GENETICS/EPIGENETICS (GEN)

GEN-03

GENOTYPE-PHENOTYPE CORRELATION IN 111 FAMILIES OF VON HIPPEL-LINDAU DISEASE IN JAPAN

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BACKGROUND AND AIM: von Hippel-Lindau (VHL) disease is a hereditary disease which manifest central nervous system (CNS) hemangioblastoma, retinal angioma, renal cell carcinoma (RCC), pheochromocytoma, endolymphatic sac tumor, and pancreas cyst. The VHL gene is located at 3p25.3 and is corresponding to 213 amino acids. Genotype-phenotype correlation analyses of VHL disease have been recently reported from several foreign countries, but the genotype-phenotype correlation has not been characterized since above 10 years ago. Therefore, this study aimed to evaluate the VHL mutation spectrum and genotype-phenotype correlations in Japanese VHL patients. METHODS: Blood samples of 111 unrelated families of VHL disease were collected and DNAs were extracted. Direct sequencing and real-time PCR analysis were performed. Consequently, the clinical manifestations and family histories of the subjects were evaluated. RESULTS: We identified VHL mutations as follows: missense 47; deletion 17; insertion 5; nonsense 8; splice-site 9; larger deletion 25. At hot-spot codon 167, 4 minsense mutations were identified, with Arg167Trp, 4 cases; Arg167Gln2, 2 cases. At codon 155, splice-site mutations were identified at 6 cases. Mutation sites were distributed in exon 1, 45; exon 2, 21; exon 3, 36. Large deletions were distributed in exon 1 & 2, 1; exon 2& 3, 1; all exons, 11. Genotype-phenotype correlation analysis revealed that age-specific risk and number of CNS hemangioblastoma were significantly higher in subjects carrying missense mutation within HIF-α binding site or non-missense mutation ($P < 0.05$). In addition, penetrance of RCC was significantly higher in subjects carrying non-missense mutation ($P < 0.05$). CONCLUSIONS: The results of this study were similar to the previous foreign studies. This study provides insight into the genotype-phenotype correlation in that amino acids substitutions in the HIF- α binding and non-sense mutations may predispose VHL patients to age-related risk and number of CNS hemangioblastoma.

GEN-06

CLINICAL COURSE AFTER TUMOR RECURRENCE OF MGMT HYPERMETHYLATED GLIOBLASTOMA

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MGMT methylation in glioblastoma is a biomarker for determining treatment responsiveness and predicting prognosis. We analyzed whether there were differences in the prognosis between glioblastoma with MGMT hypermethylation and other glioblastomas after tumor recurrence. We enrolled 184 patients who underwent radiation therapy and temozolomide chemotherapy after tumor resection for newly diagnosed glioblastoma. MGMT methylation was quantitatively analyzed using methylation-specific high resolution melting analysis. The cut-off value for MGMT methylation had a difference of 35% from the previous values. The subjects were split into three groups according to their MGMT methylation levels, 122 in the low (L) methylation group (levels of 0–34%), 40 in the medium (M) methylation group (levels of 35–69%), and 22 in the high (H) methylation group (levels of 70% or more). We mainly focused on and compared the progression after recurrence. The progression-free survival (PFS) rate and overall survival (OS) rate were significantly longer in the M and H groups than in the L group. There was no difference in PFS between group M and group H, but OS was significantly longer in group H. The details of treatment for the 16 of 22 patients who had recurrences in group H are as follows: temozolomide, n = 1; bevacizumab, n = 8; investigational drugs (peptide vaccines and immune checkpoint inhibitors), n = 3; and supportive care, n = 4. The median survival rate for these 16 patients after recurrence was 18 months. Even patients who received only supportive care had a median survival time ranging between 9 and 17 months. Our results indicate that MGMT hypermethylation in glioblastoma is effective to a certain degree with other treatments even after recurrence. Even patients who underwent only supportive care survived for a relatively longer period of time. Biologically, MGMT hypermethylation may be associated with a moderately slow-growing tumor.

GEN-13

FIREWORK PATTERN OF CANCER GENESIS FOR GLIOBLASTOMA, IDH-WILDTYPE

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Treatment of Glioblastoma (GBM), IDH-wildtype is a history of sequential failure. The cure for this disease is a distant story, and it is really the emperor of cancer. We believe that GBM should not be considered one of several cancers, and GBM is a cancer that occurs in a special environment called the central nervous system (CNS). What is the biggest difference between other cancers and cancers of the nervous system? It is thought to be neurogenesis. This presentation will review GBM genesis based on neurogensis of CNS. It also explains what the cell of origin is, what somatic mutations occur at the cell of origin, and why these somatic mutations occur. Human glioblastoma (GBM) occurs in a place without cancer tissue, that is, in the subventricular zone and have introduced the name of the firework pattern of cancer genesis, which is a metaphorical representation of the GBM genesis. So far, we have been trying to develop therapeutics focused on bulk tumors. However, in the case of GBM, IDH-wildtype, it has been found that the cell of origin is not in the tumor but is in normal SVZ, so it is now considered that the therapeutic target should also include the cell of origin.

Key words: glioblastoma, firework pattern, cell of origin

EXPERIMENTAL THERAPEUTICS (ET)

ET-02

EFFICACY OF THE SALVAGE THERAPY VIA LOMUSTINE AND NIMUSTINE FOR RECURRENT GLIOBLASTOMA WITH TEMOZOLOMIDE RESISTANCE.

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Temozolomide (TMZ) is widely used as a part of the standard treatment of glioblastomas (GBMs). However, GBM often acquires resistance for TMZ after continuous treatment with TMZ and recurs as TMZ resistance GBM (TMZ-R GBM). Other alkylating agents such as lomustine (CCNU) or nimustine (ACNU) have been sometimes used as a salvage therapy for those TMZ-R GBMs, however, their efficacy against TMZ-R GBMs has not been thoroughly investigated yet. In this study, we investigated anti-tumor effects of CCNU and ACNU for TMZ-R GBM cell lines in vitro to examine whether these agents could become alternative to TMZ in the therapy of TMZ-R GBMs. TMZ resistant clones of human GBM cell lines U87 MG (U87-R cells) and U251 MG (U251-R cells) were established as the TMZ-R GBM cell lines by cultivating U87 MG cells and U251 MG cells under continuous TMZ treatment for at least 1 year. Induction of growth arrest and apoptosis by TMZ, CCNU or ACNU against these cells were analyzed by dye exclusion assay, vital dye staining assay, and immunoblotting. The results showed that growth arrest and apoptosis were triggered upon these cells after administration of each drugs. As expected, the anti-tumor effects of TMZ for U87-R cells or U251-R cells were significantly reduced compared with those for parental U87 MG cells or U251 MG cells, respectively. On the other hand, CCNU and ACNU showed similar growth suppressive effect upon U87-R cells or U251-R cells as compared with U87 MG cells or U251 MG cells. Throughout these experiments, CCNU demonstrated strongest anti-tumor effects for all cell lines, both parental and TMZ-R GBM cell lines, and ACNU also demonstrated stronger effects than TMZ. These results suggest that CCNU or ACNU may serve as a drug of choice for salvage treatment of TMZ-R GBM.

ET-04

MOLECULAR TARGETED THERAPY AGAINST (PRO)RENIN RECEPTOR FOR GLIOBLASTOMA

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INTRODUCTION: (Pro)renin receptor(PRR) is part of the Wnt receptor complex. Wnt/β-catenin signaling pathway (Wnt signaling) plays important role in pathogenesis and self-renewal of glioblastoma (GBM), or differentiation of glioma stem cell. We previously reported that PRR activate Wnt signaling, PRR expression correlated with malignancy of glioma, and treatment with PRR siRNA reduced the proliferative capacity. This time, we have developed monoclonal antibodies against PRR and examined their effects in GBM. MATERIAL AND METHODS: We used GBM cell line (U251MG