Pituitary (2026) 29:114
https://doi.org/10.1007/s11102-026-01714-5

ORIGINAL PAPER

GH responsiveness to corticotropin-releasing hormone identifies corticotroph-like somatotroph adenomas in acromegaly

Hirotaka Itoh[1] · Kosuke Mukai[1] · Yuto Mitsui[1] · Toru Umehara[2] · Noriyuki Kijima[2] · Satoru Oshino[2] · Masaharu Kohara[3] · Eiichi Morii[3] · Atsunori Fukuhara[1,4] · Iichiro Shimomura[1]

Received: 20 April 2026 / Accepted: 10 June 2026

Abstract

Purpose Corticotropin-releasing hormone (CRH) induces an increase in growth hormone (GH) secretion in a subset of patients with acromegaly; however, the characteristics of these CRH responders remain poorly defined.

Methods 22 CRH responders were retrospectively compared with 43 nonresponders.

Results CRH responders exhibited significantly larger tumors and more frequent visual field impairment than nonresponders, despite comparable baseline GH and insulin-like growth factor 1 (IGF-1) levels, and disease duration. Tumor volume and diameter were positively correlated with the GH increase ratio in CRH test, whereas GH and IGF-1 per tumor volume or diameter were significantly lower in CRH responders, indicating reduced GH secretory capacity relative to tumor size. Immunohistochemical analyses revealed higher corticotropin-releasing hormone receptor 1 (CRHR1) and lower CRHR2 expression in CRH responders. In addition, T-box transcription factor (TPIT) and adrenocorticotropic hormone (ACTH) expression were significantly more frequent in adenomas from CRH responders, suggesting a corticotroph-like phenotype. GH responses to CRH were significantly correlated with those to luteinizing hormone–releasing hormone but not thyrotropin-releasing hormone or oral glucose tolerance testing. GH responses to CRH tended to be inversely correlated with somatostatin receptor subtype 2 expression as a predictor of first-generation somatostatin receptor ligand efficacy but not with octreotide response or MRI signal intensity.

Conclusions These findings support that GH responsiveness to CRH identifies a biologically distinct subset of somatotroph adenomas characterized by corticotroph-like features, larger tumor size, and reduced GH secretory capacity. GH responsiveness to CRH may serve as a noninvasive indicator of intrinsic tumor biology and behavior.

Keywords Acromegaly · Corticotropin-releasing hormone · Somatotroph · Pituitary adenoma · TPIT · Adrenocorticotropic hormone

Introduction

We have reported the clinical characteristics in acromegaly with an increased growth hormone (GH) response to the oral glucose tolerance test (OGTT), thyrotropin-releasing hormone (TRH) or luteinizing hormone–releasing hormone (LHRH) [1–3]. Furthermore, other groups have demonstrated similar results regarding the response to OGTT [4–6]. Corticotropin-releasing hormone (CRH) induces an increased GH response in some patients with acromegaly (CRH responders) [7]. However, the clinical characteristics of CRH responders have not been examined before.

CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) from corticotrophs in the normal pituitary gland. Pituitary adenomas in CRH responders may exhibit

✉ Kosuke Mukai
mukai@endmet.med.osaka-u.ac.jp

1 Department of Metabolic Medicine, The University of Osaka Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

2 Department of Neurosurgery, The University of Osaka Graduate School of Medicine, Osaka, Japan

3 Department of Pathology, The University of Osaka Graduate School of Medicine, Osaka, Japan

4 Department of Biomedical Informatics, The University of Osaka Graduate School of Medicine, Osaka, Japan

Published online: 01 July 2026

both somatotroph and corticotroph phenotypes (corticotropin-releasing hormone receptor [CRHR], ACTH, and T-box transcription factor [TPIT, a corticotroph transcription factor] expression) despite acromegaly because CRH can stimulate GH secretion from the pituitary adenoma in these patients. The increased GH responsiveness to LHRH is also associated with both somatotroph and gonadotroph phenotypes (gonadotropin-releasing hormone receptor [GnRHR], LH, and Steroidogenic factor 1 [SF1, a gonadotroph transcription factor] expression) [3]. The World Health Organization (WHO) reclassified pituitary adenomas according to their transcription factors in 2022 [8]. Pituitary adenomas coexpressing PIT1 and TPIT would be classified as plurihormonal adenomas. However, the clinical and biological characteristics of these adenomas have not been fully elucidated.

In the present study, we investigated the clinical and pathological characteristics of CRH responders, including TPIT, CRHR, and ACTH expression.

Subjects and methods

Subjects

We conducted a retrospective review of patients with acromegaly admitted to the University of Osaka Hospital from April 2004 through July 2025, including patients previously reported in prior studies [1–3]. A total of 65 individuals comprised the study cohort. Patients who had received any treatment before undergoing the oral glucose tolerance test (OGTT), thyrotropin-releasing hormone (TRH) test, luteinizing hormone–releasing hormone (LHRH) test, corticotropin-releasing hormone (CRH) test, bromocriptine test, or octreotide test were excluded from the analysis. The diagnosis of acromegaly was established based on a combination of clinical features, failure of GH suppression below 0.4 ng/mL in a 75-g OGTT, elevated insulin-like growth factor 1 (IGF-1) levels above the upper normal limit, and the presence of a pituitary tumor on magnetic resonance imaging (MRI) [9, 10]. The cohort comprised 28 men and 37 women with a median age of 53 years (interquartile range [IQR], 40.5–60 years). The study protocol was approved by the institutional ethics committee of the University of Osaka (approval No. 24451) and was performed in compliance with the Declaration of Helsinki.

Endocrinological evaluation

Baseline fasting serum levels of GH, IGF-1, adrenocorticotropic hormone (ACTH) and cortisol were measured prior to any medical therapy or surgical intervention for acromegaly. Given that physiological variations in GH levels can reach up to 30% [11], we defined CRH responders as individuals exhibiting a GH increase of 30% or more. Additionally, an increase in GH response to the 75-g OGTT and 0.1 mg LHRH was defined as an increase of more than 30% over baseline [1, 3].

An increase in GH response to 0.5 mg TRH was defined as a $\geq$ 100% increase from baseline, as previously described [2]. Responses to medical agents were also assessed: after administration of 2.5 mg oral bromocriptine or 50 µg subcutaneous octreotide, serial GH levels were measured at 1, 2, 4, 6, 8, 12, and 24 h, and the percentage change from baseline to nadir was calculated. The OGTT, TRH test, LHRH test, CRH test, bromocriptine test, and octreotide test were performed in 65 patients, except for the LHRH test, which was conducted in 64 patients.

Serum GH concentrations were determined using an immunoradiometric assay kit (GH kit Daiichi; Daiichi Radioisotope Laboratories, Tokyo, Japan) up to April 2007, a chemiluminescent enzyme immunoassay kit (Access hGH kit; Beckman Coulter, Tokyo, Japan) from May 2007 to April 2017, and an electrochemiluminescence immunoassay kit (ECLusys hGH; Roche Diagnostics, Tokyo, Japan) thereafter until the end of the study. To ensure consistency among measurement systems, the results obtained by the first and second assays were standardized to those from the third method using the linear regression–derived equation: $y = 1.4x$ (y: converted value, x: measured value using the first or second kit). GH levels measured using the third assay kit were used directly without any adjustment. Serum IGF-1 concentrations were measured using an immunoradiometric assay kit (Daiichi Radioisotope Laboratories) until October 2019, and subsequently with an electrochemiluminescence immunoassay kit (ECLusys IGF-1; Roche Diagnostics, Tokyo, Japan) through the study period. The IGF-1 standard deviation score (IGF-1 SD score) was calculated according to standardized centile curves and reference ranges established for healthy Japanese individuals [12]. To assess GH secretory capacity relative to tumor size, GH and IGF-1 levels were divided by tumor volume or maximum tumor diameter and expressed as secretion indices (GH/tumor volume, IGF-1/tumor volume, GH/tumor diameter, and IGF-1/tumor diameter). Postoperative biochemical remission and biochemical control were defined as normalization of IGF-1 levels within the age- and sex-adjusted reference range after surgery, together with GH levels of < 0.4 ng/mL and < 1.0 ng/mL, respectively, based on either the nadir GH during an OGTT or a random GH measurement [9, 10].

Immunohistochemical evaluation

Pathological analyses were performed for 22 CRH responders and 39 nonresponders. One patient who underwent pituitary surgery at another institution and three patients who did not undergo pituitary surgery after the CRH test were excluded. Surgical specimens for histopathological evaluation were available from 61 patients who underwent surgery at our institution, including 20 who had received preoperative SRL therapy and one who had received preoperative cabergoline monotherapy. Tissue sections were immunostained according to validated protocols using antibodies against T-box transcription factor (TPIT), CRHR1, CRHR2, ACTH, cytokeratin (CAM5.2), and somatostatin receptor subtypes 2 (SSTR2) and 5 (SSTR5). Immunohistochemical studies were performed using the DAKO Autostainer Link 48 system (EnVision FLEX Mini kit, High pH, K8023; Dako A/S, Glostrup, Denmark). The sections were incubated with anti-TBX19 (Invitrogen Mouse# MA5-31431, RRID: AB_2787067), anti-ACTH (Agilent Technologies mouse# M3501, RRID: AB_2166039), anti-CRHR1 (LifeSpan Biosciences Rabbit# LS-A6687, RRID: AB_591128), anti-CRHR2 (Sigma-Aldrich Rabbit# ABN433, RRID: AB_2814852), anti-cytokeratin (BD Biosciences Cat# 349205, RRID: AB_2134314), anti-SSTR2A (Abcam Cat# ab134152, RRID: AB_2737601), and anti-SSTR5A (Abcam Cat# ab109495, RRID: AB_10859946). For double immunohistochemical staining, sections were first incubated with an anti-GH primary antibody (Santa Cruz Biotechnology, Mouse monoclonal, Cat# sc-374266, RRID: AB_10989917), and immunoreactivity was visualized using DAB. The primary antibody was then removed using VectorPlex Antibody Removal Reagent (Vector Laboratories, Cat# VRK-1000), followed by incubation with an anti-TPIT primary antibody. The transcription factor TPIT immunoreactivity was subsequently visualized using the DISCOVERY Purple Kit (Roche Diagnostics, Cat# 760 − 229). TPIT was considered positive when 10% or more of the cell nuclei exhibited staining as previously described [13]. Similarly, ACTH expression was defined as positive when staining was observed in 10% or more of the cell cytoplasm. We evaluated the cytoplasmic cytokeratin distribution pattern and the expression of somatostatin receptor subtype 2 (SSTR2) as potential predictive factors for the efficacy of first-generation somatostatin receptor ligand (fg-SRL) [14]. Cytokeratin staining patterns were classified as densely granulated (DG), sparsely granulated (SG), or intermediate (IM) phenotypes as previously described [15]. The expression levels of SSTR2, SSTR5, CRHR1, and CRHR2 were assessed using the standardized immunoreactive score (IRS) system, which integrates staining intensity and the proportion of immunopositive cells to yield a total score ranging from 0 to 12, as previously described [16, 17].

Evaluation of pituitary tumors on magnetic resonance imaging (MRI)

Preoperative tumor size was measured by MRI. Tumor volume was measured using radiotherapy treatment planning support software SYNAPSE Radiotherapy (FUJIFILM Corporation). The T2-weighted MRI signal intensity of each tumor was evaluated as a potential predictive factor for the efficacy of fg-SRL therapy [14]. In accordance with a previous report [18], T2-weighted hypointensity was defined as a signal intensity lower than that of the white matter, whereas hyperintensity was defined as a signal intensity higher than that of the gray matter. Isointensity was defined as a signal intensity greater than that of the white matter but lower than that of the gray matter. Additionally, basal level of GH and IGF-1 per tumor size was evaluated as GH secretory capacity per tumor volume.

Statistical analysis

Continuous variables are expressed as the median and IQR (first and third quartiles), while categorical variables are presented as frequencies and percentages. Between-group comparisons were performed using the Wilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data. Associations between continuous variables were explored via Pearson correlation coefficient. A two-sided P value < 0.05 was deemed statistically significant. Statistical computations were conducted using JMP Student Edition 19.1.1 (SAS Institute, Cary, NC).

Results

Clinical characteristics of CRH responders and nonresponders

The clinical characteristics of CRH responders ($n = 22$) and nonresponders ($n = 43$) are summarized in Table 1. No significant differences were observed between the two groups regarding age, sex, body mass index, or disease duration. Endocrinological parameters, including baseline GH, IGF-1, cortisol, and DHEA-S, also showed no significant differences between groups, although ACTH levels tended to be lower in CRH responders [32.0 pg/mL (IQR, 24.0–48.0) vs. 22.5 pg/mL (IQR, 17.0-43.8), $p = .07$]. Peak ACTH levels following CRH administration were similar between CRH responders and nonresponders [80.5 pg/mL (IQR, 55.0–129.3) vs. 83.0 pg/mL (IQR, 61.0–120.0), $p = .95$]. Among

Table 1 Clinical characteristics of CRH nonresponders and responders

	CRH nonresponder	CRH responder	*p* value
Patients	43 (66.2)	22 (33.8)	
Sex			
Male/Female	22 (51.2)/21 (48.8)	6 (27.3)/16 (72.7)	0.11
Age (years)	53.0 (39.0–62.0)	51.0 (42.0–60.0)	0.72
Body mass index (kg/m^2)	24.2 (22.4–27.8)	23.4 (20.7–25.4)	0.12
Disease duration (years)	7.5 (5.0–19.8)	9.0 (6.0–12.5)	0.69
Endocrinological data			
GH (ng/mL)	12.7 (4.22–38.5)	9.14 (4.09–13.1)	0.11
IGF-1 (ng/mL)	542 (345–916)	485 (294–601)	0.18
IGF-1 SD score	6.00 (4.70–9.60)	5.20 (3.58–7.10)	0.14
Basal ACTH (pg/mL)	32.0 (24.0–48.0)	22.5 (17.0–43.8)	0.07
Basal cortisol (μg/dL)	10.0 (7.80–13.2)	8.10 (6.45–10.5)	0.18
Basal DHEA-S[a] (μg/dL)	134.6 (73.15–266.9)	117.3 (90.3–226.5)	0.95
Peak ACTH in CRH test	83.0 (61–120)	80.5 (55.0–129.3)	0.95
Complications			
Central hypothyroidism[b]	23 (54.8)/19 (45.2)	11 (50.0)/11 (50.0)	0.79
Central adrenal insufficiency	23 (53.5)/20 (46.5)	14 (63.6)/8 (36.4)	0.60
Central hypogonadism[c]	25 (62.5)/15 (37.5)	9 (40.9)/13 (59.1)	0.12
Postoperative biochemical remission	20 (51.3)/19 (48.7)	11 (50)/11 (50)	1.00

Data presented as number of patients, median (IQR) or n/N (%)

[a]Data were available in 37 nonresponders and 18 responders

[b]Data were available in 42 nonresponders and 22 responders

[c]Data were available in 40 nonresponders and 22 responders

the complications, there were no significant differences between the two groups in other complications, including hypertension, dyslipidemia, central hypothyroidism, central adrenal insufficiency, and central hypogonadism. Postoperative biochemical remission and biochemical control did not differ significantly between the two groups (51.3% vs. 50.0%, $p = 1.00$, and 59.0% vs. 63.6%, $p = .79$, respectively).

Pathological findings of corticotroph-like phenotype

CRH responders showed higher CRH receptor 1 (CRHR1) expression immunoreactive score (IRS) [2 (IQR, 0–4) vs. 4 (IQR, 3–6), $p < .001$; Fig. 1a] and lower CRHR2 expression IRS [2 (IQR, 0–4) vs. 0 (IQR, 0–2), $p < .01$; Fig. 1b]. CRHR1 expression showed a positive correlation with the GH increase ratio, while CRHR2 expression showed a negative correlation ($r = .34$, $p < .01$; and $r = -.27$, $p < .05$, respectively; Fig. 1c, d). Immunohistochemical analysis revealed significantly higher proportion of patients with TPIT and ACTH expression in CRH responders compared to nonresponders (Fig. 1e, f; TPIT, 50.0% vs. 10.3%, $p < .001$; ACTH, 72.7% vs. 25.6%, $p < .001$). Representative immunohistochemistry of pituitary adenomas in acromegaly patients is shown in Supplementary Fig. 1. Double immunostaining for GH and TPIT demonstrated regions with concomitant expression of both TPIT and GH, as well as areas with TPIT positivity alone within the same tumor.

Association of GH responsiveness to CRH with pituitary tumor progression

CRH responders tended to have larger tumor diameters [tumor diameter: 18.9 mm (IQR, 12.4–25.3) vs. 13.2 mm (IQR, 10.1–17.5), $p = .06$; figure not shown]. Furthermore, the tumor volume of CRH responders was significantly larger than that of nonresponders [tumor volume: 2.41 cm³ (IQR, 0.75–6.62) vs. 0.81 cm³ (IQR, 0.28–1.86), $p < .01$; Fig. 2a]. Additionally, a significant positive correlation was observed between the GH increase ratio following CRH administration and tumor diameter, as well as between the GH increase ratio and tumor volume (tumor diameter: $r = .32$, $p < .05$; figure not shown; tumor volume: $r = .32$, $p < .001$; Fig. 2b). Visual field impairment was observed more frequently in CRH responders compared to nonresponders [4/22 (18.2%) vs. 1/43 (2.3%), $p = .04$; Fig. 2c]. There was also a trend toward a higher prevalence of Knosp grade 3–4 in the responder group [6/22 (27.3%) vs. 4/43 (9.3%), $p = .08$; Fig. 2d]. No significant difference was observed in the Ki-67 labeling index (Fig. 2e).

Association of GH responsiveness to CRH with GH secretory capacity per tumor size

GH/tumor volume and IGF-1/tumor volume were also significantly lower in CRH responders than in nonresponders [6.27 (IQR, 1.26–10.9) vs. 18.2 (IQR, 8.30–39.1), $p < .001$; and 233.2 (IQR, 41.0–778.1) vs. 536.2 (IQR, 314.2–1324.4), $p < .005$; Fig. 3a and b, respectively]. Both indices showed strong negative correlations with the GH increase ratio ($r = .62$, $p < .001$; and $r = -.48$, $p < .001$; Fig. 3c and d). Similarly, GH/tumor diameter and IGF-1/tumor diameter were significantly lower in CRH responders than in nonresponders [0.39 (IQR, 0.27–0.89) vs. 1.01 (IQR, 0.39–2.27), $p < .01$; and 29.1 (IQR, 10.4–43.8) vs. 37.9 (IQR, 23.8–55.5), $p < .05$, respectively]. Both indices were significantly and

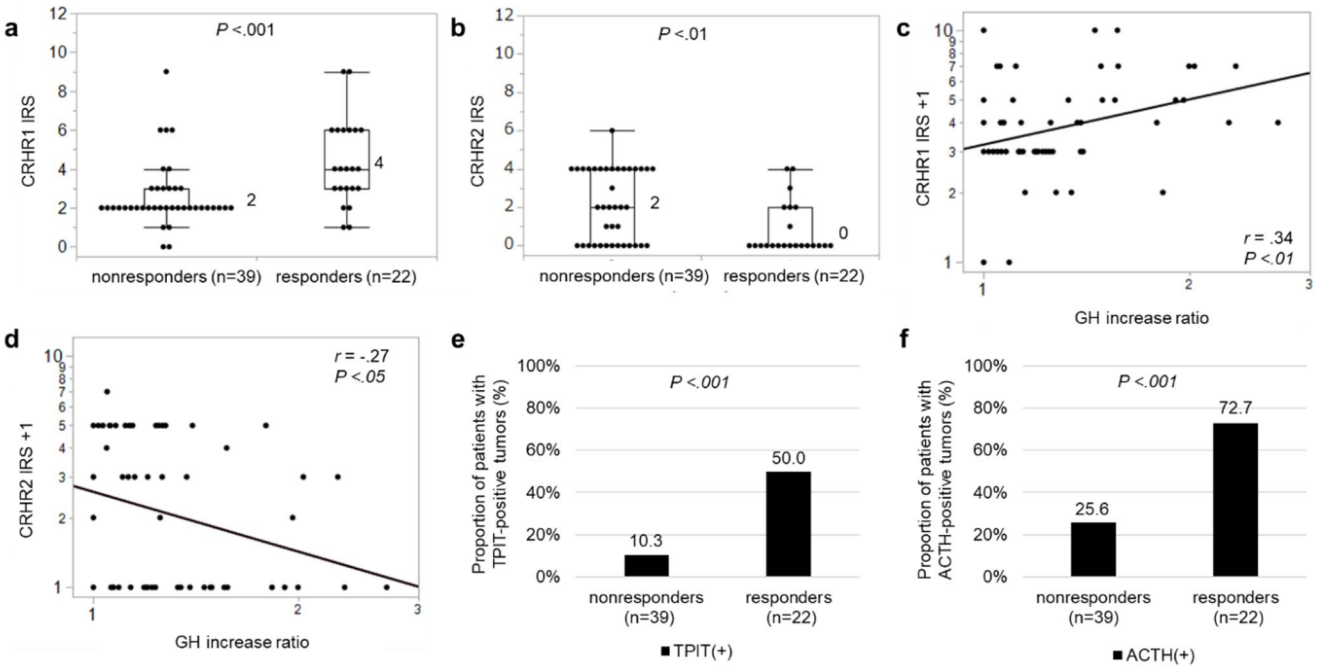

Fig. 1 Association between GH responsiveness to CRH and corticotroph-like features. (**a**),(**b**) CRH receptor (CRHR) immunoreactive score (IRS) in CRH nonresponders and responders; (**a**) CRHR1 and (**b**) CRHR2. Data are presented as box plots for individual patients. (**c**),(**d**) Correlations between GH increase ratio in CRH test and CRHR IRS in all patients, including CRH nonresponders ($n=39$) and responders ($n=22$); (**c**) CRHR1 and (**d**) CRHR2. (**e**),(**f**) TPIT and ACTH expression in CRH nonresponders and responders; (**e**) TPIT and (**f**) ACTH

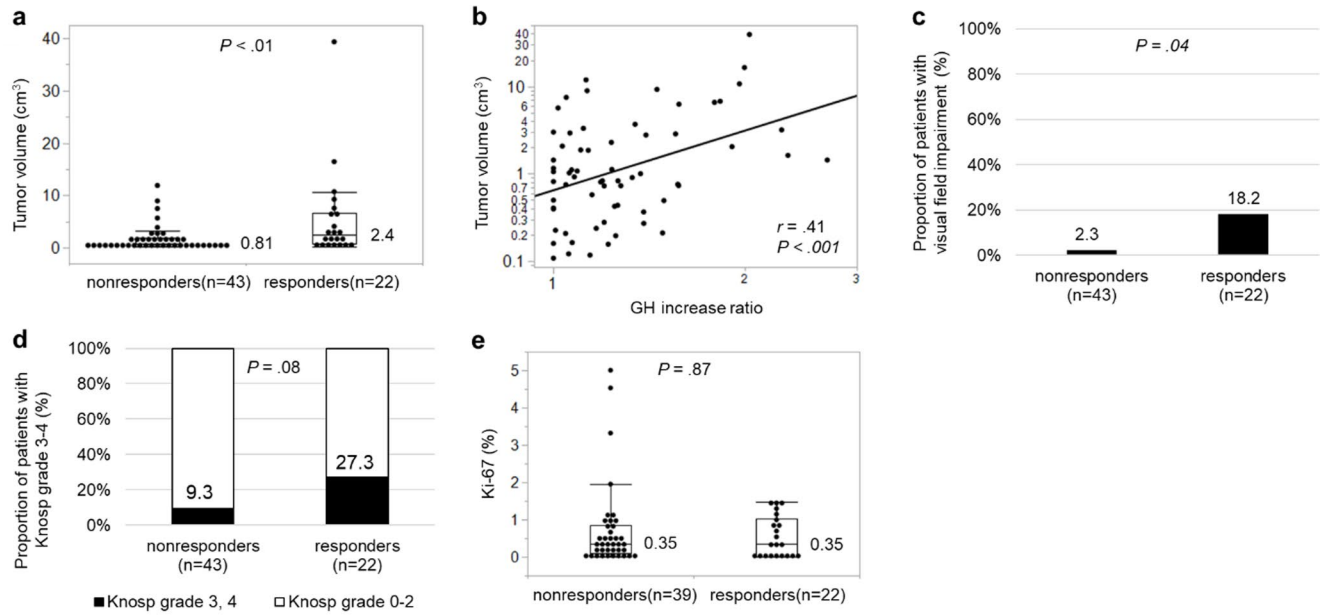

Fig. 2 Association between GH responsiveness to CRH and pituitary tumor progression. **(a)**, **(c)**, **(d)**, **(e)** Pituitary tumor progression parameters in CRH nonresponders and responders; **(a)** tumor volume, **(c)** visual field impairment, **(d)** Knosp grade, and **(e)** Ki-67 index. **(b)** Correlation between GH increase ratio in CRH test and pituitary tumor volume in all patients, including CRH nonresponders ($n=43$) and responders ($n=22$)

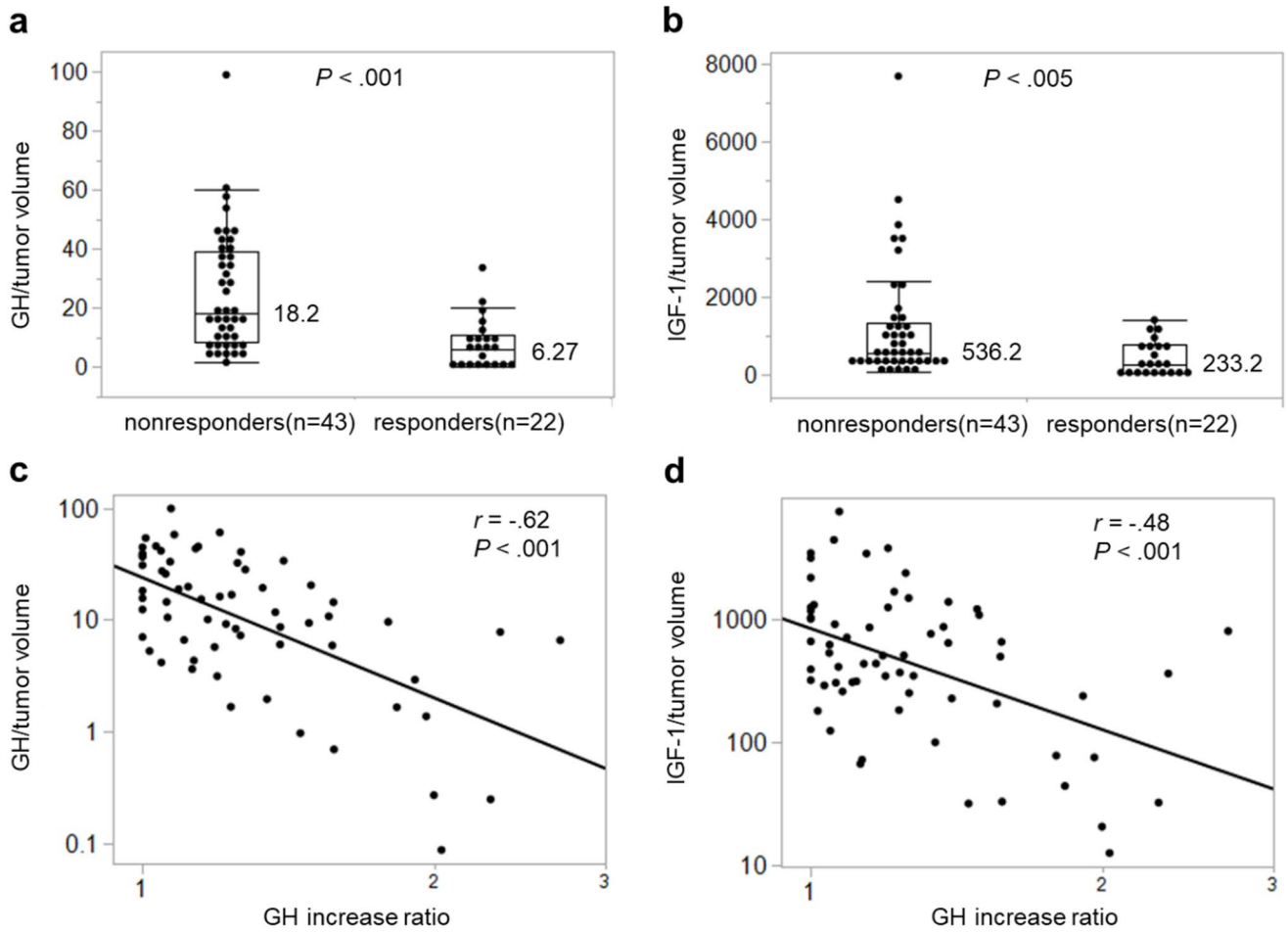

Fig. 3 Association between GH responsiveness to CRH and GH secretory capacity per tumor volume. **(a)**, **(b)** GH secretory capacity per tumor volume in CRH nonresponders and responders; **(a)** GH/tumor volume and **(b)** IGF-1/tumor volume. **(c)**, **(d)** Correlations between the GH increase ratio in CRH test and GH secretory capacity per tumor volume; **(c)** GH/tumor volume and **(d)** IGF-1/tumor volume

negatively correlated with the GH increase ratio in response to CRH ($r = –.42$, $p < .001$; and $r = –.38$, $p < .005$; figure not shown).

Relationship between GH responsiveness to CRH and those in other endocrinological tests

The GH response to CRH stimulation was significantly correlated with the GH response to the LHRH stimulation test ($n=64$, $r=.41$, $p < .001$; Fig. 4a). In contrast, no significant correlations were observed between the GH response to CRH and responses to either the TRH stimulation test ($n=65$, $r = –.14$, $p=.26$; Fig. 4b) or the OGTT ($n=65$, $r=.10$, $p=.42$; Fig. 4c).

Association of GH responsiveness to CRH with predictors of medical therapy response

There were no significant differences in GH suppression following administration of octreotide (Suppl Fig. 2a) or bromocriptine (Suppl Fig. 2b) between CRH responders and nonresponders. A trend toward a negative correlation was observed between SSTR2 expression and the GH increase ratio in the CRH stimulation test ($r = –.24$, $p=.06$; Suppl Fig. 2c), whereas no significant correlation was found between the GH increase ratio and SSTR5 expression ($r=.14$, $p=.27$; Suppl Fig. 2 d). There were no significant differences in MRI signal intensity or cytoplasmic cytokeratin distribution pattern between CRH responders and nonresponders (Suppl Fig. 2e, f).

Discussion

In the present study, we demonstrated that CRH responders exhibited significantly higher CRHR1 expression in pituitary tumors than CRH nonresponders. In addition, TPIT and ACTH expression were more frequently observed in tumors from CRH responders. Collectively, these findings

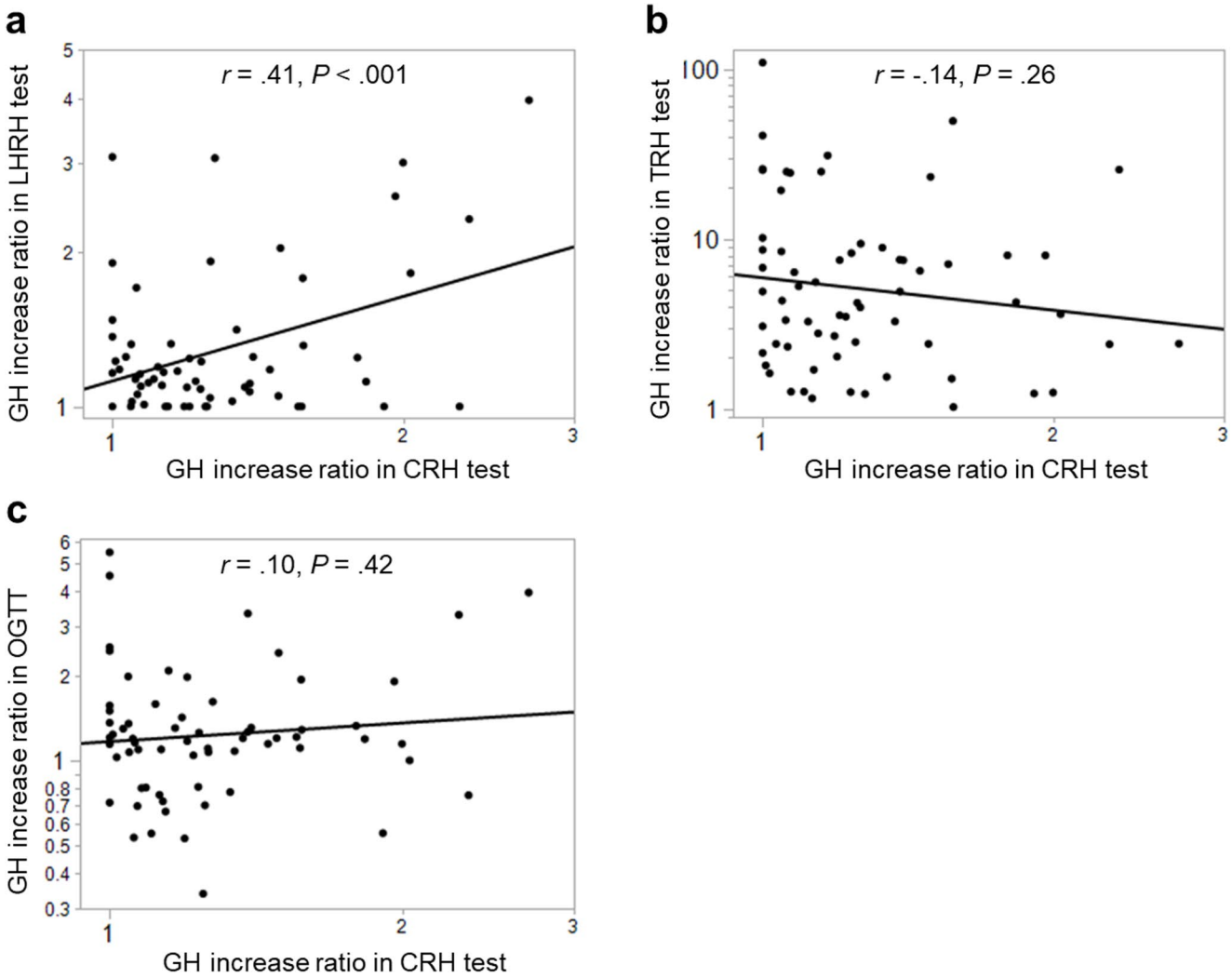

Fig. 4 Correlation between GH increase ratio in the CRH test and those in other endocrinological tests; **(a)** LHRH test ($n=64$), **(b)** TRH test ($n=65$), and **(c)** OGTT ($n=65$)

suggest that somatotroph tumors in CRH responders possess a corticotroph-like phenotype. Furthermore, CRH responders showed significantly larger tumor volumes and lower GH per tumor volume compared with nonresponders, indicating distinctive biological characteristics.

CRH responders displayed both higher GH responsiveness to CRH and increased CRHR1 expression. GH responsiveness to CRH in CRH responders could be attributed to the pituitary adenoma rather than to normal somatotroph cells, because CRH does not stimulate GH secretion in healthy individuals [19]. A previous study demonstrated that CRH directly activated PKC in somatotroph tumors from CRH responders [20]. With respect to CRH receptors, CRH preferentially binds to CRHR1 and stimulates ACTH secretion via CRHR1 signaling in corticotrophs, but not via CRHR2 signaling [21]. Therefore, GH responsiveness to CRH in CRH responders may be mediated by CRHR1 signaling, reflecting the coexistence of somatotroph and corticotroph-like features in these adenomas.

Although somatotroph adenomas are classically defined by PIT1 expression according to the 2022 WHO classification [8], acromegaly is increasingly recognized as a heterogeneous disease that includes adenomas with atypical lineage characteristics, such as PIT1/SF1 coexpression [22–24]. In this context, the TPIT and ACTH expression observed in CRH responders suggests that these adenomas may not be fully encompassed within the conventional PIT1-lineage somatotroph category but instead may represent a clinically relevant biological subset characterized by corticotroph-like differentiation, potentially reflecting lineage plasticity. Additionally, the heterogeneous staining pattern of GH and TPIT observed on double immunostaining may suggest heterogeneity in lineage plasticity within the same tumor.

Our results further revealed that CRH responders had significantly larger tumor volumes and more visual field impairments. In contrast, previous reports demonstrated that TRH responders [2, 6] and OGTT responders tend to have smaller tumor sizes [6]. The larger tumor volume in CRH responders may reflect enhanced proliferative potential, although no significant difference in Ki-67 labeling index was observed. Therefore, the tumor size should be carefully monitored. Interestingly, CRHR1 activation in gastrointestinal malignancies has been associated with tumor growth, whereas CRHR2 signaling is linked to suppression of tumor progression [25–28]. Thus, the combination of higher CRHR1 and lower CRHR2 expression observed in CRH responders may contribute to their larger tumor size.

Another possible explanation for the larger tumor size in CRH responders is their lower GH secretory capacity per tumor volume. Small tumors with low GH secretory capacity per tumor volume may fail to generate sufficient total GH excess to cause marked IGF-1 elevation or overt acromegalic features, thereby delaying clinical recognition. As tumor size increases, total GH secretion may eventually become sufficient to elevate IGF-1 levels and reveal the disease. This may account for the larger tumor size in CRH responders despite similar disease duration and IGF-1 levels compared with nonresponders. Supporting this interpretation, silent corticotroph adenomas—characterized by clinically silent ACTH production—have been reported to exhibit larger tumor sizes than functioning corticotroph adenomas [29]. This observation suggests that an incomplete or attenuated secretory phenotype may represent a shared mechanism underlying larger tumor size across distinct pituitary adenoma subtypes.

The lower GH secretory capacity observed in CRH responders may reflect a phenotype that is less closely related to the somatotroph lineage, as corticotrophs do not arise from PIT1 lineage progenitors. The aberrant co-activation of TPIT in these tumors may thus interfere with PIT1-driven somatotroph differentiation, resulting in the lower GH secretory capacity per tumor volume observed in CRH responders. In contrast, higher GH secretory capacity per tumor volume has been reported in TRH responders [2] and OGTT responders [4]. TRH is physiologically associated with thyrotrophs and lactotrophs, both of which, together with somatotrophs, arise from PIT1 lineage progenitors. This developmental relationship may partly account for the higher GH secretory capacity observed in TRH responders. Furthermore, paradoxical GH responsiveness during OGTT is specific to somatotrophs, suggesting that OGTT responders may retain a stronger somatotroph phenotype. Consistent with this interpretation, GH responses to CRH were not correlated with those to TRH or OGTT, whereas GH responses to CRH and LHRH were significantly correlated.

Regarding therapeutic implications, CRH responsiveness was not associated with predictors of fg-SRL efficacy, including octreotide responsiveness or MRI signal intensity. Notably, SSTR2 IRS, which is generally associated with favorable responses to fg-SRL therapy, tended to show an inverse correlation with the GH response to CRH. Furthermore, GH responsiveness to CRH was not associated with GH suppression in the acute bromocriptine test (a surrogate marker for dopamine agonist responsiveness) or SSTR5 expression (related to pasireotide response). These findings suggest that GH responsiveness to CRH does not directly predict responsiveness to currently available medical therapies for acromegaly.

Several limitations of this study should be acknowledged. First, its retrospective design limits causal inference, and prospective studies are required for validation. Second, although baseline clinical characteristics were comparable between groups, the sample size was relatively small due to the rarity of acromegaly. Furthermore, autonomous ACTH secretion in CRH responders could not be evaluated using the dexamethasone suppression test because of the retrospective nature of the study, although basal ACTH and cortisol levels, as well as peak ACTH levels during the CRH test, did not differ between CRH responders and nonresponders. Larger and multicenter studies will be necessary to confirm the clinicopathological significance of CRH responsiveness.

In conclusion, the present study demonstrates that increased GH responsiveness to CRH in acromegaly is associated with a corticotroph-like adenoma phenotype, larger tumor size, and reduced GH per tumor volume. Although the CRH test has limited utility in the diagnosis of acromegaly, GH responsiveness to CRH may serve as a noninvasive biomarker of intrinsic tumor biology and behavior.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11102-026-01714-5.

Acknowledgements The authors are grateful to the Center for Medical Research and Education, Graduate School of Medicine, the University of Osaka, for providing access to its equipment.

Author contributions Conceptualization: H.I. and K.M.; Data curation: H.I, K.M., and Y.M.; Formal analysis: H.I.; Funding acquisition: K.M.; Investigation: H.I., K.M., and M.K.; Methodology: M.K.; Project administration: K.M.; Resources: S.O., K.M., N.K., T.U., and E.M.; Supervision: I.S. and A.F.; Writing – original draft: H.I., K.M., A.F., and I.S.; Writing – review and editing: All authors.

Funding Open Access funding provided by The University of Osaka. This work was supported by the Japan Society for the Promotion of Science (KAKENHI grant number 24K18397); the Ministry of Health, Labour and Welfare FC Program (grant number JPMH26FC1041); and the Foundation for Growth Science (Research of Nordiscience).

Data availability Some or all datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval This study was approved by the Ethics Committee of the University of Osaka (Approval No. 24451) and conducted in accordance with the Declaration of Helsinki.

Consent The requirement for written informed consent was waived by the Ethics Committee of the University of Osaka because of the retrospective nature of the study. Information regarding the present study was published on the department website to provide patients with an opportunity to opt out.

Competing interests The authors declare no competing interests.

References

1. Mukai K, Otsuki M, Tamada D, Kitamura T, Hayashi R, Saiki A, Goto Y, Arita H, Oshino S, Morii E, Saitoh Y, Shimomura I (2019) Clinical characteristics of acromegalic patients with paradoxical GH response to oral glucose load. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2018-00975
2. Arita H, Kinoshita M, Oshino S, Kitamura T, Otsuki M, Kasayama S, Shimokawa T, Shimomura I, Yoshimine T, Saitoh Y (2012) Biological characteristics of growth hormone-producing pituitary adenomas are different according to responsiveness to thyrotropin-releasing hormone. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2012-1125
3. Mitsui Y, Mukai K, Otsuki M, Oshino S, Saitoh Y, Kohara M, Morii E, Fukuhara A, Shimomura I (2024) Growth hormone increase by luteinizing hormone-releasing hormone reflects gonadotroph-related characteristics in acromegaly. Pituitary. https://doi.org/10.1007/s11102-024-01410-2
4. Scaroni C, Albiger N, Daniele A, Dassie F, Romualdi C, Vazza G, Regazzo D, Ferraù F, Barresi V, Maffeis V, Gardiman MP, Cannavò S, Maffei P, Ceccato F, Losa M, Occhi G (2019) Paradoxical GH increase during OGTT is associated with first-generation somatostatin analog responsiveness in acromegaly. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2018-01360
5. Atquet V, Alexopoulou O, Maiter D (2021) Characteristics and treatment responsiveness of patients with acromegaly and a paradoxical GH increase to oral glucose load. Eur J Endocrinol. https://doi.org/10.1530/EJE-21-0324
6. De Marinis L, Chiloiro S, Mancini A, Giambò P, Giampietro A, Bianchi A, Pontecorvi A, Giustina A (2026) To test or not to test: what we have learnt from 50 years of dynamic testing in acromegaly. Pituitary. https://doi.org/10.1007/s11102-026-01649-x
7. Colao A, Merola B, Ferone D, Calabrese MR, Longobardi S, Spaziante R, Di Renzo G, Annunziato L, Lombardi G (1994) Effect of corticotrophin-releasing hormone administration on growth hormone levels in acromegaly: in vivo and in vitro studies. Eur J Endocrinol. https://doi.org/10.1530/eje.0.1310014
8. Asa SL, Mete O, Perry A, Osamura RY (2022) Overview of the 2022 WHO classification of pituitary tumors. Endocr Pathol. https://doi.org/10.1007/s12022-022-09703-7
9. Katznelson L, Laws ER Jr., Melmed S, Molitch ME, Murad MH, Utz A, Wass JAH (2014) Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2014-2700
10. Giustina A, Biermasz N, Casanueva FF, Fleseriu M, Mortini P, Strasburger C, van der Lely AJ, Wass J, Melmed S (2024) Consensus on criteria for acromegaly diagnosis and remission. Pituitary. https://doi.org/10.1007/s11102-023-01360-1
11. Lawrence AM, Goldfine ID, Kirsteins L (1970) Growth hormone dynamics in acromegaly. J Clin Endocrinol Metab. https://doi.org/10.1210/jcem-31-3-239
12. Isojima T, Shimatsu A, Yokoya S, Chihara K, Tanaka T, Hizuka N, Teramoto A, Tatsumi KI, Tachibana K, Katsumata N, Horikawa R (2012) Standardized centile curves and reference intervals of serum insulin-like growth factor-I (IGF-I) levels in a normal Japanese population using the LMS method. Endocr J. https://doi.org/10.1507/endocrj.EJ12-0110
13. Lenders NF, Chui J, Low J, Inder WJ, Earls PE, McCormack AI (2022) Development of a cost-effective diagnostic algorithm incorporating transcription factor immunohistochemistry in the evaluation of pituitary tumours. Pituitary. https://doi.org/10.1007/s11102-022-01284-2
14. Marazuela M, Martínez-Hernandez R, Marques-Pamies M, Biagetti B, Araujo-Castro M, Puig-Domingo M (2024) Predictors of biochemical response to somatostatin receptor ligands in acromegaly. Best Pract Res Clin Endocrinol Metab. https://doi.org/10.1016/j.beem.2024.101893
15. Obari A, Sano T, Ohyama K, Kudo E, Qian ZR, Yoneda A, Rayhan N, Mustafizur Rahman M, Yamada S (2008) Clinicopathological features of growth hormone-producing pituitary adenomas: difference among various types defined by cytokeratin distribution pattern including a transitional form. Endocr Pathol. https://doi.org/10.1007/s12022-008-9029-z
16. Ilie MD, Tabarin A, Vasiljevic A, Bonneville JF, Moreau-Grangé L, Schillo F, Delemer B, Barlier A, Figarella-Branger D, Bisot-Locard S, Santos A, Chanson P, Raverot G (2022) Predictive factors of somatostatin receptor ligand response in acromegaly—a prospective study. J Clin Endocrinol Metab. https://doi.org/10.1210/clinem/dgac512
17. Borota OC, Heck A, Schulz S, Nesland JM, Ramm-Pettersen J, Lekva T, Alafuzoff I, Bollerslev J (2013) Expression of SSTR2a, but not of SSTRs 1, 3, or 5 in somatotroph adenomas assessed by monoclonal antibodies was reduced by octreotide and correlated with the acute and long-term effects of octreotide. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2013-2145
18. Heck A, Ringstad G, Fougner SL, Casar-Borota O, Nome T, Ramm-Pettersen J, Bollerslev J (2012) Intensity of pituitary adenoma on T2-weighted magnetic resonance imaging predicts the response to octreotide treatment in newly diagnosed acromegaly. Clin Endocrinol. https://doi.org/10.1111/j.1365-2265.2011.04286.x
19. Raza J, Massoud AF, Hindmarsh PC, Robinson IC, Brook CG (1998) Direct effects of corticotrophin-releasing hormone on stimulated growth hormone secretion. Clin Endocrinol (Oxf). https://doi.org/10.1046/j.1365-2265.1998.3821204.x
20. Ishizuka T, Morita H, Mune T, Daidoh H, Hanafusa J, Yamamoto M, Shibata T, Yasuda K (1995) Growth hormone secretion in human acromegalic pituitary adenomas: cyclic adenosine

monophosphate and protein kinase C responses. Metabolism. https://doi.org/10.1016/S0026-0495(96)90055-4
21. Vuppaladhadiam L, Ehsan C, Akkati M, Bhargava A (2020) Corticotropin-releasing factor family: a stress hormone-receptor system's emerging role in mediating sex-specific signaling. Cells. https://doi.org/10.3390/cells9040839
22. Rymuza J, Kober P, Rusetska N, Mossakowska BJ, Maksymowicz M, Nyc A, Baluszek S, Zieliński G, Kunicki J, Bujko M (2022) Transcriptomic classification of pituitary neuroendocrine tumors causing acromegaly. Cells. https://doi.org/10.3390/cells11233846
23. Asa SL, Mete O, Riddle ND, Perry A (2023) Multilineage pituitary neuroendocrine tumors (PitNETs) expressing PIT1 and SF1. Endocr Pathol. https://doi.org/10.1007/s12022-023-09777-x
24. Dottermusch M, Ryba A, Ricklefs FL, Flitsch J, Schmid S, Glatzel M, Saeger W, Neumann JE, Schüller U (2024) Pituitary neuroendocrine tumors with PIT1/SF1 co-expression show distinct clinicopathological and molecular features. Acta Neuropathol. https://doi.org/10.1007/s00401-024-02686-1
25. Lee Y, Ma EL, Patel M, Kim G, Howe C, Pothoulakis C, Kim YS, Im E, Rhee SH (2021) Corticotropin-releasing hormone receptor alters the tumor development and growth in Apcmin/+ mice and in a chemically-induced model of colon cancer. Int J Mol Sci. https://doi.org/10.3390/ijms22031043
26. Fang X, Hong Y, Dai L, Qian Y, Zhu C, Wu B, Li S (2017) CRH promotes human colon cancer cell proliferation via IL-6/ JAK2/ STAT3 signaling pathway and VEGF-induced tumor angiogenesis. Mol Carcinog. https://doi.org/10.1002/mc.22691
27. Sato N, Motoi F, Tajiki H, Kawaguchi K, Ohtsuka H, Takadate T, Nakagawa K, Takagi K, Suzuki T, Katayose Y, Fukudo S, Unno M (2022) Expression of corticotropin-releasing hormone and its receptors may be associated with survival rate in pancreatic cancer. Gastro Hep Adv. https://doi.org/10.1016/j.gastha.2022.09.003
28. Rodriguez JA, Huerta-Yepez S, Law IKM, Baay-Guzman GJ, Tirado-Rodriguez B, Hoffman JM, Iliopoulos D, Hommes DW, Verspaget HW, Chang L, Pothoulakis C, Baritaki S (2015) Diminished expression of CRHR2 in human colon cancer promotes tumor growth and EMT via persistent IL-6/Stat3 signaling. Cell Mol Gastroenterol Hepatol. https://doi.org/10.1016/j.jcmgh.2015.08.001
29. Sahakian N, Goetz L, Appay R, Graillon T, Raingeard I, Piazzola C, Regis J, Castinetti F, Brue T, Dufour H, Cuny T (2024) Outcome of non-functioning ACTH pituitary tumors: silent does not mean indolent. Pituitary. https://doi.org/10.1007/s11102-024-01428-6