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Is the early-onset torsion dystonia (EOTD) linked to *TOR1A* gene as frequent as expected in France?

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Abstract Early onset torsion dystonia are rare movement disorders. Molecular defect is known for only a subgroup, consisting of a unique and recurrent mutation in the *TOR1A* gene. We undertook a nationwide census of French *TOR1A*-

mutation carriers and the assessment of clinical associated signs. Overall, 53 index cases and 104 relatives were studied and haplotypes linked to the mutation constructed. The previously reported Ashkenazi-Jewish haplotype was

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found in 11 families with the remainder carrying distinct haplotypes suggesting independent mutation events. This study demonstrates the scarcity of this disease in France with estimated disease frequency of 0.13:100,000 and mutation frequency of 0.17:100,000.

Keywords Early onset torsion dystonia (EOTD) · *DYT1* · *TORIA* · Population study

Introduction

Primary dystonia are rare disorders caused by involuntary twisting and repetitive movements, or abnormal postures in the absence of other neurological symptoms or secondary causes. In “typical” idiopathic early onset torsion dystonia (EOTD), symptoms develop first in the arm or leg in middle to late childhood and frequently progress to generalized dystonia within about 5 years [1, 2]. Currently, the only identified gene for EOTD is the *TORIA* gene that encodes the torsinA protein [3]. The majority of cases from

various ethnic groups are caused by a unique and recurrent autosomal dominantly inherited deletion of 3 bp (c.907delGAG) in exon 5 of this gene [1, 3, 4]. Low penetrance (30%) is reported regardless of ethnic origin [5–7]. In expressing individuals, there is a strong clinical variability, ranging from children profoundly handicapped to obligate carriers of the disease gene showing only a few signs of the disorder [8–10]. *TORIA* mutations are estimated to account for about 30–60% of early onset dystonia in non-Jews and about 80–90% in Ashkenazi-Jews (AJ) due to a founder effect [11]. In other populations, the presence of *TORIA*-linked haplotypes different from the AJ and from each other [12] argues for the occurrence of multiple independent events that have given rise to the deletion [1, 13] even though some studies identified a restricted number of distinct haplotypes [14–16].

Previous epidemiological surveys associated with screening of the mutation have allowed estimation of the prevalence of *TORIA*-linked dystonia among non-Jews to about 1/10,000 to 1/30,000 [17]. In a previous study, we investigated the incidence at birth of the c.907delGAG

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mutation in a population of 12,000 newborns from South-eastern France. Whereas we expected between one and four positive carriers of the mutation, only one positive was found suggesting that the prevalence of the disease would be situated in the lowest values (1/30,000) in France [18]. This observation is in accordance with the latest estimation in the general population of Europe of 0.3 to 0.5:100,000 [19].

The healthcare system organization in France, with the clear identification of referent laboratories for the molecular diagnosis of rare diseases, gives us the opportunity to identify the four laboratories involved in the detection of the *TOR1A* mutation in Lille, Lyon, Paris and Montpellier. Collaborations were set up to collect DNA samples and clinical data on symptomatic or asymptomatic mutation carriers. The purpose of this study was threefold: (1) to evaluate the number of families and individuals carrying the c.907delGAG deletion in the *TOR1A* gene in France, (2) to characterize the associated French *TOR1A* haplotypes, and (3) to estimate the mutation penetrance from identified symptomatic and asymptomatic mutation carriers.

Materials and methods

Patients and controls

The majority of the patients included in this study are currently under follow-up or had been previously examined by a neurologist trained in analysis of movement disorders. Blood was sampled with informed consent. Physicians were contacted to examine the available clinical notes at last follow-up. Available clinical data for each symptomatic relative of a *TOR1A* mutation carrier were also collected. Whenever possible, the presence of the deletion was investigated in each parent. Careful examination was performed to characterize mild symptomatic dystonia. Ninety French unrelated individuals from all over the country were used as the control population to characterize allele frequencies for each marker.

Molecular analysis

The c.907delGAG mutation was assayed, or confirmed, by polymerase chain reaction followed by electrophoresis on a ABI3130XL and then by DHPLC as previously described [18]. Five polymorphic microsatellites surrounding the *TOR1A* locus were studied (Fig. 1) by using oligonucleotide primer pairs previously described [20]. Products were analyzed on an ABI3130XL sequencer with Genemapper software. To allow comparison of our results with those previously reported, we analyzed an Ashkenazi-Jewish DNA sample and assigned allele numbers accordingly. For each locus, the other alleles were numbered accordingly

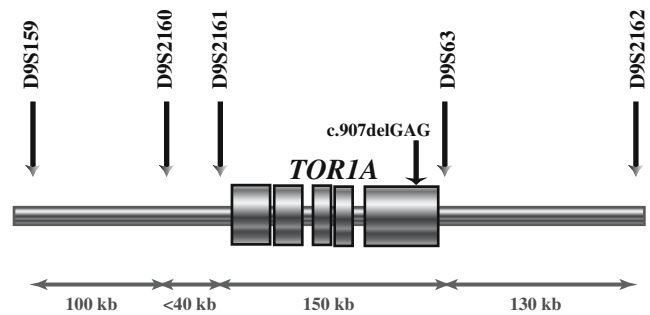


Fig. 1 Physical map of the 9q region surrounding the *TOR1A* gene. Position and physical distance between the five polymorphic microsatellites studied surrounding the *TOR1A* locus. The unique and recurrent mutation of the gene, c.907delGAG, is located in exon 5 of the gene

to their size. The control individual 1347-02 from the Centre d'Etudes du Polymorphisme Humain (CEPH) was also analyzed, and the size of observed alleles is given in Supplementary Table 1. DNA samples from the two French Canadian families [12] and from the Parisian family in which a second French AJ haplotype was previously described (PAR-11) [13] were reanalyzed for comparison of allele sizes. Marker allele frequencies were estimated by counting alleles in characterized disease-bearing chromosomes and in control individuals.

Results

Characterization of the c.907delGAG mutation-carrier population

Fifty-three index cases of EOTD carrying the c.907delGAG mutation have been identified (Supplementary Table 1). Most of the families are Caucasian and of European ancestry (PAR-05, MON-18 and MON-23 being of Polish origin). Four additional families are of Maghrebian origin (PAR-07, MON-08, MON-13, and MON-20) and one of Caribbean origin (PAR-12). AJ origins are reported in eight families: LYO-01, PAR-01, PAR-11, PAR-13, PAR-21, MON-02, MON-14, and MON-26. For 30 patients (30/53, 56.6%), relatives with dystonia were already known. In the 23 apparently isolated cases, whenever both parents could be analyzed (five cases), a carrier was always found excluding the hypothesis of the de novo occurrence of the deletion (in 14 index cases, no samples was available for both parents, and in four cases, only one parent could be studied and excluded as carrier). After identification of the *TOR1A* gene mutation in the probands ($N=53$), genetic counseling was proposed in the families, and 104 relatives were further included in the study (Fig. 2). Among the 32 affected relatives, all but two were found to carry the mutation. The first one, a relative in the MON-21 family presents with only limb motor difficulties after exercise, as

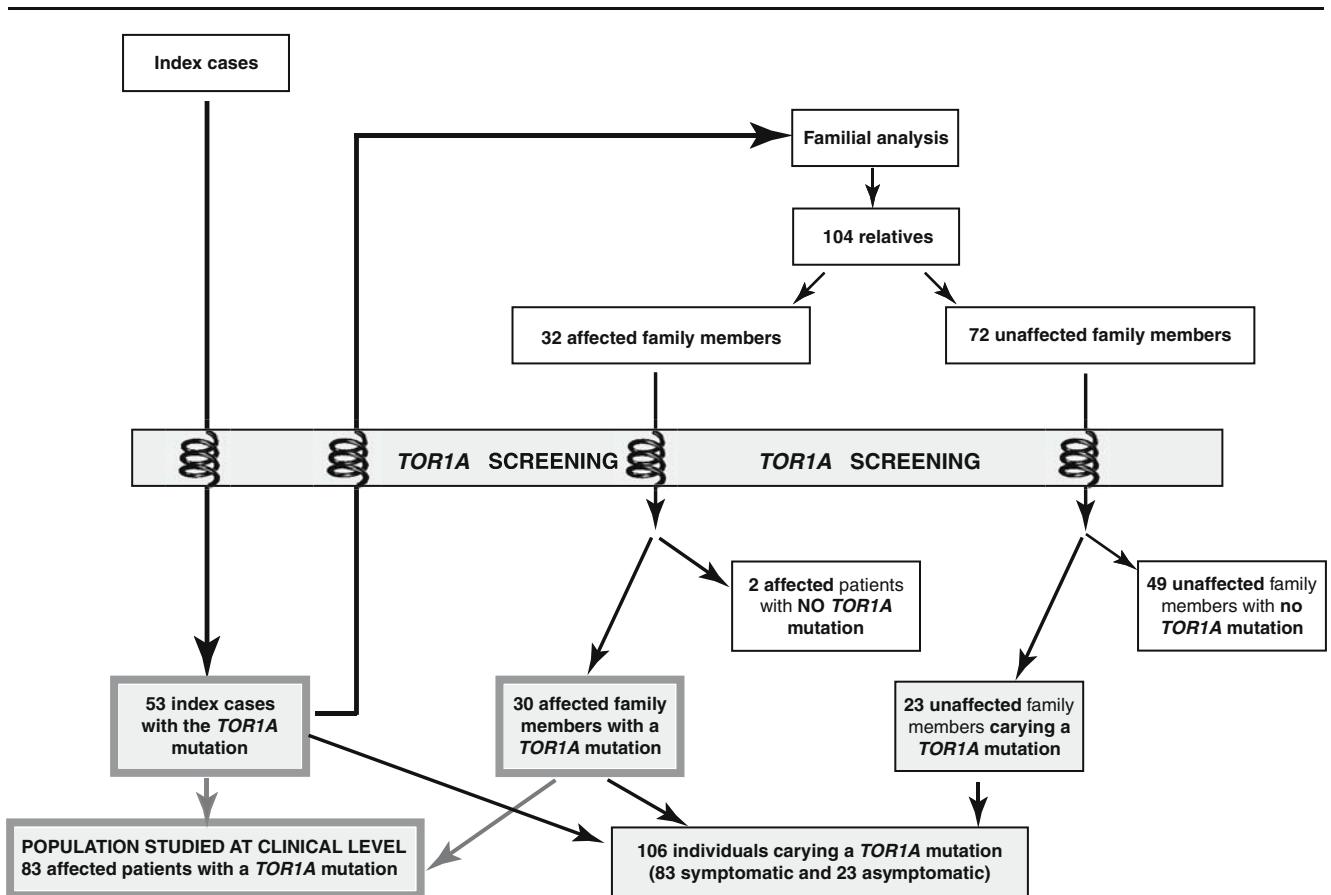


Fig. 2 Organigram summary of the study of early onset torsion dystonia (EOTD) linked to TOR1A gene in France

does his father who is a mutation carrier. The other one, a relative in the PAR-02 family, shows slight dysarthria, dystonia of both hands, the left upper limb, and the left lower limb. Among the 72 non-affected family members who were tested, 23 were found to carry the mutation, and 49 were not carriers (Fig. 2). Finally, in our French cohort, 106 individuals carry the mutation, and among them, only 23 were asymptomatic (21.7%; Fig. 2).

Clinical evaluation

Among the 53 identified index cases, 19 underwent deep brain stimulation (10 were not operated and data are missing for 24). When studying family history of each index case, a population of 109 individuals presenting with clinical signs of dystonia was initially identified (eight were excluded from this clinical study because of incomplete clinical data, and 16 because of unknown molecular status; Fig. 2). Also, the two reported affected individuals tested negative for the TOR1A mutation (families MON-21 and PAR-02) were not included in the subsequent clinical study. Clinical characteristics of this *genetically ascertained population* corresponding to the 53 index cases and 30 affected relatives ($N=83$, 41 males and 42 females) are given in Table 1. A total of 91.0% had onset of symptoms

in a limb (leg in 26.47% and arm in 64.7%), while symptom onset rarely involved neck, cranial, or truncal muscles (9.0%). The mean age at onset is 12.0 years \pm 8.2 years and ranges from 5 to 55 years, with only three cases of onset after 28 years old. The first case is a male patient developing writer's cramp at 41 years old, whereas his brother presented with generalized dystonia. The second one is an individual with generalized dystonia whose onset was at 30 years old. This woman is a member of a large dystonia family with onset ranging between 15 years and late onset. The third case is the father of an affected child. He developed writer's cramp at 55 years old, whereas his child had generalized dystonia at an early age.

The site of onset was known for 67 out of the 83 patients studied. For patients with initial leg involvement, ($N=18$, average age at onset 9.7 \pm 4 years, average follow-up duration 20.75 \pm 18 years), 55.6% ($N=10$) show a rapid rate of progression to generalized dystonia (2.25 years \pm 1.2 years, maximum 5 years; Table 1). It is noteworthy that those patients tend to have an earlier age of onset (7.8 \pm 1.15) than those who do not generalize ($N=8$, 13.6 \pm 5). The majority of the patients with no progression are now adults (30.5 \pm 24 years). Although the rate of progression is extremely variable from patient to patient, it is usually more rapid within the first 5 to 10 years after symptom

Table 1 Comparison of French patients' clinical characteristics with different ethnic groups (population genetically ascertained c.907delGAG carriers)

Clinical characteristics	Asian (N=22)	American Ashkenazi-Jewish (N=45)	American non-Jewish (N=45)	French with no JA haplotype (N=64)	French with JA haplotype (N=19)	French (N=83)
Leg onset	59.1% (13/22)	36.5%	60.0%	23.08%	40.00%	26.47%
Arm onset	31.8% (7/22)	59.6%	35.5%	65.38%	60.00%	64.70%
Neck onset	4.5% (1/22)	1.9%	4.4%	7.69%	0.00%	5.88%
Cranial onset	0%	1.9%	0%	1.92%	0.00%	1.47%
truncal onset	4.5% (1/22)	0%	0%	1.92%	0.00%	1.47%
Generalized dystonia	54.5% (12/22)	48.1%	66.7%	57.14%	50.00%	54.88%
Multifocal dystonia/ hemi-dystonia	9.1% (2/22)	11.5%	8.9%	7.94%	23.53%	12.20%
Segmental dystonia	18.2% (4/22)	15.4%	8.9%	7.94%	17.65%	9.76%
Focal dystonia	13.6% (3/22)	25.0%	15.6%	26.98%	11.76%	23.17%
Leg involvement	72.7% (16/22)	59.6%	77.8%	63.16%	83.33%	68.42%
Arm involvement	86.4% (19/22)	96.2%	95.6%	85.96%	77.78%	84.21%
Trunk involvement	62.5% (10/16 ^a)	26.9%	48.8%	47.37%	38.89%	44.74%
Neck involvement	62.5% (10/16 ^a)	25.0%	24.4%	40.35%	22.22%	35.53%
Cranial involvement	18.8% (10/16 ^a)	7.7%	11.1%	31.58%	27.78%	30.26%
Age of onset (year)	11.5±7.5		14.0±9.0 ^b	12.3±9.2	11.3±4.8	12.1±8.2
Age at last examination (year)	28.1±18.3		–	32.6±17.0	31.8±17.0	32.2±16.8
Duration	16.6±15.6		25±15.7	15.1±15.3	18.7±16.3	15.8±15.5

French: data from ours. Asian: data from Im et al. 22, Ikeuchi et al. 21, Nomura et al. 24, and Matsumoto et al. 23. Ashkenazi and non-Jewish: data from Bressman et al. 1.

^aData from Matsumoto et al. 23 omitted (no comment on axial and cranial muscle involvement).

^bNo significant difference is reported between American Ashkenazi Jewish and American non-Jewish subjects in their age-at-onset. – Missing data

onset. Therefore, one can expect that dystonia remains localized in most of these patients.

Patients whose symptoms initially affect an arm ($N=43$) have a later age of onset compared to the group with leg onset (12.3 ± 10 years, average follow-up duration 20.20 ± 13.5 years). The dystonia progressed to a generalized form in 55.8% of patients ($N=24$). In contrast to the group with leg onset, the rate of progression was slower (5.45 years ± 6.5 years, maximum 21 years), and no difference in the age of onset was observed between the group with generalization (21.9 ± 3.75) and the other group (17.9 ± 14.24). Once more, in the subset of patients who do not progress to a generalized form, the majority are also now adults.

We compared the clinical characteristics of our *TOR1A* positive patients to those reported in the literature (Table 1). The Asian patients (Korean and Japanese, $N=22$) [21–24] with a *TOR1A* mutation showed greater onset in the leg than in the arm, less focal dystonia similar to non-Jewish patients ($N=45$), and more segmental dystonia akin to Jewish patients ($N=52$). On the contrary, the French *TOR1A* patients ($N=83$) are more comparable with Jewish patients who showed more arm onset, less onset in the leg, and a higher proportion of focal dystonia.

Haplotypes linked to c.907delGAG TOR1A mutation

Five microsatellites D9S159, D9S2160, D9S2161, D9S63, and D9S2162 were studied in 157 patients and their family members (53 index cases and 104 relatives) and in 90 unrelated controls. Haplotypes were constructed in families under the assumption of minimum recombination. We were able to identify the chromosome associated with the mutation by inheritance in 28 families and the most likely associated haplotype in ten individuals (Table 2). Comparison of allele frequencies in these two groups showed no significant difference (Supplementary Table 2).

Six families shared strong similarity to the common AJ haplotype (12–4–5–16–4) previously described [20]: one family, PAR-02, showed the entire AJ haplotype while five others (MON-14, PAR-03, MON-09, PAR-16, and MON-24) shared two to four contiguous alleles and thus might share a common founder chromosome with AJ patients. Surprisingly, among these families, Jewish ancestries were known only for MON-14. In isolated cases, the entire AJ haplotype was suggested for four individuals (PAR-21, MON-17, the Polish patient MON-18 and LYO-01), and one other shared four of the five alleles (PAR-01). Based on

allele distribution in the control population (Supplementary Table 2), the calculated frequency of the 12-4-5-16-4 haplotype is 3.9×10^{-4} , demonstrating the rarity of this particular haplotype.

One other AJ haplotype was reported by Lebre et al. [13] in the previously reported French family PAR-11. This haplotype differs only for the marker D9S2161 (12-4-3-16-4), suggesting that a mutation has probably occurred in the microsatellite locus in the common AJ haplotype (12-4-5-16-4). Among our reconstructed haplotypes, we found that this mutated 12-4-3-16-4 haplotype was potentially shared by three other isolated patients (PAR-06, PAR-07, and PAR-13). Only PAR-13 has known AJ origins. Once more, the observed frequency is statistically higher than expected (4.7×10^{-4}).

Two families, MON-07 and LIL-01, in the absence of a known family link, share a common haplotype (6-5-3-12-1) that is also partly found in family PAR-08 (X-5-3-12-X). The calculated frequency of this haplotype is 8×10^{-5} . Therefore, with an observed frequency of 0.06%, there is a strong association between this haplotype and the mutation.

In our series, no similarity was found with the two previous haplotypes (14-4-2-14-4 and 12-6-4-0-2) found in French Canadian families [12]. This result suggests that either the mutation arose after migration of French to Canada or that these peculiar haplotypes have been lost in the French population. Finally, no other common haplotype could be deduced in the 15 other isolated individuals.

Discussion

In this paper, we report the first exhaustive nationwide study corresponding to the largest genetically ascertained population of *TOR1A* carriers. Fifty-three index cases were initially recruited allowing subsequent analysis of 32 affected family members and 72 at-risk asymptomatic family members (Fig. 2). Overall, we have identified the mutation in 106 individuals, 23 corresponding to asymptomatic relatives. Two reported affected relatives were in fact phenocopies as they were not found to carry the *TOR1A* mutation (other genes might be implicated).

Table 2 Disease haplotypes at 5 microsatellite loci in the French population

Haplotypes	TOR1A					Def (family)	Prob	Total
	D9S159	D9S2160	D9S2161	D9S63	D9S2162			
1	12	4	5	16	4	1 (PAR-02,)	4 (PAR-21 ^a , MON-17, MON-18, LYO-01 ^a)	5
2	12	4	5	12	4		1 (PAR-01 ^a)	1
3	12	4	5	12	4/5	1 (MON-14 ^a)		1
4	6	4	5	16	4	1 (PAR-03)		1
5	16	3/4	5	16	4	1 (MON-09)		1
6	14	5	5	16	2	1 (PAR-16)		1
7	16	3	5	18/16	5	1 (MON-24)		1
8	12	4	3	16	4	1 (PAR-11 ^{a,b})	3 (PAR-06, PAR-07, PAR-13 ^a)	4
9	6	5	3	12	1	2 (MON-07, LIL-01)		2
10	16	5	3	12	-1	1 (PAR-08)		1
11	16	4	5	0	4	1 (MON-11)		1
12	16	5	4	0	2	1 (LYO-03)		1
13	6	6	5	8	2	1 (MON-03 ^b)		1
14	12	6	5	0	2	1 (MON-04)		1
15	12	3	4	0	5	1 (PAR-04)		1
16	12	5	4	18	-1	1 (PAR-05)		1
17	12	5	4	12	0	1 (PAR-14)		1
18	14	5	4	2	1	1 (MON-06)		1
19	8	2	4	14	4	1 (PAR-15 ^b)		1
20	14	1	3	20	1	1 (MON-22)		1
21	4	4	2	20	5		1 (MON-19)	1
22	14	5	2	0	2	1 (MON-01)		1
23	16	5	2	4	3	1 (MON-10)		1
24	12	5	1	0	3	1 (MON-05 ^b)		1
25	20	5	7	20	4		1 (PAR-09)	1
26	10/12	4	5	2	3	1 (MON-13)		1
27	12	3	5	2/0	1	1 (MON-15)		1
28	4	5	4/2	14	5	1 (PAR-10 ^b)		1
29	12	3	3/4	0	5	1 (MON-25)		1
30	8	4	4	8	1/2	1 (MON-12)		1
Total						28	10	38

Def Phased disease-bearing chromosomes determined by inheritance, Prob phased disease-bearing chromosomes not determined by inheritance

^a Indicated families with Ashkenazi-Jewish origins

^b Previously described in Lebre et al. (13)

Taking into account that (1) EOTD prevalence in Europe is between 0.3 and 0.5:100,000 [19], 2) *TOR1A* mutations are estimated to account for only 30–60% of EOTD in non-Jews, (3) a population of 61,538,322 inhabitants in metropolitan France in January 2007, and finally (4) a mutation penetrance of 30%, we would expect a number of symptomatic *TOR1A* mutation carriers ranging from 55 to 184 and a total number of mutation carriers (symptomatic and asymptomatic) from 184 to 613. Whereas the small number of identified symptomatic carriers ($N=83$) is in the calculated range, a lower number of asymptomatic carriers ($N=23$) than expected has been identified. This result can likely be explained by the difficulty to achieve exhaustive inclusion of all asymptomatic relatives of *TOR1A* mutation carriers in clinical and genetic studies. Moreover, pre-symptomatic diagnosis is only authorized in adults in France when no direct benefit is expected for the patient. The proportion of symptomatic carriers should not be modified by studying focal forms of the disease in which *TOR1A* mutation have been rarely found [13, 25, 26]. Even though the penetrance of the c.907delGAG mutation cannot be accurately defined, our results allow the estimation of minimum mutation frequency of 0.17:100,000 (106 mutation carriers for 61,538,322 inhabitants) and a *TOR1A*-linked dystonia frequency of 0.13:100,000 (83 symptomatic *TOR1A* mutation carriers for 61,538,322 inhabitants).

The collection of clinical data in the 83 genetically ascertained patients (Fig. 2) showed a large intra and inter-familial clinical heterogeneity, from paucity of symptoms to extremely severe forms resulting in death. When comparing our data with those previously published for distinct populations like Asian [21–24], AJ, and non-AJ American populations [1], the French characteristics most closely resemble what was reported for the AJ population with a majority of involvement in the limbs, a higher prevalence of site of onset in the arms, and a lower occurrence of onset in trunk, neck, and cranial muscles (Table 1). These results are not due to the unexpectedly high frequency in our series (20.7%, 11/53) of the particular haplotype reported to be associated with a founder effect in the AJ population, as they were replicated when families with an AJ haplotype were removed. Only four of these families had known Jewish origins. These data confirm that clinical manifestations of the *TOR1A* mutation probably vary according to different ethnicities, suggesting population-specific disease-modifying factors. The presence of only one recurrent haplotype among the remaining disease chromosomes suggests that the mutation probably occurred independently in the French population even if de novo cases could not be demonstrated in our series [27, 28]. Finally, the identification of only 53 *TOR1A* families argues for the scarcity of this disease in the French population.

Databases

OMIM: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>.

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