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NOD2/CARD15 mutations and phenotypic expression of Crohn`s Disease in Malta

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Background: Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract with variations in localization and behaviour. Mutations in the NOD2/CARD15 gene on chromosome 16q have been implicated in the pathogenesis of the disease and three main sequence variants, all single nucleotide polymorphisms (SNPs), have been identified in North American and European populations. Data from mainland Europe has demonstrated a prevalence of 25-50% within CD patients. The genetic structure of the Maltese population includes Near Eastern Arab, Mediterranean and North African genetic components.

Aims: The aim of the study was to analyse the prevalence of the Arg702Trp, Gly908Arg and Leu1007insC mutations in the NOD2/Caspase- activation recruitment domain 15 (CARD15) gene and their correlation with the phenotypic expression in Maltese CD patients.

Method: Patients with a histological diagnosis of CD were consecutively recruited. Their phenotypic features, medications, investigations, surgical interventions were recorded in a dedicated database. All patients were genotyped for Arg702Trp, Gly908Arg and Leu1007fsinsC.

Results: 83 patients (42 female) were recruited. Their current mean age was 39 years (7-73 years). They hada CD duration post-diagnosis of 8.98 years (range:12 months to 32 years). 80.7 % of patients were having immunomodulator (IM) therapy. 26 patients were being administered azathioprine; 8 patients were being administered methotrexate; 15 patients were being administered infliximab and 18 patients were on dual IM therapy - azathioprine and infliximab. 16 patients were having 5-ASA as their only medication. 24.1% (20) of CD patients required surgery due to their underlying disease. In total, they had 27 surgical interventions. Extra-gastrointestinal manifestations were present in 21.7% of patients. 10 patients (12%) had genetic mutations: Arg702Trp- 3 patients;Gly908Arg – 3 patients and Leu1007fsinsC – 4 patients. Comparitive analysis of phenotype characteristics and the above genetic mutations did not demonstrate any relationship between the presence of these mutations and disease location, disease behaviour, age of onset and the use of immunomodulator treatment. However patients with the NOD2/CARD15 mutations were more likely to require CD related surgery (p- 0.01 – Fisher exact 2-tailed test) than those patients without any mutations.

Conclusions: In our study group only 12% of our patients had one of the mutations. Confidence intervals (quadratic equation of Fliess) demonstrated a statistically lower prevalence of the NOD2/CARD15 mutations compared to other European populations (p:<0.05). This data from Maltese patients with CD demonstrates the low prevalence of this mutation in our population when compared to other European countries. Our future research on the innate immune pathway will be directed towards TLR4 and CARD 9 mutations.