22q13

Genome-wide association study (GWAS) have transformed our understanding of glioma susceptibility, but individual studies have had limited power to identify risk loci.

Melin et al. performed a meta-analysis of existing GWAS and two new GWAS, which totaled 12,496 cases and 18,190 controls. They identified five new loci for glioblastoma (Glioblastoma) at 1p31.3 (rs12752552; P = 2.04 × 10-9, odds ratio (OR) = 1.22), 11q14.1 (rs11233250; P = 9.95 × 10-10, OR = 1.24), 16p13.3 (rs2562152; P = 1.93 × 10-8, OR = 1.21), 16q12.1 (rs10852606; P = 1.29 × 10-11, OR = 1.18) and 22q13.1 (rs2235573; P = 1.76 × 10-10, OR = 1.15), as well as eight loci for non-Glioblastoma tumors at 1q32.1 (rs4252707; P = 3.34 × 10-9, OR = 1.19), 1q44 (rs12076373; P = 2.63 × 10-10, OR = 1.23), 2q33.3 (rs7572263; P = 2.18 × 10-10, OR = 1.20), 3p14.1 (rs11706832; P = 7.66 × 10-9, OR = 1.15), 10q24.33 (rs11598018; P = 3.39 × 10-8, OR = 1.14), 11q21 (rs7107785; P = 3.87 × 10-10, OR = 1.16), 14q12 (rs10131032; P = 5.07 × 10-11, OR = 1.33) and 16p13.3 (rs3751667; P = 2.61 × 10-9, OR = 1.18). These data substantiate that genetic susceptibility to Glioblastoma and non-Glioblastoma tumors are highly distinct, which likely reflects different etiology [1)].

By integrating omics analyses in 50 matched samples, Ha et al. uncover in Taiwanese patients a predominant mutation signature associated with cytidine deaminase APOBEC, which correlates with the upregulation of APOBEC3A expression in the APOBEC3 gene cluster at 22q13 [2)].

Ha et al. describe two patients with novel chromosomal anomalies involving chromosome 22q13, a locus also associated with Phelan-McDermid syndrome (PMS).

They aim to characterize the novel phenotypic and genotypic findings of two patients with 22q13 microdeletions, distinct from PMS, comparing and contrasting with features of PMS.

Case 1 is a 4-year-old boy with global developmental delay, esotropia, moderate aortic root dilation, genu valgum, and in-toeing gait. MRI brain for evaluation of neonatal hypotonia revealed a left cerebellopontine angle arachnoid cyst. He referred on newborn hearing screening, and diagnostic auditory brainstem response (ABR) showed left profound retrocochlear hearing loss. Surgical intervention for the arachnoid cyst was deferred, with spontaneous resolution at age two years without hearing recovery. CMA revealed a novel, de novo 5.1 Mb microdeletion of 22q13.31q13.33 not involving SHANK3, a gene typically deleted in PMS. Case 2 is a 6-year-old girl with some features also seen in patients with PMS but also several atypical features. She has a complex chromosomal rearrangement including a 5.3 Mb 22q13 microdeletion (not including SHANK3) and de novo 2.1 Mb gain of 22q11.

As diagnostic sensitivity improves, smaller chromosomal imbalances will be detectable related to milder or different phenotypes. They present two patients with novel deletions of chromosome 22q13 associated with multiple congenital anomalies and features distinct from PMS [3)].

LOH at 22q13 was seen in 48%, 60%, and 60% in benign, atypical, and anaplastic meningiomas, respectively. LOH results at 1p32 and 17p13 showed statistically significant differences between benign and non-benign meningiomas.

LOH at 1p32 and 17p13 showed a strong correlation with tumor progression. On the other hand, LOH at 7q21 and 7q31 may not contribute to the development of the meningiomas [4].

Loss of chromosome 22 and gain of 1q are the most frequent genomic aberrations in ependymomas, indicating that genes mapping to these regions are critical in their pathogenesis. Using real-time quantitative PCR, we measured relative copy numbers of 10 genes mapping to 22q12.3-q13.33 and 10 genes at 1q21-32 in a series of 47 pediatric intracranial ependymomas. Loss of one or more of the genes on 22 was detected in 81% of cases, with RAC2 and C22ORF2 at 22q12-q13.1 being deleted most frequently in 38% and 32% of ependymoma samples, respectively. Combined analysis of quantitative-PCR with methylation-specific PCR and bisulphite sequencing revealed a high rate (>60% ependymoma) of transcriptional inactivation of C22ORF2, indicating its potential importance in the development of pediatric ependymomas. Increase of relative copy numbers of at least one gene on 1q were detected in 61% of cases, with TPR at 1q25 displaying relative copy number gains in 38% of cases. Patient age was identified as a significant adverse prognostic factor, as a significantly shorter overall survival time (P = 0.0056) was observed in patients <2 years of age compared with patients who were >2 years of age. Loss of RAC2 at 22q13 or amplification of TPR at 1q25 was significantly associated with shorter overall survival in these younger patients (P = 0.0492 and P = < 0.0001, respectively). This study identifies candidate target genes within 1q and 22q that are potentially important in the pathogenesis of intracranial pediatric ependymomas [5].

Ependymomas are glial cell-derived tumors characterized by varying degrees of chromosomal abnormalities and variability in clinical behavior. Cytogenetic analysis of pediatric ependymoma has failed to identify consistent patterns of abnormalities, with the exception of monosomy of 22 or structural abnormalities of 22q. In this study, a total of 19 pediatric ependymoma samples were used in a series of expression profiling, quantitative real-time PCR (Q-PCR), and loss of heterozygosity experiments to identify candidate genes involved in the development of this type of pediatric malignancy. Of the 12,627 genes analyzed, a subset of 112 genes emerged as being abnormally expressed when compared to three normal brain controls. Genes with increased expression included the oncogene WNT5A; the p53 homologue p63; and several cell cycle, cell adhesion, and proliferation genes. Underexpressed genes comprised the NF2 interacting gene SCHIP-1 and the adenomatous polyposis coli (APC)-associated gene EB1 among others. We validated the abnormal expression of six of these genes by Q-PCR. The subset of differentially expressed genes also included four underexpressed transcripts mapping to 22q12.313.3. By Q-PCR we show that one of these genes, 7 CBX7(22q13.1), was deleted in 55% of cases. Other genes mapping to cytogenetic hot spots included two overexpressed and three underexpressed genes mapping to 1q31-41 and 6q21-q24.3, respectively. These genes represent candidate genes involved in ependymoma tumorigenesis. To the authors' knowledge, this is the first time microarray analysis and Q-PCR have been linked to identify heterozygous/homozygous deletions [6].

In the majority of the other half chromosome 22 is lost. In higher grade meningiomas this loss is followed by characteristic secondary chromosome aberrations. Regarding the molecular findings in Schwannomas, homozygous loss or mutation of the NF2 gene located on chromosome 22, was supposed also to be the primary event in meningioma development. However, in nearly all high grade but in only a minority of low grade meningiomas the loss of the NF2 protein is observed. Therefore, both the hypothetical combined heterozygous loss of or inactivation of two or more tumour

suppressor genes (at least one of them located on chromosome 22) or the homozygous loss of a regulatory gene on chromosome 22 different from NF2 was discussed. In search for microdeletions or/and structural recombinations of chromosome 22 we investigated primary cell cultures of 43 meningiomas by conventional G-banding (26 without, 17 with loss of chromosome 22). Twenty-seven tumours were analysed with spectral karyotyping (SKY) and 16 with fluorescence in situ hybridisation (FISH) with DNA probes for the chromosomal regions of 22q11.2, 22q11.23q12.1, 22q12.1 and 22q13.3. SKY analysis confirmed G-banding data for chromosome 22 and could specify marker chromosomes and translocations containing material from chromosome(s) 22. Confirming our assumption microdeletions on chromosome 22 were detected by FISH in 6/8 cytogenetically non-aberrant meningiomas. Surprisingly, in 2/8 cases we observed gains of the 22q13.3 and in 2/8 gains of the 22q12.1 region. Here we present first evidence for an uncommon mechanism during early meningioma development at least for a meningioma subgroup: i) duplication and translocation of sequences from chromosome 22 to different chromosomes. ii) deletion of the original sequences on chromosome 22, resulting in disomy again (only visible as translocation in metaphase FISH). iii) loss of chromosome 22 [7)].

A high-resolution allelotype study of 21 cases of primary Glioblastoma was performed by PCR-based loss of heterozygosity (LOH) analysis. Three hundred and eighty-two fluorescent dye-labeled microsatellite markers covering all 22 autosomes were applied. The mean genetic distance between two flanking markers was about 10 cM. RESULTS: LOH was observed on all 39 nonacrocentric autosomal arms examined in this study. The LOH frequencies of 10q, 10p, 9p, 17p and 13q were the highest (> 50%). Furthermore, high LOH frequencies were detected in the regions containing known TSGs including PTEN, DMBT1, p16, p15, p53 and RB; the LOH frequencies on 14q, 3q, 22q, 11p, 9q, 19q were also high (> 40.5%). Our study observed the following commonly deleted regions: 9p22-23, 10p12.2-14, 10q21.3, 13q12.1-14.1, 13q14.3-31, 17p11.2-12, 17p13, 3q25.2-26.2, 11p12-13, 14q13-31, 14q32.1, 14q11.1-13, 22q13.3, 4q35, 4q31.1-31.2, 6q27 and 6q21-23.3. CONCLUSIONS: The molecular pathogenesis of Glioblastoma is very complicated and associated with a variety of genetic abnormalities on many chromosomal arms. The most closely related chromosomal arms to the pathogenesis of Glioblastoma are 10q, 10p, 9p, 17p and 13q. Besides the well-known TSGs including PTEN, DMBT1, p16, p15, p53 and RB, multiple unknown TSGs associated with Glioblastoma may be present on the commonly deleted regions detected in the present study [8)].

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a 69 year old man with two simultaneous meningiomas in different compartment of neural axis, in both of which 22q13 locus is lost. Histologically the two tumours appeared to be different; meningotheliomatous and transitional with psammoma bodies, respectively. No numerical or structural chromosome abnormalities were seen in karyotype analysis of the cultured spinal and cranial meningioma samples. Since long arm structural aberrations and/or whole loss of chromosome 22 are frequently reported abnormalities of meningiomas, the tumours were also analysed by fluorescence in situ hybridisation (FISH) with different colour-labelled probes in respect to relevant chromosome. The metaphases and interphase nuclei of the samples were evaluated by the combined biotinylated 22q11 and digoxigenin-labelled 22q13 locus specific FISH probes, and 22q13 deletion was revealed in both of spinal and cranial tumour cells. In conclusion, since both tumours from the presented case show the same genetic alterations, multiplicity may be derived from the same clone of cells, and support the theory of development of multiple meningiomas from the spreading of tumour cells via cerebrospinal fluid as a possible mechanism [9)].

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