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Review article

Gigantism: X-linked acrogigantism and *GPR101* mutations

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ABSTRACT

X-linked acrogigantism (XLAG) is a recently identified condition of early-onset GH excess resulting from the germline or somatic duplication of the *GPR101* gene on chromosome Xq26.3. Thirty patients have been formally reported so far. The disease affects mostly females, occurs usually sporadically, and is characterised by early onset and marked overgrowth. Most patients present with concomitant hyperprolactinaemia. Histopathology shows pituitary hyperplasia or pituitary adenoma with or without associated hyperplasia. XLAG-related pituitary adenomas present peculiar histopathological features that should contribute to raise the suspicion of this rare condition. Treatment is frequently challenging and multi-modal. While females present with germline mutations, the sporadic male patients reported so far were somatic mosaics with variable levels of mosaicism, although no differences in the clinical phenotype were observed between patients with germline or somatic duplication. The *GPR101* gene encodes an orphan G protein-coupled receptor normally expressed in the central nervous system, and at particularly high levels in the hypothalamus. While the physiological function and the endogenous ligand of GPR101 are unknown, the high expression of *GPR101* in the arcuate nucleus and the occurrence of increased circulating GHRH levels in some patients with XLAG, suggest that increased hypothalamic GHRH secretion could play a role in the pathogenesis of this condition. In this review, we summarise the published evidence on XLAG and *GPR101* and discuss the results of recent studies that have investigated the potential role of *GPR101* variants in the pathogenesis of pituitary adenomas.

1. Introduction

X-linked acrogigantism (XLAG) is a recently identified condition of early-onset pituitary gigantism due to pituitary hyperplasia or mixed somatotroph/lactotroph adenomas [1–3]. The initially published patients harboured microduplications of Xq26.3 spanning an area of approximately 500 kb encompassing four genes (*CD40LG*, *ARHGEF6*, *RBMX* and *GPR101*) [1,2]. Among these, only one, *GPR101*, encoding an orphan G protein-coupled receptor (GPCR), was found to be significantly overexpressed in these patients' pituitary samples. More recently, we have described one patient with a typical phenotype whose microduplication allowed to define a new smallest region of overlap of duplications to an area encompassing *GPR101* only [3], while the other three genes involved in previously published patients were not duplicated, thus proving the causative role of *GPR101*.

2. Clinical features

In two recently published large series of patients with pituitary gigantism, XLAG accounted for 7.8% and 10% of all cases respectively [3,4]. These patients had been screened for mutations in the *AIP* gene as well, allowing a comparison of the clinical features of XLAG patients with *AIP* mutation carriers and patients without an identified genetic predisposing mutation. XLAG patients were predominantly females, were significantly younger and presented with higher height *Z*-scores at diagnosis compared with *AIP* mutation carriers and genetically negative patients [3,4]. Moreover, in one of these studies, XLAG patients had a lower rate of pituitary adenoma invasion and extension compared with the two other groups of patients [4]. There was no statistically significant difference in tumour size, although none of the XLAG patients presented with giant adenomas, as opposed to 11–29% of patients in the other two groups [3,4]. Hyperprolactinaemia was significantly more prevalent among XLAG patients [3,4].

To date, 30 XLAG patients have been described [1–3,5–7]. Available clinical data from most patients are summarised in Table 1. The clinical phenotype of these patients is remarkably distinct. In all cases, disease onset was before the age of four. Most affected subjects were females

Abbreviations: XLAG, X-linked acrogigantism; GPCR, G protein-coupled receptor; GHRHR, Growth hormone releasing hormone receptor; FoSTeS/MMBIR, Fork stalling and template switching/microhomology-mediated break-induced replication; aCGH, Comparative genomic hybridization array; HD-aCGH, High-density comparative genomic hybridization array; ddPCR, Droplet digital PCR; ExAC, Exome Aggregation Consortium; G_s, G stimulatory protein; G_i, G inhibitory protein; CRE, cAMP response element; EGF, Epidermal growth factor.

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Table 1
Clinical features of XLAG patients reported in the literature with available data. OGTT, oral glucose tolerance test; ULN, upper limit of normal; SSA, somatostatin analogue; DA, dopamine agonist; PEG-V, pegvisomant; Sx, surgery; GK, gamma-knife; DI, diabetes insipidus; PA, pituitary adenoma; PRL, prolactin; RT, radiotherapy (conventional); NA, not available; ND, not determined; ↑, 2–10 xULN; ↑↑, 10–50 xULN; ↑↑↑, >50 xULN.

Case (original study ID)	Sex	Sporadic/ familial	Germline/ somatic	Age at onset (months)	Age at diagnosis (years)	GH	OGTT suppression	IGF-1 (xULN)	Prolactin (xULN)	Tumour/hyperplasia size (mm)	Treatment	Histology	Disease controlled	Hypopituitarism (axis)	Age at last follow-up	References
1 (I)	F	Sporadic	Germline	18	4.1	↑↑	No	NA	↑	>10	Intrasellar yttrium implants ×3, SSA	Mixed cell adenoma (acidophilic/chromophobic)	Yes	Yes (ACTH, TSH, LH)	50	[3,32,33]
2 (II)	F	Sporadic	Germline	12	3.8	↑	No	3.9	Normal	Diffuse enlargement	SSA, DA, PEG-V	No surgery	Yes	No	12	[3]
3 (III)	F	Sporadic	Germline	24	12	↑↑	Paradoxical increase	1.2	NA	13 × 12	Sx, GK, SSA, DA	NA	Yes	Yes (TSH, LH)	25	[3]
4 (IV)	F	Sporadic	Germline	9	1.5	↑	No	2.9	↑	Diffuse enlargement	DA, SSA, hemihypophysectomy, DA, SSA, completion of hypophysectomy	Somatotroph, lactotroph and mammosomatotroph hyperplasia	Yes	Yes (ACTH, TSH, LH, GH, DI)	30	[3,8]
5 (V)	F	Sporadic	Germline	30	5.7	↑	NA	3	↑	12 × 13 × 15	Sx	PA, GH+ PRL+	Yes	Yes (DI)	8	[3]
6 (VI)	F	Sporadic	Germline	24	7	↑	No	1.9	↑	16 × 19 × 12	Sx, GK, SSA, DA	PA, GH+ PRL+	Yes	No	10	[3]
7 (VII)	F	Sporadic	Germline	21	2.8	↑	NA	5	↑↑	32 × 13 × 8	Sx, GK, SSA, DA	PA, GH+ PRL+	Yes	No	12	[3]
8 (VIII)	M	Sporadic	Somatic	48	7	NA	NA	NA	Normal	>10	Sx ×3, SSA, DA, Sx, RT, GK, PEG-V	PA, GH+ PRL+	No	Yes (ACTH, TSH, LH)	33	[3,34]
9 (IX)	M	Sporadic	Somatic	24	4.7	↑	No	2	↑↑	15 × 18 × 13	SSA, DA, PEG-V	Somatotroph, lactotroph and mammosomatotroph hyperplasia	Yes	No	11	[3,7]
10 (X)	F	Sporadic	Germline	15	2.7	↑	Paradoxical increase	2.9	↑	18 × 15 × 9	SSA, DA, Sx	PA, GH+ PRL+, Ki-67 2%	Yes	Yes (ACTH, TSH, GH, DI)	6	[3]
11 (XI)	F	Sporadic	Germline	36	3.5	↑↑ ↑	No	2.2	↑↑↑	24	SSA, DA, Sx, RT, DA, PEG-V	PA, GH+ PRL+	Yes	Yes (ACTH, TSH, LH)	12	[2,3,35]
12 (XII)	F	Sporadic	Germline	7	1.6	↑↑ ↑	NA	3.9	↑↑	>10	DA, Sx	PA, GH+ PRL+	Yes	Yes (ACTH, TSH, LH, GH, DI)	15	[1–3]
13 (S1)	M	Sporadic	Somatic	6	4.7	↑↑ ↑	No	4.4	↑↑↑	27	Sx, SSA, DA, PEG-V	PA, GH+ PRL+, Ki-67 3%	Yes	Yes (ACTH, TSH, DI)	7	[2]
14 (S2)	F	Sporadic	Germline	12	3.3	↑	ND	4.9	↑	15	Sx, DA, SSA, PEG—V, Sx, SSA	PA, GH+ PRL+, Ki-67 < 1%	Yes	Yes (TSH, DI)	18	[2]
15 (S3)	F	Sporadic	Germline	18	3.5	↑	No	2.4	↑↑	17	Sx, DA, SSA, GK	PA, GH+ PRL+	No	No	7.5	[2]
16 (S4)	F	Sporadic	Germline	2	1.9	↑↑	ND	5.2	↑↑	17 × 8 × 8	DA, SSA, Sx	PA, GH+ PRL+ with hyperplasia, Ki-67 5%	Yes	Yes (ACTH, TSH)	3.5	[2,6]
17 (S6)	F	Sporadic	Germline	6	3	↑↑ ↑	Paradoxical increase	3.1	↑↑	39	DA, Sx ×2, SSA, PEG-V	PA, GH+ PRL+, Ki-67 < 1%	Yes	Yes (DI)	6	[2]
18 (S7)	F	Sporadic	Germline	36	5.3	↑	NA	NA	NA	10	Sx, SSA, DA, RT, Sx, SSA	PA, GH+ FSH+, Ki-67 < 1%	Yes	Yes (TSH)	30	[2]
19 (S8)	F	Sporadic	Germline	11	2.8	↑↑ ↑	Paradoxical increase	3.3	↑	18	DA, Sx × 2, RT, SSA	Eosinophilic PA	No	No	8	[2]
20 (S9)	F	Sporadic	Germline	3	2.8	↑↑	No	3.4	↑↑	18	DA, Sx	Hyperplasia	Yes	Yes (ACTH, TSH, LH, GH, DI)	11	[2]
21 (S11)	M	Sporadic	Somatic	31	5.7	↑↑ ↑	No	4.4	↑↑	33 × 24 × 29	Sx, SSA, DA, PEG-V	PA, GH+ PRL+, Ki-67 3.5%	No	Yes (ACTH, TSH, LH, DI)	12	[2,5]
22 (S12)	F	Sporadic	Germline	10	4	↑	No	NA	↑	25	Sx, SSA, DA, RT, PEG-V	PA, GH+ PRL+	Yes	Yes (ACTH, TSH, LH)	35	[2]
23 (S13)	F	Sporadic	Germline	48	7.6	↑	Paradoxical increase	2.6	↑	17	SSA, DA, Sx	Hyperplasia	Yes	NA	8	[2]
24 (F1A)	F	Familial	Germline	12	2.6	↑↑	No	NA	↑↑	>10	Sx	Eosinophilic PA	Yes	Yes (ACTH, TSH, GH)	45	[2]
25 (F1B)	M	Familial	Germline	12	1.5	↑↑	No	3.3	↑↑↑	15	SSA, DA, Sx ×3	PA, GH+ PRL+ with hyperplasia	Yes	Yes (ACTH, TSH, GH)	18	[2]
26 (F1C)	M	Familial	Germline	14	1.2	↑	Paradoxical increase	1.9	↑	Diffuse enlargement	DA, Sx	PA (microadenoma), GH+ PRL+ with hyperplasia	Yes	Yes (ACTH, TSH)	13	[2]
27 (F2A)	M	Familial	Germline	48	8	↑	No	NA	↑	19	Sx	PA, GH+ PRL+	Yes	Yes (DI)	23	[2]
28 (F2B)	F	Familial	Germline	NA	22	↑	No	NA	↑	>10	Sx	PA, GH+ PRL+	Yes	Yes (ACTH, TSH, LH)	26	[2]