High prevalence of genetic predisposition in young men and women with lactotroph adenomas.

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Background: Prolactinomas represent 46 to 66% of pituitary adenomas, but the prevalence of germline mutations is poorly known. We presented here the first study focusing on hereditary predisposition to prolactinomas.

Objective: We studied the prevalence of germline mutations in a large cohort of patients with isolated prolactinomas.

Material and methods: We retrospectively analyzed the genetic data of patients addressed for genetic testing of *MEN1 (NM_130799), AIP (NM_003977),* and *CDKN1B (NM_004064)* between 2003 and 2020. We sequenced *SF3B1* by Sanger in genetically-negative patients.

Results: 507 patients with prolactinoma were included: 81 with microprolactinoma (16%), 379 with macroprolactinoma (75%), 47 unknowns, 49/507 in a family context (10%).

	Total	Patients in a sporadic context	Patients with macroprolactinoma before 30 yo in a sporadic context	Patients in a family context
n	507	458	258	49
Men/Women (n, (%))	250/257	233 /225	126 / 132	17/32
	(49%/51%)	(51%/49%)	(49% / 51%)	(35%/65%)
Mean age at diagnosis of prolactinoma (years)	26 (2-77)	25 (2-77)	15.9 (11-21)	30 (12-71)
prolactinoma before 30 years (n, (%))	363 (72%)	335 (73%)	258 (100%)	28 (57%)
prolactinoma after 30 years (n, (%))	144 (28%)	123 (27%)		21 (43%)
Size of prolactinoma:				
macroprolactinoma (n, (%))	379 (75%)	358 (78%)	258 (100%)	21(43%)
microprolactinoma (n, (%))	81 (16%)	59 (13%)		22 (45%)
not available	47 (9%)	41 (9%)		6 (12%)
Patients with (likely) pathogenic variant (n, (%))	15 (3%)	12 (3%)	11 (4%)	3 (6%)
AIP (n, (%))	8 (2 %)	6 (1 %)	5 (2%)	2 (4%)
MEN1 (n, (%))	7 (1%)	6 (1%)	6 (2%)	1 (2%)
CDKN1B (n, (%))	0	0	0	0

Table 1: Clinical and genetic characteristics in the 507 patients according to the sporadic or family context. Macroaprolactinoma is defined by a maximal diameter of the tumor ≥ 10 mm; microprolactinoma is defined by a diameter <10 mm

Among them, 15 (2.9%) had a (likely) pathogenic variant in *MEN1* or *AIP*, none in *CDKN1B.*

Among positive patients, none was over 30 years old at the prolactinoma diagnosis, all developed macroprolactinomas except one Comorian teenager who carried an *AIP* mutation with a founder effect in this population.

N°	Sex	Size of adenoma	Age at diagnosis (yrs)	Family context	Gene	Nucleotide nomenclature	Protein nomenclature	Variant classification	Reference
1	M	macro	13	no	*MEN1*	c.249_252del	p.(Ile85Serfs*85)	VP	Chandrasekharappa et al, Science 1997
2	M	macro	12	yes	*MEN1*	c.402del	p.(Phe134Leufs*51)	VP	Chandrasekharappa et al, Science 1997
3	W	macro	17	no	*MEN1*	c.415del	p.(His139Thrfs*15)	VP	Wautot et al, Hum Mutat, 2002
4	W	macro	11	no	*MEN1*	c.574 C>T	p.(Gln192*)	VP	Jager et al, Mol Cell Endocrinol, 2006
5	M	macro	15	no	*MEN1*	c.788T>G	p.(Leu263Arg)	VPP	Not previously reported
6	M	macro	16	no	*MEN1*	c.1546del	p.(Arg516Glyfs*43)	VP	Agarwal et al, Hum Mol Genet, 1997
7	W	macro	15	no	*MEN1*	c.1546dup	p.(Arg516Profs*15)	VP	Agarwal et al, Hum Mol Genet, 1997
8	M	macro	22	no	*AIP*	c.55C>T	p.(Gln19*)	VP	Mougel et al, Eur J Endocrinol, 2020
9	M	micro	14	no	*AIP*	c.350del	p.(Gly117Alafs*39)	VP	Tichomirowa et al, Eur J Endocrinol, 2011
10	W	macro	17	no	*AIP*	c.350del	p.(Gly117Alafs*39)	VP	Tichomirowa et al, Eur J Endocrinol, 2011
11	M	macro	18	yes	*AIP*	c.404del	p.(His135Leufs*21)	VP	Cazabat et al, Eur J Endocrinol, 2012
12	M	macro	10	no	*AIP*	c.442dup	p.(Leu148Pro*75)	VP	Not previously reported
13	W	macro	27	yes	*AIP*	c.645+2 T>C	p.(?)	VP	Not previously reported
14	M	macro	21	no	*AIP*	c.805_825dup	p.(Phe269_His275dup	VP	Leontiou et al, J Clin Endocrinol Metab, 2006
15	M	macro	15	no	*AIP*	c.811C>T	p.(Arg271Trp)	VP	Daly et al, J Clin Endocrinol Metabl, 2007

Table 2: Clinical and genetic characteristics of the 15 patients harboring a likely pathogenic or pathogenic variant.

M, man; W, woman; macro, macroadenoma, micro: microadenoma.

Classification of sequence variants according to the ACMG guidelines; VP: pathogenic variant; VPP: probably pathogenic variant

The prevalence of germline mutations in patients with isolated macroprolactinoma before 30 years was 4% (11/258) in a sporadic context, and 15% (3/20) in a family context. In sporadic case before 18 years, it was 15% in men (5/33) and 7% in women (4/57).

		Total		Sporadic context		Family context	
All patients	Total (n)	278		258		20	
	Germline (n, %)	14 (5%)		11 (4%)		3 (15%)	
	Sex (M/W)	M	W	M	W	M	W
	Total (n)	135	143	126	132	9	11
	Germline (n, %)	9 (7%)	5 (4%)	7 (6%)	4 (3%)	2 (2%)	1 (9%)
Age < 18 years	Total (n)	95		90		5	
	Germline (n, %)	10 (12%)		9 (10%)		1 (20%)	
	Sex (M/W)	M	W	M	W	M	W
	Total (n)	35	60	33	57	2	3
	Germline (n, %)	6 (17%)	4 (7%)	5 (15%)	4 (7%)	1 (50%)	0
Age between 18 and 30 yrs	Total (n)	176		168		8	
	Germline (n, %)	4 (2%)		2 (1%)		2 (25%)	
	Sex (M/W)	M	W	M	W	M	W
	Total (n)	95	81	93	75	2	6
	Germline (n, %)	3 (3%)	1 (1%)	2 (2%)	0	1 (50%)	1 (17%)
Age >30 yrs	Germline /total	0/7		-		0/7	

Table 3: Clinical and genetic characteristics of patients with macroprolactinomas according to the family or sporadic context, to the age at the prolactinoma diagnosis, and to the gender. Germline: patients harbored a pathogenic or likely pathogenic variant. M, men; W, Women

No R625H *SF3B1* germline mutation was identified in 264 patients with macroprolactinomas.

Conclusion: This data confirms that 30 years is a good cut-off age for genetic testing in patients with macroprolactinoma.

Special attention should be paid to young patients and patients in a family context.

There is no evidence to recommend genetic testing in sporadic patients with microprolactinoma