

Polymorphisms in the p53 pathway are enriched in cancer susceptibility loci and share characteristics with somatic pathway mutations

G. Stracquadanio¹, M. Wallace¹, A.M. Grawenda¹, P. Zhang¹, J. Hewitt¹, J. Zeron-Medina³, F. Castro-Giner⁴, I.P. Tomlinson⁴, C.R. Goding¹, K.J. Cygan^{5,6}, W.G. Fairbrother^{5,6}, L.F. Thomas⁸, P. Sætrom^{7,8}, F. Gemignani⁹, S. Landi⁹, B. Schuster-Boeckler¹, D.A. Bell², G.L. Bond¹.

¹Ludwig Institute for Cancer Research, University of Oxford, Nuffield Department of Clinical Medicine, ²Environmental Genomics Group, Genome Integrity and Structural Biology, National Institute of Environmental Health Sciences, ³Vall d'Hebron University Hospital, Oncology Department, Barcelona, Spain, ⁴Molecular and Population Genetics Laboratory, The Wellcome Trust Centre for Human Genetics, University of Oxford, ⁵Center for Computational Molecular Biology, Brown University, Providence, ⁶Department of Molecular Biology, Cell Biology, and Biochemistry, ⁷Department of Computer and Information Science, Norwegian, University of Science and Technology, ⁸Department of Cancer Research and Molecular Medicine, Norwegian, University of Science and Technology, ⁹Genetics- Department of Biology, University of Pisa, Pisa, Italy

Commonly inherited genetic variants, such as single nucleotide polymorphisms (SNPs) hold great promise as easily obtainable and measurable biomarkers. Over one thousand SNPs associate with cancer in genome-wide association studies (GWAS). However, the limited understanding of the biology behind these associations has restricted their utility. Attributing GWAS SNPs to well-studied signaling pathways proven to be important in cancer could serve to accelerate our biological understanding and maximize utility. Decades of research have proven that human genetic variants in the p53 stress response pathway can play key roles in the incidence and survival of many cancers. However, most evidence has been restricted to rare inherited mutations and common somatic mutations. Here, we demonstrate that newly abundant genomic data support a model, wherein commonly inherited genetic variants in the p53 pathway also contribute to the heterogeneity of human cancer. Our results from a pathway enrichment analysis demonstrate that p53 pathway genes are more significantly enriched in cancer susceptibility loci compared to other signaling pathways. Moreover, these commonly inherited variants show strikingly similar characteristics with the well-studied somatic pathway mutations. We have found that both classes of genetic variants occur in a high proportion of p53 pathway genes relative to other pathways, in multiple cancer types, and in similar pathway genes, thereby suggesting that a relatively high proportion of particular p53 pathway genes are highly sensitive to heritable and somatic genetic variants resulting in altered tumor suppression to a broad cancer spectrum. These results allow for insights into p53-mediated tumor suppression in humans and into the potential utility for susceptibility SNPs as biomarkers for progression.