Reviewer's report

Title: Linkage Analysis of HLA and Candidate Genes for Celiac Disease in a North American Family-Based Study

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Version: 1 Date: 16 Oct 2001

Reviewer: Dr Jukka Partanen

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after revision, which I do not need to see

The manuscript by Neuhausen and co-workers describes a systematic attempt to study certain candidate genes for celiac disease, a common multifactorial disease. They have collected 62 families from US/Canada with at least two affected individuals. The standard linkage analysis included the HLA region plus certain candidate regions. They conclude that only the HLA region was found to be linked to the susceptibility. As the authors themselves state it is possible that the relatively low number of families (for this kind of study) may explain some of the negative findings. The main aspects of the article are well-based.

Some comments:
- as only one or a few markers at best were typed for each candidate region, can this low level of information cause some of the negative results?
- the HLA DQ alleles were not typed; as virtually all patients have the DQ2 or DQ8 heterodimer, their typing would help to check the diagnosis (particularly for non-biopsy diagnoses).
- only 1/2 of families showed linkage to HLA (last lines of Results); this is surprising as the DQ2 and DQ8 are found in almost all patients. It would be of interest to know whether in these non-linked families the patients anyway were positive for the known risk alleles (i.e. they can be i.b.s. rather than i.b.d.). Also, it would be interesting to know whether these patients had solid diagnoses (biopsy) or only antibody positivity.
- a minor point in Introduction: The HLA association is not strictly-speaking to DQA1*0501 and DQB1*0201, but 'merely' to DQA1*05 and DQB1*02, since the DQA1* allele in DR5 haplotypes is in fact DQA1*0505 and DQB1 allele in DR7 haplotype is DQB1*0202.

Competing interests:

None declared.