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The p.Asp216His *TOR1A* Allele Effect Is Not Found in the French Population

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Abstract: DYT1 dystonia are one of the exceptions in human genetics with its unique and recurrent mutation (c.907delGAG). In this rare movement disorder, the mutation is associated with incomplete penetrance as well as great clinical variability, making this disease a benchmark to search for genetic modifiers. Recently, Risch et al. have demonstrated the implication of the rs1801968 SNP in disease penetrance. We attempted to replicate this

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result in an exhaustive DYT1 French population with no success. Our results argue that the rs1801968 H allele effect is not part of the modifiers in the French population of DYT1 patients and that others have to be identified in our population.

Key words: TOR1A; DYT1; population studies; genetic modifiers; movement disorders; dystonia

In a recent American report (published in June 2007), Risch and colleagues looked for both *trans* and *cis* effects of rs1801968 *TOR1A* SNP in DYT1 dystonia.¹ This study is based on previous experiments of Kock et al.² on torsinA, the protein encoded by the *TOR1A* gene and supposed to have a role in nuclear envelope and endoplasmic reticulum organization.³ Kock et al. have demonstrated that cells overexpressing torsinA with the rs1801968 H allele (called 216H allele) developed inclusions that were reduced when the c.907delGAG mutation was coexpressed (216H allele was introduced *in cis* of the mutation). In their study, Risch et al. analyzed 22 index cases and their family members (population corresponding to 17 independent families of European descent including 2/3 with Ashkenazi origin as well as 3 Asian, 1 African American, and 1 Mexican families). They showed that the rs1801968 H allele (216H allele) was more frequent in *trans* in asymptomatic *TOR1A* mutation carriers (Non Manifesting Carriers, NMC) (Table 1, *) and less frequent in symptomatic carriers (Manifesting Carriers, MC) (Table 1, ^S), when compared to controls (Normal Controls, NC) (Table 1, ^E). They deduced from these results a highly protective effect of the H allele when in *trans* with the c.907delGAG deletion. Furthermore, as they found the rs1801968 D allele (216D allele) in the 21/22 independ-

ent c.907delGAG carrier chromosomes studied (one individual was not typed: “D or H ?”), they suspected that allele D was required in *cis* for disease penetrance. This article opened a new avenue with the first description of a clinically relevant modifier of DYT1 dystonia.

We have started a large and exhaustive study of *TOR1A* mutation carriers in France⁴ after the surprising demonstration of the scarcity of the mutation in a population of 12,000 French newborns.⁵ Fifty-three index cases carrying the c.907delGAG mutation have been identified. Most of the families are Caucasian and of European ancestry. Ashkenazi Jew origins are reported in eight families. Four additional families are of Maghrebian origin and one of Caribbean origin. We have confirmed that *TOR1A*-linked dystonia clinical manifestations probably vary according to different ethnicities, suggesting population-specific disease-modifying factors. We then attempted to replicate the results from Risch and colleagues in our population. Haplotypes linked to the mutation (*cis*) or inherited from the non-carrier parent (*trans*) were determined from 53 independent families. Seventy-five *TOR1A* symptomatic mutation carriers and 20 asymptomatic mutation carriers were included. The rs1801968 allele frequency was also analyzed in a control population of comparable size (227 nonrelated individuals versus 197 in Risch et al.). No difference in the allele distribution was observed between the two control populations. We first found that all carriers of the *TOR1A* mutation also had the rs1801968 D allele in *cis*, as described in the American study (Table 2). However, when looking at *trans* effect of this specific allele, we did not find any H allele in asymptomatic carriers of the mutation. This H allele distribution was not related to a particularly

TABLE 1. Allele frequencies for rs1801968 SNP in *trans* (non c.907delGAG carrier chromosomes)

	Symptomatic carriers (manifesting carriers)		Asymptomatic carriers (nonmanifesting carriers)		Control individuals (normal controls)	
	D allele	H allele	D allele	H allele	D allele	H allele
French study						
75 MC's chromosomes, 20 NMC's chromosomes, 454 NC chromosomes	73 (97%)	2 (3%)	20 (100%)	0	404 (89%)	50 (11%)
American study						
119 MC's chromosomes, 113 NMC's chromosomes, 394 NC chromosomes	117 (98.3%)	2 (1.7%) ^S	89 (78.8%)	24 (21.2%)*	337 (85.6%)	57 (14.4%) ^E
German and Italian population studies						
42 MC's chromosomes, 24 NMC's chromosomes	42 (100%)	0	Likely: 18 (75%)	6 (25%)	Not done	

Note that in the American and the French studies, the specific allele associated in *trans* of the mutation has been determined, whereas it was not specified in the German and Italian population studies.

TABLE 2. Allele frequencies for rs1801968 SNP in *cis* (c.907delGAG carrier chromosomes)

	D allele	H allele
French study (53 independent families)	53 (100%)	0
American study (22 independent families)	21 (or 22?)	0 (or 1?)
German and Italian population studies (35 independent families)	Likely: 35 (100%)	0

Note that in the American and the French studies, the specific allele associated in *cis* of the mutation has been determined, whereas it was not specified in the German and Italian population studies.

low frequency in the French population as no difference in the allele distribution was observed between the two control populations. Even if the population studied is smaller than the one of Risch et al. (20 versus 113, respectively), the difference in the distribution of rs1801968 alleles between these two populations is statistically significant (Fisher's Exact Test $P = 0.0237$).

Very recently, the American study has been confirmed in a mixed German and Italian population of 42 symptomatic individuals carrying the *TOR1A* c.907delGAG deletion and 24 asymptomatic mutation carriers from 35 families.⁶ Unfortunately, haplotypes linked to the mutation (*cis*) or inherited from the noncarrier parent (*trans*) could not be determined (C. Kamm, personal communication). They identified the 216H allele in asymptomatic patients in 6/48 chromosomes (*trans* or *cis*). Nevertheless, as all the symptomatic carriers of the *TOR1A* mutation have been demonstrated to be homozygous for the 216D allele, it is likely that the asymptomatic carriers from the same families have also a 216D allele in *cis*. The six 216H alleles would then be localized in *trans* of the mutation.

In the present study, we did not observe the high frequency of rs1801968 H allele in nonmanifesting carriers of the c.907delGAG mutation, reported by others, suggesting that other modifiers should explain the incomplete penetrance of the c.907delGAG mutation in the French population.

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