Lysine demethylase *KDM1A* and ectopic expression of GIP-receptor in somatotroph adenomas

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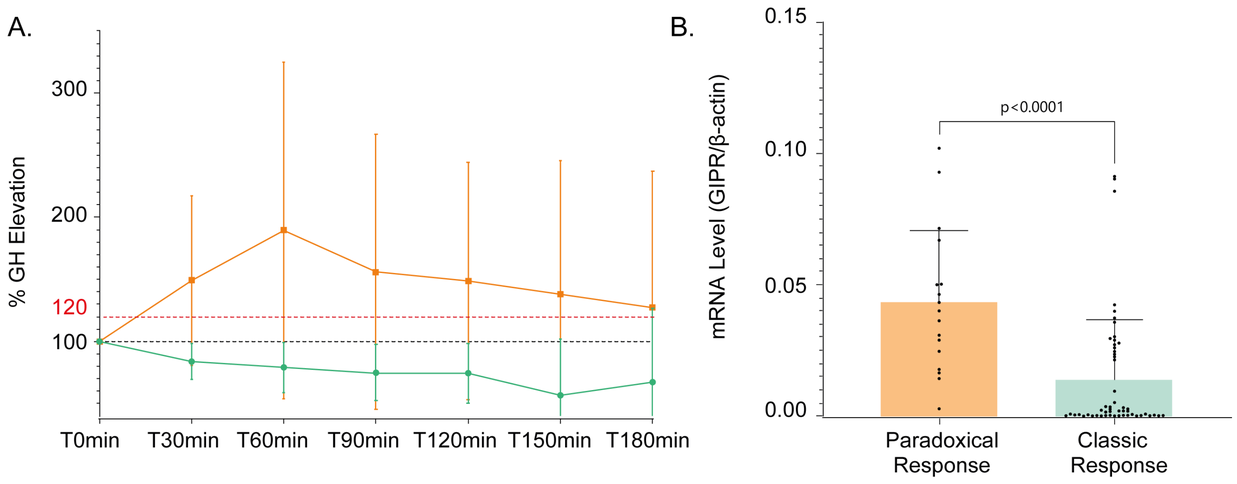
Context

Paradoxical increase of GH after oral glucose load has been described in around 10-30% of patients with acromegaly and is related to the ectopic pituitary expression of GIP-receptor (GIPR). We identified that Primary bilateral macronodular adrenal hyperplasia with GIP-dependent Cushing's syndrome and ectopic adrenal expression of GIPR is caused by germline pathogenic variant and loss of heterozygosity of *KDM1A*. The ectopic expression of GIPR in both adrenal and pituitary tissues suggests a common molecular mechanism, therefore, we aimed to identify the implication of KDM1A in the ectopic GIPR expression in somatotropinomas.

Figure 1: Characterization of GH response to oral glucose tolerance test (OGTT)
(A) mean ± SD of GH levels during OGTT in both group of patients. GH values after OGTT are expressed as a percentage of basal GH levels: patients with a normal response are shown in green (n=100, 67%) and patients paradoxical rise of GH are shown in orange (n=39, 26%). Data was not available for 11 patients (7%).
(B) Distribution of relative GIPR expression quantified in somatotropinomas samples obtained by qRT-PCR and normalized to the β-actin is displayed in both groups. Quantification of GIPR expression was available in 53 patients with a classical response and 17 patients with a paradoxical rise. Histograms represents mean ± SD.



Aim

Our aim was to identify if pathogenic variants and loss of heterozygosity of *KDM1A* was involved in the ectopic pituitary GIPR expression in patient with paradoxical rise of GH after OGTT in a large cohort of acromegaly patients.

Table 1: characteristics of patients with paradoxical rise of GH after OGTT
Abbreviations: DM, diabetes mellitus; IGT, impaired glucose tolerance test; ULN, upper limit of normal.

	Paradoxical Response of GH after OGTT n= 39 (26 %)	Normal Response of GH after OGTT n=100 (67 %)	P Value
Clinical parameters			
Age, y (Median, Percentile 25% - 75 %)	47 [36; 55]	44 [33; 52]	0.23
Male, n (%)	22 (56)	51 (51)	0.58
Preoperative medical treatment, n (%)	12/36 (33)	30/93 (32)	>0.99
Residual tumor after surgery, n (%)	11/20 (55)	23/66 (35)	0.12
Gigantism	0	3	0.56
Biological parameters			
IGF-1 % ULN, (mean ± SD)	**370 ± 112 %**	**313 ± 110 %**	**0.01**
IGT-DM, n (%)	3-4/23(13-17)	3-13/71/12 (4/18)	0.32
Prolactine, µg/l (mean SD)	16 ± 17	33 ± 105	0.32
Radiological parameters			
Invasive Tumor, n (%)	10/23 (43)	41/64 (64)	0.14
Maximum tumor diameter at diagnosis, mm (Mean ± SD)	**15 ± 6**	**18 ± 9**	**0.03**
Macroadenoma, n (%)	30/37 (81)	84/94 (89)	0.25
Histological parameters			
Mixed or plurihormonal tumor, n (%)	12/38 (32)	45/92 (49)	0.07
Ki67 (mean %)	2-3%	3 %	0.06

Figure 2: Mutational landscape and array CGH analysis from 150 somatotropinomas. *Samples are displayed in column and each row represents an event. First line show both groups: in orange patients with a paradoxical rise and in grey patients without available data. Lines 2 and 3 represent arrayCGH results on the short arm of the chromosome 1 and the KDM1A locus: red are deletions and blue are duplications. GNAS activating variants are displayed in green. AIP pathogenic variants are displayed in pink. Other genetic variants are displayed according to their ACMG classification: light orange represents VUS and red represents pathogenic variants.*

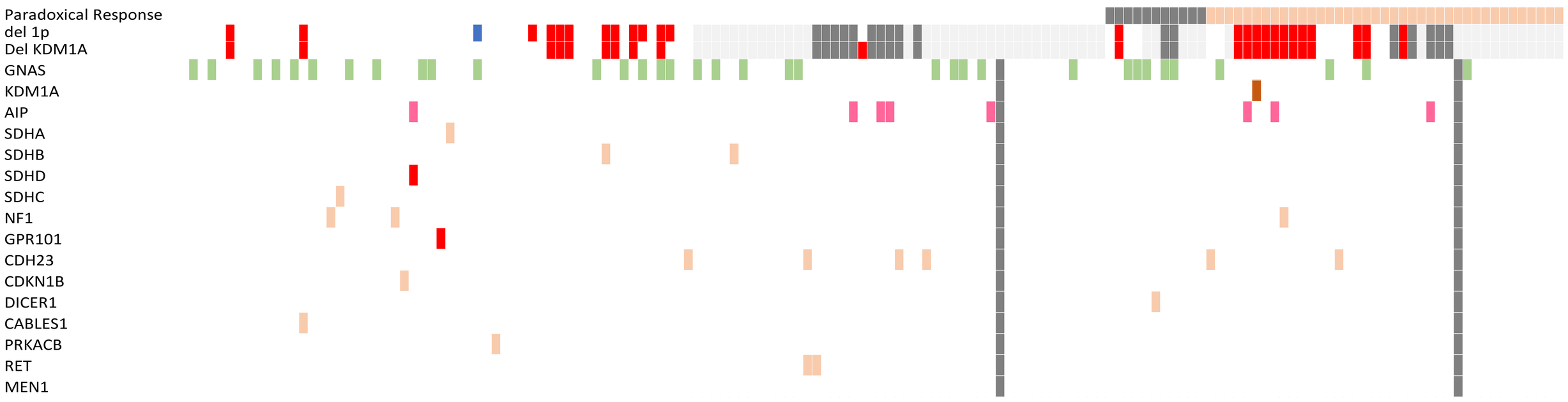
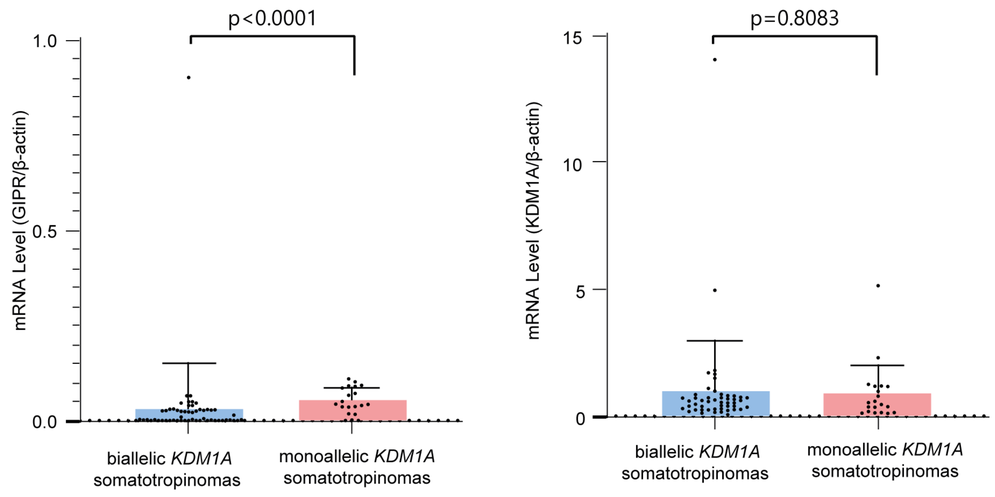


Figure 4: *Quantification of GIPR and KDM1A expression was available in 50 patients with both KDM1A alleles and in 20 patients with a monoallelic KDM1A profile in their somatotropinomas. Histograms represents mean ± SD.*



Conclusion

We did not identify somatic KDM1A pathogenic variants in somatotropinomas with ectopic GIPR expression, however, the recurrent chromosome loss of the locus of *KDM1A* in some somatotropinomas suggests that KDM1A haploinsufficiency may contribute to GIPR expression in those tumors by partially derepressing transcription of targeted genes including GIPR.