BIOGRAPHICAL SKETCH

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NAME: Shendure, Jay Ashok

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

POSITION TITLE: Professor of Genome Sciences

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
Princeton University	A.B.	Jun 1996	Molecular Biology
Harvard University	Ph.D.	Aug 2005	Genetics
Harvard Medical School	M.D.	Jun 2007	Medicine

A. Personal Statement

My background includes the development of a broad range of impactful technologies for genetics, genomics, and molecular biology. Technologies, or applications thereof, to which I and/or my lab made major contributions include next-generation DNA sequencing (2005); multiplex targeted sequence capture (2007, 2009, 2013); exome sequencing (2009) and its application to Mendelian disorders (2009, 2010) and autism (2011, 2012, 2012); massively parallel reporter assays (2009) and their application to enhancers (2012); subassembly, also known as synthetic long reads (2010); haplotype-resolved genome sequencing (2011), including of the HeLa cell line (2013); non-invasive inference of fetal genomes from cell-free DNA (2012); exploiting chromatin interactions for chromosome-scale *de novo* genome assembly (2013) or metagenome deconvolution (2014); genome-wide frameworks for interpreting genetic variants (CADD: 2014) and for mapping gene regulation (CRISPR-QTL: 2019); epigenetic maps and tissue-of-origin inference from cell-free DNA (2016); whole organism lineage tracing by genome editing (GESTALT: 2016); combinatorial cellular indexing for genome assembly (2014) and for single cell profiling of chromatin accessibility (2015), nuclear architecture (2017), gene expression (2017, 2019), genome sequence (2020), co-assays (2018) and chemical transcriptomics (2020); saturation genome editing (2014) and its application to prospective functional interpretation of variants of uncertain significance in *BRCA1* (2018); organism-scale, single cell atlases of gene expression (worm: 2017, mouse: 2019, human: 2020) and chromatin accessibility (fly: 2018, mouse: 2018, human: 2020).

More detail and a subset of citations are provided in the “Contributions to Science” section below.

B. Positions and Honors

Professional Experience

- 2017 – Present Scientific Director, Brotman Baty Institute for Precision Medicine
- 2017 – Present Scientific Director, Allen Discovery Center for Cell Lineage Tracing
- 2015 – Present Investigator, Howard Hughes Medical Institute
- 2015 – Present Full Professor (with tenure), Dept. of Genome Sciences, University of Washington
- 2010 – Present Affiliate Professor, Division of Human Biology, Fred Hutchinson Cancer Research Center
- 2011 – 2015 Associate Professor (with tenure), Dept. of Genome Sciences, University of Washington

- 2007 – 2011 Assistant Professor, Department of Genome Sciences, University of Washington
- 1998 – 2007 Medical Scientist Training Program (MSTP), Dept. of Genetics, Harvard Medical School
- 1997 – 1998 Research Scientist, Vaccine Division, Merck Research Laboratories (Rahway, NJ)
- 1996 – 1997 Fulbright Scholar to India, Dept. of Pediatrics, Sassoon General Hospital (Pune, India)

Honors, Awards, Named Lectures

- 2019 Richard Lounsbery Award, National Academy of Sciences
- 2019 Jeffrey M. Trent Lectureship in Cancer Research, NHGRI, National Institutes of Health
- 2019 Paul D. Gottlieb Distinguished Lectureship, University of Texas, Austin
- 2019 Fellow, American Association for the Advancement of Science
- 2018 Allan C. Wilson Memorial Lectures, University of California, Berkeley
- 2018 Richard and Carol Hertzberg Prize for Technology Innovation, UC San Diego
- 2018 Dr. Nancy C. Andrews Physician-Scientist Lectureship, Duke University
- 2017 British Society of Genetic Medicine Lectureship, British Society of Genetic Medicine
- 2015 HHMI Investigator (2015 – present)
- 2014 40 under 40, Cell 40th Anniversary, Cell Press
- 2014 7th Annual Scripps Genomic Medicine Award, Scripps Health
- 2014 HudsonAlpha Prize for Life Sciences, HudsonAlpha Institute for Biotechnology
- 2013 FEDERAprijs, Federation of Dutch Medical Scientific Societies
- 2013 NIH Director's Pioneer Award, National Institutes of Health
- 2012 Curt Stern Award, American Society of Human Genetics
- 2010 Lowell Milken Young Investigator (2010-2013), Prostate Cancer Foundation
- 2008 Science in Medicine New Investigator Lecture, University of Washington
- 2007 James Tolbert Shipley Prize, Harvard Medical School
- 2006 TR35 Young Innovator Award, M.I.T. Technology Review
- 1998 Medical Science Training Program Fellowship, National Institutes of Health
- 1996 Fulbright Scholarship, U.S. State Department
- 1996 *summa cum laude*, Princeton University
- 1996 Honorary Major in Anthropology, Princeton University
- 1996 Sigma Chi Book Award for Molecular Biology Senior Thesis, Princeton University
- 1996 Senior Prize for Best Thesis in Anthropology, Princeton University
- 1996 Phi Beta Kappa, Princeton University
- 1992 National Merit Scholar, Solon High School

Academic Scientific Advisory Roles & Consortium Leadership

- 2018 – present Allen Institute for Immunology, Scientific Advisory Board
- 2018 – present Chan Zuckerberg Initiative, Human Cell Atlas Science Advisory Board
- 2017 – present Advisory Committee to NIH Director (ACD), National Institutes of Health
- 2017 – present Science, Board of Reviewing Editors
- 2017 – present Allen Institute for Cell Science, Stem Cells and Gene Editing Advisory Council
- 2015 Advisory Committee to NIH Director: Working Group on US Precision Medicine Initiative
- 2014 – 2018 NIH/NHGRI National Advisory Council for Human Genome Research
- 2015 – present NIH/NHGRI Center of Excellence in Genomic Science (Stanford University; PI: Howard Chang) (Scientific Advisory Board)
- 2015 – 2018 NIH/OD 4D Nucleome Network (Steering Committee)
- 2014 – 2019 NIH/NIAID Center of Excellence in Translational Research (Harvard School of Public Health; PI: Megan Murray) (Scientific Advisory Board)
- 2012 – 2014 Joint Genome Institute, Department of Energy (Scientific Advisory Board)

- 2012 – 2015 NIH/NHGRI Centers for Mendelian Genomics (Steering Committee)
- 2009 – 2012 NIH/NHLBI Exome Sequencing Project (Steering Committee)

C. Contributions to Science

My major scientific achievements comprise methodological advances that promise to or already have had broad impacts in human genetics and molecular biology. I am sole or joint corresponding author on all publications referenced below.

1. Next-generation DNA sequencing: My doctoral research laid the conceptual groundwork and achieved early milestones for massively parallel or next-generation DNA sequencing (NGS), including the first proof-of-concept of NGS for genome resequencing in 2005. After establishing my lab in 2007, I led the development and application of a diversity of enabling methods in genome sequencing, *e.g.* haplotype-resolved genome sequencing and its application to infer the genome of a fetus via samples obtained non-invasively from its parents; chromatin contact-based scaffolding of genome assemblies and its application to the HeLa genome; etc. We have also sought to apply NGS in creative ways, *e.g.* the inference of nucleosome positions and tissues-of-origin of cell-free DNA based on fragmentation patterns, and the use of that information for cancer diagnostics.

a. **Shendure J*#**, Porreca GJ*#, Reppas NB, Lin X, McCutcheon JP, Rosenbaum AM, Wang MD, Zhang K, Mitra RD, Church GM. Accurate Multiplex Polony Sequencing of an Evolved Bacterial Genome. *Science* 2005 Sep 9;309(5741):1728-32.

b. Kitzman JO#, Snyder MW, Ventura M, Lewis AP, Qiu R, Simmons LE, Gammill HS, Rubens CE, Santillan DA, Murray JC, Tabor HK, Bamshad MJ, Eichler EE, **Shendure J#**. Noninvasive whole-genome sequencing of a human fetus. *Science Translational Medicine* 2012 Jun 6;4(137):137ra76.

c. Adey A#*, Burton JN*, Kitzman JO*, Hiatt JB, Lewis AP, Martin BK, Qiu R, Lee C, **Shendure J#**. The haplotype-resolved genome and epigenome of the aneuploid HeLa cancer cell line. *Nature* 2013 Aug 8;500(7461):207-11.

d. Snyder MW*, Kircher M*, Hill AJ, Daza RM, **Shendure J#**. Cell-free DNA Comprises an In Vivo Nucleosome Footprint that Informs Its Tissues-Of-Origin. *Cell* 2016 Jan 14;164(1-2):57-68.

2. Exome sequencing and Mendelian genetics: My lab pioneered the development of exome sequencing as well as its earliest applications to identify the genetic basis of Mendelian disorders that resist conventional analysis. This paradigm that has been widely adopted in human genetics since we first reported it in 2009 and has been used to identify the genes underlying hundreds of rare diseases. In related work, we co-developed *de novo* mutation-focused approaches for discovering and validating genes underlying autism spectrum disorders.

a. Ng SB#, Turner EH, Robertson PD, Flygare SD, Bigham AW, Lee C, Shaffer T, Wong M, Bhattacharjee A, Eichler EE, Bamshad M, Nickerson DA, **Shendure J#**. Targeted capture and massively parallel sequencing of 12 human exomes. *Nature* 2009 Sep 10;461(7261):272-6.

b. Ng SB*, Buckingham KJ*, Lee C, Bigham AW, Tabor HK, Dent KM, Huff CD, Shannon PT, Jabs EW, Nickerson DA, **Shendure J#,** Bamshad MJ#. Exome sequencing identifies the cause of a mendelian disorder. *Nature Genetics* 2010 Jan;42(1):30-5.

c. O'Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, Levy R, Ko A, Lee C, Smith JD, Turner EH, Stanaway IB, Vernot B, Malig M, Baker C, Reilly B, Akey JM, Borenstein E, Rieder MJ, Nickerson DA, Bernier R, **Shendure J#**, Eichler EE#. Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature* 2012 Apr 4;485(7397):246-50.

d. O'Roak BJ, Vives L, Fu W, Egertson JD, Stanaway IB, Phelps IG, Carvill G, Kumar A, Lee C, Ankenman K, Munson J, Hiatt JB, Turner EH, Levy R, O'Day DR, Krumm N, Coe BP, Martin BK, Borenstein E, Nickerson DA, Mefford HC, Doherty D, Akey JM, Bernier R, Eichler EE#, **Shendure J#**. Multiplex Targeted Sequencing Identifies Recurrently Mutated Genes in Autism Spectrum Disorders. *Science* 2012 Dec 21;338(6114):1619-22.

3. Mutational analysis: My lab pioneered a new generation of methods for experimentally measuring or computationally predicting the functional consequences of mutations, including massively parallel reporter assays and saturation genome editing. We also developed combined annotation dependent depletion (CADD), a unifying and widely used framework for prioritizing variants observed in human genomes.

We are applying these methods to goals including the prospective functional interpretation of variants of uncertain significance, *e.g.* at the *BRCA1* locus.

a. Patwardhan RP#, Lee C, Litvin O, Young DL, Pe'er D, **Shendure J#.** High-resolution analysis of DNA regulatory elements by synthetic saturation mutagenesis. *Nature Biotechnology* 2009 Dec;27(12):1173.

b. Kircher M*, Witten DM*, Jain P, O'Roak BJ, Cooper GM#, **Shendure J#**. A general framework for estimating the relative pathogenicity of human genetic variants. *Nature Genetics* 2014 Mar;46(3):310.

c. Findlay GM#*, Boyle EA*, Hause RJ, Klein JC, **Shendure J#**. Saturation editing of genomic regions by multiplex homology-directed repair. *Nature* 2014 Sep 4;513(7516):120-3.

d. Findlay GM, Daza RM, Martin B, Zhang MD, Leith AP, Gasperini M, Janizek JD, Huang X, Starita LM#, **Shendure J#**. Accurate classification of BRCA1 variants with saturation genome editing. *Nature* 2018 Oct;562(7726):217-222.

4. Molecular methods: My lab has a long-standing and ongoing interest in developing new molecular methods for a broad range of goals in genomics and biomedical research more broadly. Recent examples include single cell combinatorial indexing ("sci-") assays or co-assays, genome editing of synthetic target arrays for lineage tracing (GESTALT), and a genome-wide framework for mapping gene regulation (CRISPR-QTL).

a. McKenna A*, Findlay GM*, Gagnon JA*, Horwitz MS, Schier AF#, **Shendure J#**. Whole organism lineage tracing by combinatorial and cumulative genome editing. *Science* 2016 Jul 29;353(6298):aaf7907.

b. Cusanovich DA, Daza R, Adey A, Pliner H, Christiansen L, Gunderson KL, Steemers FJ, Trapnell C, **Shendure J#.** Multiplex single-cell profiling of chromatin accessibility by combinatorial cellular indexing. *Science* 2015 May 22;348(6237):910-4.

c. Cao J, Cusanovich DA*, Ramani V*, Aghamirzaie D, Pliner HA, Hill AJ, Daza RM, McFaline-Figueroa JL, Packer JS, Christiansen L, Steemers FJ, Adey AC, Trapnell C#, **Shendure J#**. Joint profiling of chromatin accessibility and gene expression in thousands of single cells. *Science* 2018 Aug 30. pii: eaau0730.

d. Gasperini M#, Hill AJ, McFaline-Figueroa JL, Martin B, Kim S, Zhang MD, Jackson D, Leith A, Schreiber J, Noble WS, Trapånell C, Ahituv N, **Shendure J#.** A Genome-wide Framework for Mapping Gene Regulation via Cellular Genetic Screens. *Cell* 2019 Jan 10;176(1-2):377-390.e19.

5. Global views of development: Recently, we have begun applying single cell profiling and lineage tracing methods developed in the lab towards obtaining global views of development across a range of key organisms, including worm, fly, mouse and human.

a. Cao J*, Packer JS*, Ramani V, Cusanovich DA, Huynh C, Daza R, Qiu X, Lee C, Furlan SN, Steemers FJ, Adey A, Waterston RH#, Trapnell C#, **Shendure J#**. Comprehensive single-cell transcriptional profiling of a multicellular organism. *Science* 2017 Aug 18;357(6352):661-667.

b. Cusanovich DA, Hill AJ, Aghamirzaie D, Daza RM, Pliner HA, Berletch JB, Filippova GN, Huang X, Christiansen L, DeWitt WS, Lee C, Regalado SG, Read DF, Steemers FJ, Disteche CM, Trapnell C#, **Shendure J#**. A Single-Cell Atlas of In Vivo Mammalian Chromatin Accessibility. *Cell* 2018 Aug 23;174(5):1309-1324.e18.

c. Cusanovich DA*, Reddington JP*, Garfield DA*, Daza RM, Aghamirzaie D, Marco-Ferreres R, Pliner HA, Christiansen L, Qiu X, Steemers FJ, Trapnell C, **Shendure J#**, Furlong EEM#. The cis- regulatory dynamics of embryonic development at single-cell resolution. *Nature* 2018 Mar 22;555(7697):538-542.

d. Cao J*, Spielmann M*, Qiu X, Huang X, Ibrahim DM, Hill AJ, Zhang F, Mundlos S, Christiansen L, Steemers FJ, Trapnell C#, **Shendure J#**. The single-cell transcriptional landscape of mammalian organogenesis. *Nature* 2019 Feb;566(7745):496-502.

Complete List of Published Work:

http://www.ncbi.nlm.nih.gov/pubmed/?term=shendure%5Bau%5D

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

Investigator Award 09/01/15 – 08/31/21
Howard Hughes Medical Institute (Shendure)
No specific projects are associated with this funding. However, Dr. Shendure receives 100% of his salary and fringe benefit (FB) compensation from the Howard Hughes Medical Institute (HHMI). HHMI support is broadly being used to develop and apply new genomic technologies.

Paul G. Allen Frontiers Foundation 09/01/17 – 08/31/21
Allen Discovery Center for Cell Lineage (MPI: Shendure, Elowitz, Schier *et al.*)
The goal of this project is to develop and implement novel technologies for whole organism lineage tracing to zebrafish and mouse.
Role: PI, Director

1UM1HG011586 (NIH/NHGRI) 09/01/20 – 08/31/25
UW 4-Dimensional Genomic Organization of Mammalian Embryogenesis Center (MPI: Noble, Disteche, Shendure)
The UW 4D Genome Organization of Mammalian Embryogenesis Center (UW 4D GENOME) will carry out systematic generation of sequencing and imaging data during mouse embryogenesis, summarizing and visualizing the resulting data using machine learning models.
Role: PI (MPI award)

1UM1HG009408 (NIH/NHGRI) 02/01/17 – 01/31/21
Massively parallel reporter assays and genome editing of ENCODE predicted regulatory elements (MPI: Ahituv, Shendure)
This project will implement `in genome' massively parallel functional assays to characterize over 100,000 ENCODE-based candidate regulatory elements, to confirm and quantify their activities as well as to link many of them to their target genes.
Role: PI (MPI award)

1U54HL145611 (NIH/NHLBI) 09/01/18 – 08/31/22
A spatially resolved molecular atlas of human endothelium (MPI: Cai, Shendure, Trapnell)
The goals of the project are: 1) Evaluation and optimization of high-throughput single cell and spatial genomics methodologies for spatial atlas generation. 2) Optimization of highly multiplexed in situ seqFISH imaging to determine spatial distribution of cell types. 3) Generation of a multi-scale atlas to enable multidimensional cellular, morphological and molecular mapping of endothelial cells in different organs. 4) Integration of sci-RNAseq and seqFISH data.
Role: PI (MPI award)

1R01HG009136 (NIH/NHGRI) 04/21/17 – 01/31/21
Predictive modeling of alternative splicing and polyadenylation from millions of random sequences (MPI: Seelig, Shendure)
This project aims to develop predictive models of alternative splicing and polyadenylation by learning from millions of synthetic constructs. These models will be applied for understanding the consequences of genetic variation in humans and how this variation can lead to disease.
Role: PI (MPI award)

1R01HG010632 (NIH/NHGRI) 08/1/19 – 07/31/23
Versatile, exponentially scalable methods for single cell molecular profiling (Shendure)
The major goal of the project is to develop a much broader range of single cell methods than is currently available.
Role: PI