An association study of Huntington's disease and HLA

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SUMMARY HLA antigens were determined in a sample of 47 patients with the diagnosis and family history of Huntington's disease (HD). Two groups consisting of 20 and 11 unrelated patients respectively were investigated. In the first group an increased frequency of HLA-Bw44 ($p < 0.05$) and of HLA-A11 ($p < 0.05$) was found, but after correcting for multiple inferences the differences were no longer statistically significant. No correlation was found between sex, age of onset, initial symptom, and HLA type. In order to find out if the increased frequency of HLA-Bw44 was real or due to chance, the second group of patients was investigated. In this group the frequency of HLA-Bw44 did not differ from the normal population and a strong association between HLA and HD could be excluded.

Huntington's disease (HD) is an autosomal dominantly inherited disorder with a late age of onset. The pathogenesis is unknown and there is no reliable means of identifying gene carriers who will develop the disease.

In recent years, associations between different diseases and certain HLA antigens have been reported, for instance, between multiple sclerosis and HLA-B7 and HLA-Dw2.¹ Such associations may be of value in elucidating the pathogenesis of a disease and, in cases of strong association, in identifying persons at risk.

One of the characteristics of HD is its late onset, the cause of which is unknown. One possibility is that the symptoms appear after an infection, perhaps with a virus. Thus, Husby *et al*^{2,3} found a positive association between the duration of clinical disease for more than 7 years and titres of 1:2 or greater of antibody reacting with neuronal cytoplasm; they suggested that an environmental or infectious factor may be involved in the expression of HD. Barkley and Hardiwidjaja⁴ found striking parallels between some aspects of HD and infection in mice with murine C type virus and they concluded that endogenous virus involvement in HD should be considered. Because of these findings we undertook a study to search for a possible association between HLA and HD, and if such an association were found, to correlate this to age of onset and initial symptom. Our findings are compared with the findings of Foerster and Freudenberg,⁵ who found

a non-significant increased frequency of HLA-Bw16.

Materials and methods

The material comprised 68 Danish subjects with the diagnosis of HD, referred to us from psychiatric and neurological departments in different parts of the country. The diagnosis was verified by a specialist in neurology. Of these patients, 47 fulfilled the criterion of a family history of HD, which is necessary for a definite diagnosis. The disease in their relatives was ascertained from hospital records and, where possible, necropsy reports. The investigation was restricted to these 47 patients. In the first part of the study 28 patients were investigated (group 1). Twenty patients fulfilled the criterion of being unrelated, which is necessary for the study of a possible association with HLA, while the remaining eight patients were related to four of the former 20. These four patients were in each case the first patients examined in their respective families. Because of an increased frequency of HLA-Bw44 found in group 1 (see Results), a second group of patients was investigated. Group 2 comprised 19 patients, of whom 11 fulfilled the criterion of being unrelated, and none of these patients was related to the group 1 patients. Eight patients in group 2 were related to some of these 11 patients or the group 1 patients. Genealogical studies carried out for each person excluded that the 20 patients in group 1 and 11 patients in group 2 were related.

HLA typing was carried out by the standard NIH microlymphocytotoxicity technique⁶ on peripheral blood lymphocytes after separation into B and T lymphocytes according to the method of Pellegrino *et al.*⁷

Evaluation of a possible association was carried out by the method of Woolf⁸ and corrected for multiple inferences. As normal control material for HLA we used the data given by Ryder *et al.*⁹

Results

An increased number of HLA-A11 ($p < 0.05$) and HLA-Bw44 ($p < 0.05$) types was found among the 20 HD patients in group 1 in comparison with the normal population, but after correcting for multiple inferences the differences were no longer statistically significant.

The five patients with HLA-A11 were all females and the sex ratio of the HLA-Bw44 was eight females to two males. In comparison to the 14:6 ratio of the total group these differences are not significant.

The mean age at which the first symptom appeared was 37.0 ± 8.8 years. Abnormal movements were the first symptom in four patients and psychiatric symptoms in 11, while four patients had both neurological and psychiatric symptoms at the onset

of the disease. No data were available about the first symptom in one patient. There was no correlation between age of onset, initial symptom, and HLA type.

In the eight relatives belonging to group 1, HLA-A11 was found in one patient. HLA-Bw44 was found in five patients of whom three were related to case 6. Part of the pedigree is shown in the figure, from which it can be seen that HLA-Bw44 was found in two sib pairs (6+21 and 23+24, respectively). Two patients related to case 6 were HLA-Bw44 negative.

HLA-Bw44 was found in four of the 11 patients of group 2. This was not significantly different from the normal population.

Discussion

In investigations of HD and HLA one could look for genetic linkage and for association. The benefit of linkage would be the use of linkage relationships in carrier detection for genetic counselling purposes in persons at risk and in prenatal diagnosis. Very close linkage of HD with HLA has been excluded¹⁰ and our results of the family shown in the figure are in agreement with this finding.

The findings of an association between HD and HLA might elucidate the pathogenesis of the

FIGURE The HLA types in six members of a family with Huntington's disease.

disease and because of the possibility of virus involvement in HD this study was done.

In the search for an association between a disease and a genetic marker it is important that the patients, as well as the controls, are unrelated. It is also important that the patients represent a homogeneous group with respect to the disease under investigation, and an exact diagnosis is necessary. As the mutation rate at the HD locus is considered to be very low,¹¹ and because of the autosomal dominant inheritance, one might expect that the vast majority of cases of HD would be familial. In our material as many as 21 of 68 patients (about 30%) had no definite case of HD among their relatives, and this could indicate that in some of these cases the diagnosis had been misclassified. Because of this we have chosen to study only the patients with a definite family history of HD.

We found an increased frequency of HLA-A11 and HLA-Bw44 among the patients in group 1. Because of the small number of patients investigated and because of the large number of antigens tested our findings could be chance occurrences. This may be likely for HLA-A11 as only one case with this type was observed among the affected relatives. In contrast, HLA-Bw44 was found in five of the eight relatives in group 1. The observations in the family shown in the figure supports the possibility of an association between HD and HLA-Bw44. This type was found in two sib pairs and the probability that the Bw44 type in these originated from a common ancestor is only 1.5%. The findings in this family was another reason to investigate a new group of patients to see if the observations of increased frequency of HLA-Bw44 were real or due to chance. In group 2, the frequency of HLA-Bw44 was increased but not statistically significant, which suggests that a strong association between HLA and HD does not exist. In group 1 we found no correlation between age of onset, initial symptom, and HLA type.

Only Foerster and Freudenberg⁵ have reported a study concerning association between HLA and HD, but they did not specify whether their patients were familial or sporadic cases, so their results cannot be directly compared to ours. They tested for HLA-B12, which includes the splits -Bw44 and -Bw45, but they found no increased frequency of HLA-B12. They found an increased frequency of HLA-Bw16, significant at the 1% level, but after correcting for multiple inferences, it was no longer statistically significant. We found no increased frequency of HLA-Bw16 among the familial cases of the two groups combined. Owing to the lack of a monospecific antiserum defining that antigen,

we cannot exclude that two more cases were HLA-Bw16 positive, but even so the number would not be significantly increased.

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