BIOGRAPHICAL SKETCH

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NAME: Adam J. de Smith

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

POSITION TITLE: Assistant Professor of Clinical Preventive Medicine

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
University of Bristol, UK	BSc.	06/2005	Zoology
Imperial College London, UK	MSc.	09/2006	Human Molecular Genetics
Imperial College London, UK	Ph.D.	10/2010	Human Genetics
University of California, San Francisco	Postdoctoral training	07/2014	Molecular epidemiology of childhood leukemia

A. Personal Statement

The research carried out during my PhD was focused on human genomic copy number variation and its role in obesity risk, and I gained extensive training in the utilization and analysis of various molecular genetics techniques. This work led to the publication of 15 manuscripts, 6 as first author, including a number of high impact scientific contributions. Keen to pursue a career in cancer genetics, I joined Dr. Joseph Wiemels' lab at UCSF as a postdoctoral scholar, with a focus on the role of inherited genetic variation and development of the neonatal immune system in the etiology of acute lymphoblastic leukemia (ALL), the most common cancer in children. Since joining UCSF, I published 7 first author papers, with a focus on genetic variation associated with ALL risk and development. In 2014, I was appointed to the Professional Research Series at UCSF, with Principal Investigator status, reflecting the support of my department. That year I also received an ALSF "A" Award grant to fund a comprehensive investigation into the etiology of ALL in children with Down syndrome (DS). To make this study feasible, I initiated a multi-institutional and global collaboration to obtain sufficient DNA samples, and am currently analyzing the first GWAS of DS-ALL. Further, I received a grant from the UCSF Cancer Center, the "UCSF 500 Cancer Genes Sequencing Pilot Program", to carry out targeted sequencing of high hyperdiploid (HD) ALL patient tumor samples, to investigate novel driver genes in this leukemia subtype. This enhanced my expertise in analysis techniques for next-generation sequencing data, and resulted in one first author manuscript describing the somatic mutational landscape in HD-ALL, with another first author manuscript reporting a novel ALL predisposition gene in preparation. My research also utilizes tumor genomic data to identify environmental risk factors for ALL, and I am Principal Investigator of two recently funded projects: 1) to investigate the association between in utero tobacco smoke exposure and tumor gene deletion frequency in childhood ALL; and 2) to discover an infectious etiology of the APOBEC mutational signature in childhood ALL.

B. Positions and Honors

Positions and Employment

2006	Intern, Agilent Technologies, Santa Clara, CA
2006-2010	PhD student, Imperial College London, UK
2009-2010	Course Tutor, MSc in Human Molecular Genetics, Imperial College London, UK
2011	Postdoctoral Researcher, Imperial College London, UK
2011-2014	Postdoctoral Researcher, University of California San Francisco, CA
2014-2018	Assistant Professional Researcher, University of California San Francisco, CA
2018-	Assistant Professor, University of Southern California, CA

Other Experience and Professional Memberships

2012-	Member, American Society of Human Genetics
2013-2015	Scientific Board, Diploid (formerly Gentle Labs), Leuvin, Belgium
2014-2018	Associate Member, UCSF Helen Diller Family Comprehensive Cancer Center
2017-	Member, American Society of Hematology

Honors

2006	MSc. in Human Molecular Genetics with Distinction, Imperial College London, UK
2014	Alex's Lemonade Stand Foundation 'A' Award

C. Contributions to Science

1. In 2006, research into human genomic copy number variation was still in its infancy. We carried out one of the first studies using array CGH to investigate copy number variants (CNVs) in the genomes of healthy individuals, and discovered over 1000 novel CNV loci. I carried out the array CGH experiments for this study and was involved in the analysis and manuscript preparation. At the time, our study was the highest resolution array CGH investigation of CNVs, and was one of the earlier studies to be included in the Database of Genomic Variants (http://dgv.tcag.ca/dgv/app/home). Subsequently, I was interested in characterizing the breakpoints of small deletion CNVs. I discovered that they had stable breakpoints across samples that suggested ancient origins, and also found that they frequently were associated with *Alu* elements, which suggested a role for these repeat elements in the formation of these CNVs.

a) **de Smith AJ**, Tsalenko A, Sampas N, Scheffer A, Yamada NA, Tsang P, Ben-Dor A, Yakhini Z, Ellis RJ, Bruhn L, Laderman S, Froguel P, Blakemore AI. Array CGH analysis of copy number variation identifies 1284 new genes variant in healthy white males: implications for association studies of complex diseases. Hum Mol Genet. 2007 Dec 1;16(23):2783-94.
b) **de Smith AJ**, Walters RG, Coin LJ, Steinfeld I, Yakhini Z, Sladek R, Froguel P, Blakemore AI. Small deletion variants have stable breakpoints commonly associated with alu elements. PLoS One. 2008 Aug 29;3(8):e3104.
c) **de Smith AJ**, Trewick AL, Blakemore AI. Implications of copy number variation in people with chromosomal abnormalities: potential for greater variation in copy number state may contribute to variability of phenotype. Hugo J. 2010 Dec;4(1-4):1-9.

2. Using high resolution array CGH, we investigated a group of approximately 40 children who presented with phenotypes associated with syndromic obesity but for whom no chromosomal aberrations had been detected previously. We identified causative microdeletions in 3 of these children. The first patient had apparent Prader-Willi syndrome (PWS), which had not been confirmed by karyotyping or FISH. We identified a microdeletion at the PWS region at chromosome 15q11-13, and using PCR and sequencing I validated this deletion and determined a minimum critical region for PWS of ~100Kb that encompassed a group of small nucleolar RNAs (snoRNAs). In another patient, we found a ~600Kb deletion at chromosome 16p11.2 that was subsequently identified in additional undiagnosed syndromic obesity children in other cohorts. Genome-wide SNP data was used to predict the presence of this deletion in obesity case-control datasets, and I used multiplex ligation-

dependent probe amplification to validate the presence of deletions in some of these cases. The deletion was found to account for ~1% of morbid obesity cases. I helped to write the manuscript, which was published in *Nature* and has been cited over 100 times. I identified a third case with a microdeletion at chromosome 19p13.3, with both breakpoints lying within genes associated with congenital disease. Subsequent studies have confirmed this locus as underlying a novel syndrome (eg. PMID: 25853300).

a) **de Smith AJ**, Purmann C, Walters RG, Ellis RJ, Holder SE, Van Haelst MM, Brady AF, Fairbrother UL, Dattani M, Keogh JM, Henning E, Yeo GS, O'Rahilly S, Froguel P, Farooqi IS, Blakemore AI. A deletion of the HBII-85 class of small nucleolar RNAs (snoRNAs) is associated with hyperphagia, obesity and hypogonadism. Hum Mol Genet. 2009 Sep 1;18(17):3257-65.
b) Walters RG, Jacquemont S, Valsesia A, **de Smith AJ**, Martinet D, Andersson J, Falchi M, Chen F, Andrieux J, Lobbens S, Delobel B, Stutzmann F, El-Sayed Moustafa JS, Chèvre JC, Lecoeur C, Vatin V, Bouquillon S, Buxton JL, Boute O, Holder-Espinasse M, Cuisset JM, Lemaitre MP, Ambresin AE, Brioschi A, Gaillard M, Giusti V, Fellmann F, Ferrarini A, Hadjikhani N, Campion D, Guilmatre A, Goldenberg A, Calmels N, Mandel JL, Le Caignec C, David A, Isidor B, Cordier MP, Dupuis-Girod S, Labalme A, Sanlaville D, Béri-Dexheimer M, Jonveaux P, Leheup B, Ounap K, Bochukova EG, Henning E, Keogh J, Ellis RJ, Macdermot KD, van Haelst MM, Vincent-Delorme C, Plessis G, Touraine R, Philippe A, Malan V, Mathieu-Dramard M, Chiesa J, Blaumeiser B, Kooy RF, Caiazzo R, Pigeyre M, Balkau B, Sladek R, Bergmann S, Mooser V, Waterworth D, Reymond A, Vollenweider P, Waeber G, Kurg A, Palta P, Esko T, Metspalu A, Nelis M, Elliott P, Hartikainen AL, McCarthy MI, Peltonen L, Carlsson L, Jacobson P, Sjöström L, Huang N, Hurles ME, O'Rahilly S, Farooqi IS, Männik K, Jarvelin MR, Pattou F, Meyre D, Walley AJ, Coin LJ, Blakemore AI, Froguel P, Beckmann JS. A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. Nature. 2010 Feb 4;463(7281):671-5.
c) **de Smith AJ**, van Haelst MM, Ellis RJ, Holder SE, Payne SJ, Hashim SK, Froguel P, Blakemore AI. Chromosome 19p13.3 deletion in a patient with macrocephaly, obesity, mental retardation, and behavior problems. Am J Med Genet A. 2011 May;155A(5):1192-5.

3. There are few known causes of childhood acute lymphoblastic leukemia (ALL). Genome-wide association studies have revealed heritable SNP associations in a handful of genes. At *CDKN2A*, we identified a germline missense mutation that underlies most of the chr9p21.3 association with ALL in our case-control study. I developed a novel methodology utilizing droplet digital PCR to show that the SNP risk allele is preferentially retained in tumor samples with hemizygous loss of *CDKN2A*, suggesting tumor selection of this variant. This is the first example of preferential allelic imbalance (PAI) in leukemia. I then used this method (termed Somatic Mutation Allelic Ratio Test using ddPCR = “SMART-ddPCR”) to investigate PAI in other childhood ALL-associated SNPs. I also led the first investigation into the combination of killer immunoglobulin receptor (KIR) and HLA alleles on childhood ALL risk, and found significant associations that varied by ethnicity. I carried out all of the analyses in this manuscript. Finally, I assessed the frequency of common ALL tumor gene deletions in Latino and non-Latino white ALL patients, and found association between self-reported parental tobacco smoking and ALL gene deletion frequency that was validated with a biomarker of *in utero* tobacco smoke exposure. This supports a role for early-life tobacco smoke exposure in the etiology of childhood ALL.

a) Walsh KM*, **de Smith AJ***, Hansen HM, Smirnov IV, Gonseth S, Endicott AA, Xiao J, Rice T, Fu CH, McCoy LS, Lachance DH, Eckel-Passow JE, Wiencke JK, Jenkins RB, Wrensch MR, Ma X, Metayer C, Wiemels JL. A heritable missense polymorphism in *CDKN2A* confers strong risk of childhood acute lymphoblastic leukemia and is preferentially selected during clonal evolution. Cancer Research. 2015 Nov 15;75(22):4884-94. *joint first authors
b) **de Smith AJ**, Walsh KM, Ladner MB, Zhang S, Xiao C, Cohen F, Moore TB, Chokkalingam AP, Metayer C, Buffler PA, Trachtenberg EA, Wiemels JL. The role of KIR genes and their cognate HLA class I ligands in childhood acute lymphoblastic leukemia. Blood. 2014 Apr 17;123(16):2497-503.
c) **de Smith AJ**, Kaur M, Gonseth S, Endicott A, Selvin S, Zhang L, Roy R, Shao X, Hansen HM, Kang AY, Walsh KM, Dahl GV, McKean-Cowdin R, Metayer C, Wiemels JL. Correlates of prenatal and early-life tobacco smoke exposure and frequency of common gene deletions in childhood acute lymphoblastic leukemia. Cancer Research. 2017 Apr 1;77(7):1674-1683.

Complete list of published work in PubMed:
http://www.ncbi.nlm.nih.gov/pubmed/?term=de+smith+a

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

Ongoing Research Support

High Impact Research Project Award (de Smith) 08/01/2017-08/01/2019
Tobacco-Related Disease Research Program (TRDRP)
Prenatal tobacco smoke exposure and somatic alterations in childhood ALL
We recently found an association between in utero tobacco smoke exposure and frequency of somatic gene deletions in childhood ALL. The first goal of this project is to replicate this association in an independent set of ALL patients using an epigenetic biomarker of in utero tobacco exposure at the AHRR gene. The second goal is to investigate a predicted mechanism through which tobacco smoke may generate deletions, via the whole genome sequencing and deletion breakpoint analysis in tumors from ALL patients with high tobacco exposure and in tumors from unexposed patients.
Role: Principal Investigator

Completed Research Support

'A' Award Grant (de Smith) 01/15/2015– 01/14/2018
Alex's Lemonade Stand Foundation
Investigating the role of genetic and epigenetic variation in risk of childhood acute lymphoblastic leukemia in Down syndrome
The goal of this project is to determine genetic and epigenetic variants that are associated with increased risk of acute lymphoblastic leukemia (ALL) in children with Down syndrome (DS). The project includes genome-wide assessment of both single nucleotide polymorphisms and copy number variants, with a focus on chromosome 21 variation, in a set of DS-ALL cases and DS non-ALL controls. Genome-wide methylation analysis will also be carried out in these same subjects.
Role: Principal Investigator

Emerging Investigator Fellowship Grant (de Smith) 01/01/2017-12/31/2017
Pediatric Cancer Research Foundation (PCRF)
Biological underpinnings of heritable risk imposed by GWAS significant SNPs in childhood acute lymphoblastic leukemia.
The purpose of this research is to elucidate the biological mechanisms through which childhood ALL-associated genetic variants contribute to leukemogenesis. Fine-mapping of known GWAS hit loci will be carried out via targeted imputation, in addition to bioinformatic analysis of candidate SNPs with a particular focus on long-range chromosomal interactions and enhancer overlap of noncoding variants.
Role: Principal Investigator

New Idea Award (de Smith) 10/01/2016-10/01/2017
Leukemia & Lymphoma Society
APOBEC mutagenesis: a causal link between infections and childhood ALL?
This project aims to investigate whether the APOBEC mutational signature found in a subset of childhood ALL tumor genomes is associated with increased frequency of medically-diagnosed infections in the first year of life. Whole genome sequencing will be used to assess mutational signatures in 25 ALL patients with a high number of early life infections compared with 25 patients with zero infections. Results may provide a mechanistic link between infections and childhood ALL.
Role: Principle Investigator