Published in final edited form as:

Best Pract Res Clin Endocrinol Metab. 2010 June ; 24(3): 439–449. doi:10.1016/j.beem.2010.02.002.

Endocrine tumours in neurofibromatosis type 1, tuberous sclerosis and related syndromes

Maya B. Lodish, MD and Constantine A. Stratakis, MD, D (med)Sci

Section on Endocrinology Genetics, Program on Developmental Endocrinology Genetics, Eunice Kennedy Shriver National Institute of Child Health and Paediatric Endocrinology Inter-Institute Training Program, National Institutes of Health, Bethesda, MD 20892

Abstract

Neurofibromatosis type 1 (NF-1) and tuberous sclerosis complex (TSC) are two familial syndromes known as phakomatoses that may be associated with endocrine tumors. These hereditary cutaneous conditions affect the central nervous system and are characterized by the development of hamartomas. Over the past 20 years, there have been major advances in our understanding of the molecular basis of these diseases. Both NF-1 and TSC are disorders of unregulated progression through the cell cycle, in which causative genes behave as characteristic tumor suppressor genes. The pathogenesis of these familial syndromes is linked by the shared regulation of a common pathway, the protein kinase mammalian target of rapamycin (mTOR). Additional related disorders that also converge on the mTOR pathway include Peutz-Jeghers syndrome and Cowden syndrome. All of these inherited cancer syndromes are associated with characteristic skin findings that offer a clue to their recognition and treatment. The discovery of mTOR inhibitors has led to a possible new therapeutic modality for patients with endocrine tumors as part of these familial syndromes.

Keywords

phakomatoses; neuroendocrine tumours; tumour suppressor; mammalian target of rapamycin; Cowden; Peutz-Jegher

INTRODUCTION

The inherited syndromes neurofibromatosis type 1 (NF-1), tuberous sclerosis complex (TSC), Cowden syndrome, and Peutz-Jeghers syndrome (PJS) are all associated with increased susceptibility to tumours, including endocrine-related malignancies. These conditions share defects involving skin pigmentation, and have related molecular etiologies. The types of endocrine tumors found in each of these syndromes, as well as the diagnosis and management of these conditions, will be outlined in this review.

Corresponding Author and reprints: Maya Lodish, 10 Center Dr., CRC Room 1-3330, Bethesda, MD 20892, USA, Tel: 301-451-7175, Fax: 301-402-0574 lodishma@mail.nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure statement: The authors have nothing to disclose

Conflict of interest statement: The authors have no conflict of interest to report

NF-1

CLINICAL DESCRIPTION

NF-1 affects about 1 in 4000 individuals worldwide. (1) NF-1 is clinically characterized by multiple café-au-lait spots and associated cutaneous neurofibromas. The National Institutes of Health Consensus Conference developed diagnostic criteria that require at least two of the following clinical features, as outlined in Table 1, in order to diagnose NF-1. (2–4) These features include café-au-lait macules, neurofibromas, axillary freckling, optic gliomas, iris hamartomas, and bony abnormalities.

TYPES OF ENDOCRINE TUMORS IN NF-1

Patients with NF1 are at an approximately 2–4 fold higher risk of developing tumors than the general population with a risk of malignancy estimated at between 5 and 15 percent. (5,6) The gastrointestinal tract may be involved in NF-1 and includes mucosal and myenteric nerve hyperplasia, gastrointestinal stromal tumors (GIST), carcinoids, pheochromocytomas, paragangliomas, as well as pancreatic neuroendocrine tumors (Table 3). (7)

Gastrointestinal Stromal Tumor—GISTs are mesenchymal tumors of the gastrointestinal tract that originate from the interstitial cells of Cajal. The lifetime risk for patients with NF-1 developing a GIST is 1–6%. (8,9) In the setting of NF-1, the majority of GISTs arise in the small intestine and are not associated with somatic mutations in the *KIT* proto-oncogene or platelet derived growth factor alpha (*PDGFA*) genes, and are therefore usually not responsive to tyrosine kinase inhibitor therapy. (10)

Pheochromocytoma—NF1 patients have a lifetime risk of 1–5% for the development of a pheochromocytoma. (11,12) NF-1 associated pheochromocytomas are predominantly epinephrine-producing, and thus patients may present with paroxysmal symptoms due to stimulation of β_2 receptors and subsequent vasodilatation. (11) Sustained hypertension is a feature of approximately 60% of patients with pheochromocytoma in the setting of NF-1. (13) These tumors are almost exclusively localized to one or both adrenal glands and are rarely malignant; in most patients, the tumor is cured by surgery. (11) Biochemical testing via serum fractionated metanepherines should be performed in symptomatic patients with a genetic predisposition for pheochromocytoma. (11) If biochemical testing is positive, computed tomography (CT), magnetic resonance imaging (MRI), and functional imaging with I^{123} MIBG may be utilized to further characterize the tumor.

Somatostinoma—Inherited pancreatic endocrine tumors, especially duodenal carcinoids (somatostatinomas) can occur as part of NF-1, with a penetrance of approximately 1%. (14–17). Somatostatinomas in NF-1 characteristically cause biliary dilatation and pancreatitis and are associated with jaundice, nausea, pain, bleeding, or vomiting. (17) Over the past thirty years, fifty patients with NF1 and somatostatinomas have been identified. (18,19) Metastatic disease to lymph nodes or liver is present in approximately 30% of patients. (15) Gastrinomas, insulinomas, and nonfunctioning pancreatic endocrine tumors have also been reported in NF-1 patients. (20–23) First-line treatment for pancreatic endocrine tumors in NF-1 is via surgical resection. (17)

Optic Pathway Gliomas—Optic pathway gliomas (OPGs) occur in 15 percent of children under the age of six with NF-1. (24) OPGs involve the optic nerves, chiasm, and optic tracts and may be associated with visual problems. Although not tumors of endocrine tissue, these tumors may involve the hypothalamus and can lead to either premature or delayed puberty caused by hypothalamic involvement. (25)

SURVEILLANCE FOR ENDOCRINE TUMORS IN NF-1

The American Academy of Pediatrics has published diagnostic and health supervision guidelines for children with NF1. (26) These include checking blood pressure on an annual basis, as well as assessing children for precocious puberty by evaluating growth and sexual development. The detection of precocious puberty in patients with NF-1 is crucial in order to ameliorate accelerated linear bone growth and premature sexual development. As optic gliomas usually develop before the age of 6, all children with NF-1 under the age of 8 should have annual ophthalmologic examinations, which may be spaced out to once every 2 years between the ages of 8 and 18.(25) Any child with visual symptoms or physical signs such as proptosis, decreased vision, or precocious puberty warrants an MRI to investigate for an OPG. Specific recommendations for surveillance of patients with NF-1 for other endocrine tumors do not exist. However, due to the association of NF-1 with endocrine tumors, physicians should have a high index of suspicion in patients with symptoms suggestive of a neuroendocrine tumor. For example, patients with NF-1 and hypertension should have screening for their plasma metanepherine levels as part of the evaluation.

MOLECULAR PATHWAYS IN NF-1

NF-1 is an autosomal dominant disorder caused by a mutation of the gene encoding neurofibromin, which is located on chromosome 17q11.2. (27,28) Half of the mutations in the *NF1* tumor suppressor gene occur de novo. Neurofibromin is a tumor suppressor that plays a key role in the control of intracellular signaling and regulation of cell growth, acting as a negative regulator of the p 21 ras proto-oncogene. (29) Loss-of function mutations in *NF-1* therefore cause increased activation of ras and increased signaling via downstream pathways, including the mitogen-activated protein kinase (MAPK) pathway and the mammalian target of rapamycin (mTOR) pathway. (30) Many of the regulatory components of this pathway have been elucidated and are outlined in Figure 1. (31) mTOR is a member of the phosphoinositide-3-kinase-related family, and serves as a critical mediator of cell growth and proliferation, responsible for stimulating cell growth and controlling cellular energy levels. (32) (31) mTOR is highly conserved throughout evolution and regulates ribosomal biogenesis, protein translation, and formation of the actin cytoskeleton. (33) Individuals with NF-1 are born with one functional and one mutated NF-1 gene, whereby inactivation of the functional gene leads to loss of neurofibromin expression and tumor formation. Pathogenic mutations of neurofibromin lead to constitutive activation of downstream pathways and subsequent tumor development. (34)

The majority of children with NF-1 meet diagnostic criteria by age 8 via clinical evaluation, thus genetic confirmation of the diagnosis is rarely indicated.(4,35) In addition, mutational analysis is not recommended due to the large size of the *NF-1* gene that spans more than 50 exons and 300 kb of genomic sequence. (36) Evidence supporting NF-1 as the cause of associated endocrine tumors comes from molecular analysis of a malignant insulinoma found in an NF-1 patient in which loss of heterozygosity of the wild type *NF-1* allele was seen in the tumor, and neurofibromin protein expression was absent in the tumor tissue.(22)

TARGETED THERAPUTIC INTERVENTIONS IN NF-1

Tumor cell lines derived from NF1 patients are highly sensitive to the mTOR inhibitor rapamycin, which may serve as a promising therapy for NF1.(34) Drugs that block mTOR and ras are currently under investigation for treatment of NF-1 associated malignancies. A summary of the clinical trials involving the targeted therapies using mTOR inhibitors in NF-1 as well as neuroendocrine tumors outside of NF-1 are presented in tables 4 and 5. A phase II study of the mTOR inhibitor sirolimus in NF-1 related plexiform neurofibromas is currently underway. Farnesyl transferase inhibitors such as tipifarnib interfere with the activation of ras,

which is dysregulated in NF-1. Phase 1 clinical trials of tipifarnib are being performed in patients with plexiform neurofibromas (Table 4). (37)

TUBEROUS SCLEROSIS COMPLEX

CLINICAL DESCRIPTION

Tuberous sclerosis (TSC) is an autosomal dominant neurocutaneous disorder with an incidence of approximately 1 in 5,000 to 10,000 live births. (38) Approximately 70–80% of TSC patients represent sporadic cases. (38,39) TSC is a multisystem disorder with involvement of the brain, eyes, skin, heart, lungs and kidneys with characteristic hamartomatous lesions. The classic TSC triad, known as Vogt's triad, includes mental retardation, seizures, and facial angiofibromas. (40) The diagnostic criteria for TSC include the presence of two major features, or one major and two minor features, as outlined in Table 2. (40,41)

TYPES OF ENDOCRINE TUMORS IN TSC

TSC is associated with an increased risk of benign as well as malignant tumors, especially in the kidneys, brain, and soft tissues. The relative risk of malignancy in children with TSC is approximately 18-fold higher than the general population. (42) Although neuroendocrine tumors have been reported in patients with TSC, they are not currently considered one of the major features TSC. (43) A number of case reports have documented endocrine tumors in patients with TSC, and a recent systematic review summarized the available articles on this association. (43) Pituitary tumors have been reported in four patients with TSC, including adrenocorticotrophic hormone, growth hormone, and prolactin secreting tumors. (44–47) Both parathyroid adenoma and parathyroid hyperplasia have been reported. (48–50) Rarely, pancreatic endocrine tumors including gastrinoma and insulinomas have also been described in TSC. (51–59) There is a single report of a pheochromocytoma in a patient with TSC, as well as a single report of carcinoid occurring together with TSC. (60,61)

SURVEILLANCE FOR ENDOCRINE TUMORS IN TSC

Recommendations exist for the diagnostic evaluation for TSC, and genetic mutation analysis is commercially available. (41) Children with suspected TSC require evaluation for seizures and developmental delay. In addition, magnetic resonance brain imaging, renal ultrasound, and electrocardiogram are indicated at the time of presentation. (41) Genetic testing for TSC mutations is helpful in clinical diagnosis and counseling, however there is a 15% false negative rate for DNA testing as well as an approximately 2% prevalence of germline mosaicism in TSC. (62) Practice guidelines for the surveillance of neuroendocrine tumors in patients with TSC have not been developed. Although current recommendations for evaluation of TSC patients do not include screening for neuroendocrine tumors, given the multiple reports of endocrine tumors in TSC patients, those patients with symptoms suggestive of hypoglycemia or hypercalcemia should lead to a higher level of suspicion of associated NET. (43)

MOLECULAR PATHWAYS IN TSC

Tuberous sclerosis is caused by mutations of two tumor suppressor genes, *TSC1* and *TSC2*. The *TSC1* gene maps to chromosome 9q34 and encodes the protein hamartin. (63,64) The *TSC2* gene maps to chromosome 16p13.3 and encodes the tuberlin protein. (65,66) Hamartin and tuberlin together form a complex that acts to negatively regulate the cell cycle. (67) *TSC* functions as a tumor suppressor gene, as evidenced by the presence of inactivating mutations of *TSC* and loss of heterozygosity of *TSC1* and *TSC2* in tumors associated with TSC. (68,69) Loss-of-function mutations of the tuberlin-hamartin complex impair GTPase activity, leading to constitutive activation of these proteins. The hamartin-tuberlin complex functions as an inhibitor of downstream cellular signaling via the mTOR pathway, and the development of

tumors in patients with TSC is the result of dysregulated signaling of mTOR to downstream targets.(67)

The function of the mTOR pathway in neuroendocrine tumorigenesis in TSC has been demonstrated with molecular studies. The serine-threonine kinase Akt (protein kinase B) is responsible for phosphorylation and inactivation of TSC2, leading to subsequent activation of mTOR.(67,70). Enhanced protein kinase B/Akt signaling has been found in pituitary tumors, and increased activation of the Ras-B-Raf MAP kinase pathway has been demonstrated in pituitary adenomas. (71) (72) In addition, both tuberlin and hamartin are expressed in most cell types and tissues, with increased levels of hamartin found in the endocrine pancreas(73). One pancreatic neuroendocrine tumor was found to have loss of heterozygosity at chromosome 16p13, and absence of expression of tuberlin in the tumor was shown, supporting the role of tuberlin in the development of pancreatic neuroendocrine tumors (NETs) in TSC. (56)

TARGETED THERAPUTIC INTERVENTION IN TSC

Resection of a pancreatic tumor is the first line of treatment, however the optimal systemic treatment for advanced pancreatic NETs continues to be debated. Systemic chemotherapy, somatostatin analogue therapy, and radionuclide therapy are all treatment modalities for endocrine pancreatic tumors (7). As constitutive activation of mTOR contributes to the growth of tuberous sclerosis lesions and endocrine tumors, treatment with mTOR inhibitors may provide promising treatment for this disorder.(74) Two mTOR inhibitors sirolimus and everolimus are both being investigated in other tumour types associated with TSC, as well as in neuroendocrine tumors in general (Tables 4 and 5). Recent evidence has demonstrated some efficacy of mTOR inhibitors in patients with TSC-associated tumors. The use of sirolimus for treatment of angiomyolipomas in patients with TSC was recently reported. The authors found that angiomyolipomas regressed somewhat during sirolimus therapy but tended to increase in volume after the therapy was stopped. (75) Sirolimus has been used in TSC associated paediatric central nervous system tumors. (37,76) The use of the mTOR inhibitor everolimus was reported in four cases of patients with progressive malignant paraganglioma/phaeochromocytoma. (77) Report of the use of everolimus in thirty-three patients with metastatic pancreatic cancer (not specific to TSC patients) was recently published (78). No complete or partial treatment responses were noted, and only seven patients (21%) had stable disease at the first restaging scans performed at 2 months; median progression-free survival and overall survival were 1.8 months and 4.5 months, respectively. The authors concluded that although well tolerated, everolimus administered as a single-agent had minimal clinical activity in patients with metastatic pancreatic cancer.

RELATED SYNDROMES

COWDEN SYNDROME

Another related syndrome associated with hamartomas and endocrine tumour formation is Cowden syndrome. Diagnostic criteria for Cowden syndrome include skin findings such as papillomas and acral keratoses. Patients are susceptible to breast cancer, follicular thyroid cancer, and endometrial carcinoma. (79) Major criteria include breast and thyroid cancer, macrocephaly, and Lhermitte-Duclos disease (hamartomatous growths of the cerebellum with associated ataxia). Minor criteria include thyroid disease (adenoma and goiter), gastrointestinal hamartomas, lipomas, fibromas, genitourinary tumors, fibrocystic breast disease, and developmental delay. (80) Up to 10 percent of patients with Cowden syndrome develop follicular carcinoma, and 50–75% will manifest benign thyroid disease (81,82). In order to diagnose Cowden syndrome, patients must have one major and three minor criteria. Like NF-1 and TSC, Cowden syndrome is also associated with loss-of-function mutations in a tumor suppressor gene leading to constitutive mTOR activation. Approximately 80 percent of patients

with Cowden syndrome are found to have associated mutations in the phosphate and tensin gene (*PTEN*) on chromosome 10q23.31, which codes for a neuroendocrine developmental regulator protein. (79,83) The role of *PTEN* in the mTOR pathway is outlined in Figure 1. Management of Cowden syndrome includes cancer screening including annual mammograms and thyroid examinations, and annual thyroid ultrasounds may also be indicated. (81)

PEUTZ-JEGHERS SYNDROME

Another autosomal dominant hamartomatous disorder associated with endocrine tumour development is Peutz-Jeghers syndrome (PJS). Patients with PJS characteristically have hyperpigmented macules involving the mucocutaneous membranes, and gastrointestinal polyposis. This disorder is characterized by an increased susceptibility to endocrine tumors, including thyroid cancer, benign ovarian sex cord tumors, calcifying sertoli tumors of the testis, cervical cancer, breast cancer, gastrointestinal cancer, pancreatic cancer, endometrial cancer. (84) (85) The Sertoli cell tumors may be associated with gynecomastia. (86) PJS represents another disease that involves dysregulated signalling in the pathway upstream of mTOR (Figure 1). In over one half of cases, PJS is due to mutations in the serine-threonine kinase *STK11/LKB1* tumour suppressor gene, located on 19p13(85). Tumour surveillance includes regular endoscopy and colonoscopy beginning at age 10, as well as mammograms, and testicular examinations and testicular ultrasounds.

PRACTICE POINTS

- A number of tumour suppressor genes have been implicated in endocrine tumour formation. The genetic defects leading to NF-1, TSC, Cowden syndrome, and PJS interact with the same molecular pathway responsible for cell growth and proliferation; loss-of-function mutations in these genes lead to constitutive mTOR activation.
- Therapies targeting the vascular endothelial growth factor pathway and mTOR are currently being evaluated in large randomized studies for the use in many neuroendocrine tumors, and in other tumour types associated with NF-1, TSC, Cowden syndrome, and PJS (Tables 4 and 5).
- Specific guidelines for screening patients with these inherited tumour susceptibility conditions exist, however they do not include clear guidelines for the surveillance of endocrine tumors.

RESEARCH AGENDA

- Future studies are needed to investigate the efficacy of targeted therapies for endocrine tumors associated with activation of the mTOR pathway
- The optimal screening recommendations for endocrine tumors in patients with the inherited tumour susceptibility conditions NF1, TSC, Cowden syndrome, and PJS remains to be determined.

SUMMARY

A number of diseases have been found to involve dysregulated signalling in the pathway upstream of mTOR. The genes *NF-1*, *TSC1*, *TSC2*, *PTEN*, and *LKB1* are components of the mTOR pathway, and mutations in these genes cause NF-1, TSC, Cowden syndrome, and PJS, respectively. These syndromes are all associated with increased susceptibility to tumour development and pigmentation defects, and have converging molecular pathways. All of these syndromes are characterized by tumors involving the endocrine system. Because in vitro studies have implicated the mTOR pathway in the pathogenesis of neuroendocrine tumors, mTOR inhibitors are in clinical use via a number of clinical trials.

Acknowledgments

This work was supported by....

REFERENCES

1. Rasmussen SA, Friedman JM. NF1 gene and neurofibromatosis 1. *Am J Epidemiol* 2000 Jan 1;151(1):33–40. [PubMed: 10625171]
2. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol* 1988 May;45(5):575–578. [PubMed: 3128965]
3. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics* 2000 Mar;105(3 Pt 1):608–614. [PubMed: 10699117]
4. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997 Jul 2;278(1):51–57. [PubMed: 9207339]
5. Sorensen SA, Mulvihill JJ, Nielsen A. Long-term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. *N Engl J Med* 1986 Apr 17;314(16):1010–1015. [PubMed: 3083258]
6. Walker L, Thompson D, Easton D, Ponder B, Ponder M, Frayling I, et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. *Br J Cancer* 2006 Jul 17;95(2):233–238. [PubMed: 16786042]
7. Alexakis N, Connor S, Ghaneh P, Lombard M, Smart HL, Evans J, et al. Hereditary pancreatic endocrine tumours. *Pancreatology* 2004;4(5):417–433. discussion 34–5. [PubMed: 15249710]
8. Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. *Am J Surg Pathol* 2006 Jan;30(1):90–96. [PubMed: 16330947]
9. Zoller ME, Rembeck B, Oden A, Samuelsson M, Angervall L. Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. *Cancer* 1997 Jun 1;79(11):2125–2131. [PubMed: 9179058]
10. Mussi C, Schildhaus HU, Gronchi A, Wardelmann E, Hohenberger P. Therapeutic consequences from molecular biology for gastrointestinal stromal tumor patients affected by neurofibromatosis type 1. *Clin Cancer Res* 2008 Jul 15;14(14):4550–4555. [PubMed: 18628470]
11. Zelinka T, Eisenhofer G, Pacak K. Pheochromocytoma as a catecholamine producing tumor: implications for clinical practice. *Stress* 2007 Jun;10(2):195–203. [PubMed: 17514588]
12. Toumpanakis CG, Caplin ME. Molecular genetics of gastroenteropancreatic neuroendocrine tumors. *Am J Gastroenterol* 2008 Mar;103(3):729–732. [PubMed: 18341492]
13. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. von Recklinghausen's disease and pheochromocytomas. *J Urol* 1999 Nov;162(5):1582–1586. [PubMed: 10524872]
14. Dayal Y, Tallberg KA, Nunnemacher G, DeLellis RA, Wolfe HJ. Duodenal carcinoids in patients with and without neurofibromatosis. A comparative study. *Am J Surg Pathol* 1986 May;10(5):348–357. [PubMed: 2422964]
15. Mao C, Shah A, Hanson DJ, Howard JM. Von Recklinghausen's disease associated with duodenal somatostatinoma: contrast of duodenal versus pancreatic somatostatinomas. *J Surg Oncol* 1995 May;59(1):67–73. [PubMed: 7745981]
16. Anlauf M, Garbrecht N, Bauersfeld J, Schmitt A, Henopp T, Komminoth P, et al. Hereditary neuroendocrine tumors of the gastroenteropancreatic system. *Virchows Arch* 2007 Aug;451 Suppl 1:S29–S38. [PubMed: 17684762]
17. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 2008 Oct 1;113(7 Suppl):1807–1843. [PubMed: 18798544]
18. Caiazzo R, Mariette C, Piessen G, Jany T, Carnaille B, Triboulet JP. Type I neurofibromatosis, pheochromocytoma and somatostatinoma of the ampulla. Literature review. *Ann Chir* 2006 Jul–Aug;131(6–7):393–397. [PubMed: 16426562]

19. Cappelli C, Agosti B, Braga M, Cumetti D, Gandossi E, Rizzoni D, et al. Von Recklinghausen's neurofibromatosis associated with duodenal somatostatinoma. A case report and review of the literature. *Minerva Endocrinol* 2004 Mar;29(1):19–24. [PubMed: 15258554]
20. Lee WS, Koh YS, Kim JC, Park CH, Joo YE, Kim HS, et al. Zollinger-Ellison syndrome associated with neurofibromatosis type 1: a case report. *BMC Cancer* 2005;5:85. [PubMed: 16042772]
21. Chagnon JP, Barge J, Henin D, Blanc D. Recklinghausen's disease with digestive localizations associated with gastric acid hypersecretion suggesting Zollinger-Ellison syndrome. *Gastroenterol Clin Biol* 1985 Jan;9(1):65–69. [PubMed: 3920107]
22. Perren A, Wiesli P, Schmid S, Montani M, Schmitt A, Schmid C, et al. Pancreatic endocrine tumors are a rare manifestation of the neurofibromatosis type 1 phenotype: molecular analysis of a malignant insulinoma in a NF-1 patient. *Am J Surg Pathol* 2006 Aug;30(8):1047–1051. [PubMed: 16861979]
23. Coskey RL, Tranquada RE. Insulinoma and Multiple Neurofibromatosis: Report of a Case. *Metabolism* 1964 Apr;13:312–318. [PubMed: 14143154]
24. Lewis RA, Gerson LP, Axelson KA, Riccardi VM, Whitford RP. von Recklinghausen neurofibromatosis. II. Incidence of optic gliomata. *Ophthalmology* 1984 Aug;91(8):929–935. [PubMed: 6436764]
25. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol* 2007 Mar;61(3):189–198. [PubMed: 17387725]
26. Hersh JH. Health supervision for children with neurofibromatosis. *Pediatrics* 2008 Mar;121(3):633–642. [PubMed: 18310216]
27. Cawthon RM, Weiss R, Xu GF, Viskochil D, Culver M, Stevens J, et al. A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. *Cell* 1990 Jul 13;62(1):193–201. [PubMed: 2114220]
28. Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulino AM, et al. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. *Science* 1990 Jul 13;249(4965):181–186. [PubMed: 2134734]
29. Martin GA, Viskochil D, Bollag G, McCabe PC, Crosier WJ, Haubruck H, et al. The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21. *Cell* 1990 Nov 16;63(4):843–849. [PubMed: 2121370]
30. Brems H, Beert E, de Ravel T, Legius E. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. *Lancet Oncol* 2009 May;10(5):508–515. [PubMed: 19410195]
31. Rosner M, Hanneder M, Siegel N, Valli A, Fuchs C, Hengstschlager M. The mTOR pathway and its role in human genetic diseases. *Mutat Res* 2008 Sep–Oct;659(3):284–292. [PubMed: 18598780]
32. Kwiatkowski DJ, Manning BD. Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways. *Hum Mol Genet* 2005 Oct 15;14(Spec No. 2):R251–R258. [PubMed: 16244323]
33. Sandsmark DK, Pelletier C, Weber JD, Gutmann DH. Mammalian target of rapamycin: master regulator of cell growth in the nervous system. *Histol Histopathol* 2007 Aug;22(8):895–903. [PubMed: 17503347]
34. Johannessen CM, Reczek EE, James MF, Brems H, Legius E, Cichowski K. The NF1 tumor suppressor critically regulates TSC2 and mTOR. *Proc Natl Acad Sci U S A* 2005 Jun 14;102(24):8573–8578. [PubMed: 15937108]
35. Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI, Eldridge R. NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). *Ann Intern Med* 1990 Jul 1;113(1):39–52. An update. [PubMed: 2112353]
36. Viskochil D, Buchberg AM, Xu G, Cawthon RM, Stevens J, Wolff RK, et al. Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell* 1990 Jul 13;62(1):187–192. [PubMed: 1694727]
37. Widemann BC, Salzer WL, Arceci RJ, Blaney SM, Fox E, End D, et al. Phase I trial and pharmacokinetic study of the farnesyltransferase inhibitor tipifarnib in children with refractory solid tumors or neurofibromatosis type I and plexiform neurofibromas. *J Clin Oncol* 2006 Jan 20;24(3):507–516. [PubMed: 16421428]
38. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci* 1991;615:125–127. [PubMed: 2039137]

39. Rosser T, Panigrahy A, McClintock W. The diverse clinical manifestations of tuberous sclerosis complex: a review. *Semin Pediatr Neurol* 2006 Mar;13(1):27–36. [PubMed: 16818173]
40. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol* 1998 Dec;13(12):624–628. [PubMed: 9881533]
41. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. *J Child Neurol* 1999 Jun;14(6):401–407. [PubMed: 10385849]
42. Narod SA, Stiller C, Lenoir GM. An estimate of the heritable fraction of childhood cancer. *Br J Cancer* 1991 Jun;63(6):993–999. [PubMed: 2069856]
43. Dworakowska D, Grossman AB. Are neuroendocrine tumours a feature of tuberous sclerosis? A systematic review. *Endocr Relat Cancer* 2009 Mar;16(1):45–58. [PubMed: 18978035]
44. Tigas S, Carroll PV, Jones R, Bingham E, Russell-Jones D, Powell M, et al. Simultaneous Cushing's disease and tuberous sclerosis; a potential role for TSC in pituitary ontogeny. *Clin Endocrinol (Oxf)* 2005 Dec;63(6):694–695. [PubMed: 16343106]
45. Nandagopal R, Vortmeyer A, Oldfield EH, Keil MF, Stratakis CA. Cushing's syndrome due to a pituitary corticotropinoma in a child with tuberous sclerosis: an association or a coincidence? *Clin Endocrinol (Oxf)* 2007 Oct;67(4):639–641. [PubMed: 17596199]
46. Hoffman WH, Perrin JC, Halac E, Gala RR, England BG. Acromegalic gigantism and tuberous sclerosis. *J Pediatr* 1978 Sep;93(3):478–480. [PubMed: 211218]
47. Bloomgarden ZT, McLean GW, Rabin D. Autonomous hyperprolactinemia in tuberous sclerosis. *Arch Intern Med* 1981 Oct;141(11):1513–1515. [PubMed: 7197143]
48. Mortensen LS, Rungby J. Tuberous sclerosis and parathyroid adenoma. *J Clin Pathol* 1991 Nov;44(11):961–962. [PubMed: 1752991]
49. Ilgren EB, Westmoreland D. Tuberous sclerosis: unusual associations in four cases. *J Clin Pathol* 1984 Mar;37(3):272–278. [PubMed: 6142060]
50. Yin W, Zhu DM, Wang DS, Wang DX, Wu EH, Zhu XY. Parathyroid adenoma with primary hyperparathyroidism and tuberous sclerosis. A case report. *Chin Med J (Engl)* 1984 Aug;97(8):599–602. [PubMed: 6440749]
51. Davoren PM, Epstein MT. Insulinoma complicating tuberous sclerosis. *J Neurol Neurosurg Psychiatry* 1992 Dec;55(12):1209. [PubMed: 1479404]
52. Boubaddi NE, Imbert Y, Tissot B, Chapus JJ, Dupont E, Gallouin D, et al. [Secreting insulinoma and Bourneville's tuberous sclerosis]. *Gastroenterol Clin Biol* 1997;21(4):343. [PubMed: 9208005]
53. Eledrisi MS, Stuart CA, Alshanti M. Insulinoma in a patient with tuberous sclerosis: is there an association? *Endocr Pract* 2002 Mar–Apr;8(2):109–112. [PubMed: 11942775]
54. Schwarzkopf G, Pfisterer J. Metastasizing gastrinoma and tuberous sclerosis complex. Association or coincidence? *Zentralbl Pathol* 1994 Feb;139(6):477–481. [PubMed: 8161496]
55. Merritt JL 2nd, Davis DM, Pittelkow MR, Babovic-Vuksanovic D. Extensive acrochordons and pancreatic islet-cell tumors in tuberous sclerosis associated with TSC2 mutations. *Am J Med Genet A* 2006 Aug 1;140(15):1669–1672. [PubMed: 16835931]
56. Francalanci P, Diomedi-Camassei F, Purificato C, Santorelli FM, Giannotti A, Dominici C, et al. Malignant pancreatic endocrine tumor in a child with tuberous sclerosis. *Am J Surg Pathol* 2003 Oct;27(10):1386–1389. [PubMed: 14508401]
57. Kim H, Kerr A, Morehouse H. The association between tuberous sclerosis and insulinoma. *AJNR Am J Neuroradiol* 1995 Aug;16(7):1543–1544. [PubMed: 7484652]
58. Verhoef S, van Diemen-Steenen R, Akkersdijk WL, Bax NM, Ariyurek Y, Hermans CJ, et al. Malignant pancreatic tumour within the spectrum of tuberous sclerosis complex in childhood. *Eur J Pediatr* 1999 Apr;158(4):284–287. [PubMed: 10206124]
59. Gutman A, Leffkowitz M. Tuberous sclerosis associated with spontaneous hypoglycaemia. *Br Med J* 1959 Nov 21;2(5159):1065–1068. [PubMed: 13830461]
60. Sato T, Seyama K, Kumasaka T, Fujii H, Setoguchi Y, Shirai T, et al. A patient with TSC1 germline mutation whose clinical phenotype was limited to lymphangioleiomyomatosis. *J Intern Med* 2004 Aug;256(2):166–173. [PubMed: 15257730]

61. Stern J, Friesen A, Bowering R, Babaryka I. Multiple bilateral angiomyolipomas of the kidneys in tuberous brain sclerosis in association with pleomorphic pheochromocytoma. *Fortschr Med* 1982 Oct 21;100(39):1809–1812. [PubMed: 7152417]
62. Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. *J Child Neurol* 2004 Sep;19(9):643–649. [PubMed: 15563009]
63. van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. *Science* 1997 Aug 8;277(5327):805–808. [PubMed: 9242607]
64. Lamb RF, Roy C, Diefenbach TJ, Vinters HV, Johnson MW, Jay DG, et al. The TSC1 tumor suppressor hamartin regulates cell adhesion through ERM proteins and the GTPase Rho. *Nat Cell Biol* 2000 May;2(5):281–287. [PubMed: 10806479]
65. Wienecke R, Konig A, DeClue JE. Identification of tuberlin, the tuberous sclerosis-2 product. Tuberlin possesses specific Rap1GAP activity. *J Biol Chem* 1995 Jul 7;270(27):16409–16414. [PubMed: 7608212]
66. Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell* 1993 Dec 31;75(7):1305–1315. [PubMed: 8269512]
67. Tee AR, Fingar DC, Manning BD, Kwiatkowski DJ, Cantley LC, Blenis J. Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. *Proc Natl Acad Sci U S A* 2002 Oct 15;99(21):13571–13576. [PubMed: 12271141]
68. Carbonara C, Longa L, Grosso E, Borroni C, Garre MG, Brisigotti M, et al. 9q34 loss of heterozygosity in a tuberous sclerosis astrocytoma suggests a growth suppressor-like activity also for the TSC1 gene. *Hum Mol Genet* 1994 Oct;3(10):1829–1832. [PubMed: 7849708]
69. Green AJ, Smith M, Yates JR. Loss of heterozygosity on chromosome 16p13.3 in hamartomas from tuberous sclerosis patients. *Nat Genet* 1994 Feb;6(2):193–196. [PubMed: 8162074]
70. Manning BD, Tee AR, Logsdon MN, Blenis J, Cantley LC. Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberlin as a target of the phosphoinositide 3-kinase/akt pathway. *Mol Cell* 2002 Jul;10(1):151–162. [PubMed: 12150915]
71. Ewing I, Pedder-Smith S, Franchi G, Ruscica M, Emery M, Vax V, et al. A mutation and expression analysis of the oncogene BRAF in pituitary adenomas. *Clin Endocrinol (Oxf)* 2007 Mar;66(3):348–352. [PubMed: 17302867]
72. Musat M, Korbonits M, Kola B, Borboli N, Hanson MR, Nanzer AM, et al. Enhanced protein kinase B/Akt signalling in pituitary tumours. *Endocr Relat Cancer* 2005 Jun;12(2):423–433. [PubMed: 15947113]
73. Johnson MW, Kerfoot C, Bushnell T, Li M, Vinters HV. Hamartin and tuberlin expression in human tissues. *Mod Pathol* 2001 Mar;14(3):202–210. [PubMed: 11266527]
74. El-Hashemite N, Zhang H, Henske EP, Kwiatkowski DJ. Mutation in TSC2 and activation of mammalian target of rapamycin signalling pathway in renal angiomyolipoma. *Lancet* 2003 Apr 19;361(9366):1348–1349. [PubMed: 12711473]
75. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008 Jan 10;358(2):140–151. [PubMed: 18184959]
76. Lam C, Bouffet E, Tabori U, Mabbott D, Taylor M, Bartels U. Rapamycin (sirolimus) in tuberous sclerosis associated pediatric central nervous system tumors. *Pediatr Blood Cancer* 2009 Oct;23
77. Druce MR, Kaltsas GA, Fraenkel M, Gross DJ, Grossman AB. Novel and evolving therapies in the treatment of malignant pheochromocytoma: experience with the mTOR inhibitor everolimus (RAD001). *Horm Metab Res* 2009 Sep;41(9):697–702. [PubMed: 19424940]
78. Wolpin BM, Hezel AF, Abrams T, Blaszkowsky LS, Meyerhardt JA, Chan JA, et al. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol* 2009 Jan 10;27(2):193–198. [PubMed: 19047305]
79. Eng C. PTEN: one gene, many syndromes. *Hum Mutat* 2003 Sep;22(3):183–198. [PubMed: 12938083]
80. Stratakis CA, Kirschner LS, Taymans SE, Tomlinson IP, Marsh DJ, Torpy DJ, et al. Carney complex, Peutz-Jeghers syndrome, Cowden disease, and Bannayan-Zonana syndrome share cutaneous and

- endocrine manifestations, but not genetic loci. *J Clin Endocrinol Metab* 1998 Aug;83(8):2972–2976. [PubMed: 9709978]
81. Nose V. Familial non-medullary thyroid carcinoma: an update. *Endocr Pathol* 2008 Winter;19(4):226–240. [PubMed: 18931957]
82. Blumenthal GM, Dennis PA. PTEN hamartoma tumor syndromes. *Eur J Hum Genet* 2008 Nov;16(11):1289–1300. [PubMed: 18781191]
83. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet* 2000 Nov;37(11):828–830. [PubMed: 11073535]
84. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res* 2006 May 15;12(10):3209–3215. [PubMed: 16707622]
85. Stratakis CA. Genetics of Carney complex and related familial lentiginoses, and other multiple tumor syndromes. *Front Biosci* 2000 Mar 1;5:D353–D366. [PubMed: 10704431]
86. Winterfield L, Schultz J, Stratakis CA, Cowen EW. Gynecomastia and mucosal lentigines in an 8-year-old boy. *J Am Acad Dermatol* 2005 Oct;53(4):660–662. [PubMed: 16198789]

Figure 1. Components of the mTOR regulatory pathway

The tumour-suppressor genes LKB1, PTEN, NF1, and TSC 1 and 2 all exert inhibitory effects on signalling through the TSC complex that inactivates mTOR. Each of these tumour suppressor genes is mutated in distinct syndromes that are characterized by increased malignancy risk. LKB1, serine/threonine kinase 11; AMPK, AMP-activated protein kinase; PTEN, phosphatase and tensin homolog; P13K, 1-phosphatidylinositol 3-kinase; PDK1, pyruvate dehydrogenase kinase isozyme 1; AKT, protein kinase B; NF1, neurofibromatosis type 1; MEK, mitogen activated protein kinase kinase; ERK, extracellular signal-regulated kinase; RSK1, p90 ribosomal S6 kinase; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2; mTOR, mammalian target of rapamycin.

Table 1

Diagnostic criteria for NF-1

Diagnostic criteria for NF-1	
<ul style="list-style-type: none">• Six or more café-au-lait macules >5 mm in longest diameter in prepubertal and >15 mm in longest diameter in postpubertal individuals• Two or more neurofibromas of any type or one plexiform neurofibroma• axillary or inguinal freckling• Optic glioma• Two or more Lisch nodules (iris hamartomas)• A distinctive bony lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis• A first-degree relative with NF1 based upon the above criteria	

Table 2

Diagnostic criteria for TSC

Major clinical features of TSC	Minor clinical features of TS
<ul style="list-style-type: none"> • Facial angiofibromas or forehead plaques • Shagreen patch (connective tissue nevus) • Three or more hypomelanotic macules • Nontraumatic ungual or periungual fibromas • Lymphangiomyomatosis • Renal angiomyolipoma • Cardiac rhabdomyoma • Multiple retinal nodular hamartomas • Cortical tuber • Subependymal nodules • Subependymal giant cell astrocytoma 	<ul style="list-style-type: none"> • Confetti skin lesions (multiple 1 to 2 mm hypomelanotic macules) • Gingival fibromas • Pits in dental enamel • Hamartomatous rectal polyps • Multiple renal cysts • Nonrenal hamartomas • Bone cysts • Retinal achromic patch • Cerebral white matter radial migration lines

Table 3

Characteristics of four phakamotoses

Syndrome	Risk of other malignancy	Skin lesion	Types of endocrine tumors	Genotype	Frequency
Peutz-Jeghers	Gastrointestinal hamartomas Breast cancer	Lentigines	Thyroid Testicular Ovarian	STK11/LKB1 (19q13)	1 in 25,000
Tuberous sclerosis	Renal-cell carcinoma Angiomyolipomas Astrocytoma	Angiofibromas Ash-leaf macules Shagreen patch Fibroma	Pancreatic neuroendocrine tumors	TSC1 (9q34) TSC2 (16p13)	Prevalence 1 per 5,000–10,000
Cowden Syndrome	Prostate cancer Bladder cancer Glioblastoma multiforme Colon cancer	Keratosis Papillomatosis of oral mucosa	Breast cancer Follicular thyroid cancer, endometrial cancer Ovarian cancer	PTEN (10q23.31)	1 in 200,000
Neurofibromatosis type 1	Optic gliomas Meningioma Astrocytoma Neurofibrosarcoma Rhabdomyosarcoma Pheochromocytoma Duodenal carcinoid	Café au lait macules Neurofibromas Axillary freckling	Somatostatin/insulin producing NET, duodenal NET, GIST	NF2 (17q11.2)	Prevalence 1 per 4–5,000

Table 4

Clinical trials with targeted therapy for the phakomatoses

Disease	Tumour Type	Drug	Mechanism	Identifier	Status
NF-1	Plexiform neurofibromas	Sunitinib	mTOR inhibitor	NCT00634270 NCT00652990	Recruiting
NF-1	Plexiform neurofibromas	Tipifarnib	Farnesyltransferase inhibitor	NCT00029354	Suspended
NF-1	Gliomas	Tarceva/ Rapamycin	EGFR inhibitor and mTOR inhibitor	NCT00901849	Enrolling
NF-1	Plexiform neurofibromas	Sorafenib	Multikinase inhibitor with activity against raf, VEGFR, and PDGFR	NCT00727233	Recruiting
Peutz-Jeghers Syndrome	Gastrointestinal polyps	Everolimus	mTOR Inhibitor	NCT00811590	Recruiting
Cowden Syndrome	Benign and malignant tumors, site not specified	Sunitinib	mTOR inhibitor	NCT00971789 NCT00722449	Recruiting
TSC	Giant cell astrocytoma	Everolimus	mTOR inhibitor	NCT00789828 NCT00411619	Recruiting/ ongoing
TSC	Angiomyolipoma	Everolimus	mTOR inhibitor	NCT00790400 NCT00457964 NCT00457808	Recruiting/ Completed
TSC	Angiomyolipoma	Sunitinib	mTOR inhibitor	NCT00490789	Active, not recruiting

Table 5

Studies for neuroendocrine tumors involving mTOR inhibitors

Drug	Mechanism	Identifier	Status
Everolimus	mTOR inhibitor	NCT00510068 NCT00363051 NCT00688623 NCT00936858	Active, not recruiting Active, not recruiting Recruiting Recruiting
Everolimus Plus Octreotide	mTOR inhibitor and Somatostatin analogue	NCT00113360 NCT00412061	Active, not recruiting Ongoing, not recruiting
Everolimus and Avastatin	mTOR inhibitor, angiogenesis inhibitor	NCT00607113	Active, not recruiting
Everolimus and Sorafenib	mTOR inhibitor Multikinase inhibitor with activity against raf, VEGFR, and PDGFR	NCT00942682	Recruiting
Everolimus and Erlotinib	mTOR inhibitor EGFR tyrosine kinase inhibitor.	NCT00843531	Recruiting
Everolimus and Pasireotide	mTOR inhibitor and somatostatin analogue	NCT00804336	Recruiting
Everolimus and Temozolomide	mTOR inhibitor and alkylating agent	NCT00576680	Recruiting
Temsirolimus	mTOR inhibitor	NCT00093782	Active, not recruiting

Legend: NF-1, Neurofibromatosis; TSC, tuberous sclerosis complex; mTOR, mammalian target of rapamycin; EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor;