BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Alexander Eckehart Urban

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

POSITION TITLE: Associate Professor

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
Freie Universitaet Berlin, Germany	B.Sc. (equiv.)	07/1996	Biochemistry
Yale University, New Haven, CT	M.A.	05/2002	Mol., Cell. And Dev. Bio.
Yale University, New Haven, CT	Ph.D.	12/2007	Mol., Cell. And Dev. Bio.

A. Personal Statement

I have more than two decades of experience in developing and applying high-throughput and high-resolution genomics analysis tools and procedures, in particular in the context of studying genomic sequence variation in brain development and function. I have been involved on numerous occasions in using a large-scale and high-throughput setup for genomics analyses as well as carrying out analyses over several levels of genomics and epigenomics information. This includes for example participation in the ENCODE and 1000 Genomes projects and also in the Brain Somatic Mosaicism Network (BSMN) consortium project and the PsychENCODE consortium. I have extensive experience with developing and applying state-of-the-art and emerging genomics and epigenomics technologies for the analysis of gene expression, genomic DNA sequence and structure, DNA methylation and chromatin modification, in human cells and human cell culture systems, including stem cell culture models. For example I was co-first author of the paper in Science (Korbel, Urban, Affourtit et al., 2007, PMID 17901297) on developing next-generation-sequencing based paired-end mapping of CNVs and SVs, an approach that is now a standard part of whole-human-genome sequencing projects and also a critical component of advanced RNA-Seq approaches, the study of long-range chromatin interactions, and for the detection of mobile element insertions into the human genome.

Two main, and connected, directions of research in my laboratory are the investigation of the molecular effects of large genome sequence variants during neuronal development using iPSC model systems and the study of the nature and effects of somatic genome variation using tissue culture models and primary tissue samples. I have been mentoring multiple students and postdoctoral fellows since starting my own laboratory and, for example, four of these postdoctoral fellows have since started on faculty positions.

Ongoing and recently completed projects that I would like to highlight include:

U01 (MH116529)   04/01/2019 – 03/31/2024
Integrated, cell type specific functional genomics analyses of regulatory sequence elements and their dynamic interaction networks in neuropsychiatric brain tissues (PsychENCODE)
Create epigenomic maps of regulatory genomic elements and their interactions in neuropsychiatric disorders (schizophrenia, autism, bipolar disorder), using scRNA-Seq, scATAC-Seq, sorted HiChIP, phased whole-genome sequencing, nuclear proteomics and advanced approaches for data analysis.
Role: Contact-PI. MPIs: Urban, Hallmayer, Snyder

P50 (HG00773506) 07/01/2019 – 06/30/2024
Center of Excellence in Genomic Science (CEGS): Center for Personal Dynamic Regulomes
Use a transposase-based method for genome-wide analysis of open chromatin states. Map the interactions between lncRNAs, DNA methylation, high order chromosome interactions and genome sequence variation.
Role: Co-Investigator/Project Director. PI: Chang (renewal of P50 HG007735-01)

Jaswa Innovator Award 12/15/2019 – 12/15/2022
Bringing to light the dark genetic 'jumping' elements that are variable between individual human genomes and strongly implicated in psychiatric disorders
Explore the feasibility of using Nanopore sequencing to analyze retrotransposon elements in the germline genome.
Role: PI

Uytengsu-Hamilton 22q11 Neuropsychiatry Research Award 01/01/2020 – 12/31/2023
A genome analysis method to detect and resolve the exact boundaries of the 22q11 deletion
We will develop a novel method, CRISPR-Catch/Long-Read-Sequencing, and use it to
resolve for the first time the exact rearrangements in the SegDups around microdeletions in 22q11.2.
Role: PI

Simons Foundation SFARI Research Award 09/01/2016 – 08/31/2020
Somatic mosaicism in autism spectrum disorders
Explore the role of somatic genome variation in brain cells in autism spectrum disorders.
Role: Subcontract-PI. MPI: Vaccarino (Yale) and Abyzov (Mayo)

R01 (MH100914-01A1) 09/01/2013 – 12/31/2018
Genomic mosaicism in the developing human brain
Provide a comprehensive estimate of the allelic frequency of genomic variation in somatic cells of the brain.
Role: Subcontract-PI. MPI: Vaccarino, Sestan, Gerstein (all Yale)

R01 (MH100900-01) 09/01/13 – 07/31/19
Integrative Molecular and Phenotype Analysis of 22q11.2 Deletion Syndrome
Study neurons derived from human induced pluripotent stem cells (iPSCs), from patients with 22q11DS.
Role: Co-Investigator. PI: Hallmayer

U19 (MH104172-01) 04/01/2014 – 01/31/2020
Multimodal analysis of high-risk psychosis mutations in induced neurons (NCRCRG consortium)
Use induced neuronal (iN) cells, to model defects in synaptic function due to three engineered or naturally-occurring CNVs that increase the risk of schizophrenia: NRXN1 exonic, 22q11.2, and 16p11.2.
Role: Co-Investigator. MPI: Levinson, Südhof, Wernig

U01 (MH106876-01) 04/01/2015 – 03/31/2020
Somatic Mosaicism in the Brain of Tourette Syndrome (Brain Somatic Mosaicism Network, BSMN)
Analyze somatic genome variation in Tourette Syndrome.
Role: Subcontract-PI. PI: Vaccarino (Yale)

Publications with particular relevance to the project (for more publications see Section C):
   a) Zhu X, Zhou B, Pattni R, Gleason K, …, Abyzov A, Vogel H, Brain Somatic Mosaicism Network, Moran JV, Vaccarino FM, Tamminga CA, Levinson DF, **Urban AE**. Machine learning reveals bilateral distribution of somatic L1 insertions in human neurons and glia. ***Nature Neuroscience***. 2021 Feb;24(2):186-196. doi: 10.1038/s41593-020-00767-4. Epub 2021 Jan 11. PMID: 33432196.

   b) Abyzov A, Mariani J*, Palejev D*, Zhang Y*, Haney MS*, Tomasini L*, Rosenberg-Belmaker L, Ferrandino A, Wilson M, Grigorenko EL, Huttner A, Weissman SM, **Urban AE**‡, Gerstein M‡, Vaccarino FM‡. Somatic copy number mosaicism in human skin revealed by induced pluripotent stem cells. ***Nature***. 2012 Dec 20; 492(7429):438-42. doi: 10.1038/nature11629. PMCID: PMC3532053.

c) Bae T, Fasching L, Wang Y, Shin JH, …, Huttner A, Kleinman JE, Hyde TM, Straub RE, Walsh CA, Brain Somatic Mosaicism Network, **Urban AE**, Leckman JF, Weinberger DR[‡], Vaccarino FM[‡], Abyzov A[‡]. <u>Analysis of somatic mutations in 131 human brains reveals aging associated hypermutability.</u> ***Science.*** *In press.*

d) Zhou B, Shin G, Greer SU, Vervoort L, Huang Y, Pattni R, Ho M, Wong WH, Vermeesch JR, Ji HP[‡], **Urban AE[‡]**. <u>Complete and haplotype-specific sequence assembly of segmental duplication-mediated genome rearrangements using CRISPR-targeted ultra-long read sequencing (CTLR-Seq).</u> ***BioRxiv.*** Doi: https://doi.org/10.1101/2020.10.23.349621

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021–present   Associate Professor (with tenure), Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, and Department of Genetics; Member, Stanford Center for Genomics and Personalized Medicine, and Program in Genetics of Brain Function

2011–2021   Assistant Professor, Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, and Department of Genetics; Member, Stanford Center for Genomics and Personalized Medicine, and Program in Genetics of Brain Function

2008–2010   Postdoctoral Associate, Yale University School of Medicine, Department of Genetics

<u>**Honors**</u>
2020 One Mind Bipolar Research Award
2019 Uytengsu-Hamilton 22q11 Neuropsychiatry Research Award
2019 Jaswa Innovator Scholar
2017 Finalist NIH Director's Pioneer Award
2016 Tashia and John Morgridge Faculty Scholar
2013 Stanford Psychiatry Department Award for Advancing Science
2013 National Ataxia Foundation Young Investigator Award
2012 NIH Director's New Innovator Award
2012 NARSAD Young Investigator Award
2008 John Spangler Nicholas Prize

C. Contributions to Science

(*these authors contributed equally or [‡]are co-corresponding authors*)
1) Developed high-resolution array technology for discovery and fine-mapping of benign and pathogenic copy number variants (CNVs) in the genome. CNVs could only be mapped with very low resolution. We increased mapping resolution by several orders of magnitude, in the process we determined for the first time the exact breakpoint in an (atypical) case of 22q11-Deletion-Syndrome and increased by several fold the resolution for partial-trisomy-21 breakpoints; high-density oligomer array CGH is today the standard first-line method in clinical cytogenetics.

a) **Urban AE***, Korbel JO*, Selzer R, Richmond T, Hacker A, Popescu GV, Cubells JF, Green R, Emanuel BS, Gerstein MB, Weissman SM[‡], Snyder M[‡]. <u>High-resolution mapping of DNA copy alterations in human chromosome 22 using high-density tiling oligonucleotide arrays.</u> ***Proc Natl Acad Sci U S A****. 2006 Mar 21;103(12):4534-9. PMCID: PMC1450206.

b) Korbel JO*, **Urban AE***, Grubert F, Du J, Royce TE, Starr P, Zhong G, Emanuel BS, Weissman SM, Snyder M, Gerstein MB. <u>Systematic prediction and validation of breakpoints</u> associated with copy-number variants in the human genome. ***Proc Natl Acad Sci U S A****. 2007 Jun 12;104(24):10110-5. PMID: 17551006. PMCID: PMC1891248.

c) Korbel JO*, Tirosh-Wagner T*, **Urban AE***, Chen XN, Kasowski M, Dai L, Grubert F, Erdman C, … , Warburton D, Weissman S, Gerstein MB, Snyder M[‡], Korenberg JR[‡]. <u>The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies.</u> *Proc Natl Acad Sci U S A*. 2009 Jul 21;106(29):12031-6. Epub 2009 Jul 13. PMCID: PMC2709665.

d) Haraksingh RR, Abyzov AA, **Urban AE**. <u>Comprehensive performance comparison of high-resolution array platforms for genome-wide CNV analysis in humans.</u> ***BMC Genomics***. 2017 Apr 24;18(1):321. PMCID: PMC5402652.

2) Developed next-generation-sequencing based paired-end mapping and read-depth analysis of the human genome sequence. Massively-parallel ("next-generation") sequencing platforms had just become available and we developed two basic procedures to use them in the genome-wide analysis of CNV and SV – i.e. paired-end mapping (PEM) and read-depth analysis (RDA). We demonstrated the power of PEM by detecting large numbers of SVs in normal genomes; both methods are now standard components of human whole-genome sequencing and for example were used by the 1000 Genomes Project to which we were standing contributors.

a) Korbel JO*, **Urban AE***, Affourtit JP*, Godwin B, Grubert F, Simons JF, Kim PM, Palejev D, Carriero NJ, Du L, Taillon BE, Chen Z, Tanzer A, Saunders AC, Chi J, Yang F, Carter NP, Hurles ME, Weissman SM, Harkins TT, Gerstein MB, Egholm M[‡], Snyder M[‡]. <u>Paired-end mapping reveals extensive structural variation in the human genome.</u> *Science*. 2007 Oct 19;318(5849):420-6. Epub 2007 Sep 27. PMCID: PMC2674581.

b) Abyzov A, **Urban AE**, Snyder M, Gerstein M. <u>CNVnator: An approach to characterize and genotype atypical CNVs using high-throughput sequencing coupled with population and family structure.</u> *Genome Research*. 2011 Jun; 21(6): 974–984. PMCID: PMC3106330.

c) 1000 Genomes Project Consortium[1], Durbin RM, Abecasis GR, Altshuler DL, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. <u>A map of human genome variation from population scale sequencing.</u> *Nature*. 2010 Oct 28;467(7319):1050-1. PMCID: PMC3042601.
[1] The 1000 Genomes Project had more than 540 co-authors, with only the writing teams being listed in the short format references; Dr. Urban is a co-author as a member of both the analytical and structural variation groups of the 1000 Genomes Consortium.

d) Zhou B*, Arthur JG*, Pattni R, Ho SS, Wong WH[‡], **Urban AE**[‡]. <u>Deep sequencing with multiple strategies unlocks the Venter/HuRef genome as reference for genomics tools development and benchmarking.</u> *Scientific Data.* 2018 Dec 18;5:180261. PMCID: PMC6298255.

3) Developed advanced genomics and epigenomics analysis methods on cutting-edge platforms.
I have contributed to the development or improvement of advanced methods for genomics and epigenomics analysis, always based on the most cutting-edge array and sequencing platforms.

a) Zhou B, Ho S, Zhang X, Pattni R, Haraksingh RR, Abyzov A, **Urban AE**. <u>Whole-genome sequencing analysis of genomic copy number variation (CNV) using low-coverage and paired-end strategies is highly efficient and outperforms array based CNV analysis.</u> ***J Med Genetics***. 2018 Nov;55(11):735-743. PMCID: PMC8131063.

b) Zhou B, Ho S, Zhu X, Zhang X, Spies N, Byeon S, Arthur JG, Pattni R, Ben-Efraim N, Haney MS, Haraksingh RR, Song G, Perrin D, Wong WH, Abyzov A, **Urban AE**. <u>Comprehensive, Integrated, and Phased Whole-Genome Analysis of the Primary ENCODE Cell Line K562.</u> *Genome Research.* 2019 2019 Mar;29(3):472-484. PMCID: PMC6396411.

c) Zhou B, Ho S, Greer SU, Spies N, Bell JM, …, Pattni R, Ben-Efraim N, Huang Y, Song G, Perrin D, Wong WH, Abyzov A, **Urban AE**. <u>Haplotype-resolved and integrated genome analysis of the cancer cell line HepG2.</u> *Nucleic Acids Research.* 2019 May 7;47(8):3846-3861. PMCID: PMC6486628.

d) Robakis TK[‡], Zhang S, Rasgon NL, Li T, Wang T, Roth MC, Humphreys KL, Gotlib IH, Ho M, Khechaduri A, Watson K, Roat-Shumway S, Budhan VV, Davis KN, Crowe SD, Ellie Williams K, **Urban AE[‡]**. Epigenetic signatures of attachment insecurity and childhood adversity provide evidence for role transition in the pathogenesis of perinatal depression. *Translational Psychiatry.* 2020 Feb 3;10(1):48. doi: 10.1038/s41398-020-0703-3. PMCID: PMC7026105.

4) Multilevel and integrated genomics and epigenomics analyses. I am frequently using cutting edge genomics and epigenomics methods in an integrative fashion, i.e. combining data across multiple levels of genomic and epigenomic information and control. For example, using this approach we recently discovered that large CNVs that are strongly associated with neuropsychiatric disorders can affect chromatin states and chromosome folding patterns not just locally but also globally and indirectly across the cell's nucleus.

a) Zhang X*, Zhang Y*, Zhu X*, Purmann C, Haney MS, Ward TR, Yao J, Weissman SM, **Urban AE**. Local and global chromatin interactions are altered by large genomic deletions associated with human brain development. *Nature Communications.* 2018 Dec 17;9(1): 5356. PMCID: PMC6297223.

b) Leung LC, Wang GX, Madelaine R, Kawakami K, Deisseroth K, **Urban AE**, Mourrain P. Neural signatures of sleep in zebrafish. *Nature.* 2019 Jul;571(7764):198-204. PMCID: PMC7081717.

c) Zhang X*, Hong D*,[‡], Ma S, Ward T, Ho M, Pattni R, Duren Z, Stankov A, Bade Shrestha S, Hallmayer J, Wong WH[‡], Reiss AL[‡], **Urban AE[‡]**. Integrated functional genomics analyses of Klinefelter and Turner syndromes reveal global network effects of altered X chromosome dosage. *Proc Natl Acad Sci U S A*. 2020 Mar 3;117(9):4864-4873. Doi: 10.1073/pnas.1910003117. PMCID: PMC7060706.

d) Zhang S, Zhang X, Ma S, Purmann C, Davis K, Wong WH, Bernstein J, Hallmayer JF, **Urban AE**. Network effects of the neuropsychiatric 15q13.3 microdeletion on the transcriptome and epigenome in human induced neurons. *Biological Psychiatry.* 2020 Jul 1:S0006-3223(20)31710-8. PMID: 32919612.

5) Genome variation in somatic tissues and stem cell model systems. *(Also see end of Section A)*
The emerging genomics platforms enable us for the first time to comprehensively detect and study the presence and effects of CNVs and retrotranspositions as somatic variants, in stem cell systems, primary tissues and in a combination of these tissues. We have developed and established novel approaches to harness the full potential of the genomics platforms in combination with these model systems and tissues.

a) O'Huallachain M, Karczewski KJ, Weissman SM, **Urban AE**, Snyder MP. Extensive genetic variation in somatic human tissues. *Proc Natl Acad Sci U S A*. 2012 Oct 30;109(44):18018-23.

b) McConnell M*, Moran JV*, Abyzov A, Akbarian S, Bae T, Erwin JA, Fasching L, Flasch DA, Freed D, Ganz J, Kwan KY, …, Weinberger DR, **Urban AE**, Gage FH, Lehner T, Senthil G, Walsh C, Chess A, Courchesne E, Gleeson JG, Kidd JM, Park PJ, Pevsner J, Vaccarino FM, Brain Somatic Mosaicism Network. Intersection of diverse neuronal genomes and neuropsychiatric disease: the Brain Somatic Mosaicism Network. *Science*. 2017 Apr 28;356(6336). PMCID: PMC5558435.

c) Bae T, Tomasini L, Mariani J, Zhou B, Roychowdhury T, Franjic D, Pletikos M, Pattni R, Chen BJ, Venturini E, Riley-Gillis B, Sestan N, **Urban AE**, Abyzov A[‡], Vaccarino FM[‡]. Different mutational rates and mechanisms in human cells at pregastrulation and neurogenesis. *Science*. 2018 Feb 2;359(6375):550-555. PMCID: PMC6311130.

d) Sekar S, Tomasini L, Proukakis C, Bae T, Manlove L, Jang Y, Scuderi S, Zhou B, Kalyva M, Amiri A, Mariani J, Sedlazeck FJ, **Urban AE**, Vaccarino FM, Abyzov A. Complex mosaic structural variation in human fetal brains. *Genome Res.* 2020 Dec;30(12):1695-1704. PMID: 33122304

(*these authors contributed equally or [‡]are co-corresponding authors*)
Above: 24 publications selected from 78 publications, updated list of published work on MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/alexander.urban.2/bibliography/public/?page=1