Unraveling the intrafamilial correlations and heritability of tumor types in MEN1: a Groupe d'étude des Tumeurs Endocrines study

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Abstract

Background: MEN1, which is secondary to the mutation of the *MEN1* gene, is a rare autosomal-dominant disease that predisposes mutation carriers to endocrine tumors. Most studies demonstrated the absence of direct genotype-phenotype correlations. The existence of a higher risk of death in the Groupe d'étude des Tumeurs Endocrines-cohort associated with a mutation in the JunD interacting domain suggests heterogeneity across families in disease expressivity. This study aims to assess the existence of modifying genetic factors by estimating the intrafamilial correlations and heritability of the six main tumor types in MEN1.

Methods: The study included 797 patients from 265 kindred and studied seven phenotypic criteria: parathyroid and pancreatic neuroendocrine tumors (NETs) and pituitary, adrenal, bronchial, and thymic (thNET) tumors and the presence of metastasis. Intrafamilial correlations and heritability estimates were calculated from family tree data using specific validated statistical analysis software.

Results: Intrafamilial correlations were significant and decreased along parental degrees distance for pituitary, adrenal and thNETs. The heritability of these three tumor types was consistently strong and significant with 64% (s.e.m.=0.13; $P<0.001$) for pituitary tumor, 65% (s.e.m.=0.21; $P<0.001$) for adrenal tumors, and 97% (s.e.m.=0.41; $P=0.006$) for thNETs.

Conclusion: The present study shows the existence of modifying genetic factors for thymus, adrenal, and pituitary MEN1 tumor types. The identification of at-risk subgroups of individuals within cohorts is the first step toward personalization of care. Next generation sequencing on this subset of tumors will help identify the molecular basis of MEN1 variable genetic expressivity.

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Introduction

MEN1 (OMIM 131100) is an autosomal dominant disorder secondary to *MEN1* mutations that predispose carriers to endocrine tumors (1). The tumors mainly develop from endocrine tissues and may arise from parathyroid glands (90–100%), the pancreas (50–70%), pituitary gland (20–40%), and adrenal glands (20–40%), and at a lower frequency from the bronchi and thymus (<15%) (2, 3). Survival is limited in approximately 60% of patients because of MEN1 disease evolution (4). More than half of MEN1-related deaths are associated with tumors that are difficult to diagnose (5). These critical tumors, such as pancreatic neuroendocrine tumors (pNETs) or thymic tumors (thNETs), are characterized by frequent synchronous metastasis at diagnosis (5, 6, 7, 8, 9). Familial clustering of specific tumors has been reported in the literature, as well as mild/late MEN1 phenotypes. Prolactinomas are specifically overrepresented in the Burin families, suggesting the existence of a founder effect (10). Gender is recurrently shown to modify tumor development in patients, notably for pituitary or thNETs (8, 11, 12, 13). Additionally, several families from various ethnic origins are reported to present recurrent thNETs (11, 14, 15). Nevertheless no direct genotype-phenotype

correlation in MEN1 disease regarding the tumor types has ever been found (16, 17, 18).

A recent genotype-phenotype study highlighted a global trend for intrafamilial correlations in disease expressivity (19). This previous study reported a higher risk of death in patients carrying *MEN1* mutations affecting the JunD interacting domain. JunD, which regulates the transcriptional activity in interaction with the MENIN complex, is known to be pro-oncogenic in various cancer types. In families carrying mutations within the JunD interacting domain, patient survival was significantly lower, with a twofold increased risk of dying from MEN1-related cancers (19). The existence of intrafamilial correlations in MEN1 disease was also identified for most of the tumor types, and this hypothesis was in accordance with literature data (13). Nevertheless, the statistical approach was dedicated to genotype-phenotype association analysis and did not allow accurate estimations of intrafamilial correlations – that is to say, correlations according to the degree of the family relationship (i.e., parent-offspring, siblings, etc.). Indeed, one hypothesis is that people from the same family may share genetic variations accounting for shared

intrafamilial tumor patterns. Besides, the progressive genetic dilution through generations within families (i.e., parental degree distance) should lead to the progressive disappearance of their influence together with the different expressivity (20). Thus, intrafamilial correlations should decrease with the degree of the relationship, which is the strongest between pairs of monozygotic twins, important between parents and children and between siblings, decreasing between second-degree relatives (namely, grandparents vs grandchildren, cousins) and third degree relatives (for instance, avuncular relatives, defined as uncle vs nephew), and finally tend toward zero for distant relatives in the same family. Tumor heritability should also be estimated for a better understanding of the genetic background of MEN1 tumors. Heritability estimation is a complementary genetic approach that aims to quantify the proportion of the phenotypic expression that is attributable to gene effects (21). Although intrafamilial correlations in MEN1 disease were suggested by rare observations reported in the literature, statistical estimates of intrafamilial correlations or heritability have never been provided in MEN1 disease. Therefore, the aims of this new genetic study were to quantify intrafamilial correlations and heritability among the six main MEN1-related tumors using the French MEN1/Groupe d'étude des Tumeurs Endocrines (GTE) cohort (19).

Patients and methods

Population

The GTE network for MEN1, created in February 1991, groups together clinical centers in France and Belgium and the four molecular genetics laboratories in charge of MEN1 diagnosis in these countries. In 2011, the GTE cohort for MEN1 included a total of 912 patients from 278 families. From these patients, we selected subjects with *MEN1* mutations (Table 1). Overall, 823 patients had a genetic diagnosis. Among these, 26 patients (2.1%) from 16 different families were excluded from the analysis because of missing data. Three families needed to be divided because of a missing common genealogical ancestor. The analysis finally included 797 patients from 265 kindred (Table 1).

A copy of each patient's file was obtained, anonymized, and stored at the Clinical Investigation Center of Dijon CHU. A case report form was created, filled in, and regularly updated from copies of the patients' medical files and regular visits by the surgeon in charge

Table 1 Prevalence of MEN1 clinical features according to gender and age categories (GTE cohort, 797 patients, 2014).

	MEN1 tumor type										Metastatic MEN1 tumor				Total	
	Parathyroid		Pancreatic		Pituitary		Adrenal		Bronchial		Thymic		n	%	n	%
	n	%	n	%	n	%	n	%	n	%						
Age at last follow-up	29	32%	12	13%	14	15%	3	3%	0	0%	0	0%	1	1%	91	11%
	194	78%	100	40%	77	31%	23	9%	1	0%	6	2%	17	7%	250	31%
	289	92%	206	65%	125	40%	77	24%	18	6%	15	5%	76	24%	315	40%
	125	89%	92	65%	41	29%	40	28%	13	9%	1	1%	30	21%	141	18%
	Gender															
Male	289	78%	196	53%	92	25%	68	18%	15	4%	21	6%	69	19%	369	46%
Female	348	81%	214	50%	165	39%	75	18%	17	4%	1	0%	55	13%	428	54%
Total	637	80%	410	51%	257	32%	143	18%	32	4%	22	3%	124	16%	797	100%

to 797.

of the database (P G). This cohort was approved by the Consultative Committee on Treatment of Information in Health Research (CCTIRS), file number 12.364) and the Commission nationale de l'informatique et des libertés (CNIL, authorization number DR 2013-348). Written informed consent was not required, but patients were informed about their inclusion in the GTE cohort and had the right to withdraw their data.

Phenotypes

Seven phenotypic traits were studied, tumor aggressiveness (presence of metastasis) and six MEN1 lesion types: parathyroid, pNETs, pituitary, adrenal, bronchial, and thNETs. Descriptive analysis was performed according to the gender and the age at last follow-up. The follow-up duration and the age of first occurrence for each phenotypic criterion was described by medians and inter-quartiles range.

Familial correlations and heritability

Familial correlation coefficients, according to the degree of the family relationship (parent–offspring, siblings, avuncular, and cousin), were estimated using the FCOR program of Statistical Analysis for Genetic Epidemiology Version 6.0.1 (SAGE v6.0.1 Software) (22). Correlations were calculated between the residual trait values, after adjusting for gender and age at last follow-up. The asymptotic S.E.M. of a given correlation was estimated by using a second-order Taylor series expansion and replacing all correlation parameters with their respective estimates(20). As a prerequisite for this analysis, the homogeneity of correlations among subtypes (e.g., mother–offspring and father–offspring) and main types (e.g., parent–offspring) was tested; no intra-subtype heterogeneity was found.

Heritability for binary traits was estimated through the liability threshold polygenic model as implemented in the Polygenic command of the Sequential Oligogenic Linkage Analysis Routines Version 6.6.2 (SOLAR v6.6.2) computer package (21, 23). This method uses a mixed effects model that incorporates fixed effects for known covariates (gender and age at last follow-up in the present study) and variance components for unknown genetic effects. Estimates were obtained by maximum likelihood methods and significance was determined by likelihood ratio tests. Interpretation was guided by the concordance between significant intrafamilial correlations among first-degree relatives (sibling and parents/offspring pairs) followed by

Table 2 Adjusted intrafamilial correlation coefficients for seven clinical features of MEN1 (GTE cohort, 797 patients, 2014).

	Parents:offspring (355 pairs)			Siblings (396 pairs)			Avuncular (466 pairs)			Cousin (282 pairs)		
	CE	± s.d.	P	CE	± s.d.	P	CE	± s.d.	P	CE	± s.d.	P
Parathyroid	–0.02	±0.06	0.768	0.35	±0.07	<0.001†	0.05	±0.09	0.609	0.22	±0.11	0.048*
Pancreatic	0.04	±0.06	0.498	0.16	±0.06	0.011*	0.01	±0.06	0.831	–0.01	±0.07	0.940
Pituitary	0.16	±0.06	0.009†	0.20	±0.07	0.003†	0.17	±0.07	0.016*	0.08	±0.09	0.340
Adrenal	0.16	±0.06	0.004†	0.14	±0.07	0.047*	0.14	±0.06	0.029*	0.04	±0.1	0.662
Bronchial	0.08	±0.06	0.202	0.07	±0.06	0.199	–0.07	±0.05	0.215	0.02	±0.06	0.737
Thymic	0.15	±0.05	0.006†	0.13	±0.06	0.036*	0.08	±0.05	0.154	–0.05	±0.06	0.396
Metastasis	–0.08	±0.06	0.191	0.14	±0.06	0.022*	–0.02	±0.07	0.778	0.08	±0.08	0.324

*0.01 < P < 0.05; †0.001 < P < 0.01; ‡P < 0.001.

both a decrease in intrafamilial correlations with genetic dilution and strong and significant heritability estimates.

Results

Among the 265 families totaling 797 patients, kindred sizes ranged from 2 to 50 patients, with a median of 3 patients per kindred. Median follow-up was 46 years (inter-quartile range: 30–59 years). The prevalence of phenotypic criteria according to gender and age are shown in Table 1.

Familial correlations

Intrafamilial correlations were significant for 12 of the 28 tested conditions (Table 2, Fig. 1). In three different tumor types – namely the pituitary, adrenal, and thNETs – intrafamilial correlation strength and significance decreased with genetic dilution. For pituitary tumors, the intrafamilial correlation estimate (CE) was strong and highly significant for parents/offspring and sibling, grouped in first-degree relatives (CE=0.16, $P=0.009$ and CE=0.20, $P=0.003$, respectively). It decreased but remained significant for second-degree relatives (CE=0.17, $P=0.016$ for avuncular). Finally, the intrafamilial CE was very weak and not significant for third-degree relatives (CE=0.08, $P=0.34$ for cousin). The same phenomenon

was observed for adrenal and thNETs tumor types (Table 2, Fig. 1). This information is summarized in Fig. 1 in which two graphical patterns were presented. The top graph concerns pituitary, adrenal, and thNET tumor types with a strong and significant CE between first-degree relatives (parents/offspring and sibling) followed by a decreasing in strength and significance along the genetic dilution (avuncular then cousin). Conversely, the other phenotypes (parathyroid, pancreatic, bronchial tumor types and metastasis) are presented in the bottom graph, with irregular evolution of the intrafamilial correlation strength and significance showing no evidence for the existence of genetic modifying factors for these MEN1 phenotypes.

Heritability

The heritability of these three tumor types was strong and significant: pituitary tumor heritability was of 64% (S.E.M.=0.13; $P<0.001$), adrenal tumor heritability, 65% (S.E.M.=0.21; $P<0.001$), and thNET heritability 97% (S.E.M.=0.41; $P=0.006$). There was no significant heritability for metastasis. Borderline heritability was observed for bronchial tumors. The heritability of parathyroid and pancreatic tumors was significant but this result was not confirmed by intrafamilial correlations (Table 3).

Figure 1

Representation of intrafamilial correlation estimates and decrease with genetic dilution within family pairs. Dots represent correlation estimates. Vertical lines represent their 95% CIs. Dashed lines represent their regression trend and the

shaded area their CIs. A genetic component is suspected in the case of a significant correlation at the parents:offspring degree followed by a correlation decrease with familial genetic dilution.

Table 3 Heritability estimates for seven clinical features of MEN1 (GTE cohort, 797 patients, 2014).

	Heritability		
	Estimate	($\pm$ s.d.)	P
Parathyroid	88%	(± 0.18)	<0.001
Pancreatic	37%	(± 0.14)	0.001
Pituitary	64%	(± 0.13)	<0.001
Adrenal	65%	(± 0.21)	<0.001
Bronchial	60%	(± 0.35)	0.037
Thymic	97%	(± 0.41)	0.006
Metastasis	19%	(± 0.16)	0.104

Discussion

The estimation of the genetic components of MEN1 disease expressivity requires a dedicated statistical approach on a large cohort of patients. This estimation has become possible using one of the largest MEN1 cohorts, totaling 797 patients from 265 kindred. The intrafamilial correlation and trait heritability for six tumor types and metastasis were calculated and a significant genetic component was evidenced in three of them, namely, thNETs, pituitary, and adrenal tumors. In addition to mutations affecting the JunD interacting domain, the aforementioned results suggest the existence of additional genetic markers allowing the definition of at-risk groups of individuals (18).

The MEN1 GTE cohort has already been described and is deemed representative of MEN1 disease in Western Europe (18). There were no major differences in terms of lesion prevalence compared with the independent German and Netherlands cohorts (18, 24). The GTE cohort had a median follow-up of 47 years and thus allowed us to study the age-dependent expressivity of MEN1 disease with time-to-event techniques (4, 19). During this analysis, we showed intrafamilial correlations without direct phenotype-genotype correlations. In addition, we reported the first arguments for the implication of genetic factors able to modify MEN1 disease expression. Indeed, a global trend for heterogeneity across families was observed, suggesting the existence of other genetic factors able to modify MEN1 disease expressivity, as expected since the discovery of the *MEN1* gene (13, 14, 19). These preliminary results were a first step toward unraveling the genetic determinants of MEN1 disease expressivity. Estimation of a trait's heritability in a familial disease with variable expressivity depends on the partitioning of a trait into genetic and environmental factors (25). The balance between genes and environmental effects in the

phenotypic variance in MEN1 traits was estimated with a robust statistical approach previously applied to neurofibromatosis type 1 (26, 27, 28). Two complementary methods were used to quantify intrafamilial correlations. As expected from the existence of familial clusters of thNETs in the literature (11, 12, 14), a strong genetic component was identified regarding thNETs. While these tumors are diagnosed in 5–7% of MEN1 patients, the first series of genotyped patients with thNETs revealed that 15/150 cases were familial (3, 11, 12, 14, 18). The pedigree shown in Fig. 2 consistently highlights the pseudo-dominant inheritance of thNETs in a familial cluster (heritability estimate 97%, s.e.m.=0.47). No correlation decrease was found for parathyroid and pancreatic tumors and no genetic dilution was noted. The heritability of pNETs was significant but weak (37%). This result may be related to the heterogeneity of pNET subtypes. However, the statistical power was insufficient to test each subtype separately. In contrast, parathyroid tumor heritability was strong (Table 3), but this finding may merely reflect the high prevalence of parathyroid tumors in MEN1 patients (637/797 patients, 80% of the GTE cohort).

Besides the thNET results, both intrafamilial correlations and heritability were significant regarding pituitary and adrenal tumors. These unsuspected results may have direct clinical implications. Current recommendations related to the detection of these tumors advise regular workups and starting a follow-up program at 10 years old for pituitary and adrenal tumors and 15 years old for thNETs (29, 30). Nevertheless, real life shows that updated recommendations are not always correctly applied for

Figure 2

Example of a family tree harboring an aggregate of three thymic tumors (¶) among the 15 MEN1 carriers (black boxes). Known individual from the family but without available clinical information are represented with gray boxes.

many good and bad reasons. This study reminds us that pituitary adenomas, adrenal tumors, and thNETs must be regularly screened for, particularly among relatives of patients affected by these tumors. This strategy is well known for thNETs because thNET clusters were evidenced early. The right imaging tool to detect this tumor is still debated because yearly CT scans of the chest could be harmful, but it is known and accepted that we must pay particular attention to the relatives of patients with thNETs (11, 12, 14, 15). Pituitary adenomas and adrenal tumors are underdiagnosed tumor types in MEN1. A recent study showed that young men between 15 and 20 years old with MEN1 may harbor large pituitary adenomas, and the clinical experience of the GTE cohort shows that compliance with follow-up is not easy at this age (30). Therefore, this group at risk must be particularly screened when pituitary adenomas have already been found in the same family. Adrenal tumor screening should be carefully performed when this lesion already exists in the family. There are several reasons why adrenal tumors may be under-evaluated during follow-up: the prevalence is low and adrenal tumors are present in only 24% of patients aged 40–60 years; these tumors are rarely aggressive; and abdominal imaging usually focuses on the pancreas and liver because pNETs are the main challenge for abdominal surgery in terms of cancer development and spread.

To conclude, the current recommendations for screening and follow-up regarding thNET, pituitary, and adrenal tumors must be strictly followed among relatives of affected patients. This study is an additional step toward unraveling the genetic contribution to variable expressivity of MEN1 disease and a more personalized follow-up for MEN1 families. As far as genetic research is concerned, families with multiple occurrences of these tumor types should be the best candidates for the identification of genetic factors able to modify MEN1 expressivity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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