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DNA Repair Polymorphisms in Glioblastoma Susceptibility

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Introduction

Glioblastoma accounts for about 70% of gliomas and is the most common and aggressive primary malignant brain tumour in adults [1]. Despite the better understanding of glioma biology and the improvements in therapeutic approaches, patients diagnosed with glioblastoma have a median survival of only 12-14 months [2]. Although several alterations in core signalling pathways have been involved in development and progression of glioblastoma tumours [3], the aetiology of most of glioblastoma cases is still poorly understood [2]. The only established environmental risk factor is the exposure to high doses of ionizing radiation [4], and also an increased risk of glioma is associated with inherited familial disorders such as Li-Fraumeni and Turcot syndromes, neurofibromatosis and tuberous sclerosis [4]. Nevertheless, they only account for a small proportion of cases suggesting that complex interactions among genetic abnormalities and unknown environmental factors predispose individuals to glioma [2,5].

DNA repair function is critical in maintaining genome stability and integrity. Thus, deficiencies in DNA repair capability may affect susceptibility to cancer [6]. Several polymorphisms in DNA repair genes have been associated with small variations in the efficacy of DNA repair that may facilitate glioma development [7-10]. However, in many cases these association studies have yield inconclusive results due to insufficient sample sizes, differences in population ethnicity or environmental exposure, or even they might be influenced by possible gene-environment interactions [11]. In addition, most of the studies investigated mixed histologic subtypes of glioma with different genetic background (low-grade astrocytomas, anaplastic astrocytomas, glioblastomas and oligodendrogliomas), and only a few studies have specifically evaluated the relation of DNA repair polymorphism in glioblastoma susceptibility.

In that regard, the article by Rodriguez-Hernandez and colleagues [12] investigated the role of several common polymorphisms in relevant genes to four major DNA repair pathways in modulating glioblastoma risk. The authors showed that the homozygous Gln/Gln genotype of ERCC2 rs13181 polymorphism was associated with a protective effect of developing glioblastoma. Moreover, the authors found that the haplotype containing the C allele of ERCC2 rs13181 polymorphism and the T allele of ERCC1 rs11615 polymorphism was significantly associated with a protective effect of developing glioblastoma [12]. Both ERCC2 and ERCC1 genes are involved in the same DNA repair pathway, the nucleotide excision repair (NER) pathway, and are located on the same chromosomal region (19q13.32), suggesting that they may have a collective effect on DNA repair outcome and the 19q chromosomal region could be important in glioblastoma pathogenesis. This is supported by the fact that different expression profiles and copy number alterations in this region have been found in familial and sporadic gliomas and are also related to glioma patients' survival [3,13-15]. However, although the ERCC2 rs13181 polymorphism is one of the most studied polymorphisms in ERCC2 gene, its functional significance is still not clear [16-18] and its association with glioma, and in particular with glioblastoma risk, is also controversial [7-9,19-22]. In addition, several meta-analysis have attempted to clarify the role of ERCC2 rs13181 polymorphism in modulating glioma risk, but the results are not conclusive or depend on the different ethnic population investigated [23-25]. Larger studies with more specified information in pathological types of glioma are needed to clarify the contribution of ERCC2 rs13181 polymorphism to glioblastoma susceptibility.

On the other hand, Rodriguez-Hernandez et al. [12] found that the MLH1 rs1800734 AA genotype conferred an increased risk of glioblastoma. The MLH1 rs1800734 polymorphism, located in an important region for MLH1 transcription regulation, has been widely investigated in colon, breast and lung cancer susceptibility [26-28]. Interestingly, the authors were the first group to identify its association with glioblastoma risk [12,29].

In conclusion, their results pointed out that both ERCC2 rs13181 and MLH1 rs1800734 polymorphisms might constitute glioblastoma susceptibility factors, although more studies in larger glioblastoma populations with functional studies are needed to validate the role of these polymorphisms in glioblastoma development. The identification of genetic and molecular biomarkers is critical for shedding light on the complex pathogenesis of glioblastoma tumours and might improve early diagnosis and/or help in the development of personalized therapies for these patients with a dismal prognosis.

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