Bone Reports 13 (2020) 100299

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Case Report

GNAS mutated thyroid carcinoma in a patient with Mc Cune Albright syndrome

M.A. Legrand[a,b,*], G. Raverot[c], M. Nicolino[d], R. Chapurlat[a,b]

[a] INSERM UMR 1033, Université de Lyon, Hospices Civils de Lyon, Hôpital E Herriot, 69437 Lyon, France
[b] Centre national de référence de la dysplasie fibreuse des os, Hôpital E Herriot, 69437 Lyon, France
[c] Fédération d'Endocrinologie, Centre de Référence Maladies Rares Hypophysaires (HYPO), Groupement Hospitalier Est, Hospices Civils de Lyon, Bron, France
[d] Endocrinologie, Diabétologie, Nutrition Pédiatriques, Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, F-69677 Bron, France

ARTICLE INFO

Keywords:
Fibrous dysplasia
Mc Cune Albright syndrome
GNAS mutation
Thyroid
Thyroid carcinoma

ABSTRACT

Mc Cune-Albright syndrome (MAS) is a rare disorder defined by the triad of polyostotic fibrous dysplasia, "café au lait" skin hyperpigmentation and hyperfunctioning endocrinopathies, such as precocious puberty.

MAS is caused by an activating post zygotic somatic mutation of GNAS gene, coding for the alpha-subunit of the stimulatory G protein (Gsalpha). In endocrine tissues, this mutation results in overproduction of hormones and endocrine cell hyperfunction and proliferation.

Whereas the association of hyperthyroidism and thyroid adenomas is well known in MAS, the relation with thyroid carcinoma has rarely been observed.

We report the occurrence of a thyroid carcinoma in an 18-years old woman with MAS, revealed by subclinical hyperthyroidism detected during her systematic annual follow-up. Ultrasound and thyroid scintigraphy revealed the presence of a nodule in the right lobe. Pathology on hemithyroidectomy revealed an unexpected thyroid follicular carcinoma. Neoplastic thyroid cells harbored the GNAS R201C activating mutation. This observation suggests that MAS may predispose patients to thyroid carcinomas and supports the importance of thyroid assessment by physical examination, hormonal blood test and ultrasound, in the follow-up of patients with MAS. Because ultrasound diagnostic is challenging in MAS, needle puncture of palpable nodules should be advised.

1. Introduction

Mc Cune Albright Syndrome (MAS) is a rare disorder defined by the classical triad of polyostotic fibrous dysplasia (FD), "café-au-lait" skin hyperpigmentation and hyperfunctioning endocrinopathies, such as precocious puberty.

MAS is caused by an activating post zygotic somatic mutation of GNAS gene, coding for the alpha-subunit of the stimulatory G protein (Gsalpha), involved in the cAMP cascade, referred to as a gsp mutation (Weinstein et al., 1991). This mutation leads to elevated levels of intracellular cAMP and activation of downstream-dependent pathways. In endocrine tissues, this mutation results in overproduction of hormones and endocrine cell hyperfunction and proliferation.

MAS is associated with hyperfunction of multiple endocrine tissues, including excess of growth hormone (GH) secretion (Cremonini et al., 1992), hyperthyroidism (Feuillan et al., 1990; Congedo and Celi, 2007; Tessaris et al., 2012; Sallum et al., 2008; Mastorakos et al., 1997) or Cushing's syndrome (Brown et al., 2010).

Whereas the association of hyperthyroidism or thyroid adenomas (Feuillan et al., 1990; Congedo and Celi, 2007; Tessaris et al., 2012; Sallum et al., 2008; Mastorakos et al., 1997) is well known in MAS, the relationship with thyroid carcinoma has rarely been observed (Collins et al., 2003; Collins et al., 2012; Yang et al., 1999).

We report a new case of GNAS mutated thyroid carcinoma in a patient with MAS.

2. Case report

A 18 years old woman with known MAS presented with subclinical hyperthyroidism during her annual follow-up work up.

Her MAS was diagnosed at age 6 because of abnormal bleeding in relation with precocious puberty. She also had skin "café au lait" spots, polyostotic FD, renal phosphate wasting and growth hormone excess.

At age 18, her systematic follow up measurement showed subclinical hyperthyroidism with suppressed serum TSH, less than 0.01 mUI/ml (normal 0.4–3.1), elevated T3 level at 5.2 pmol/L (normal

* Corresponding author at: Centre national de référence de la dysplasie fibreuse des os, Hôpital E Herriot, 5 place d'Arsonval, 69003 Lyon, France.
E-mail address: melanie.legrand@chu-lyon.fr (M.A. Legrand).

https://doi.org/10.1016/j.bonr.2020.100299
Received 22 March 2020; Received in revised form 13 July 2020; Accepted 15 July 2020
Available online 18 July 2020

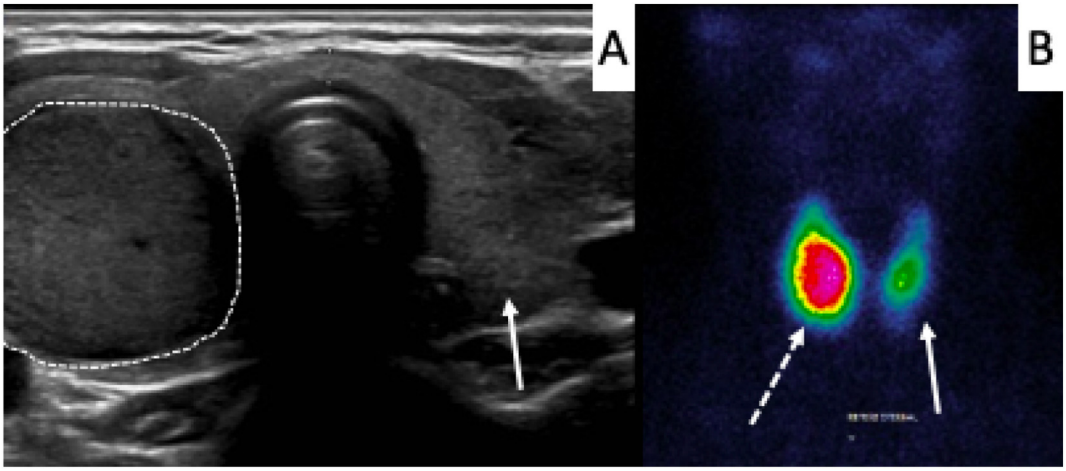

Fig. 1. Thyroid imaging.
(A) Thyroid ultrasonography showed the largest thyroid nodule in the right lobe (25 ∗ 20 ∗ 35 mm) classified TIRADS 3 and the normal left lobe (arrow).
(B) This nodule showed as excess trapping of isotope in technetium-99 m pertechnetate scintigraphy (dashed arrow) against a low background of the thyroid (arrow).

2.9–4.9) and a slight decrease of T4 concentration (11.2 pmol/L – normal 12–22) suggestive of autonomous functioning thyroid nodule producing T3. She had no symptoms of thyrotoxicosis. There was no history of radiation exposure to the neck.

Her mother had an history of toxic multinodular goiter.

Neck ultrasonography showed hypertrophy of the right lobe and 3 nodules including one hypervascularized nodule of 25 × 20 × 30 mm in the right lobe, classified TIRADS 3.

A technetium-99 m pertechnetate thyroid scintigraphy scan showed a strong hyperfixation at the location of the nodule (Fig. 1). The patient underwent a right hemithyroidectomy and the pathology revealed a follicular thyroid neoplasm. Genetics analysis using next generation sequencing showed the presence of the R201C GNAS mutation in neoplastic thyroid cells. No other mutation (including BRAF and N RAS) was detected. The surgery will be extended to a total thyroidectomy. An initial surgical treatment was preferred over iodine treatment because of the increased risk of sarcomatous transformation of skull FD lesions in context of MAS and GH excess that has been observed in case of radiotherapy (Mock and Rosen, 1986; Hansen and Moffat, 2003; Ruggieri et al., 1994).

3. Discussion

Somatic mutations of GNAS have been implicated in various sporadic endocrine and non - endocrine tumors, such as pituitary adenomas (Landis et al., 1989; Yoshimoto et al., 1993; Riminucci et al., 2002; Vortmeyer et al., 2012; Freda et al., 2007), thyroid adenomas and carcinomas (Collins et al., 2003; Yoshimoto et al., 1993; Lyons et al., 1990; O'Sullivan et al., 1991; Palos-Paz et al., 2008; Lu et al., 2016), Leydig cell tumors (Fragoso et al., 1998), ovarian tumors (Boussaïd et al., 2013; Chevalier et al., 2015), breast cancer (Collins et al., 2012; Scanlon et al., 1980; Tanabeu et al., 1998; Majoor et al., 2018), pancreatic and hepatobiliary tumors (Parvanescu et al., 2014; Gaujoux et al., 2014; Gaujoux et al., 2019) leading to the term “gsp oncogene”.

Regarding thyroid tumors, somatic GNAS mutations have been reported in thyroid carcinomas, out of the context of MAS/FD. Indeed, O'Sullivan et al. (1991), have analyzed the presence of activating Gs mutations in 38 differentiated human thyroid benign tumors by polymerase chain reaction amplification and oligonucleotide hybridization. Activating Gs mutations were identified in 5 of 13 (38%) autonomously functioning adenomas, but in none of other thyroid tumors (non-functioning adenomas, papillary carcinomas or follicular carcinomas). In this study, authors had concluded that the *gsp* oncogene was involved in the pathogenesis of autonomously functioning tumors but did not support a role in other thyroid tumors.

Yoshimoto et al. (1993), have screened Gs alpha mutations (at codons 201 and 227) by PCR and the mutation was present in 4 of 66 thyroid tumors (30 papillary carcinomas) and these 4 thyroid tumors were papillary carcinomas. They concluded that Gs alpha mutations at these two loci may play a role in the pathogenesis of a small population of papillary thyroid carcinomas.

Lu et al. (2016), reported the observation of a follicular thyroid carcinoma, with both NRAS pQ61K and GNAS pR201H mutation in a 79 year old-man with history of Grave's disease. NRAS and GNAS mutations were only found in neoplastic thyroid tissue.

The presence of thyroid abnormalities in MAS, such as hyperthyroidism, goiter and thyroid adenomas is well known (Collins et al., 2012): hyperthyroidism is the second most common endocrinopathy in MAS. At the National Institute of Health (NIH), approximately 2/3 of the patients with MAS had involvement of thyroid, when assessed by thyroid ultrasound (US) (Collins et al., 2012).

Activating GNAS mutation in thyroid tissue results in activation of the TSH/G protein/cAMP pathway which is leading to hyperplasia and thyroid hormone production and increased conversion from T4 to T3 (Combest and Russell, 1983; Celi et al., 2008).

However, association of MAS with thyroid malignancies is rare. So far, two cases of thyroid cancer have been described in MAS patients (1.3%) from the NIH cohort (Collins et al., 2012): one case of papillary thyroid cancer in a 14 year old girl and another case of clear cells thyroid carcinoma in a 42 year old woman. In both instances, the Gs mutation was found in the neoplastic tissue. Interestingly, the Gs mutation was not found in adjacent normal tissue. This data supports the oncogenic role of GNAS mutation on endocrine tissue (Collins et al., 2003).

Another case of lipid-rich follicular carcinoma of the thyroid was reported by Yang GC et al., in a 41 year old woman with MAS (Yang et al., 1999).

Incidence of thyroid carcinomas is low, and MAS is also a rare disease. Therefore, in this observation, it is unlikely that the presence of GNAS mutated thyroid carcinomas and MAS was incidental.

Malignancies can involve other endocrine tissues of patients with MAS.

Indeed, women with polyostotic fibrous dysplasia and/or MAS have an increased risk of breast cancer (Collins et al., 2012; Scanlon et al., 1980; Tanabeu et al., 1998; Majoor et al., 2018). In a cohort of women with FD from Netherlands and United States (Majoor et al., 2018), breast cancer risk was 3.9 fold increased (95% CI 1.2–8.2) compared with the general population. Risk of breast cancer was increased at a

younger age, especially in polyostotic FD and thoracic FD lesions. GNAS mutations were identified in pathological specimens of breast tumors in 4 of 9 patients with fibrous dysplasia (44%) compared with less than 1% reported incidence of GNAS positive breast cancer in the general population. Thus, authors recommended screening for breast cancer in women with FD, at a younger age than women in the general population.

In the same way, MAS is associated with GH excess and pituitary adenomas (Akintoye et al., 2002) and GNAS mutations have been identified in human pituitary tumors in non-MAS patients (Landis et al., 1989; Yoshimoto et al., 1993; Lyons et al., 1990). Thus, a pituitary MRI is indicated in case of abnormal hormonal blood tests (IGF1, GH, prolactin) (Javaid et al., 2019).

Rare cases of testicular and ovarian malignancies were described in MAS: one patient with testicular cancer (both embryonal carcinoma and a seminoma) was reported by the NIH (Boyce et al., 2012). One case of ovarian virilizing sclerosing-stromal tumor and one case of ovarian epithelial tumor harboring a GNAS mutation were reported (Boussaïd et al., 2013; Chevalier et al., 2015).

The putative pathogenic effect of GNAS in these tumors is supported by the identification of the R201C mutation in ovarian and testicular Leydig cell tumors, in non-MAS patients (Fragoso et al., 1998).

Gastrointestinal malignancies with hepatobiliary (liver adenomas and choledochal cysts) and pancreatic neoplasms (intraductal papillary mucinous neoplasms - IPMNs) have also been reported in FD (Parvanescu et al., 2014; Gaujoux et al., 2014; Gaujoux et al., 2019). IPMNs occur in up to 50% in patients with MAS (Robinson et al., 2018) whereas pancreatic adenocarcinoma appears to be a rare development in this population, with only 2 reported cases. In these two cases of IPMNs related colloid pancreatic adenocarcinoma in MAS patients, genetic analysis revealed GNAS mutation of the tumor (Parvanescu et al., 2014; Gaujoux et al., 2019).

Out of the context of MAS/FD, somatic activating GNAS mutations have also been reported in digestive sporadic tumors, such as hepatocellular adenoma, hepatocellular carcinoma, cholangiocarcinoma and in up to 70% of pancreatic IPMNs (Nault et al., 2012; Wu et al., 2011; Kanda et al., 2013; Furukawa et al., 2011).

These elements support, on the one hand, the involvement of GNAS mutation in tumorigenesis of hepatobiliary and pancreatic tissue and, on the other hand, the association between MAS and pancreatic neoplasms (IPMNs).

In total, GNAS mutation can affect any tissue and be responsible for malignancy in these.

MAS patients with endocrinopathies should be enrolled in a specific neoplastic screening program. The first step of endocrine malignancies screening is the physical examination (with thyroid, breast, abdomen and testicular palpation) and the biochemistry (with at least, GH, IGF1, prolactin, TSH, T3 and T4). Then, specific imaging exams should be performed, depending on clinical and biological findings, and according to the endocrine organ involved: for instance, pituitary assessment should be completed with an MRI in case of GH excess at biochemistry, and all male with MAS should have baseline testicular ultrasounds (Javaid et al., 2019).

Concerning thyroid, according with recommendations, all patients should have an ultrasound exam, in order to characterize subclinical involvement consistent with MAS (Javaid et al., 2019). Because of the increased risk of thyroid cancer and diagnostic difficulties encountered with ultrasound in patients with MAS (diffusely abnormal thyroid gland making difficult the identification of malignant changes) (Collins et al., 2012), we believe that, in case of palpable nodule, needle puncture should be advised. Indeed, in this observation, histology revealed thyroid carcinoma whereas ultrasound data was reassuring, with a low risk of malignancy (2–4%) according to TIRADs classification.

Currently, no specific screening is recommended for digestive tumor including IPMNs, but we believe that the most severe cases of MAS and FD (e.g., polyostotic FD, GH excess) should have baseline hepatopancreatobiliary MRI, as suggests by Parvanescu and al (Parvanescu et al., 2014). Finally, colon cancer screening may be performed in case of excess GH (Katznelson et al., 2014).

4. Conclusion

We report the fourth case of thyroid carcinoma GNAS mutated associated with a Mc Cune Albright Syndrome. Outside the context of FD/MAS, a GNAS mutation in thyroid carcinoma has been demonstrated in molecular studies, suggesting that MAS may predispose patients to thyroid carcinomas.

Physicians should keep in mind that the risk of thyroid cancer is higher, but the ultrasound diagnostic is challenging in MAS, guiding to needle puncture of palpable nodules.

Consent

The patient has provided consent for publication of this case report.

Declaration of competing interest

All authors state that they have no conflicts of interest.

References

Akintoye, S.O., Chebli, C., Booher, S., Feuillan, P., Kushner, H., Leroith, D., Cherman, N., Bianco, P., Wientroub, S., Robey, P.G., Collins, M.T., 2002. Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 87, 5104–5112. https://doi.org/10.1210/jc.2001-012022.

Boussaïd, K., Meduri, G., Maiza, J.-C., Gennero, I., Escourrou, G., Bros, A., Leguevaque, P., Bennet, A., Caron, P., 2013. Virilizing sclerosing-stromal tumor of the ovary in a young woman with McCune Albright syndrome: clinical, pathological, and immunohistochemical studies. J. Clin. Endocrinol. Metab. 98, E314–E320. https://doi.org/10.1210/jc.2012-3551.

Boyce, A.M., Chong, W.H., Shawker, T.H., Pinto, P.A., Linehan, W.M., Bhattacharryya, N., Merino, M.J., Singer, F.R., Collins, M.T., 2012. Characterization and management of testicular pathology in McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 97, E1782–E1790. https://doi.org/10.1210/jc.2012-1791.

Brown, R.J., Kelly, M.H., Collins, M.T., 2010. Cushing syndrome in the McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 95, 1508–1515. https://doi.org/10.1210/jc.2009-2321.

Celi, F.S., Coppotelli, G., Chidakel, A., Kelly, M., Brillante, B.A., Shawker, T., Cherman, N., Feuillan, P.P., Collins, M.T., 2008. The role of type 1 and type 2 5′-deiodinase in the pathophysiology of the 3,5,3′-triiodothyronine toxicosis of McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 93, 2383–2389. https://doi.org/10.1210/jc.2007-2237.

Chevalier, N., Paris, F., Fontana, S., Delotte, J., Gaspari, L., Ferrari, P., Sultan, C., Fénichel, P., 2015. Postpubertal persistent hyperestrogenemia in McCune-Albright syndrome: unilateral oophorectomy improved fertility but detected an unexpected borderline epithelial ovarian tumor. J. Pediatr. Adolesc. Gynecol. 28, e169–e172. https://doi.org/10.1016/j.jpag.2015.04.001.

Collins, M.T., Sarlis, N.J., Merino, M.J., Monroe, J., Crawford, S.E., Krakoff, J.A., Guthrie, L.C., Bonat, S., Robey, P.G., Shenker, A., 2003. Thyroid carcinoma in the McCune-Albright syndrome: contributory role of activating Gs alpha mutations. J. Clin. Endocrinol. Metab. 88, 4413–4417. https://doi.org/10.1210/jc.2002-021642.

Collins, M.T., Singer, F.R., Eugster, E., 2012. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 7 (Suppl. 1), S4. https://doi.org/10.1186/1750-1172-7-S1-S4.

Combest, W.L., Russell, D.H., 1983. Alteration in cyclic AMP-dependent protein kinases and polyamine biosynthetic enzymes during hypertrophy and hyperplasia of the thyroid in the rat. Mol. Pharmacol. 23, 641–647.

Congedo, V., Celi, F.S., 2007. Thyroid disease in patients with McCune-Albright syndrome. Pediatr. Endocrinol. Rev. 4 (Suppl. 4), 429–433.

Cremonini, N., Graziano, E., Chiarini, V., Sforza, A., Zampa, G.A., 1992. Atypical McCune-Albright syndrome associated with growth hormone-prolactin pituitary adenoma: natural history, long-term follow-up, and SMS 201-995–bromocriptine combined treatment results. J. Clin. Endocrinol. Metab. 75, 1166–1169. https://doi.org/10.1210/jcem.75.4.1400888.

Feuillan, P.P., Shawker, T., Rose, S.R., Jones, J., Jeevanram, R.K., Nisula, B.C., 1990. Thyroid abnormalities in the McCune-Albright syndrome: ultrasonography and hormonal studies. J. Clin. Endocrinol. Metab. 71, 1596–1601. https://doi.org/10.1210/jcem-71-6-1596.

Fragoso, M.C., Latronico, A.C., Carvalho, F.M., Zerbini, M.C., Marcondes, J.A., Araujo, L.M., Lando, V.S., Frazzatto, E.T., Mendonca, B.B., Villares, S.M., 1998. Activating mutation of the stimulatory G protein (gsp) as a putative cause of ovarian and testicular human stromal Leydig cell tumors. J. Clin. Endocrinol. Metab. 83, 2074–2078. https://doi.org/10.1210/jcem.83.6.4847.

Freda, P.U., Chung, W.K., Matsuoka, N., Walsh, J.E., Kanibir, M.N., Kleinman, G., Wang,

Y., Bruce, J.N., Post, K.D., 2007. Analysis of GNAS mutations in 60 growth hormone secreting pituitary tumors: correlation with clinical and pathological characteristics and surgical outcome based on highly sensitive GH and IGF-I criteria for remission. Pituitary. 10, 275–282. https://doi.org/10.1007/s11102-007-0058-2.

Furukawa, T., Kuboki, Y., Tanji, E., Yoshida, S., Hatori, T., Yamamoto, M., Shibata, N., Shimizu, K., Kamatani, N., Shiratori, K., 2011. Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. Sci. Rep. 1, 161. https://doi.org/10.1038/srep00161.

Gaujoux, S., Salenave, S., Ronot, M., Rangheard, A.-S., Cros, J., Belghiti, J., Sauvanet, A., Ruszniewski, P., Chanson, P., 2014. Hepatobiliary and pancreatic neoplasms in patients with McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 99, E97–101. https://doi.org/10.1210/jc.2013-1823.

Gaujoux, S., Pasmant, E., Silve, C., Mehsen-Cetre, N., Coriat, R., Rouquette, A., Douset, B., Prat, F., Leroy, K., 2019. McCune Albright syndrome is a genetic predisposition to intraductal papillary and mucinous neoplasms of the pancreas associated pancreatic cancer in relation with GNAS somatic mutation - a case report. Medicine (Baltimore) 98, e18102. https://doi.org/10.1097/MD.0000000000018102.

Hansen, M.R., Moffat, J.C., 2003. Osteosarcoma of the skull base after radiation therapy in a patient with McCune-Albright syndrome: case report. Skull Base. 13, 79–83. https://doi.org/10.1055/s-2003-820562.

Javaid, M.K., Boyce, A., Appelman-Dijkstra, N., Ong, J., Defabianis, P., Offiah, A., Arunde, P., Shaw, N., Pos, V.D., Underhil, A., Portero, D., Heral, L., Heegaard, A.-M., Masi, L., Monsell, F., Stanton, R., Dijkstra, P.D.S., Brandi, M.L., Chapurlat, R., Hamdy, N.A.T., Collins, M.T., 2019. Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Orphanet J Rare Dis. 14, 139. https://doi.org/10.1186/s13023-019-1102-9.

Kanda, M., Knight, S., Topazian, M., Syngal, S., Farrell, J., Lee, J., Kamel, I., Lennon, A.M., Borges, M., Young, A., Fujiwara, S., Seike, J., Eshleman, J., Hruban, R.H., Canto, M.I., Goggins, M., 2013. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. Gut. 62, 1024–1033. https://doi.org/10.1136/gutjnl-2012-302823.

Katznelson, L., Laws, E.R., Melmed, S., Molitch, M.E., Murad, M.H., Utz, A., Wass, J.A.H., 2014. Endocrine Society, acromegaly: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 99, 3933–3951. https://doi.org/10.1210/jc.2014-2700.

Landis, C.A., Masters, S.B., Spada, A., Pace, A.M., Bourne, H.R., Vallar, L., 1989. GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. Nature. 340, 692–696. https://doi.org/10.1038/340692a0.

Lu, J.-Y., Hung, P.-J., Chen, P.-L., Yen, R.-F., Kuo, K.-T., Yang, T.-L., Wang, C.-Y., Chang, T.-C., Huang, T.-S., Chang, C.-C., 2016. Follicular thyroid carcinoma with NRAS Q61K and GNAS R201H mutations that had a good 131I treatment response. Endocrinol Diabetes Metab Case Rep. 2016. https://doi.org/10.1530/EDM-15-0067.

Lyons, J., Landis, C.A., Harsh, G., Vallar, L., Grünewald, K., Feichtinger, H., Duh, Q.Y., Clark, O.H., Kawasaki, E., Bourne, H.R., 1990. Two G protein oncogenes in human endocrine tumors. Science. 249, 655–659. https://doi.org/10.1126/science.2116665.

Majoor, B.C., Boyce, A.M., Bovée, J.V., Smit, V.T., Collins, M.T., Cleton-Jansen, A.-M., Dekkers, O.M., Hamdy, N.A., Dijkstra, P.S., Appelman-Dijkstra, N.M., 2018. Increased risk of breast cancer at a young age in women with fibrous dysplasia. J. Bone Miner. Res. 33, 84–90. https://doi.org/10.1002/jbmr.3286.

Mastorakos, G., Mitsiades, N.S., Doufas, A.G., Koutras, D.A., 1997. Hyperthyroidism in McCune-Albright syndrome with a review of thyroid abnormalities sixty years after the first report. Thyroid. 7, 433–439. https://doi.org/10.1089/thy.1997.7.433.

Mock, D., Rosen, I.B., 1986. Osteosarcoma in irradiated fibrous dysplasia. J. Oral Pathol. 15, 1–4. https://doi.org/10.1111/j.1600-0714.1986.tb00555.x.

Nault, J.C., Fabre, M., Couchy, G., Pilati, C., Jeannot, E., Tran Van Nhieu, J., Saint-Paul, M.-C., De Muret, A., Redon, M.-J., Buffet, C., Salenave, S., Balabaud, C., Prevot, S., Labrune, P., Bioulac-Sage, P., Scoazec, J.-Y., Chanson, P., Zucman-Rossi, J., 2012. GNAS-activating mutations define a rare subgroup of inflammatory liver tumors characterized by STAT3 activation. J. Hepatol. 56, 184–191. https://doi.org/10.1016/j.jhep.2011.07.018.

O'Sullivan, C., Barton, C.M., Staddon, S.L., Brown, C.L., Lemoine, N.R., 1991. Activating point mutations of the gsp oncogene in human thyroid adenomas. Mol. Carcinog. 4, 345–349. https://doi.org/10.1002/mc.2940040503.

Palos-Paz, F., Perez-Guerra, O., Cameselle-Teijeiro, J., Rueda-Chimeno, C., Barreiro-Morandeira, F., Lado-Abeal, J., Galician Group for the Study of Toxic Multinodular Goitre, Vilar, D. Araujo, Argueso, R., Barca, O., Botana, M., Cabezas-Agrícola, J.M., Catalina, P., Gerpe, L. Dominguez, Fernandez, T., Mato, A., Nuño, A., Penin, M., Victoria, B., 2008. Prevalence of mutations in TSHR, GNAS, PRKAR1A and RAS genes in a large series of toxic thyroid adenomas from Galicia, an iodine-deficient area in NW Spain. Eur. J. Endocrinol. 159, 623–631. https://doi.org/10.1530/EJE-08-0313.

Parvanescu, A., Cros, J., Ronot, M., Hentic, O., Grybek, V., Couvelard, A., Levy, P., Chanson, P., Ruszniewski, P., Sauvanet, A., Gaujoux, S., 2014. Lessons from McCune-Albright syndrome-associated intraductal papillary mucinous neoplasms: : GNAS-activating mutations in pancreatic carcinogenesis. JAMA Surg. 149, 858–862. https://doi.org/10.1001/jamasurg.2014.535.

Riminucci, M., Collins, M.T., Lala, R., Corsi, A., Matarazzo, P., Gehron Robey, P., Bianco, P., 2002. An R201H activating mutation of the GNAS1 (Gsalpha) gene in a corticotroph pituitary adenoma, MP. Mol. Pathol. 55, 58–60. https://doi.org/10.1136/mp.55.1.58.

Robinson, C., Estrada, A., Zaheer, A., Singh, V.K., Wolfgang, C.L., Goggins, M.G., Hruban, R.H., Wood, L.D., Noë, M., Montgomery, E.A., Guthrie, L.C., Lennon, A.M., Boyce, A.M., Collins, M.T., 2018. Clinical and radiographic gastrointestinal abnormalities in McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 103, 4293–4303. https://doi.org/10.1210/jc.2018-01022.

Ruggieri, P., Sim, F.H., Bond, J.R., Unni, K.K., 1994. Malignancies in fibrous dysplasia. Cancer. 73, 1411–1424. https://doi.org/10.1002/1097-0142(19940301)73:5<1411::aid-cncr2820730516>3.0.co;2-t.

Sallum, A.C.R., Leonhardt, F.D., Cervantes, O., Abrahão, M., Yazaki, R.K., 2008. Hyperthyroidism related to McCune-Albright syndrome: report of two cases and review of the literature. Arq Bras Endocrinol Metabol. 52, 556–561. https://doi.org/10.1590/s0004-27302008000300017.

Scanlon, E.F., Burkett, F.E., Sener, S.F., Green, O.C., Traisman, H.S., Marr, T.J., Victor, T.A., Crist, M.L., 1980. Breast carcinoma in a 11-year-old girl with Albright's syndrome. Breast. 6, 6–9.

Tanabeu, null, Nakahara, null, Mitsuyama, null, Ono, null, Toyoshima, null, 1998. Breast cancer in a patient with McCune-Albright syndrome. Breast Cancer 5, 175–178. https://doi.org/10.1007/bf02966691.

Tessaris, D., Corrias, A., Matarazzo, P., De Sanctis, L., Wasniewska, M., Messina, M.F., Vigone, M.C., Lala, R., 2012. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. Horm Res Paediatr. 78, 151–157. https://doi.org/10.1159/000342641.

Vortmeyer, A.O., Gläsker, S., Mehta, G.U., Abu-Asab, M.S., Smith, J.H., Zhuang, Z., Collins, M.T., Oldfield, E.H., 2012. Somatic GNAS mutation causes widespread and diffuse pituitary disease in acromegalic patients with McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 97, 2404–2413. https://doi.org/10.1210/jc.2012-1274.

Weinstein, L.S., Shenker, A., Gejman, P.V., Merino, M.J., Friedman, E., Spiegel, A.M., 1991. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N. Engl. J. Med. 325, 1688–1695. https://doi.org/10.1056/NEJM199112123252403.

Wu, J., Matthaei, H., Maitra, A., Dal Molin, M., Wood, L.D., Eshleman, J.R., Goggins, M., Canto, M.I., Schulick, R.D., Edil, B.H., Wolfgang, C.L., Klein, A.P., Diaz, L.A., Allen, P.J., Schmidt, C.M., Kinzler, K.W., Papadopoulos, N., Hruban, R.H., Vogelstein, B., 2011. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 3, 92ra66. https://doi.org/10.1126/scitranslmed.3002543.

Yang, G.C., Yao, J.L., Feiner, H.D., Roses, D.F., Kumar, A., Mulder, J.E., 1999. Lipid-rich follicular carcinoma of the thyroid in a patient with McCune-Albright syndrome. Mod. Pathol. 12, 969–973.

Yoshimoto, K., Iwahana, H., Fukuda, A., Sano, T., Itakura, M., 1993. Rare mutations of the Gs alpha subunit gene in human endocrine tumors. Mutation detection by polymerase chain reaction-primer-introduced restriction analysis. Cancer 72, 1386–1393. https://doi.org/10.1002/1097-0142(19930815)72:4<1386::aid-cncr2820720439>3.0.co;2-j.