

Somatic predisposition to germline mutations in the RTK/RAS/MAPK pathway

Anne Goriely, PhD

MRC-Weatherall Institute of Molecular Medicine; Nuffield Division of Clinical Laboratory Sciences, Radcliffe Department of Medicine, University of Oxford, Oxford OX3 9DS, UK

Anne.goriely@imm.ox.ac.uk

Somatic and germline mutations are traditionally viewed as separate entities. Yet, it is well established that germline variants (either inherited or occurring spontaneously) can influence cancer risk - i.e. cancer predisposition syndromes.

In this presentation, I will discuss the reverse (but complementary) concept and propose that *de novo* germline mutations in the RTK/RAS/MAPK pathway occur recurrently because they confer a selective advantage to testicular stem cells, leading to the formation of 'mole-like' mutant clones in the ageing testis. This universal mechanism called 'selfish selection' relies on principles akin to oncogenesis and explains the paternal age-effect and high birth prevalence observed for several Mendelian disorders, including Noonan (*PTPN11*), Costello (*HRAS*), Apert (*FGFR2*) syndromes and achondroplasia (*FGFR3*). I will describe the strategies we have developed to show that the human testis is a repository of pathogenic *de novo* mutations and that selfish 'moles' are prevalent in older men's testes. Our data show that the male germline is particularly vulnerable to dysregulation of the RTK/RAS/MAPK pathway. Importantly, because the germline provides a source of heritable material (unlike somatic tissues), this phenomenon has implications that extend far beyond the individual in whom it takes place, and is predicted to affect disease prevalence, genome heterogeneity and evolution of our species. This process illustrates another facet of the fascinating biology of the RAS/MAPK pathway.