MOLECULAR-GENETIC ANALYSIS OF CERULOPLASMIN IN OESOPHAGEAL CANCER

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Oesophageal Cancer (OC) is a disease characterised by the development of malignant tumours in the epithelial cells lining the oesophagus. It demonstrates marked ethnic variation, with squamous cell carcinoma (SCC) being more prevalent in the Black population and adenocarcinoma (ADC) occurring more often in Caucasians. OC is one of the leading causes of cancer-related deaths worldwide; it is the 15th most common cancer in developed nations and the 4th most common in developing countries such as South Africa. The Transkei region of South Africa is thought to be the centre of the disease in Africa, with an age standardised incidence rate (ASIR) of 46.7/100 000 for males and 19.2/100 000 for females previously being reported. OC shows clear geographic variation and occurs at a high incidence in certain areas of the world, which are termed “oesophageal cancer belts”.The aetiology of this complex disease has been attributed to a variety of factors, including an excess of iron (resulting in increased tumourigenesis), oesophageal injury and inflammation (due in part to Barrett's oesophagus and smoking, amongst others). Ceruloplasmin (CP) is a ferroxidase enzyme synthesized in the liver which catalyses the oxidation of ferrous iron (Fe2+) to ferric iron (Fe3+), thereby creating an ion gradient favouring iron export from the cells. Therefore, CP which is located primarily in the plasma is responsible for driving iron transport from stores in various tissues In this study, we aim to demonstrate the relationship between genes involved in iron metabolism (specifically CP) and the development of OC, by identifying gene variations that could potentially contribute toward iron dysregulation and subsequent disease pathogenesis. It is anticipated that the results obtained from this study will lead to a greater understanding of the role that iron homeostasis plays in the aetiology of OC. The study cohort consisted of 96 unrelated OC patients from the Black Xhosa-speaking South African population and 88 population-matched control individuals. The promoter and coding regions of the CP gene were analysed for DNA sequence variation using the polymerase chain reaction (PCR), heteroduplex single-strand conformation polymorphism (HEX-SSCP) analysis, restriction fragment length polymorphism (RFLP) analysis and semi-automated bidirectional DNA sequencing analysis. Allele and genotype frequencies were estimated by allele counting and statistical differences between patient and control groups were tested for significance by chi-squared (X2) analysis. A probability value (P) smaller than 0.05 was regarded as statistically significant. The Hardy-Weinberg equilibrium (HWE) test was performed to determine equilibrium for the genetic traits investigated in the respective populations. Fourteen previously described (5’UTR-567CÍG, 5’UTR-563TÍC, 5’UTR-439CÍT, 5’UTR-364delT, 5’UTR-354TÍC, 5’UTR-350CÍT, 5’UTR- 282AÍG, V223, Y425, R367C, D544E, IVS4-14CÍT, IVS7+9TÍC and IVS15-12TÍC) and four novel (5’UTR-308GÍA, T83, V246A and G633) variants were identified. Statistical analysis revealed that two of the novel variants identified in the patient cohort were significantly associated with OC in this study; the promoter variant 5'UTR-308GÍA (P=0.012) and the exonic variant G633 (P=0.0003). This is the first study to examine CP with respect to OC in the Black South African population. As such, these findings should serve to further our understanding of the relationship between iron metabolism and disease pathogenesis, specifically OC.