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Dr.sc.hum.

**Genetics of skin cancer: Somatic alterations in melanoma and susceptibility variants in basal cell carcinoma.**

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The first aim included the study of somatic alterations in critical genes in malignant melanoma. The genes screened in melanoma cell lines and tumor tissues included oncogenes (*B-RAF* and *N-RAS*), tumor suppressor genes (*CDKN2A, CDKN2B* and *CDK4*), *DUSP* genes (*DUSP4, DUSP* and *DUSP10*), kinase genes (*PIK3CA, c-KIT* and *EGFR*) and low penetrance genes (*MC1R* and *EDNRB*). Our results confirmed previous findings that *B-RAF* and *N-RAS* mutations constitute the largest somatic alterations in melanoma. Our results from cell lines and tumor tissues also showed highly significant concomitant *B-RAF/N-RAS* and *CDKN2A* alterations. These results augment the hypothesis that *B-RAF/N-RAS* mutations, though early events, are not sufficient for the genesis of melanoma. The loss of *CDKN2A* is required to overcome oncogene induced melanocytic senescence. In a novel finding we report a strong inverse association between *MC1R* variants and *B-RAF/N-RAS* mutations. Our results suggest a stronger role for *MC1R* variants in melanoma biology than has been so far understood. Though the mutations in other screened genes were rare, nevertheless, a subset of melanoma according to our results carried aberrations in multiple genes. This sub-set of melanoma probably constitutes a mutator phenotype with likely prognostic implications. We also found differential associations between *B-RAF* and *N-RAS* mutations and patient survival. The results from this part of study provide a scope for future use of mutations as prognostic markers.

The second aim of identifying susceptibility alleles in critical genes was attained by carrying out population based association studies. Melanoma cases and healthy controls were genotyped for polymorphisms in the melanocyte specific *MC1R* and *EDNRB* genes. While *MC1R* variants were associated with melanoma risks but not the variants in the *EDNRB* gene. Lastly, in population based case-control study on BCC

we studied 12 polymorphisms in 11 genes which included those involved in DNA repair and cell cycle regulation. We found a strong protective effect of variant allele for T241M polymorphism in the *XRCC3* gene. The variant allele was also associated with a decreased risk of multiple BCC. In a gender specific analysis we found E185Q polymorphism in the *NBS1* gene was associated with an increased risk of BCC in men. Again in men, polymorphisms in the *XRCC3* and *NBS1* genes were associated with a multiplicative increase in risk of BCC.