SPORADIC PITUITARY ADENOMAS IN YOUNG PATIENTS: CLINICAL AND MOLECULAR DESCRIPTION

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INTRODUCTION

Pituitary adenomas (PA) in pediatric and young patients comprise a rare pathology of unknown prevalence. The majority are sporadic, but 5% occur in a familial setting, either as isolated (FIPA) or as part of a syndrome (1,2). Somatic changes in *GNAS* and *USP8* have been identified in an important percentage of sporadic somatotropinomas and adrenocorticotrophic tumours (3). However, only 10–12% of young patients with sporadic PA carry germline mutations in *AIP* or *MEN1* (4). Other genes such as *CDKN1B*, *PRKAR1A*, SDHx, and *DICER1* predispose to PAs (5).

AIM

We describe the **clinical characteristics of patients with sporadic pituitary adenomas arising before the age 35 years** and perform a **thorough genetic screening for germline variants** in probands and relatives.

PATIENTS & METHODS

Patients
Clinical characteristics were collected from 276 patients (≤35 years at disease onset) with apparently sporadic PA.

Genetic screening
Genomic DNA from peripheral blood leukocytes was tested using a targeted gene panel (Thermo Fisher Scientific) including *MEN1, AIP, PRKAR1A, CDKN1B, GNAS, DICER1, SDHB, SDHC,* and *SDHD* genes. After bioinformatic analysis and in silico studies, we classified genetic changes according to recommendations (6). Patients' relatives were tested by PCR and Sanger sequencing. We performed a comparative genomic hybridization array (aCGH) and *GPR101* gene amplification on patients with gigantism/acromegaly. In cases with a corticotropinoma *CABLES1* gene was amplified by PCR and sequenced.

RESULTS

Clinical characteristics
Among the total cohort, mean age was 19.5 years and 64.1% were females. Local mass effect symptoms were present in 22.4% and prolactinomas were the most frequent type of tumour (46.3%). Genetically positive patients were younger and had larger tumor size at diagnosis (Table 1).

Genetic findings
We identified disease-causing germline variants in 20 patients (Table 2). Healthy family carriers were also identified.

	All	Positive patients	Negative patients	P-value
n	276	20	256	
Age at diagnosis (years)	19.5	16.7	20	0.04
Gender (F/M, %)	64.1/35.9	65.0/35.0	64.1/ 35.9	ns
Mass effect symptoms (%)	22.4	25	22.8	ns
Tumour size (mm)	15.3	21.4	14.7	0.02
Macroadenomas (%)	64.5	80	63.2	0.04
F/NF tumour (%)	84.8/15.2	90/10	84.7/15.3	ns
Surgery (%)	52.2	45	47.8	ns

	Case (Gender)	Age	Type of PA	Tumor size (mm)	Surgery (Yes/No)	Genetic alteration
Pediatric and adolescents (<19 years)	1 (F)	17.3	GH	30.0	Yes	AIP,c.64C>T;p.R22
	2 (M)	10.3	GH	40.0	Yes	AIP,c.811C>T;p.R271W
	3 (M)	17.9	PRL	Macroadenoma	No	AIP,c.811C>T;p.R271W
	4 (F)	13.9	ACTH	55.0	No	AIP,c.911G>A;p.R304Q
	5 (M)	12.9	GH	30.0	No	AIP,c.811C>T;p.R271W PRKAR1A,c.221G>A;p.R74H
	6 (F)	15.9	PRL	13.0	Yes	MEN1,c.1010G>A;p.R337H
	7 (M)	3.1	GH	38.0	No	CDKN1B,c.160G>C;p.E54Q
	8 (F)	15.0	ACTH	2.0	Yes	CDKN1B,c.356T>C;p.I119T
	9 (F)	15.9	PRL	16.0	Yes	SDHB,c.166_170delCCTCA;p.P56Yfs*5
	10 (F)	10.8	NF	12.0	No	PRKAR1A,c.221G>A;p.R74H
	11 (F)	11.1	PRL	26.0	No	PRKAR1A,c.221G>A;p.R74H
	12 (F)	15.1	PRL	7.8	No	PRKAR1A,c.221G>A;p.R74H
	13 (F)	15.7	PRL	13.0	Yes	PRKAR1A,c.221G>A;p.R74H
	14 (F)	3.6	GH	Enlarged sella turca	No	Xq26.3(135.615.258-136.262.002)X3
Young adults (19- 35 years)	15 (M)	23.0	PRL	10.0	No	AIP,c.26G>A;p.R9Q
	16 (M)	23.3	PRL	36.0	Yes	AIP,c.197delA;p.K66Rfs*88
	17 (M)	28.2	PRL	36.0	No	AIP,c.807C>T;p.F269=
	18 (F)	30.6	ACTH	7.0	Yes	AIP,c.26G>A;p.R9Q
	19 (F)	33.0	NF	2.5	Yes	PRKAR1A,c.221G>A;p.R74H
	20 (F)	19.0	PRL	10.0	No	CDKN1B,c.272C>T;p.P91L

CONCLUSIONS

Variants in genes associated with syndromic forms of pituitary adenomas were detected in a large cohort of apparently sporadic pituitary tumours. **Longer follow-up** of these positive patients and their relatives is essential to accentuate this statement.
We have identified **novel variants in well-known genes**, such as *CDKN1B*, and set the possibility of **incomplete disease penetrance in carriers of *MEN1* alterations or a limited clinical expression of the syndrome**.
Despite the low penetrance observed, **genetic screening of *AIP* and *MEN1* in young patients and relatives is of clinical value.**

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