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Translating genetic biomarkers for melanoma prevention and clinical practice

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Abstract

Genome wide association studies have uncovered many of the key genetic factors that underlie inherited risk for developing melanoma. A concerted effort is needed to explore the clinical and translational utility of this wealth of genetic information. To this end, we have established two major studies: a longitudinal study of childhood melanocytic nevus development (birth to 14 years of age) and a case-case melanoma study. Since nevi are intermediates for melanoma development and phenotypic risk indicators for melanoma, we collected DNA samples from 800 subjects from the greater Denver area to examine the gene-environment interactions that give rise to maximum nevus counts in childhood. As for the melanoma study, we have collected peripheral blood DNA from 1500 melanoma patients and have obtained their clinical records. We are using Sequenom MassArray and qPCR assays to genotype SNPs in the IRF4, PLA2G6, MTAP, OCA2, SLC45A2, ASIP and MC1R melanoma risk loci (among others) in subjects from both of these studies. The selected SNPs may affect nevus development and clinical presentation of melanoma. Our data identifies the key pigmentation and melanoma risk genes that interact with different UV exposure profiles to give maximal nevus counts in children. This information will be used to select individuals with nevus and melanoma susceptibility genotypes who may in turn be identified for prevention studies. Additionally, examining DNA from our melanoma patients will reveal the mutational impact of these risk genes on clinically relevant features such as age of onset, time to metastasis, number of primary melanomas, tumor site, response to treatment and survival. We obtained tumor biopsies from 400 of these melanoma patients for oncotyping. We are using qPCR arrays to identify the tumor mutational status for key melanoma genes including BRAF, NRAS, KIT, p53, GNAQ, CDKN2A, and MITF (among others). Oncotyping will enable us to determine the contribution of risk SNPs to the emerging molecular subtypes of melanoma, together with their combined impact on clinical disease presentation. These studies are particularly relevant to the emerging FDA regulated clinical genotyping assays such as BRAF, and soon KRAS and EGFR, where additional medically relevant features may be linked to particular genotypes in each cancer type. Moreover, we anticipate that these approaches will expand the demand for clinically regulated genotyping assays that will ultimately improve patient care.

Biography

Neil Box is a Assistant Professor in the Department of Dermatology at the University of Colorado Denver. He is a member of the University of Colorado Cancer Center, Skin Diseases Research Center and the Charles C. Gates Regenerative Medicine and Stem Cell Biology Center. He is an active member of the Skin Cancer Tissue Bank executive committee. He has received Research Career Development Awards from the Dermatology Foundation and the American Skin Association. Dr. Box completed his graduate school training on the genetics of human hair, skin and eye color in the laboratory of Dr. Richard Sturm at the University of Queensland, Australia. During this period he identified some of the key red hair color variants at the MC1R locus (eg. R151C, R160W). His subsequent research on this subject produced some of the seminal melanoma association and gene interaction studies for MC1R. Since moving to the USA in 2001, he performed postdoctoral trained with two leading scientists in mouse models of human disease: Dr. Monica Justice and Dr. Dennis Roop at Baylor College of Medicine. From this work, he has assembled a research program aimed at uncovering the molecular mechanisms regulating melanoma risk. Since his recruitment to the University of Colorado in 2007, he has also continued his interests in working with human melanoma risk genes to explore their potential clinical and public health applications.