BIOGRAPHICAL SKETCH

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NAME: Shendure, Jay Ashok

eRA COMMONS USER NAME: shendure

POSITION TITLE: Professor of Genome Sciences

EDUCATION/TRAINING

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 developing a broad range of impactful technologies in human genetics and molecular biology. Technologies to which I or my lab made major contributions include next-generation DNA sequencing (2005); multiplex targeted sequence capture (2007); exome sequencing (2009) and its application to Mendelian disorders (2009), cancer (2011) and autism (2011); massively parallel reporter assays (2009) and their application to enhancers (2012); subassembly or synthetic long reads (2010); haplotype-resolved genome sequencing (2011); non-invasive inference of fetal genomes from sequencing of cell-free DNA (2012); dial-out PCR (2012); using chromatin interactions for chromosome-scale *de novo* genome assembly (2013) or metagenome deconvolution (2014); combined annotation dependent depletion or CADD for interpreting genetic variants (2014); saturation genome editing (2014); multiplex programming of allelic series and prospective functional interpretation of variants of uncertain significance (2015); high-throughput determination of RNA structure by proximity ligation (2015); nucleosome maps and tissue-of-origin inference from sequencing of cell-free DNA (2016); whole organism lineage tracing by combinatorial and cumulative genome editing (2016); and combinatorial cellular indexing for genome assembly (2014), single cell epigenetics (2015) or single cell transcriptomes (2017). More detail and 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 Director, Allen 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 and Awards

- 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

- 2017 – present Advisory Committee to NIH Director (ACD), National Institutes of Health
- 2017 – present Board of Reviewing Editors, Science
- 2017 – present Stem Cells and Gene Editing Advisory Council, Allen Institute for Cell Science
- 2015 Advisory Committee to NIH Director: Working Group on US Precision Medicine Initiative
- 2014 – present NIH/NHGRI National Advisory Council for Human Genome Research
- 2015 – present NIH/OD 4D Nucleome Network (Steering Committee)
- 2015 – present NIH/NHGRI Center of Excellence in Genomic Science (Stanford University; PI: Howard Chang) (Scientific Advisory Board)
- 2014 – present 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 next-generation DNA sequencing (NGS), including the first proof-of-concept of NGS for genome resequencing in 2005. After establishing my own lab in 2007, I led development of early methods for selective capture and NGS of genomic subsets, *e.g.* exome sequencing, as well as methods for library preparation including Tn5-based *in vitro* transposition and subassembly/synthetic long reads.

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. Turner EH, Lee C, Ng SB, Nickerson DA, **Shendure J#.** Massively parallel exon capture and library-free resequencing across 16 genomes. *Nature Methods* 2009 May;6(5):315-6.

c. 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.

d. Hiatt JB*[#], Patwardhan RP*, Turner EH, Lee C, **Shendure J**[#]. Parallel, tag-directed assembly of locally derived short sequence reads. *Nature Methods* 2010 Feb;7(2):119-22.

2. Mendelian and autism genetics: My lab pioneered the application of exome sequencing to identify the genetic basis of Mendelian disorders that resist conventional analysis, a paradigm that has been widely adopted in human genetics since we first reported it in 2009. We also co-developed *de novo* mutation-focused approaches for discovering and validating genes underlying autism spectrum disorders.

a. 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.

b. Ng SB*, Bigham AW*, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, Beck AE, Tabor HK, Cooper GM, Mefford HC, Lee C, Turner EH, Smith JD, Rieder MJ, Yoshiura KI, Matsumoto N, Ohta T, Niikawa N, Nickerson DA, Bamshad MJ[#], **Shendure J**[#]. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. *Nature Genetics* 2010 Sep;42(9):790-3.

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 developed several cutting-edge methods for experimentally measuring or computationally predicting the functional consequences of mutations. For example, we pioneered massively parallel reporter assays for multiplex saturation mutagenesis of *cis*-regulatory elements, as well as 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 continuing to develop methods for multiplex functional analysis of proteins, regulatory elements, and loci, with the goal of prospective functional interpretation of variants of uncertain significance.

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. Patwardhan RP*, Hiatt JB*, Witten DM, Kim MJ, Smith RP, May D, Lee C, Andrie JM, Lee SI, Cooper GM, Ahituv N[#], Pennacchio LA[#], **Shendure J**[#]. Massively parallel functional dissection of mammalian enhancers in vivo. *Nature Biotechnology* 2012 Feb 26;30(3):265-70.

c. 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

d. 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.

4. Haplotypes and contiguity in genome re-sequencing and *de novo* assembly: We developed some of the first methods for haplotype-resolved genome sequencing, and we also recently showed how long-range chromatin interactions facilitate chromosome-scale *de novo* genome assembly and metagenome convolution. We have also sought to demonstrate the utility of these methods. For example, we used haplotype-resolved genome sequencing towards achieving the first whole genome sequencing of a human fetus using samples obtained non-invasively from the parents during pregnancy. We also reported the first haplotype-resolved genome and epigenome of a human cancer, the aneuploid HeLa cancer cell line.

a. Kitzman JO[#], Mackenzie AP, Adey A, Hiatt JB, Patwardhan RP, Sudmant PH, Ng SB, Alkan C, Qiu R, Eichler EE, **Shendure J[#]**. Haplotype-resolved genome sequencing of a Gujarati Indian individual. *Nature Biotechnology* 2011 Jan;29(1):59-63.

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. Burton JN[#], Adey A, Patwardhan RP, Qiu R, Kitzman JO, **Shendure J[#]**. Chromosome-scale scaffolding of de novo genome assemblies based on chromatin interactions. *Nature Biotechnology* 2013 Dec;31(12):1119-25.

d. 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.

5. Molecular methods: My lab has a long-standing and ongoing interest in developing new molecular methods for a broad range of goals in biomedical research. In addition those methods described or referenced above, examples of methods which we developed include GESTALT (genome editing of synthetic target arrays for lineage tracing), combinatorial cellular indexing for multiplex single-cell profiling of chromatin accessibility, dial-out PCR for accurate gene synthesis, high-throughput determination of RNA structure by proximity ligation, and inference of nucleosome positions and tissue(s)-of-origin of cell-free DNA based on their fragmentation patterns.

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[#]**. *Science* 2017 Aug 18;357(6352):661-667.

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. 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.

d. 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.

Complete List of Published Work:

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

D. Research Support

Ongoing Research Support (PI or MPI awards only)

Investigator Award 09/01/15 – 08/31/20
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 being used to develop new genomic technologies, including for single cell analysis.

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

1DP1HG007811 (NIH/OD/NHGRI) 09/23/13 – 07/31/18
Interpreting genetic variants of uncertain significance (Shendure)

This project aims to develop novel experimental and computational paradigms for predicting the functional consequences of all possible single residue variants in clinically significant genes, thereby informing the interpretation of variants newly observed in patients.
Role: PI

1R01HG008123 (NIH/NHGRI) 03/01/15 – 02/28/18
Integrative interpretation of the organismal consequences of non-coding variation (Cooper, Shendure)
The goals are to further develop the CADD framework, to apply it in the context of ongoing genetic studies of both rare and common human diseases, and to experimentally evaluate its predictions.
Role: PI (MPI award)

1U54DK107979-01 (NIH/NIDDK) 09/01/15 – 7/31/20
University of Washington Center for Nuclear Organization and Function (MPI: Noble, Shendure)
This project will develop novel experimental and computational methods to characterize genome 3D architecture, validate the methods using mouse and human cells, and demonstrate the utility of the resulting data for improving our understanding of fundamental biology and human disease.
Role: PI (MPI award)

1R01HG009136-01A1 (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)

1UM1HG009408-01 (NIH/NHGRI) 09/01/15 – 7/31/20
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)