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## Case Report

Recurrent Acromegaly in a Patient With a *CHEK2* MutationMilica Perosevic, MD<sup>1,2,\*</sup>, Maria Martinez-Lage, MD<sup>3,5</sup>, Brooke Swearingen, MD<sup>4,5</sup>,  
Nicholas A. Tritos, MD, DSc<sup>1,5</sup><sup>1</sup> Neuroendocrine Unit and Neuroendocrine and Pituitary Tumor Clinical Center, Massachusetts General Hospital, Boston, Massachusetts<sup>2</sup> Department of Medicine, South Shore Hospital, Weymouth, Massachusetts<sup>3</sup> Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts<sup>4</sup> Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts<sup>5</sup> Harvard Medical School, Boston, Massachusetts

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## ABSTRACT

**Background/Objective:** *CHEK2* is a cell-cycle checkpoint kinase and is part of the ATM-CHEK2-p53 cascade, which is protective against carcinogenesis. We describe a germline *CHEK2* mutation in a patient with acromegaly and other tumors.**Case Report:** We present a woman with a germline *CHEK2*\* 110delC mutation previously diagnosed with fibroadenoma of the breast and papillary thyroid carcinoma. She presented with acromegaly at age 48 (insulin-like growth factor 1, 556 mcg/L [reference range, 90–360] and lack of growth hormone suppression on glucose tolerance testing) and underwent transsphenoidal resection of a somatotroph microadenoma. Four years after surgery, she developed recurrent growth hormone excess. She was treated with cabergoline, which was discontinued due to intolerance, and transitioned to lanreotide depot, which was switched to pegvisomant because of prediabetes. Her insulin-like growth factor 1 levels remained normal on pegvisomant. Follow-up magnetic resonance imaging examinations showed no evidence of tumor progression. Shortly after the diagnosis of acromegaly, the patient was diagnosed with endometrial carcinoma, bilateral ovarian cystadenomas, and uterine leiomyomas. She was additionally found to have a nonfunctioning adrenal nodule and hyperplastic and adenomatous colon polyps. There are multiple family members with malignancies, including colon, thyroid, and lung cancer.**Discussion:** This is a novel report of a patient with a pathogenic germline *CHEK2* mutation and multiple malignant and benign tumors, including recurrent acromegaly.**Conclusion:** Our data raise the possibility that *CHEK2* mutations may be involved in the development of acromegaly. Additional studies are needed to elucidate the potential role of *CHEK2* mutations in the pathogenesis of somatotroph adenomas.© 2021 AAACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Acromegaly is a consequence of long-term exposure to excess growth hormone (GH) and is typically caused by a GH-secreting adenoma, though ectopic GH-releasing hormone or ectopic GH-secreting tumors may rarely occur, leading to GH excess. In a small minority of patients with acromegaly, germline mutations of

one of several genes (including *AIP*, *CDKN1B*, *GPR101*, *MEN1*, *NF1*, *PRKAR1A*, *SDHA*, *SDHB*, *SDHC*) are present and may cause predisposition to pituitary tumorigenesis.<sup>1</sup>

*CHEK2* is a cell-cycle checkpoint kinase, which responds to DNA damage by preventing cells from entering mitosis.<sup>2</sup> The cascade ATM-CHEK2-p53 is a well-known barrier to carcinogenesis.<sup>2</sup> Patients with germline *CHEK2* gene mutations are at an increased risk of several malignancies, including breast and endometrial cancer.<sup>2</sup> A *CHEK2* gene mutation has been associated with Cushing's disease and papillary thyroid carcinoma but has not been reported in patients with acromegaly.<sup>3</sup>

Whether patients with *CHEK2* gene mutations are at risk for developing GH-secreting adenomas is unknown. This report describes a patient with recurrent acromegaly, who

**Abbreviations:** GH, growth hormone; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; OR, odds ratio.

\* Address correspondence to Dr Milica Perosevic, Massachusetts General Hospital, Neuroendocrine Unit and Neuroendocrine and Pituitary Tumor Clinical Center, 100 Blossom Street, Cox 140, Boston, MA 02114.

E-mail address: [milicaperosevic@yahoo.com](mailto:milicaperosevic@yahoo.com) (M. Perosevic).

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was found to have a deleterious mutation in the *CHEK2* gene.

**Case Report**

At age 48, the patient presented with acral enlargement, an increase in nose size, skin tags, and excessive perspiration. She had a history of fibroadenoma of the right breast (excised at age 38) and multifocal follicular variant of papillary thyroid carcinoma (largest tumor, 2.7 cm × 2.2 cm in the isthmus). She underwent total thyroidectomy at age 47 followed by radioiodine ablation (75 mCi).

There is a strong family history of various malignancies on both maternal and paternal sides (Fig. 1). Our patient underwent a genetic analysis of over 65 genes and was found to have a germline heterozygous mutation in the *CHEK2* gene (c.1100delC). No pathogenic variants were found in all other examined genes (Box).

Laboratory tests showed elevated serum insulin-like growth factor 1 (IGF-1), 400 mcg/L (reference range, 90-360), repeat IGF-1, 556 mcg/L (reference range, 90-360), normal serum thyrotropin, free thyroxine, prolactin, and gonadotropins (Table). A glucose tolerance test confirmed the diagnosis of acromegaly. A pituitary magnetic resonance imaging (MRI) examination showed an 8-mm × 7-mm hypodense lesion, consistent with microadenoma on the right side of the sella. There was no evident invasion of the cavernous sinus or compression of the optic chiasm or nerves. She was referred to our pituitary neurosurgeon and underwent trans-sphenoidal resection of the sellar mass. Gross total resection was achieved. Pathology confirmed the presence of adenoma, strongly positive for GH on immunohistochemistry (Fig. 2). Her serum IGF-1 level normalized postoperatively (IGF-1, 165 mcg/L [reference range, 90-360]), and serum GH suppressed to undetectable levels during a glucose tolerance test. However, 4 years later, she presented with hip arthralgias and was found to have a relapse of acromegaly (IGF-1, 390 mcg/L [reference range, 90-360]) (Fig. 3). A follow-up pituitary MRI examination showed a 2-mm × 2-mm sellar hypodensity. Cabergoline treatment was initiated (0.5 mg weekly) but was discontinued because of intolerance (nausea and vomiting). She then began therapy with lanreotide depot (90 mg every 4 weeks), which led to IGF-1 normalization (IGF-1, 140 mcg/L

**Box**

Genetic analysis of DNA (extracted from peripheral leukocytes) was conducted by next generation gene sequencing complemented by Sanger sequencing at a commercial laboratory. Genes analyzed have a putative role in the pathogenesis of a variety of tumors, including breast, endometrial, ovarian, and colon cancer. Some genes that were analyzed have been involved in the pathogenesis of pituitary adenomas, including *AIP*, *CDKN1B*, *MAX*, *MEN1*, *NF1*, *PRKAR1A*, *SDHA*, *SDHB*, and *SDHC*. The following 67 genes were analyzed:

*AIP, ALK, APC, ATM, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CHEK2, CDH1, CDK4, CDKN1B, CDKN2A, DICER1, EPCAM, FANCC, FH, FLCN, GALNT12, GREM1, HOXB13, MAX, MEN1, MET, MITF, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, XRCC2.*

[reference range, 90-360]). However, she developed prediabetes (HbA1c, 6.0% [42 mmol/mol]) and was switched to pegvisomant therapy (titrated to 15 mg daily). Serum IGF-1 levels have remained normal under pegvisomant therapy (Fig. 3). Follow-up pituitary MRI examinations have shown no radiographic evidence of tumor progression for over 10 years.

Meanwhile, at age 49, the patient was diagnosed with endometrial carcinoma. She underwent total hysterectomy and bilateral salpingo-oophorectomy. At age 50, she was noted to have an incidental left adrenal nodule (1.8 cm × 2.0 cm) with signal drop on out-of-phase images (high lipid content) on MRI, consistent with adenoma, which has remained stable in size on follow-up imaging. Extensive laboratory testing showed no evidence of adrenal hormone excess (Table).

Serial ultrasound examinations of the neck have shown no evidence of mass in the thyroid bed or cervical lymphadenopathy. Her latest serum thyroglobulin was detectable (0.3 mcg/L [reference range, <0.1 mcg/L in athyreotic patients]) with undetectable antithyroglobulin antibodies.

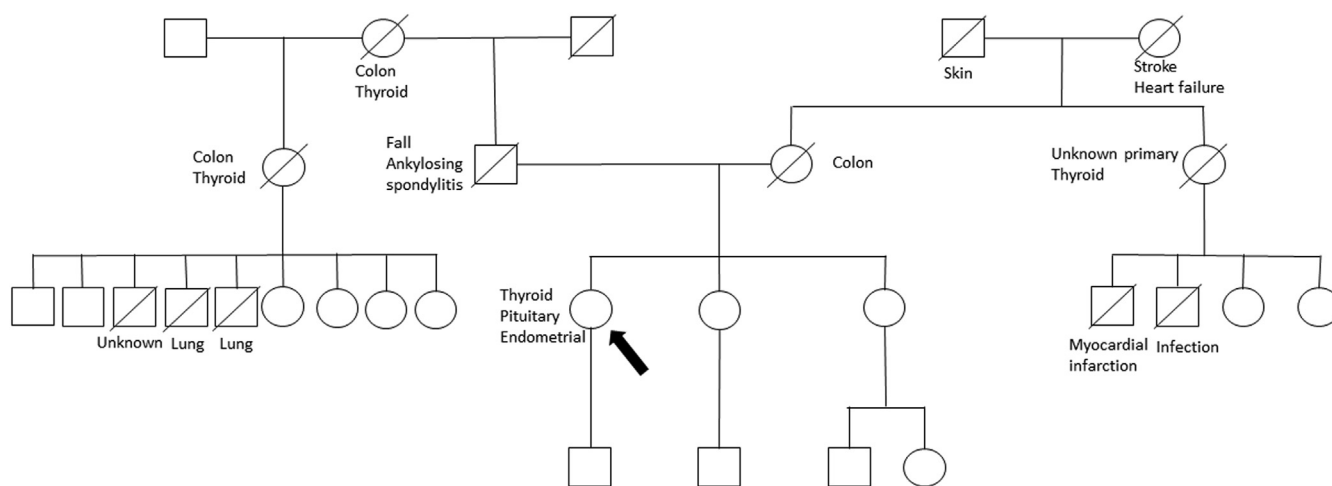


Fig. 1. Pedigree chart of the patient's family. The diagnoses of tumors and causes of death are shown. The proband is indicated by an arrow.

**Table**  
Laboratory Values at Presentation With Acromegaly, Followed by the Results of Adrenal Hormone Testing (at the Time of Diagnosis of Left Adrenal Nodule)

Analyte (serum or plasma)	Test result	Reference range
IGF-1 (mcg/L)	556 <sup>a</sup>	90-360
Nadir GH (mcg/L) during 2-hour OGTT	2 <sup>a</sup>	<0.4
TSH (mU/L)	0.5	0.5-4.5
Free T4 (ng/dL)	1.4	0.9-1.8
Prolactin (mcg/L)	10	0-20
FSH (U/L)	3.0	1-18
LH (U/L)	1.5	1-16
Calcium, total (mg/dL)	9.6	8.5-10.4
PTH (ng/L)	15	10-60
Morning cortisol (mcg/dL) after administration of dexamethasone (1 mg) the night before (11 PM)	0.8	<1.8
Aldosterone (ng/dL)	4	≤15
Renin activity (ng/ml/h)	0.9	0.2-5.8
DHEA-S (mcg/dL)	53	15-170
Metanephrine (pg/mL)	<25	≤57
Normetanephrine (pg/mL)	42	≤148

Abbreviations: DHEA-S = dehydroepiandrosterone sulfate; FSH = follicle stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; OGTT = oral glucose tolerance test; PTH = parathyroid hormone; TSH = thyroid stimulating hormone; T4 = thyroxine.

<sup>a</sup> Abnormal results.

Her most recent colonoscopy was performed at age 63, at which time adenomatous and hyperplastic polyps were removed. Mammograms and breast MRI at age 63 showed no evidence of malignancy. She has had no evidence of breast cancer to date.

The authors performed electronic literature searches using the keywords “CHEK2,” “cancer,” “pituitary adenoma,” “pituitary tumor,” and “acromegaly” to identify potentially pertinent studies.

**Discussion**

Acromegaly is usually sporadic. However, germline mutations of one of several genes (including *AIP*, *CDKN1B*, *GPR101*, *MEN1*, *NF1*, *PRKAR1A*, *SDHA*, *SDHB*, *SDHC*) are present in a minority of patients with acromegaly and may predispose to pituitary tumorigenesis.<sup>1</sup> The present report describes a patient with recurrent acromegaly and several other malignant and benign tumors, who was found to have a pathogenic germline mutation in the *CHEK2* gene.

The mutation (c. 1100delC) identified in this patient is located in coding exon 10 of the *CHEK2* gene. The deletion of one nucleotide at position 1100 causes a translational frameshift that results in a stop codon (p.T367Mfs\*15). This is located within the kinase domain

and has been reported to abolish the kinase activity of CHEK2 protein.<sup>4</sup>

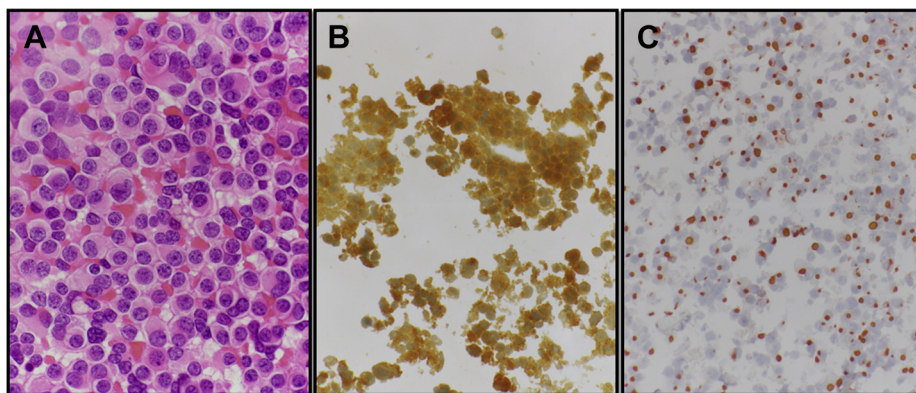
Several studies have reported an increased risk of malignancies associated with *CHEK2* mutations, including cancers of the breast (odds ratio [OR], 2.2-7.9 in different studies), colon (OR, 1.8-5.2 in different studies), endometrium, (papillary) thyroid (OR, 1.8-5.7 in different studies), and prostate (OR, 1.6-4.7 in different studies), as well as benign and malignant ovarian tumors.<sup>1</sup> Adrenal tumors have not been previously reported in association with *CHEK2* mutations. The truncating *CHEK2* mutation present in our case, 1100delC, has been reported not only in patients with breast cancer, but also in some with prostate and colorectal cancers.<sup>5</sup> Mutations 1100delC and I157T are associated with a higher risk of distant metastasis in patients with breast cancer, which makes them more likely to have poor outcomes.<sup>3,6</sup> Papillary thyroid cancer represents 80% of all thyroid tumors and overall carries a good prognosis. Three truncating mutations (1100delC, IVS2 + 1G> A, and del5395) and one missense mutation (I157T) of the *CHEK2* gene have been associated with an increased risk of papillary thyroid cancer.<sup>7</sup> The *CHEK2* I157T mutation has also been linked to endometrial cancer<sup>8</sup> and benign and low-grade malignant ovarian tumors.<sup>9</sup>

Alterations in *CHEK2* expression have been reported in pituitary adenomas.<sup>10</sup> However, acromegaly has not been previously reported in a patient with a *CHEK2* gene mutation. There was insufficient pituitary tumor tissue available for genetic testing (analysis for somatic mutations or expression profiling) in this case.

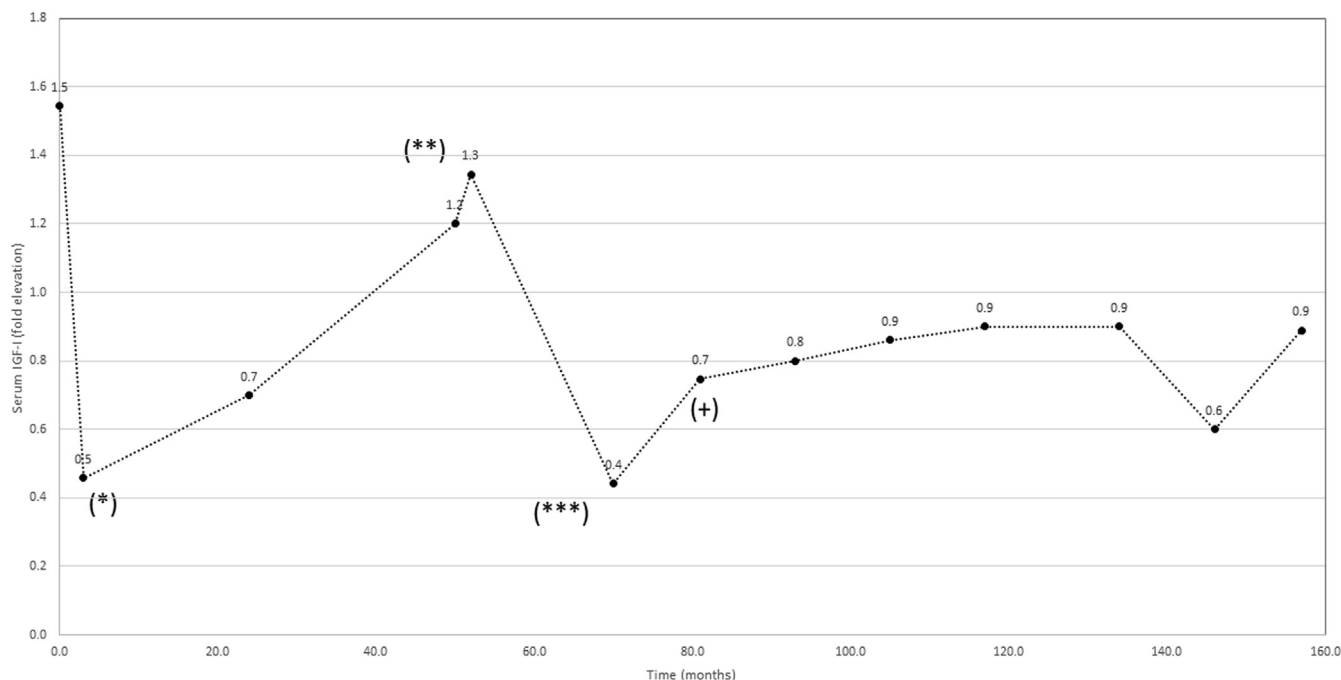
The incidence of several cancers appears to be increased in patients with acromegaly.<sup>10</sup> In these patients, estimates of the standardized incidence ratio of several malignancies are as follows: 2.6 (colorectal cancer), 9.2 (thyroid cancer), 2.0 (gastric cancer), 1.6 (breast cancer), and 1.5 (urinary tract cancer).<sup>11</sup> In our patient, it remains unclear whether the reported extrapituitary tumors are linked to the *CHEK2* mutation or the presence of GH excess.

**Conclusion**

In summary, our patient with a *CHEK2*\*1100delC mutation has had recurrent somatotroph adenoma, papillary thyroid carcinoma, endometrial carcinoma, colon polyps, ovarian cystadenomas, and an adrenal adenoma. It is conceivable that the mutation in the *CHEK2* gene could be involved in the development



**Fig. 2.** A, Hematoxylin-eosin photomicrograph from smear slide shows epithelioid cells with eosinophilic cytoplasm and nuclei with speckled chromatin, consistent with a pituitary adenoma. B, Immunohistochemistry for growth hormone shows diffuse staining of adenoma cells, confirming the diagnosis of somatotroph adenoma. C, Cam5.2 immunohistochemistry shows striking “dot-like” cytoplasmic pattern (note pale, blue-stained nuclei, which are negative) consistent with fibrous bodies, supporting the diagnosis of sparsely granulated somatotroph adenoma.



**Fig. 3.** Serum insulin-like growth factor 1 (IGF-1) data during the course of the patient’s illness. Serum IGF-1 data are expressed as “fold” elevation times the upper end of the reference range. First data point is just before surgery; subsequent data points represent IGF-1 values obtained at 3 months postoperatively (\*); at time of recurrence (\*\*); on lanreotide depot therapy (\*\*\*) and on pegvisomant therapy (+).

of at least some of these tumors, including somatotroph adenoma, in this patient. Further studies are warranted to elucidate the possible role of *CHEK2* mutations in the pathogenesis of somatotroph adenomas.

**Acknowledgment**

We thank the patient, who provided verbal informed consent for this case report.

**Disclosure**

The authors have no multiplicity of interest to disclose.

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