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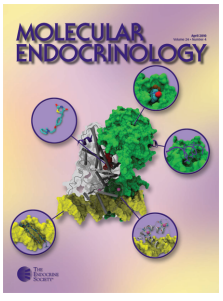


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# Clinical Characterization of Familial Isolated Pituitary Adenomas

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**Context:** Familial pituitary adenomas occur rarely in the absence of multiple endocrine neoplasia type 1 (MEN1) and Carney complex (CNC).

**Objective:** Our objective was to characterize the clinical and genealogical features of non-MEN1/CNC familial isolated pituitary adenomas (FIPA).

**Design and Setting:** We conducted a retrospective study of clinical and genealogical characteristics of FIPA cases and performed a comparison with a sporadic population at 22 university hospitals in Belgium, Italy, France, and The Netherlands.

**Results:** Sixty-four FIPA families including 138 affected individuals were identified [55 prolactinomas, 47 somatotropinomas, 28 nonsecreting adenomas (NS), and eight ACTH-secreting tumors]. Cases were *MEN1/PRKAR1A*-mutation negative. First-degree relationships predominated (75.6%) among affected individuals. A single tumor phenotype occurred in 30 families (homogeneous), and heterogeneous phenotypes occurred in 34 families. FIPA cases were younger at diagnosis than sporadic cases ($P = 0.015$); tumors were diagnosed earlier in the first *vs.* the second generation of multigenerational families. Macroadenomas were more frequent in heterogeneous *vs.* homogeneous FIPA families ($P = 0.036$). Prolactinomas from heterogeneous families were larger and had more frequent suprasellar extension ($P = 0.004$) than sporadic cases. Somatotropinomas occurred as isolated familial somatotropinoma cases and within heterogeneous FIPA families; isolated familial somatotropinoma cases represented 18% of FIPA cases and were younger at diagnosis than patients with sporadic somatotropinomas. Familial NS cases were younger at diagnosis ($P = 0.03$) and had more frequently invasive tumors ($P = 0.024$) than sporadic cases.

**Conclusions:** Homogeneous and heterogeneous expression of prolactinomas, somatotropinomas, NS, and Cushing's disease can occur within families in the absence of MEN1/CNC. FIPA and sporadic cases have differing clinical characteristics. FIPA may represent a novel endocrine neoplasia classification that requires further genetic characterization. **(*J Clin Endocrinol Metab* 91: 3316–3323, 2006)**

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Abbreviations: CNC, Carney complex; CT, computed tomography; FIPA, familial isolated pituitary adenoma; IFS, isolated familial somatotropinoma; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NS, clinically nonsecreting.

* This study was conducted with the collaboration of the Groupe d'Etude des Tumeurs Endocrines, France.

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PITUITARY ADENOMAS CAN occur in a familial setting in multiple endocrine neoplasia type 1 (MEN1) and Carney complex (CNC) (1). MEN1 is caused by an inactivating mutation in the *MEN1* gene on chromosome 11q13, which encodes the nuclear protein menin (2). The clinical presentation of MEN1 has been extensively characterized, and pituitary adenomas occur in about 40% of patients (3).All tumor phenotypes can occur, but prolactinomas predominate (3). Although more than 350 *MEN1* gene mutations

have been described, at least 10% of patients with clinical features of MEN1 do not have *MEN1* mutations (1). This suggests that other causes, such as mutations in the *MEN1* promoter region or in other regulatory genes, may be involved in the pathophysiology of MEN1. CNC is a rare condition that is linked in more than 50% of cases to an inactivating mutation in the gene encoding protein kinase A type 1A regulatory subunit (*PRKAR1A*) at 17q24; a second, as yet uncharacterized, locus at 2p16 has also been implicated (1, 4, 5). A key pathological abnormality in CNC pituitary disease is multifocal somatomammotropic cell hyperplasia (6). Hence, about 75% of patients with CNC exhibit subclinical increases in GH, IGF-I, and prolactin levels or abnormal responses to dynamic pituitary function tests, whereas clinical acromegaly occurs in less than 10% of patients (7, 8).

Isolated familial somatotropinoma (IFS) has been reported and is defined as the occurrence of at least two cases of acromegaly/gigantism in a single family in the absence of CNC or MEN1 (9); 108 affected members in 46 families have been described to date (10). To date, studies indicate that MEN1 and other candidate genes are unlikely to be directly implicated in the molecular pathogenesis of IFS (11–13). A disease locus for IFS appears to exist within a region of approximately 2.1 Mb on chromosome 11q13.3 (10, 14). Apart from IFS, a handful of reports of other isolated pituitary adenomas occurring in families have appeared in the literature (15–17). The scarcity of data regarding the characteristics of these families has limited our understanding of the clinical features and patterns of presentation of familial pituitary adenomas in patients without MEN1/CNC. To address these issues, we undertook an international, multicenter, retrospective study to identify non-MEN1/CNC families with familial isolated pituitary adenomas (FIPA). The aims of our study were to analyze the characteristics of FIPA and to describe their phenotypic presentation compared with a matched population of patients with sporadic pituitary tumors.

## Patients and Methods

### *Patient characteristics*

This retrospective study from 1970–2004 was undertaken to identify FIPA; this was defined as families with two or more confirmed members presenting with anterior pituitary tumors and no evidence of MEN1/CNC. In identified FIPA families, additional questioning was undertaken to search for other affected relatives. The study was performed at 22 centers in Belgium, France, Italy, and The Netherlands, and existing case records and databases were scrutinized for previously diagnosed familial pituitary tumor cases. Data from 15 patients have been reported previously (11, 13, 18–22). Informed consent for collection of personal and clinical data was obtained from all patients; data were anonymized before entry into a central database at the University of Liège, Belgium. Relevant demographic, genealogical, clinical, and radiological data were extracted from case records at individual study centers. Although the study period was from 1970–2004, families with patients who had been diagnosed with a pituitary tumor before 1970 were included.

Using available hormonal and clinical data, pituitary adenomas were classified as prolactinomas, GH-secreting, clinically nonsecreting (NS), ACTH-secreting, and TSH-secreting tumors, respectively. Gonadotropinomas with a high plasma FSH were included in the NS group. MEN1 was ruled out clinically by family history and the demonstration of a normal serum calcium and PTH in all cases, whereas in a subset of individuals. normal levels of gastrin, vasoactive intestinal polypeptide, and pancreatic polypeptide were also demonstrable. Patients with acromegaly underwent echocardiographic studies to exclude the presence of a cardiac myxoma related to CNC.

Neuroradiological studies consisted of a contrast-enhanced computerized tomography (CT) scan of the pituitary before 1986 and magnetic resonance imaging (MRI), predominantly with gadolinium enhancement, thereafter. Based on the maximal diameter, tumors were defined as microadenomas ($\leq$10 mm), macroadenomas (>10 mm), and giant adenomas (>40 mm). Invasion of the cavernous or sphenoidal sinuses was assessed based on CT/MRI results and/or intraoperative findings.

### *Sporadic pituitary tumors*

We compared the demographic and tumor characteristics of FIPA cases with those of the corresponding sporadic non-MEN1, non-CNC phenotype. This series of patients with sporadic pituitary adenomas was obtained from registries of patients treated from 1970–2004 in Belgium (Liège) and Italy (L'Aquila, Rome), which comprised a total of 2600 patients. Each patient from the familial group was paired with two patients with the same tumor phenotype extracted randomly from the sporadic registries (Statview 5.1 software; SAS Institute, Cary, NC). A postextraction analysis was undertaken to ensure that the familial and sporadic groups were matched with respect to year at diagnosis for each tumor phenotype; this was done to exclude bias introduced by improvements in diagnostic methods over the study period.

### *Immunohistochemistry*

Among the group of patients that underwent surgery (n = 83), tumor tissue from 74 individuals was studied by immunohistochemistry for LH, FSH, TSH, GH, prolactin, ACTH, and $\alpha$-subunit. GH-secreting adenomas were subclassified as pure GH-secreting, mixed GH/prolactin, or glycoprotein/GH adenomas, whereas NS adenomas were subclassified as null cell, gonadotroph-secreting, or silent adenomas. Silent adenomas were defined as tumors that were immunopositive for pituitary hormones in the absence of preoperative biochemical or clinical evidence of hormonal hypersecretion.

### *Genetic analysis*

Blood samples were collected in all available patients, and DNA was extracted from leukocytes. Germline mutations of the *MEN1* gene were excluded by direct sequencing of exons 1–10 in at least one affected member of each family. In addition, sequencing of the *PRKAR1A* gene was performed in one affected member of families with IFS. Informed consent for genetic studies was obtained in all cases.

### *Statistical analysis*

Unless otherwise specified, results are expressed in mean $\pm$ SD. Data were analyzed using Statview 5.1 software (SAS Institute). As noted above, to verify that the groups were correctly matched at time of diagnosis, a postextraction comparison of centile distributions of year at diagnosis in the familial and sporadic adenoma patient groups was performed. For patients with recurrent disease, only the characteristics at first presentation were retained for the study. Because different patterns of pituitary tumor phenotypes could present within the same kindred, families were divided into homogeneous (families presenting with a single tumor phenotype) and heterogeneous (at least two phenotypes per family) groups for subsequent analyses.

Intergroup analyses were performed to compare FIPA with sporadic adenomas and to distinguish between homogeneous and heterogeneous subgroups, whereas multiple comparisons were used for the comparison of homogeneous or heterogeneous tumors with their sporadic counterparts and for comparisons between tumor phenotypes (prolactinoma, somatotropinoma, NS adenoma, and Cushing's disease), respectively. The distributions of nominal data were compared using the $\chi^2$ test for single or multiple comparisons, whereas continuous variables were compared by the Mann-Whitney test for univariate analyses and by ANOVA followed by the Bonferroni/Dunn *post hoc* test for multivariate analyses. The analysis of parental transmission data was performed using $\chi^2$ to compare percentages of maternal/paternal transmission with the 50% theoretical value that would occur by chance; a $\chi^2$ test for multiple comparisons was used to analyze differences among tumor

phenotype subgroups. The level of statistical significance was $P < 0.05$ for the two-group analyses, whereas the $\alpha$-level was adjusted to compensate for multiple groups where necessary (*e.g.* $\alpha < 0.0167$ for three groups).

## Results

### *Demographics and disease characteristics*

A total of 64 families with isolated pituitary tumors were identified, which included 138 affected individuals (52 males, 86 females). Within the reference study centers, FIPA cases represented 1.9–3.2% of the total patient population with pituitary adenomas. The mean follow-up period for FIPA cases was 9.6 ± 8.0 yr (median, 7 yr; range, 1–44 yr). The sporadic group consisted of 288 patients (109 male, 179 female) with sporadic, nonfamilial, non-MEN1/CNC pituitary adenomas (Table 1). There was no difference between the FIPA and sporadic groups in terms of gender distribution, and the mean year at diagnosis in both groups was 1993. Prolactinomas and somatotropinomas were the most prevalent phenotypes among the familial group, accounting for nearly 75% of the entire series.

Fifty-five families had two affected members, eight families had three affected members, and one family had four affected members. First-degree relationships (parents, offspring, or siblings) predominated (103 of 138, 74.6%). The mean (± SD) total family size in the study was 15.4 ± 9.4 individuals, and the average degree of relatedness among the FIPA population was 0.62. When families were subdivided according to tumor phenotype, 30 families with 62 patients had homogeneous tumor expression; they consisted of 28 patients with prolactinoma in 14 families, 26 with somatotropinomas in 12 families, four with NS tumors in two families, and four patients with Cushing's disease in two families. In the 34 families (76 affected individuals) exhibiting heterogeneous tumor expression, up to three different tumor phenotypes were noted; every heterogeneous kindred had at least one prolactinoma or somatotropinoma.

### *Age at diagnosis*

The mean age at diagnosis was significantly lower in the familial group as compared with the sporadic group (38.4 ± 16.3 *vs.* 41.9 ± 15.1 yr, respectively; $P = 0.015$). This difference was predominantly because of the younger age of patients with IFS and familial NS adenomas compared with their sporadic counterparts (Table 1). Furthermore, the mean age at diagnosis in the homogeneous families was significantly lower than in the heterogeneous families ($P = 0.023$). In families distributed over two generations, tumors were diagnosed significantly earlier in the second generation compared with the first (Table 2; mean age at diagnosis, 29.0 ± 10.2 *vs.* 50.5 ± 14.2 yr, respectively; $P < 0.0001$). This generational effect was preserved after correction for homogeneous or heterogeneous in a multivariate analysis ($P < 0.0001$). Similarly, the second generation was diagnosed significantly earlier than the first generation in patients with prolactinomas, somatotropinomas, and NS adenomas occurring as part of FIPA families ($P \leq 0.02$). However, a generation effect independent of familial tumor status was seen only for prolactinomas ($P < 0.0001$).

### *Tumor characteristics*

There was no difference between FIPA and sporadic groups overall in terms of the frequency of micro- and macroadenomas, suprasellar extension, and invasiveness, although there was a trend toward a higher rate of cavernous sinus invasion in the FIPA group compared with the sporadic group ($P = 0.058$; Table 1). Macroadenomas were more frequent in heterogeneous than in homogeneous FIPA cases (71.5 *vs.* 52.5%; $P = 0.036$), perhaps related to the predominance of NS adenomas in the heterogeneous FIPA group and the low frequency of macroadenomas in the homogeneous prolactinoma group.

### *Individual tumor subtype characteristics*

The clinical characteristics of FIPA subgroups and comparison with their relative sporadic counterparts are summarized in Table 1.

### *Familial prolactinomas*

Prolactinomas were the most commonly observed tumor overall (39.9%), with 55 affected members in 40 FIPA families. The mean age at diagnosis was 32.6 ± 12.5 yr (range, 15–61 yr) with a female predominance (41 females and 14 males); the age and sex distributions of prolactinomas did not differ from those of sporadic prolactinomas. Prolactinomas were equally distributed between homogeneous families and heterogeneous families. Prolactinomas in homogeneous FIPA families were indistinguishable from sporadic prolactinomas, with 71.4% (20 of 28 patients) being females with microprolactinomas. All males (four of four) but only four of 24 females (16.7%) from homogeneous families had macroprolactinomas. In six of the 14 homogeneous prolactinoma families, mother and daughter were affected, and 83.3% of these had microprolactinomas.

Prolactinomas from heterogeneous FIPA families had more aggressive characteristics than their homogenous counterparts, with a larger maximal diameter ($P = 0.047$) and more frequent suprasellar extension ($P = 0.038$). Compared with their sporadic counterparts, heterogeneous prolactinomas were also significantly larger than their sporadic counterparts ($P = 0.0137$) and had a higher rate of suprasellar extension ($P = 0.004$). The percentage of males with prolactinomas tended to be higher in heterogeneous than in homogenous FIPA families (37 *vs.* 14.8%; $P = 0.053$); a male patient from a heterogeneous FIPA family developed a malignant prolactinoma, as described previously (22).

### *Familial somatotropinomas*

Familial somatotropinomas occurred in 47 patients divided among 31 families (34.1% of the series), were similarly distributed between homogeneous/IFS and heterogeneous FIPA families, and did not differ from sporadic cases in terms of demographic characteristics. Patients with IFS were more than 10 yr younger at diagnosis than those from either heterogeneous phenotype families ($P = 0.002$) or sporadic somatotropinoma cases ($P = 0.0023$); all five patients with gigantism belonged to IFS families. IFS patients also had more aggressive tumors, with extrasellar ($P = 0.023$) and

**TABLE 1.** Demographic and tumor characteristics in patients with FIPA (homogeneous and heterogeneous tumor presentation) and sporadic pituitary adenomas

| | Familial | Sporadic | Homogeneous familial | Heterogeneous familial | Familial *vs.* sporadic | Homogeneous *vs.* sporadic | Heterogeneous *vs.* sporadic | Homogeneous *vs.* heterogeneous |
|---|---|---|---|---|---|---|---|---|
| All tumors | | | | | | | | |
| n | 138 | 288 | 62 | 76 | | | | |
| Age at diagnosis (yr) | 38.4 ± 16.3 | 41.9 ± 15.1 | 34.2 ± 16.1 | 41.8 ± 15.8 | 0.015 | 0.0040 | NS | 0.023 |
| Sex | 52 M/86 F | 109 M/179 F | 21 M/41 F | 31 M/45 F | NS | NS | NS | NS |
| Macroadenomas (%) | 63.4 | 66.3 | 52.5 | 71.0 | NS | NS | NS | 0.036 |
| Maximal diameter (cm) (n) | 1.74 ± 1.23 (92) | 1.50 ± 1.6 (217) | 1.63 ± 1.27 (44) | 1.84 ± 1.20 (48) | NS | NS | NS | NS |
| Extrasellar extension (%) | 66/127 (53.4) | 141/281 (50.2) | 28/56 (50.0) | 38/71 (54.3) | NS | NS | NS | NS |
| Suprasellar extension (%) | 54/126 (42.9) | 113/277 (40.8) | 21/56 (37.5) | 33/70 (47.1) | NS | NS | NS | NS |
| Invasive (%) | 60/129 (46.5) | 111/282 (39.4) | 23/55 (41.8) | 37/74 (50.0) | NS | NS | NS | NS |
| Cavernous sinus invasion (%) | 42/118 (35.6) | 71/272 (26.1) | 20/54 (37.0) | 22/64 (34.4) | NS (0.058) | NS | NS | NS |
| Prolactinomas | | | | | | | | |
| n | 55 | 113 | 28 | 27 | | | | |
| Age at diagnosis (yr) | 32.6 ± 12.5 | 34.0 ± 13.2 | 32.4 ± 13.1 | 33.7 ± 13.2 | NS | NS | NS | NS |
| Sex | 14 M/41 F | 26 M/87 F | 4 M/24 F | 10 M/17 F | NS | NS | NS | NS (0.053) |
| Macroadenomas (%) | 45.5 | 47.8 | 35.7 | 55.5 | NS | NS | NS | NS |
| Maximal diameter (cm) (n) | 1.43 ± 1.12 (40) | 1.21 ± 0.91 (64) | 1.10 ± 0.69 (22) | 1.83 ± 1.50 (16) | NS | NS | 0.0137 | 0.047 |
| Extrasellar extension (%) | 24/54 (44.4) | 36/110 (32.7) | 11/28 (39.3) | 13/26 (50.0) | NS | NS | NS | NS |
| Suprasellar extension (%) | 16/53 (30.2) | 19/108 (17.6) | 5/28 (17.9) | 11/25 (44.0) | NS | NS | 0.004 | 0.038 |
| Invasive (%) | 22/55 (40.0) | 40/112 (36.4) | 9/19 (32.1) | 13/27 (48.1) | NS | NS | NS | NS |
| Cavernous sinus invasion (%) | 17/52 (32.7) | 19/85 (18.3) | 8/28 (28.6) | 9/24 (37.5) | 0.044 | NS | NS | NS |
| GH-secreting tumors | | | | | | | | |
| n | 47 | 97 | 26 | 21 | | | | |
| Age at diagnosis (yr) | 40.7 ± 19.2 | 44.1 ± 13.5 | 33.8 ± 18.9 | 49.3 ± 16.3 | NS | 0.0023 | NS | 0.002 |
| Sex | 24 M/23 F | 44 M/53 F | 13 M/13 F | 11 F/10 M | NS | NS | NS | NS |
| Macroadenomas (%) | 76.7 | 80.4 | 77.3 | 76.2 | NS | NS | NS | NS |
| Maximal diameter (cm) (n) | 1.80 ± 1.10 (26) | 1.58 ± 0.87 (64) | 2.16 ± 1.25 (10) | 1.23 ± 0.40 (16) | NS | NS | NS | NS |
| Extrasellar extension (%) | 17/38 (44.7) | 48/94 (51.0) | 13/20 (65.0) | 4/18 (22.2) | NS | NS | NS | 0.023 |
| Suprasellar extension | 16/38 (42.1) | 41/93 (44.0) | 12/20 (60.0) | 4/18 (22.2) | NS | NS | NS | 0.043 |
| Invasive (%) | 15/40 (37.5) | 36/94 (38.3) | 10/19 (52.6) | 5/21 (23.8) | NS | NS | NS | NS |
| Cavernous sinus invasion (%) | 10/34 (29.4) | 26/93 (27.9) | 8/18 (44.4) | 2/16 (12.5) | NS | NS | NS | NS |
| NS tumors | | | | | | | | |
| n | 28 | 59 | 4 | 24 | | | | |
| Age at diagnosis (yr) | 46.4 ± 15.3 | 54.0 ± 12.0 | 49.7 ± 13.3 | 45.8 ± 13.3 | 0.030 | NS | 0.0132 | NS |
| Sex | 13 M/15 F | 36 M/23 F | 2 M/2 F | 11 M/13 F | NS | NS | NS | NS |
| Macroadenomas (%) | 92.9 | 98.3 | 100 | 91.7 | NS | NS | NS | NS |
| Maximal diameter (cm) (n) | 2.50 ± 1.20 (20) | 2.16 ± 1.07 (40) | 3.9 ± 1.6 (3) | 2.28 ± 0.97 (17) | NS | NS | NS | NS |
| Extrasellar extension (%) | 24/27 (88.9) | 54/58 (93.1) | 4/4 (100) | 20/23 (86.9) | NS | NS | NS | NS |
| Suprasellar extension | 21/27 (77.8) | 52/57 (91.2) | 4/4 (100) | 17/23 (73.9) | NS | NS | NS | NS |
| Invasive (%) | 22/26 (84.6) | 34/57 (59.6) | 4/4 (100) | 18/22 (81.8) | 0.024 | NS | NS | NS |
| Cavernous sinus invasion (%) | 14/24 (58.3) | 23/56 (41.0) | 4/4 (100) | 10/20 (50.0) | NS | NS | NS | NS |
| ACTH-secreting tumors | | | | | | | | |
| n | 8 | 19 | 4 | 4 | | | | |
| Age at diagnosis (yr) | 33.9 ± 12.9 | 40.2 ± 14.2 | 33.7 ± 14.7 | 34.0 ± 13.1 | NS | NS | NS | NS |
| Sex | 2 M/6 F | 3 M/16 F | 2 M/2 F | 0 M/4 F | NS | NS | NS | NS |
| Macroadenomas (%) | 12.5 | 5.3 | 0 | 25.0 | NS | NS | NS | NS |
| Maximal diameter (cm) (n) | 0.9 ± 1.10 (6) | 0.54 ± 0.27 (18) | 0.40 ± 0.26 (3) | 1.4 ± 1.4 (3) | NS | NS | NS | NS |
| Extrasellar extension (%) | 1/8 (12.5) | 3/19 (15.6) | 0/4 (0) | 1/4 (25.0) | NS | NS | NS | NS |
| Suprasellar extension (%) | 1/8 (12.5) | 1/18 (5.5) | 0/4 (0) | 1/4 (25.0) | NS | NS | NS | NS |
| Invasive (%) | 1/8 (12.5) | 2/18 (11.0) | 0/4 (0) | 1/4 (25.0) | NS | NS | NS | NS |
| Cavernous sinus invasion (%) | 1/8 (12.5) | 1/18 (5.5) | 0/4 (0) | 1/ 4 (25.0) | NS | NS | NS | NS |

The denominator used to calculate the percentages in terms of tumor characteristics may differ from the overall number of tumors because of missing or irretrievable data in a minority of cases. The level of significance was set at $P < 0.05$ for comparisons of the entire familial group *vs.* the sporadic group and between homogeneous and heterogeneous familial groups and $P < 0.0167$ for comparisons of homogeneous or heterogeneous groups *vs.* the sporadic group. F, Female; M, male; NS, Not significant.

**TABLE 2.** Mean ages at diagnosis in the first and second generations of multigenerational families with FIPA according to tumor phenotype and pattern of presentation

| Tumor type | Age at diagnosis (first generation) | Age at diagnosis (second generation) | *P* value |
|---|---|---|---|
| Overall | | | |
| All phenotypes (n = 80 in 37 families) | 50.5 ± 14.2 | 29.0 ± 10.2 | <0.0001[a] |
| All homogeneous (n = 29 in 14 families) | 43.2 ± 12.8 | 24.4 ± 6.6 | |
| All heterogeneous (n = 51 in 23 families) | 54.4 ± 13.4 | 31.8 ± 11.0 | <0.0001[b] |
| Individual phenotypes | | | |
| All prolactinomas (n = 41 in 29 families) | 44.7 ± 8.3 | 26.7 ± 9.0 | <0.0001[a] |
| Homogeneous (n = 22 in 11 families) | 44.4 ± 9.2 | 23.3 ± 4.6 | |
| Heterogeneous (n = 19 in 18 families) | 45.7 ± 5.8 | 29.2 ± 10.7 | <0.0001[b] |
| All somatotropinomas (n = 20 in 16 families) | 53.3 ± 17.4 | 34.4 ± 12.3 | 0.02[a] |
| Homogeneous (n = 5 in 2 families) | 27.0 ± 18.4 | 26.0 ± 12.8 | |
| Heterogeneous (n = 15 in 14 families) | 58.1 ± 12.9 | 40.7 ± 8.2 | |
| All NS adenomas (n = 18 in 17 families) | 56.0 ± 15.0 | 32.1 ± 10.8 | 0.006[a] |
| Homogeneous (n = 2 in 1 family) | 63.0 | 32.0 | |
| Heterogeneous (n = 16 in 16 families) | 55.3 ± 15.6 | 32.2 ± 11.8 | |

The ages at diagnosis are expressed as mean ± SD.
[a] One-way comparison between the first and second generations.
[b] Significant difference in age after a two-way analysis after exclusion of a significant interaction between generation and familial subtype status.

suprasellar extension ($P = 0.043$) occurring more frequently than heterogeneous somatotropinoma families. Giant tumors (>40 mm maximal diameter; n = 2) occurred only in IFS kindreds.

*Familial NS adenomas*

Twenty-eight NS adenomas were observed in 26 families, including one case of a clinically active gonadotroph-secreting adenoma. Most NS adenomas (85.7%) occurred in heterogeneous families. NS adenomas were diagnosed nearly 8 yr earlier in the FIPA group as compared with the sporadic group ($P = 0.03$). NS adenomas in the FIPA group were more frequently invasive than sporadic cases (84.6 *vs.* 59.6%; $P = 0.024$).

*Familial ACTH-secreting adenomas*

Eight patients were affected by Cushing's disease in five FIPA families (homogeneous, four patients, including two siblings, in two families; heterogeneous, four patients in three families). The demographic and clinical characteristics of the familial and sporadic Cushing's disease groups did not differ significantly from one another.

*Immunohistochemistry*

The diagnosis of prolactinoma was confirmed by immunohistochemistry in all operated cases (n = 26). Immunohistochemical analysis of 40 available GH-secreting tumors demonstrated that 70% stained for GH only, 27.5% were mixed GH/prolactin staining, and 2.5% were mixed glycoprotein/GH-positive adenomas (2.5%). Among IFS families, tumors exhibiting immunopositivity for GH alone or for combinations of GH/prolactin and GH/glycoprotein hormones were found to occur. Immunohistochemistry of NS tumor tissue showed them to be null cell (n = 11), FSH/LH-positive (n = 7), GH-positive (n = 2) or β-endorphin/TSH β-subunit-positive (n = 1) adenomas. The two silent, GH-positive, NS adenomas were giant tumors from second-degree relatives in the same homogeneous NS phenotype family; the other homogeneous NS tumor family comprised a mother-son pair with silent gonadotroph-positive adenomas.

*Analysis of genealogical trees*

Pituitary adenomas occurred in one in seven individuals among the genealogies of the FIPA group overall, whereas in generations containing at least one affected member, pituitary tumors occurred at a rate of one in 2.8 individuals. A sizeable majority of patients in the FIPA group (103 of 138, 74.6%) were first-degree relatives of other affected members. Potential parental transmission was studied in 78 generations and was identified in 66 patients from 48 families. A total of 38 of 66 (57.6%) of cases indicated potential maternal transmission, which did not differ significantly from the 50% that would be expected by chance ($\chi^2 = 1.51$; $P$ value not significant). A significantly high level of potential maternal transmission was seen in 69.7% of the homogeneous FIPA group ($\chi^2 = 5.12$; $P < 0.05$). For all prolactinomas, potential maternal transmission occurred in 74.2% of cases ($\chi^2 = 7.26$; $P < 0.01$) because of frequent maternal transmission among homogeneous prolactinoma families (81.2%; $\chi^2 = 6.25$; $P < 0.02$). In IFS families, tumors occurred predominantly among siblings (65.4%), whereas data in FIPA families with NS tumors and Cushing's disease were insufficient for a robust assessment of parental transmission.

*Genetic studies*

Germline mutations in exons 1–10 of the *MEN1* gene were excluded in at least one affected member of each family (90 patients were tested); upstream and downstream elements related to *MEN1* were not assessed. Mutations in the

*PRKRA1A* gene were found to be negative in at least one member from 11 of 12 families with a homogeneous acromegaly phenotype. One homogeneous, two-member IFS family was screened for *MEN1* but was not available for *PRKRA1A* gene screening. However, the subjects had no cardiac, cutaneous, or endocrine abnormalities that were suggestive of CNC.

## Discussion

Pituitary tumors that occur in a familial setting due to MEN1, CNC, or IFS account for a minority of pituitary tumors overall. Scheithauer *et al.* (23) estimated that 2.7% of pituitary adenomas were due to MEN1, whereas acromegaly due to CNC or IFS together account for no more than a few hundred cases worldwide (1, 8, 9). The current study indicates that FIPA may account for a similar proportion (2.5%) of pituitary adenomas to MEN1, suggesting that hereditary tumor syndromes may play a role in the clinical presentation of about 5% of pituitary tumors (24).

Familial prolactinoma unrelated to MEN1 was first described by Berezin and Karasik (16). In this study, we have characterized familial prolactinoma further in a large number of patients (n = 55). In line with the epidemiology of sporadic pituitary tumors (25), prolactinoma was the most frequently encountered tumor in FIPA families (39.9% of cases). Prolactinomas in the heterogeneous FIPA group were larger and had more frequent suprasellar extension than the homogeneous group. This may have been because of the presence of relatively more males in the heterogeneous prolactinoma group, because the clinical course of prolactinoma is thought to be generally more aggressive in males (26). Somatotropinomas accounted for about one third of FIPA cases. Although IFS has been characterized previously, in this study we noted that acromegaly cases could also occur in conjunction with prolactinomas, NS adenomas, or Cushing's disease in the same family. Among the IFS group (18% of FIPA cases), six families with 14 affected individuals (two three-member families and four two-member families) have not been reported previously, increasing the reported number of IFS cases to 122 overall. Patients with IFS were diagnosed more than a decade before those with sporadic somatotropinomas or somatotropinomas occurring in heterogeneous FIPA families, whereas all five cases of gigantism occurred in families with IFS. These results are in keeping with the previously reported early median age at diagnosis (26 yr) in patients with IFS (27). Similarly, suprasellar/extrasellar extension was more frequent in IFS than in the heterogeneous FIPA groups, mirroring previous reports of acromegaly being more aggressive in younger subjects (28). In contrast to previous reports of male predominance in IFS, however, equal sex distribution of somatotropinomas was seen in our series. NS adenomas occurred predominantly as part of heterogeneous FIPA families and were diagnosed earlier and were more frequently invasive than sporadic NS adenomas. No particular characteristics could be observed in the eight patients with familial Cushing's disease.

All *MEN1* gene mutation studies performed in the patient population were negative, which strongly suggests that FIPA, including patients characterized as IFS, represents an entity/entities unrelated to MEN1. In support of this, serum calcium and PTH were normal in all cases, and no abnormalities developed throughout follow-up; normal gastrin, vasoactive intestinal polypeptide, and pancreatic polypeptide levels were observed in the subgroup tested. A pituitary-restricted form of CNC was largely ruled out by normal *PRKAR1A* sequences in IFS families, whereas CNC-related multifocal somatomammotropic hyperplasia (6) was not reported in pituitary tumor samples. Echocardiography was also negative for CNC-related atrial myxomas in patients with somatotropinomas. Although these data do not entirely exclude the role of a potential disease locus on chromosome 2p16, CNC in somatotropinoma patients in this series is unlikely.

How do the characteristics of FIPA compare with the respective characteristics of pituitary tumors that occur in the setting of MEN1? Vergès *et al.* (3) described the characteristics of 136 MEN1 patients with pituitary adenomas from a group of 324 patients with demonstrated *MEN1* mutations. Approximately 75% of pituitary adenomas were diagnosed before the age of 51 yr in FIPA, which is older than the corresponding age (46 yr) in MEN1 (3). Macroadenomas predominated in MEN1-related pituitary adenoma cases (85%), and invasion occurred in one third of tumors. These results are not mirrored by FIPA, because tumor size and invasion did not differ significantly between the overall FIPA group and the sporadic cases. Both FIPA and MEN1 pituitary adenomas have a female preponderance, with prolactinomas being the most frequent phenotype encountered. In MEN1, the percentage of prolactinomas (62.5%) is markedly higher than in FIPA (39.9%) (3). Somatotropinomas, on the other hand, accounted for 34.1% of tumors in FIPA, compared with only 8.8% of tumors in MEN1 (3).

The epidemiology of sporadic pituitary adenomas and aspects of the genealogical data in this series indicate that the occurrence of uncommon pituitary tumors within multiple members of individual families, as seen in FIPA (Fig. 1), is more likely to occur because of inherited factors rather than by chance. This has been noted previously with respect to IFS (27). The prevalence of pituitary tumors within FIPA family trees is higher (one in seven individuals) than the historical prevalence of clinically active pituitary adenomas in the general population (190–280 per million) (29, 30). Although a recent meta-analysis of MRI and autopsy data suggested a high frequency of pituitary adenomas, many of these tumors were detected incidentally (31). Analysis of genealogical trees suggests autosomal dominant inheritance with variable penetrance as a general model, as has been hypothesized previously for IFS (27). Additional epidemiological studies will be required to assess the frequency of clinically active pituitary tumors in the modern diagnostic era; such data would help to determine accurately disease risk ratios and familiality in FIPA. This point is relevant to the FIPA population overall, with 74.6% of cases occurring in first-degree relatives, and chance is even less likely in families with more than two affected members. The period of follow-up (34 yr) may not have been sufficient, however, to identify patterns of disease across many generations, which could bias reporting toward first-degree relatives. Maternal transmission

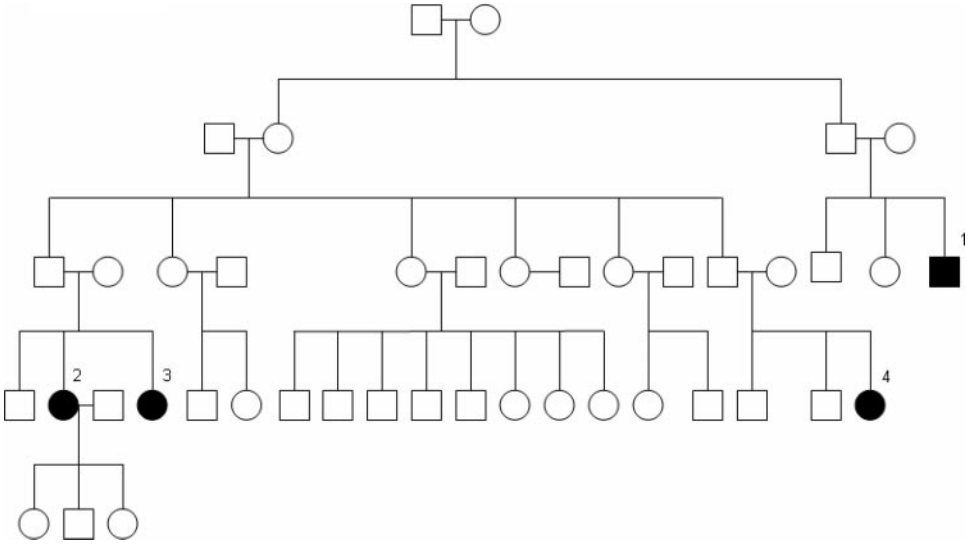


FIG. 1. The pedigree of a family exhibiting heterogeneous expression of pituitary tumors in four affected members across two generations. Affected members numbered 1 and 4 had acromegaly, whereas siblings 2 and 3 had a prolactinoma and Cushing's disease, respectively.

was significantly in excess of 50% in homogeneous prolactinoma families. The finding that patients from the second generation were diagnosed significantly earlier than the first generation in multigenerational FIPA families is intriguing and is suggestive of genetic anticipation, although a significant generational effect independent of familial tumor status could be documented reliably only for prolactinomas. Alternatively, other factors unrelated to the disease process itself may be involved, including increased awareness of symptoms within the family or improvements in diagnostic methods.

In conclusion, this multicenter, retrospective study indicates that FIPA may represent a new clinical entity/entities that includes IFS, and is unlikely to be related to MEN1 or CNC. Heterogeneous or homogeneous tumor phenotypes can occur within FIPA, which may indicate shared molecular pathophysiological mechanisms.

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