GENOME-WIDE SEARCH FOR MENINGIOMA GENES/FAMILY STUDY OF MENINGIOMA

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PROGRESS:

Funds from the Brain Science Foundation (BSF) and Meningioma Mommas (MM) allowed us to genotype the first 200 Caucasian cases from our ongoing meningioma case/control study using the Illumina Infinium HD Human610-Quad BeadChip. DNA was extracted for each of these 200 cases and sent to DeCode Genetics in Iceland for genotyping. The genotyping is complete and we have completed our quality control analyses and commenced our statistical analyses. Our preliminary SNP association analyses reveal several "hits" on a number of chromosomes and at least one replication of the findings reported by Bethke et al (J Natl Cancer Inst 2008 ;100:270-276) in their examination of variants in DNA repair genes and meningioma risk.

Over the past six months we have examined the copy number variation data generated by these analyses. Copy-number variants (CNVs), defined as genomic deletions and duplications spanning more than 1000 base-pairs, can influence human phenotype by altering the transcriptional and translational levels of the genes encompassed by the CNV. The importance of CNVs in the etiology of nervous system lesions was recently recognized when a copy-number deletion was shown to confer a 2.5-fold increased risk for neuroblastoma. As a preliminary investigation into the role of CNVs in meningioma carcinogenesis, we conducted a pilot genomewide association study using 200 meningioma cases (funded by BSF/MM) and 1056 population-based controls genotyped on the Illumina 610 Quad Chip (Funded by NIH). After restricting the sample to include only Caucasian patients passing all quality control measures, 187 cases (73% female) and 871 controls (63% female) remained for analysis. Three distinct algorithms were applied to identify CNVs using hybridization intensity and B allele frequency values extracted from the SNP array data. In total, 35531 high-confidence CNVs were identified in the case-control sample (average 33.6 CNVs/person). Comparisons were made across phenotypic classes to identify copy-number deletions or duplications substantially enriched among patients with meningioma relative to controls. Several rare genic deletions were found in multiple cases but were absent in study controls (p-values < 0.001). For one of these deletions, the reciprocal duplication was significantly enriched among controls relative to cases ($p < 0.05$), indicating that the deletion may be a risk factor for meningioma while the duplication may have a protective effect. Given that the gene contained within this CNV is highly expressed in brain, ovary and mammary tissue, this is an intriguing finding.

Our next step will be to undertake laboratory experiments to validate these associations by performing real-time quantitative PCR reactions on the case-control sample set, targeting the candidate CNVs detected in the genomewide analysis. Further work is needed to identify promising genetic risk factors for meningioma, including genotyping a larger patient population.