GC-02. CNS GERMINOMAS ARE CHARACTERIZED BY GLOBAL DEMETHYLATION, CHROMOSOMAL INSTABILITY AND MUTATIONAL ACTIVATION OF THE KIT-, RAS/RAF/ERK- AND AKT-PATHWAYS

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CNS germinomas represent a unique germ cell tumor entity characterized by uniform undifferentiated tumor cells and a high response rate to current treatment protocols. However, only limited information is available on their underlying genomic, epigenetic and biological alterations. In this study we performed a genome-wide analysis of genomic copy number alteration and allelic disbalances in 37 cases of CNS germinomas by molecular inversion profiling. In addition, CpG dinucleotide methylation was studied by immunohistochemistry with a specific antibody against methylated cytosine residues. Mutational analysis was performed by resequencing of candidate genes including KIT and RAS family members using FFPE-derived DNA. Ras/Erk and Akt pathway activation was analysed by immunostaining with specific antibodies against phospho-Erk and phospho-Akt. All germinomas coexisted Oct4 and Kit but showed an extensive global demethylation of nuclear DNA compared to other germ cell tumors and normal tissues. Molecular inversion profiling showed predominant genomic instability in 32/37 tumors with a high frequency of regional gains and losses including high level amplifications. Activating mutations of KIT exons 11, 13, 17 as well as a case with genomic KIT amplification and activating mutations or amplifications of RAS gene family members including KRAS, NRAS, RRAS2 and RHOH as well as mutation of BRAF indicated mutational activation of crucial signalling pathways. Activation of both, Ras/Erk and Akt pathways was demonstrated by immunohistochemistry of phospho-Erk and phospho-Akt in germinomas. These data suggest that CNS germinoma cells display a demethylated nuclear DNA similar to primordial germ cells in early development. This finding is associated with extensive genomic instability in the majority of germinomas. In addition, mutational activation of KIT, Ras/Raf/Erk- and Akt- pathways is characteristic indicating the biological importance of these pathways and potential targets for therapy.