ASSOCIATION BETWEEN *IFN-γ, TNF-α, FcγRIIA* AND *IL-12β* GENE POLYMORPHISMS AND SUSCEPTIBILITY TO ENDEMIC BURKITT LYMPHOMA IN CHILDREN FROM WESTERN KENYA

ABSTRACT

Endemic Burkitt lymphoma (eBL) is an aggressive paediatric B-cell lymphoma prevalent in children from holoendemic malaria regions of sub-Saharan Africa. It is associated with early primary Epstein-Barr virus (EBV) and repetitive *Plasmodium falciparum* (Pf) malaria coinfection with high incidence in western Kenya. The lymphoma is common among children aged 2-11 years with high incidence at 5-8 years and has been associated with multiple genetic variations. Endemic BL is characterized by the overexpression of the *c-MYC* oncogene, as a consequence of the t(8:14) IGH-myc translocation. However, the translocation alone is insufficient to drive the development of eBL since normal B cells also undergo *c-myc* translocation, leading to the hypothesis that other mutational variations may contribute to tumorigenesis. Polymorphic variations in cytokine genes that affect specific cytokine transcriptional levels have been shown to influence tumoral, viral and parasitic immune responses hence increasing the risk of tumour development in several cancers. The influence of cytokine polymorphisms in the aetiology of eBL has not been exhaustibly demonstrated. In this study, a retrospective case-control study design was used to investigate the association between polymorphisms within diverse genes implicated in tumoral immune surveillance: IFN-γ (+2109C/T), *TNF-α* (-1031T/C, -308G/A, -376G/A, -238G/A), *FcγRIIA* 131His/Arg and *IL-12B* +1188A/C; and the susceptibility to eBL in children from western Kenya. Specifically, the study determined the association between IFN-γ (+2109C/T), *TNF-α* (-1031T/C, -308G/A, -376G/A, -238G/A), *FcγRIIA* 131His/Arg and *IL-12B* +1188A/C genotypes and *TNF-α* (-1031 T/C, -308G/A and -238G/A) haplotypes and risk of eBL development and *IFN-γ* (+2109C/T), *TNF*-α (-1031T/C, -308G/A, -376G/A, -238G/A), *FcγRIIA* 131His/Arg and *IL-12B* +1188A/C gene polymorphism and EBV load among cases and controls from western Kenya. Based on the frequency of IL-12 +1188A/C low cytokine producing genotype within this population, a total of 113 eBL cases and 69 healthy age-matched control samples were used. Genomic DNA was extracted following the Qiagen™ DNAeasy protocol and used for TaqMan allelic discrimination and molecular inversion probes genotyping assays. EBV load was quantified using quantitative real-time PCR. The distribution of selected *IFN-γ, TNF-α, FcγRIIA* and *IL-12B* genotypes were determined by Fisher Exact test, while the association between the selected genotypes/TNF-α haplotypes and risk of eBL development were determined using logistic regression analysis. One-Way ANOVA was used to compare EBV load across the genotypes. The frequency of *IFN-γ* (+2109C/T), *TNF-α* (-1031T/C, -308G/A, -376G/A, -238G/A), *FcγRIIA* 131His/Arg and *IL-12B* +1188A/C genotypes were not significantly different between the study groups. Furthermore, no association between *IFN-γ, FcγRIIA, IL-12B* and *TNF-α* genotypes and risk of eBL diagnosis was observed. No significant difference in the EBV viral load between IFN-γ, *TNF-α*, *FcγRIIA* and *IL-12B* genotypes were also observed. Additionally, *TNF-α* haplotypic analysis were not significantly associated with the risk of eBL development. These results demonstrate that genetic variations in selected *IFN-γ, TNF-α, FcγRIIA* and *IL-12B* genes that affect levels of their respective cytokines and affinity of FcγRIIA for IgG have no association with eBL development. This suggest that other cytokine or other genetic factors may play a role in increasing susceptibility to eBL development through other mechanisms other than *IFN-γ, TNF-α, FcγRIIA* and *IL-12B* genes. Lack of association between the selected cytokine polymorphism and development of eBL suggest that these polymorphisms are not cytokine gene risks factors for genetic screening and development of cytokine therapeutics that target prevention and management of children at risk of developing eBL within malaria endemic region of western Kenya. However, the identification of other genetic variants in cytokines and their possible

association with eBL development in children from malaria endemic regions of Kenya is still critical in mapping other genetic mutations that may contribute to the pathogenesis of the lymphoma aside from the *MYC* translocation.