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LETTER TO THE EDITOR

Linkage exclusion in Italian families with hereditary essential tremor

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Sirs,

Essential tremor (ET) is a common movement disorder, with a prevalence of 0.4–3.93% in the general population [1]. Up to 96% of patients with ET have a positive family history, suggesting that ET is primarily a hereditary disease [2]. Although an autosomal dominant pattern of inheritance has been suggested, no human gene causative of ET has been identified yet [3].

Genetic studies revealed linkage of familial ET to different chromosomal locations: 3q13.3, 2p25-p22 and 6p23 in families with European and Asian ancestry [4–8]. Two independent studies excluded linkage to all previous loci in the Italian population, confirming additional underlying genetic heterogeneity [9,10].

Herein, we tested for linkage to markers in 2p, 3q and 6p four large ET Italian families, comprising 29 affected individuals. All families originated from a single Italian region (Campania). The pedigrees are shown in Fig. 1. Upon informed consent, blood samples of patients, unaffected relatives and spouses were obtained. Allele frequencies at marker loci were obtained on Italian subjects with normal neurological examination, originating from the same geographical area of patients and matched for age and gender. Two chromosomal locations (2p22-p25 and 3q13) were analysed as previously described [4,5]. Six microsatellites on chromosome 6p22.3–p24.3 and three SNPs within the ALDH5A1 gene in this interval were genotyped by specific PCRs [8,11]. Whilst some of the markers used here represented merely positional candidates, ALDH5A1 could also be considered a functional candidate. This enzyme catalyses a key step in GABA (gamma-aminobutyrate) degradation, and its severe deficiency results in a disruption of the balance between GABA and its catabolites [12,13]. Interestingly, mouse models of ET involve either a disruption of GABA receptors or ameliorations of symptoms following treatment with modulators of the GABA degradation pathway [14]. The variants herein analysed have been shown to determine a measurable reduction in the overall enzyme activity [11]. More recently, other authors have described the absence of association between GABA receptors and GABA transporter polymorphism in humans [15–18].

Parametric LOD score analysis was performed with the program Simwalk [19]. Linkage results are shown in Fig. 2.

In summary, the study did not provide any evidence of linkage to loci in 2p, 3q and 6p suggesting that the association with the disease is unlikely, in agreement with previous data on other Italian families [9,10].

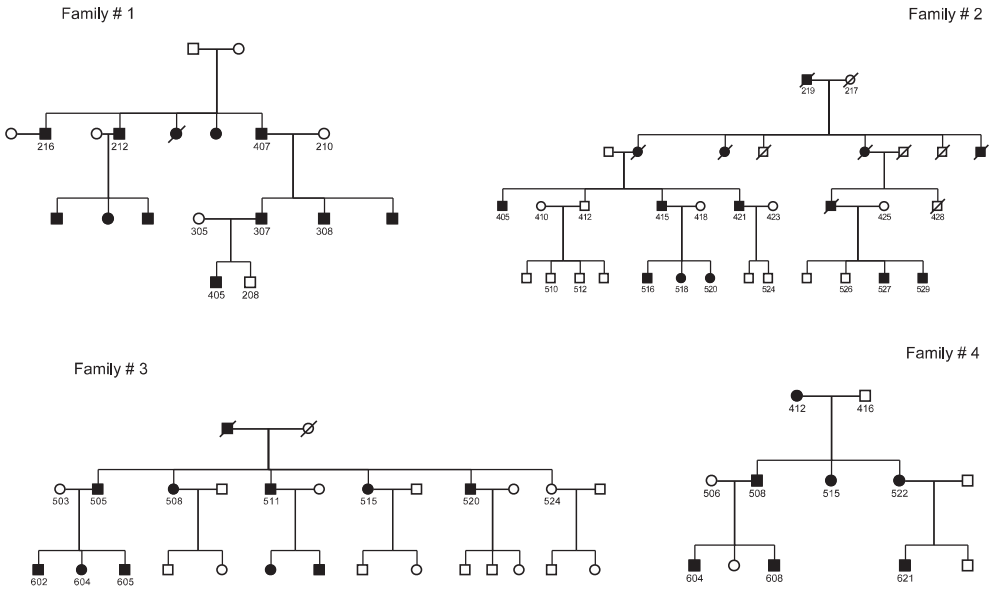

Figure 1 Pedigrees of essential tremor families. Individuals tested are indicated by a number.

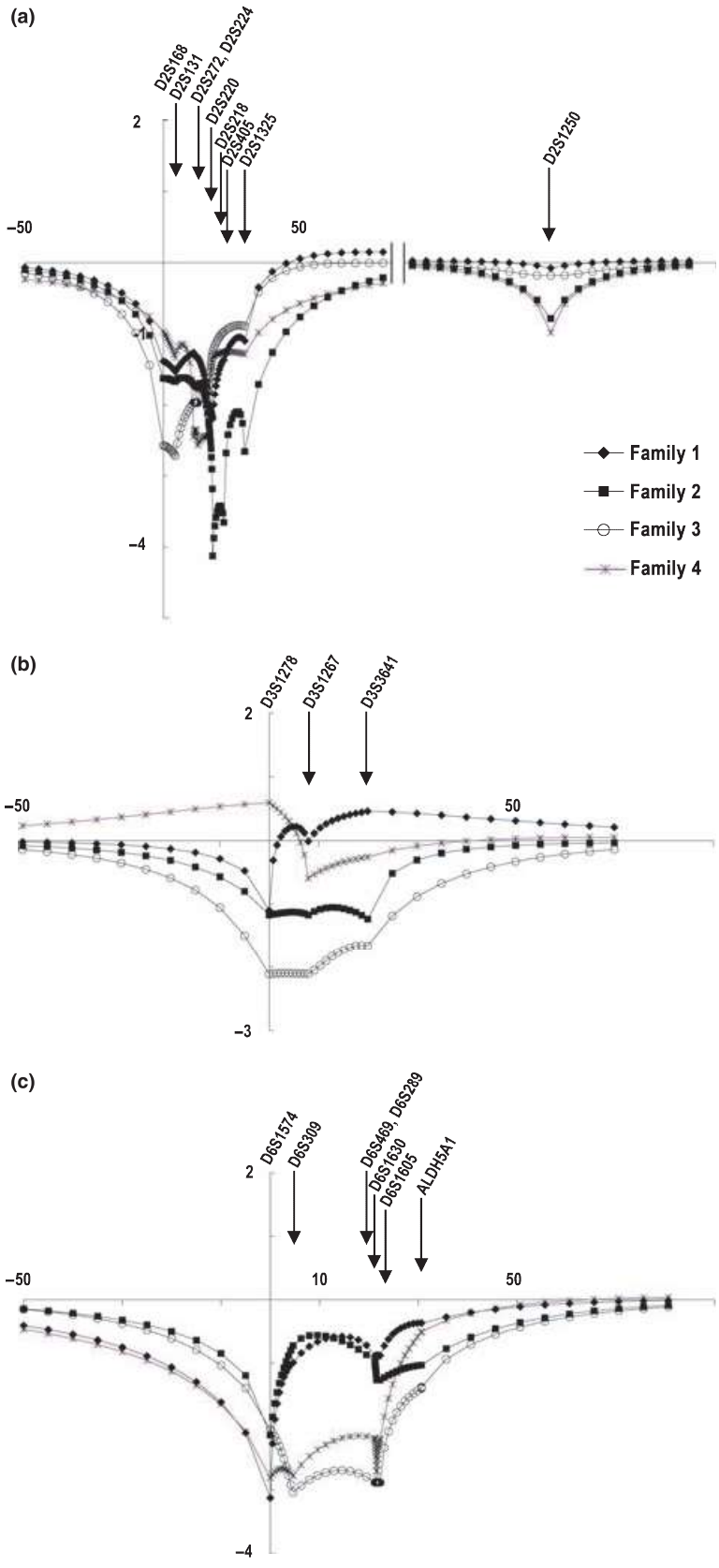

Figure 2 Location scores obtained over chromosome 2p, 3q and 6p map intervals in four essential tremor families. In each plot, the first marker is assigned position 0; arrows mark map positions of the additional markers used. Each family is identified by the same symbol in panels (a–c). Panel (a) 2p map interval. The *x* axis is interrupted to render that D2S1325 and D2S1250 are >50 cM apart; (b) 3q map interval; (c) 6p map interval. The position of markers rs4646828, rs2760118 and rs3765310 cannot be resolved and is identified by the acronym ALDH5A1. Note the different × scales in panel (a) as compared to panels (b) and (c).

Genetic dissection of this condition thus requires single pedigrees potentially able to display significant linkage.

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Ethics approval

Approval for the study was provided by the local ethics committee (Ethics Committee USL 3 – Genova).

Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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