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**_Telomerase Reverse Transcriptase_ Promoter Mutations in Melanoma, Non-Melanoma Skin Cancer and Glioma**

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Telomerase expression and the capability for infinite growths through implicated maintenance of telomeres is one of the hallmarks of cancer. This dissertation is based on a comprehensive investigation of the recently discovered mutations in the core promoter of the *telomerase reverse transcriptase* (*TERT*) gene. The study included over 1300 neoplastic lesions of various stages from three major cancer types - melanoma as well as non-melanoma skin cancer (NMSC), and adult gliomas of the brain. In all three cancer types we observed high frequencies of the *TERT* promoter mutations (melanoma 43%; NMSC 46-64%; glioma 39-80%). In melanoma, *TERT* promoter mutations were associated with later stages of the disease, more frequent in distant metastases than regional ones and distinctively absent in melanocytic nevi, which present non-obligate precursor lesions of melanoma. In adult gliomas an association with higher grades was observed and *TERT* promoter mutation frequency was highest in the most aggressive form of glioma, primary glioblastomas. Non-melanoma skin cancers also carried *TERT* promoter mutations at high frequencies; however, the mutations were also detected in benign and potentially pre-malignant lesions. The development of *TERT* promoter mutations in skin cancers can be presumed to be facilitated by UV-radiation, indicated by our observations of higher rates of CC>TT tandem mutations in skin cancers than in gliomas or other cancer types. The underlying discernible selection force behind the occurrence of the major *TERT* promoter mutations is the *de novo* creation of CCGGAA/T binding motifs for Ets/TCF transcription factors that consequently leads to higher TERT mRNA levels in tumours with *TERT* promoter mutations than without. Tumours with *TERT* promoter mutations had shorter telomeres than those without. In melanoma and glioma, the *TERT* promoter mutations were associated with clinical parameters linked to poor prognosis and mutations indicated poor patient survival, which was further influenced by a germline single nucleotide polymorphism (rs2853669). The combination of *TERT* promoter mutations with other driver mutations was found to allow for stratification of patients into subgroups with distinct survival features. In melanoma this was the case for *BRAF* mutations and the combination of *TERT* promoter and *IDH* mutations was of strong prognostic value in glioma. The *TERT* promoter mutations are among the first

functional alterations in the ‘dark matter’ of the genome. Their exceedingly high recurrence and effects on transcription and telomere length emphasise the importance of telomere biology in disease genesis.