BIOGRAPHICAL SKETCH

NAME: Ahituv, Nadav

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

POSITION TITLE: Professor, Dept. of Bioengineering and Therapeutic Sciences and Institute for Human Genetics

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tel-Aviv University	BSc	06/1996	Biology
Tel-Aviv University	PhD	09/2002	Human Genetics
Lawrence Berkeley National Laboratory	Postdoc	08/2007	Genomics

A. Personal Statement

I am a human geneticist/genomicist that uses advanced computational and genomic tools to characterize how variation in gene regulatory elements leads to various phenotypes, in particular human disease. My lab uses numerous genomic technologies (ChIP-seq, ATAC-seq, Cut&Run, RNA-seq, Hi-C and single-cell technologies) to characterize gene regulatory elements. In order to functionally characterize these elements, we use zebrafish, mouse and cell culture functional assays. In addition, we have created and continue to develop technologies that can enable the massively parallel testing of thousands of sequences for gene regulatory activity. Finally, we are also using gene regulatory elements as therapeutic targets for various human diseases.

1. Birnbaum RY, Clowney EJ, Agamy O, Kim MJ, Zhao J, Yamanaka T, Pappalardo Z, Clarke SL, Wenger AM, Nguyen L, Gurrieri F, Everman DB, Schwartz CE, Birk OS, Bejerano G, Lomvardas S, **Ahituv N**. Coding exons function as tissue-specific enhancers of nearby genes. *Genome Research* 2012,22: 1059-1068. PMCID: PMC3371700.
2. Smith RP, Taher L, Patwardhan RP, Kim MJ, Inoue F, Shendure J^, Ovcharenko I^, **Ahituv N^**. Massively parallel decoding of mammalian regulatory sequences supports a flexible organizational model, *Nature Genetics* 2013, 45: 1021-1028. PMCID: PMC3775494.
3. Eckalbar WL, Schlebusch SA, Mason MK, Gill Z, Parker AV, Booker BM, Nishizaki S, Nday CM, Terhune E, Nevonen K, Makki N, Friedrich T, VanderMeer JE, Pollard KS, Carbone L, Wall JD^, Illing N^, **Ahituv N^** Transcriptomic and epigenomic characterization of the developing bat wing, *Nature Genetics* 2016, 48:528-36. PMCID: PMC4848140.
4. Matharu N, Rattanasopha S, Tamura S, Maliskova L, Wang Y, Bernard A, Hardin A, Eckalbar WL, Vaisse C, **Ahituv N**. Promoter or enhancer activation by CRISPRa rescues haploinsufficiency caused obesity, *Science* 2019, 363: eaau0629. PMCID: PMC6570489.

^co-corresponding author

B. Positions and Honors

Positions and Employment

1997-2002 Direct Ph.D. with distinction, Tel-Aviv University, Tel-Aviv, Israel.
1997-2003 Postdoctoral Fellow, Genomics Division, Lawrence Berkeley Laboratory, Berkeley, CA, USA.
2007-2013 Assistant Professor, Dept. of Bioengineering and Therapeutic Sciences, and Institute for Human Genetics, UCSF, San Francisco, CA, USA.
2013-2016 Associate Professor, Dept. of Bioengineering and Therapeutic Sciences, and Institute for Human Genetics, UCSF, San Francisco, CA, USA.
2016- Professor, Dept. of Bioengineering and Therapeutic Sciences, and Institute for Human Genetics, UCSF, San Francisco, CA, USA.

Other Experience and Professional Memberships

2006- Member, American Society of Human Genetics
2012- Member, Society for Developmental Biology

Honors and Awards

2002 Ph.D. with distinction
2014 ASCPT Leon I. Goldberg Young Investigator Award

1. Functional genomics: While we have a large understanding of the genetic code and the functional consequences of gene coding mutations, the regulatory code remains largely unknown. The focus of my lab since its inception is to obtain an increased understanding of the regulatory code and how its aberration can lead to various phenotypes. To this end, my lab has been actively testing synthetic enhancers that ask various grammatical questions regarding the regulatory code and also developing high-throughput assays to allow the testing of thousands of candidate sequences for regulatory activity termed massively parallel reporter assays.

a. **Ahituv N**, Zhu Y, Visel A, Holt A, Afzal V, Pennacchio LA, Rubin EM Deletion of ultraconserved elements yields viable mice, *PLoS Biology* 2007; 5:e234. PMCID: PMC1964772.
b. Smith RP, Taher L, Patwardhan RP, Kim MJ, Inoue F, Shendure J^, Ovcharenko I^, **Ahituv N^**. Massively parallel decoding of mammalian regulatory sequences supports a flexible organizational model, *Nature Genetics* 2013, 45: 1021-1028. PMCID: PMC3775494.
c. Inoue F, Kircher M, Martin B, Cooper GM, Witten DM, McManus MT, **Ahituv N^**, Shendure J^. A systematic comparison reveals substantial differences in chromosomal versus episomal encoding of enhancer activity, *Genome Research*, 2017, 27: 38-52. PMCID: PMC5204343.
d. Kircher M^, Xiong C, Martin B, Schubach M, Inoue F, Bell RJA, Costello JF, Shendure J^, **Ahituv N^**. Saturation mutagenesis of twenty disease-associated regulatory elements at single base-pair resolution, *Nature Communications*, 2019, 10: 3583. PMCID: PMC6687891.

2. Genetics of obesity: Obesity is a growing epidemic and is largely caused by genetic factors. Using high-throughput sequencing, familial analysis, and functional genomics we linked numerous nucleotide variants both in genes and in enhancers with obesity susceptibility. In addition, using CRISPRa to target the unaffected allele, we have shown that we can rescue haploinsufficient caused obesity.

a. **Ahituv N**, Kavaslar N, Schackwitz WS, Ustaszewska A, Martin J, Hébert S, Doelle H, Ersoy B, Kryukov G, Schmidt S, Yosef N, Ruppin E, Sharan R, Vaisse C, Sunyaev S, Dent R, Cohen J, McPherson R, Pennacchio LA Medical sequencing at the extremes of human body mass, American Journal of Human Genetics 2007; 80: 779-791. PMC1852707.
b. Kim MJ, Oksenberg N, Hoffmann TJ, Vaisse C, **Ahituv N**. Functional characterization of SIM-associated enhancers, *Human Molecular Genetics* 2014, 23: 1700-1708. PMCID: PMC3943516.
c. Matharu N, Rattanasopha S, Tamura S, Maliskova L, Wang Y, Bernard A, Hardin A, Eckalbar WL, Vaisse C, **Ahituv N**. Promoter or enhancer activation by CRISPRa rescues haploinsufficiency caused obesity, *Science* 2019, 363: eaau0629. PMCID: PMC6570489.
d. Inoue F, Eckalbar W, Wang Y, Murphy KK, Matharu N, Vaisse C^, **Ahituv N^**. Genomic and epigenomic mapping of leptin-responsive neuronal populations involved in body weight regulation, *Nature Metabolism* 2019, *In Press*.

3. Genetics of mental disorders: Over 20% of children and nearly 6% of adults in the U.S. suffer from seriously debilitating mental disorders. Abnormal neuronal development can lead to a wide range of psychiatric disease. Gene coding mutations only explain a limited number of these cases. To uncover novel pathways and gene regulatory elements that could be involved in these disorders, we have functionally characterized an important and novel neurodevelopmental regulator, *AUTS2*, a gene that was shown to be disrupted in over 30 individuals with autism. In addition, we have characterized using various genomic technologies, including massively parallel reporter assays, numerous neurodevelopmental enhancers thus providing novel candidate regions for psychiatric disease.

a. Oksenberg N, Stevnison L, Wall J, **Ahituv N**. Function and regulation of *AUTS2*, a gene implicated in autism and human evolution, *PLoS Genetics*, 2013: e1003221. PMCID: PMC3547868.

b. Smith RP, Riesenfeld SJ, Holloway AK, Li Q, Murphy KK, Feliciano NM, Orecchia L, Oksenberg N, Pollard KS^, **Ahituv N**^. A compact, *in vivo* screen of all 6-mers reveals drivers of tissue-specific expression and guides synthetic regulatory element design, *Genome Biology*, 2013, 14: R72. PMCID: PMC4054837.
c. Oksenberg N, Haliburton GDE, Eckalbar WL, Nishizaki S, Murphy KK, Pollard KS, Birnbaum RY^, **Ahituv N**^. Genome-wide distribution of Auts2 binding localizes with active neurodevelopmental genes, *Translational Psychiatry* 2014, 2: e431. PMCID: PMC4199417.
d. Inoue F, Kreimer A, Ashuach T, **Ahituv N**^, Yosef N^. Identification and massively parallel characterization of regulatory elements driving neural induction, *Cell Stem Cell* 2019, *In Press*.

4. Gene regulatory mutations and human limb malformations: Limb malformations are the second most common human congenital abnormality with a prevalence of 1 for every 500 births. Although several mutations in genes have been identified that explain syndromic forms (associated with other symptoms) of limb malformations, the characterization of mutations causing non-syndromic/isolated limb malformations has been less successful. A variety of molecular and clinical data suggests that mutations responsible for non-syndromic limb malformations can reside in distal noncoding regulatory sequences such as enhancers. However, to date, only a few limb enhancers have been definitively linked with these malformations. Our laboratory uses functional genomics to identify novel genes and limb enhancers that could be associated with limb malformations. We have collected DNA from over 1,000 individuals with various forms of non-syndrominc limb malformations and are screening them for mutations in both genes and enhancers and have identified numerous mutations thus far. Finally, using non-model organisms with unique limb phenotypes, such as bats, we are learning how limb malformations can develop. Combined our work is providing for an increased understanding about the pathogenesis of human limb malformations and limb development and also poses as a model for the identification of causative regulatory variants in other human birth defects.

a. Birnbaum RY, Clowney EJ, Agamy O, Kim MJ, Zhao J, Yamanaka T, Pappalardo Z, Clarke SL, Wenger AM, Nguyen L, Gurrieri F, Everman DB, Schwartz CE, Birk OS, Bejerano G, Lomvardas S, **Ahituv N**. Coding exons function as tissue-specific enhancers of nearby genes. *Genome Research* 2012,22: 1059-1068. PMCID: PMC3371700.
b. VanderMeer JE, Smith RP, Jones S, **Ahituv N**. Genome-wide identification of signaling center enhancers in the developing limb, *Development* 2014, 141:4194-4198. PMCID: PMC4302890.
c. Booker BM, Friedrich T, Mason MK, VanderMeer JE, Zhao J, Eckalbar WL, Logan M, Illing N, Pollard KS^, **Ahituv N**^. Bat Accelerated Regions Identify a Bat Forelimb Specific Enhancer in the *HoxD* Locus, *PLoS Genetics* 2016, 12: e1005738. PMCID: PMC4809552.
d. Eckalbar WL, Schlebusch SA, Mason MK, Gill Z, Parker AV, Booker BM, Nishizaki S, Nday CM, Terhune E, Nevonen K, Makki N, Friedrich T, VanderMeer JE, Pollard KS, Carbone L, Wall JD^, Illing N^, **Ahituv N^** Transcriptomic and epigenomic characterization of the developing bat wing, *Nature Genetics* 2016, 48:528-36. PMCID: PMC4848140.

5. Variation in gene regulatory elements and drug response: Adverse drug effects are a leading cause of death and can be caused by genetic factors. There has been a lot of work carried out to identify mutations in gene coding mutations that lead to interindividual differences in drug response. However, not much is known about gene regulatory elements. Using computational analyses, ChIP-seq, RNA-Seq and high-throughput functional studies we are characterizing how genetic differences in regulatory sequences lead to clinical variation in drug response.

a. Choi JH, Yee SW, Kim MJ, Nguyen L, Lee JH, Hesselson S, Stryke D, Johns SJ, Kwok P, Ferrin TE, Lee MG, **Ahituv N**, Giacomini KM (2009) Identification and Characterization of Novel Polymorphisms in the Basal Promoter of the Human Transporter, MATE1, *Pharmacogenetics and Genomics*, 2009, 19: 770-780. PMIC: PMC2976711.
b. Kim MJ, Skewes-Cox P, Fukushima H, Hesselson S, Yee SW, Ramsey LB, Nguyen L, Eshragh JL, Castro RA, Wen C, Stryke D, Johns SJ, Ferrin TE, Kwok PY, Relling MV, Giacomini KM, Kroetz DL, **Ahituv N** Functional characterization of liver enhancers regulating drug-associated transporters, *Clinical Pharmacology and Therapeutics* 2011, 89: 571-578.
c. Smith RP, Eckalbar WL, Morrissey KM, Luizon MR, Hoffman TJ, Sun X, Jones SL, Force Aldred S, Ramamoorthy A, Desta Z, Liu Y, Skaar TC, Trinklein ND, Giacomini KM, **Ahituv N**. Genome-wide

discovery of drug-dependent human liver regulatory elements, *PLoS Genetics* 2014, 10:e1004648. PMCID: PMC4183418.

d. Luizon MR, Eckalbar WL, Wang Y, Jones SL, Smith RP, Laurance M, Lin L, Gallins PJ, Etheridge AS, Wright F, Zhou Y, Molony C, Innocenti F, Yee SW, Giacomini KM, **Ahituv N**. Genomic characterization of metformin hepatic response, *PLoS Genetics* 2016, 12: e1006449. PMCID: PMC5130177.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Ahituv+N

D. Research Support

Ongoing Research Support

1R01MH109907 Ahituv & Pollard (PIs) 05/01/16-02/28/21
NIMH
Massively parallel dissection of psychiatric regulatory networks
The major goal of this project is to characterize gene regulatory elements that could be associated with psychiatric disorders.
Role: PI

1P01HD084387 Ahituv, Solnica-Krezel Wise (PIs) 09/01/16-06/30/21
NICHD
Developmental mechanisms of human idiopathic scoliosis
The major goal of this project is to characterize the genetic causes of idiopathic scoliosis.
Role: PI

1UM1HG009408 Ahituv & Shendure (PIs) 02/01/17 – 01/31/21
NHGRI (ENCODE)
Massively parallel reporter assays and genome editing of ENCODE predicted regulatory elements
We plan to use massively parallel reporter assays and genome editing to characterize at least 100,000 ENCODE-annotated candidate regulatory elements for their function.
Role: PI

R35HL145235 Erle (PI) 08/01/17 – 02/28/26
NHLBI
Airway Epithelial Reprogramming in Asthma
The major goals of this project are to identify distal DNA regulatory elements (enhancers) that control gene transcription in airway epithelial cells. We will use this new knowledge to develop new strategies for selectively reprogramming the airway epithelium in asthma.
Role: Co-I

New Frontier Research Award Ahituv & Shen (PIs) 01/16/18-01/15/20
UCSF Program for Breakthrough Biomedical Research
Development of massively parallel reporter assays that use cognate promoters
The goal of this project is to develop massive parallel reporter assays so as to be able to obtain preliminary results to secure future NIH or other sources of funding.
Role: PI

1R21HG010065 Ahituv & Shen (PIs) 05/01/18-04/30/20
NHGRI
Development of massively parallel reporter assays that use cognate promoters
The major goal of this project is to develop novel massively parallel reporter assays that test enhancers alongside their target promoters.
Role: PI

1U01MH116438 Ahituv & Pollard (PIs) 07/06/18-03/31/23
NIMH (psychENCODE)
Massively parallel characterization of psychiatric disease associated regulatory elements in defined cell types
The major goal of this proposal is to functionally characterize psychiatric disease associated genes, regulatory elements and their variants.
Role: PI

1R01DK116738 Ahituv & Jorgenson (PIs) 09/15/18 – 08/31/21
NIDDK
Genetic Etiology of Abdominal Hernia Susceptibility
The major goal of this proposal is to functionally characterize hernia-associated nucleotide variants.
Role: PI

1R01HG010333 Carbone (PI) 09/14/18 – 06/30/22
NHGRI
Comparative and functional characterization of topological associating domain (TAD) rearrangements
The major goal of this proposal is to functionally characterize evolutionary conserved topological associating domains.
Role: Co-I

R01HL117004 Burchard (PI) 07/01/19 – 06/30/23
NHLBI
The Airway Functional Genomics of Bronchodilator Drug Response in Minority Children with Asthma
The major goal of this project is to understand the genetic and environmental basis of racial/ethnic differences in asthma and drug response.
Role: Co-I

629287 (P0535912) Ahituv & Bender (PI) 08/01/19 – 07/31/21
Simons Foundation
CRISPRa as a therapy to rescue ASD-associated haploinsufficiency
The major goal of this proposal is to advance CRISPRa-based technologies as a potential therapeutic in Scn2a haploinsufficiency.
Role: PI

1R21HG010683 Ahituv (PI) 08/16/19 – 07/31/21
NHGRI
Technologies for simultaneous characterization of regulatory activity and protein binding
The major goal of this proposal is to develop a technology that can simultaneously measure regulatory activity and protein binding.
Role: PI

Completed Research Support

R01 HG008123 Cooper & Shendure (PIs) 01/02/15-01/31/18
NCI
Integrative interpretation of the organismal consequences of non-coding variation
The major goal of this project is to improve our ability to identify and interpret “non-coding” variants that causally contribute to human disease.
Role: Co-I

1R01NS079231 (EUREKA) Ahituv (PI) 04/01/12-03/31/16
NINDS
Characterization of neuronal gene regulatory elements associated with epilepsy
The major goal of this project is to characterize gene regulator elements associated with epilepsy.
Role: PI