysseys for patients and their families, spanning numerous hospitalizations, medical specialties, and inconclusive tests. I have been interested in helping families with undiagnosed diseases since the start of my training in human genetics as a graduate student. Later in medical school, I was also fortunate to have the opportunity to be the first medical student to participate in a formal rotation at the NIH Undiagnosed Diseases Program with Dr. Bill Gahl and Dr. Cyndi Tifft. This was a special and memorable experience that inspired me to start a similar program during residency. During my residency, I launched the Mount Sinai Pediatric Undiagnosed Diseases Program together with Dr. Bruce Gelb, which along with a handful of other Undiagnosed Disease Programs across the country, brings new hope for families caring for children with undiagnosed diseases. So far we have enrolled 75 individuals from 25 families from across all pediatric specialties, and have found a diagnosis for ~30% of analyzed cases, consistent with the ‘solve rate’ of other undiagnosed disease programs. Among the solved cases is an entirely new autoimmune disease caused by somatic mutation of a previously unknown disease gene that happens to have an already FDA-approved targeted drug (functional studies and treatment of the patient are ongoing; unpublished). Other solved cases have identified new mutations in other ultra-rare disease genes (most of these diseases have fewer than 10 cases worldwide). For several cases, research collaborations have been initiated in order to perform specialized functional tests to confirm the diagnosis. This close interaction between the clinic and personalized research is a window into the future of pediatrics and precision medicine.

4. Initiated a comparative medicine course based at a zoo for medical students. As a student at Harvard Medical School, I initiated together with the veterinarians at the Franklin Park Zoo in Boston the first course in the country for medical students to do a veterinary medicine rotation at a zoo. The fact that nearly every disease seen in humans can be found in the animal kingdom is largely missing from medical school curricula. I was motivated to start this course by the perspective that human and veterinary medicine are intrinsically linked, two trunks of the same tree— an idea advocated by past luminaries of medicine including Rudolf Virchow and William Osler. My rotation at the zoo was a remarkable experience, with many exciting ideas for research in plain sight by asking the simple questions: “why is this animal’s disease prevalent in this species and how is it different or similar in humans?” Moreover, this experience taught me that there are countless variations in how bodies can function and get sick, and that each species, including humans, is susceptible to each disease to a different degree due to its particular genetics and physiology. For example, desert tortoises get bladder stones, bongos are susceptible to amyloidosis, cardiomyopathy is common in meerkats, and humans have cholesterol-induced atherosclerosis even though our closest great ape relatives do not. Yet medical students and physicians are rarely exposed to this comparative medicine approach, which could spur novel avenues for research and provide significant insight into why certain diseases affect certain species such as humans but not others. I wrote an article about my time at the zoo (**JAMA** 316(7):713-4), and as a result of

my experience, it was established as a formal course for medical students at Harvard. The course, and the experiences that I and subsequent participating students have had, has been featured in the **New York Times** ("Doctor, Your Patient Is Waiting. It's a Red Panda"; cover of Science section; June 29, 2018) and other media. This course, and others like it that may start as a result at other medical schools, will help bridge human and veterinary medicine in a mutually beneficial way and will stimulate research ideas and broad critical thinking early in medical students' careers, especially among aspiring physician-scientists.

Evrony GD. A Wild Rotation, **JAMA**. 316(7):713-4. 2016. PMCID: 5179038

5. Developed a nanoparticle drug delivery system targeted to neurons: As an undergraduate, I worked in the laboratory of Professor Robert S Langer (MIT) in collaboration with Professor Robert H Brown (MGH) to create nanoparticles targeted to neurons to enable versatile delivery of therapeutics to degenerating motor neurons in Amyotrophic Lateral Sclerosis (ALS). The surfaces of the nanoparticles were engineered to bind Tetanus toxin C fragment to cause retrograde transport of the nanoparticles from primary motor neurons to the central nervous system. I further assisted in developing a similar system containing contrast agent to image the speed of retrograde transport in spinal cords of ALS patients as a potential early diagnostic/biomarker for the disease.

Townsend SA*, Evrony GD*, Gu FX, Schulz MP, Brown RH Jr, Langer R. Tetanus toxin C fragment-conjugated nanoparticles for targeted drug delivery to neurons, **Biomaterials**. 28 (34): 5176-84. 2007. (* co-first authors) PMCID: 2435502

Complete List of Published Works in 'My Bibliography':
http://www.ncbi.nlm.nih.gov/sites/myncbi/1vc6IUcamxI5F/bibliography/40007148/public/?sort=date&direction=descending

D. Research Support

Ongoing

American Epilepsy Society Seed Grant: 01/2018 – 01/2019
Investigating somatic mutations in Rasmussen's encephalitis by high-depth and single-cell sequencing

Completed

T32GM007753 (NIH/NIGMS): Medical Scientist Training Program 07/2007 – 05/2015