Chapter 25
Pheochromocytoma and NF1

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25.1 Introduction

Neurofibromatosis type 1 (NF1), or von Recklinghausen disease, is a common autosomal dominant inherited disorder associated with pheochromocytoma, a rare neuroendocrine, catecholamine-producing tumor. Pheochromocytomas occur sporadically but are also a feature of numerous familial cancer syndromes. Neurofibromatosis type 1 is the oldest known classic inherited pheochromocytoma-associated syndrome, a group of disorders that also includes multiple endocrine neoplasia type 2 (MEN2), von Hippel–Lindau disease (VHL), the pheochromocytoma/paraganglioma syndromes (PGL1–4), and the familial pheochromocytoma syndromes. They are characterized by their typical clinical features and their molecular genetic basis. Pheochromocytomas associated with these syndromes differ in terms of their age at diagnosis, their tumor localization, and their malignant potential. Sustained or intermittent hypertension, which can be life-threatening, is the classic symptom of pheochromocytoma. Hypertension is also a frequent finding in NF1 patients and in half of these patients pheochromocytomas are causative. Neurofibromatosis type 1 is a rare cause of pheochromocytomas which are only found in a small number of NF1 patients. However, NF1 and pheochromocytomas have a long history and share some striking features.

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25.2 Historical Background

NF1 was the first described pheochromocytoma-associated syndrome. The first clinical description of a patient with neurofibromatosis and the first clinical description of a patient with pheochromocytoma were not only published in the same century but also in the same decade. Friedrich Daniel von Recklinghausen (1833–1910), a German pathologist, published a detailed description of neurofibromatosis in 1882 and lent his name to the disease (von Recklinghausen 1882). Four years later, in 1886, Felix Fränkel published an article about the clinical history of the 18-year-old Minna Roll with "bilateral adrenal sarcoma and angiosarcoma" (Fränkel 1886). This article has traditionally been considered to be the first description of a pheochromocytoma, but 121 years later, that case has been identified with current knowledge and technology to be a patient with MEN2 (Neumann et al. 2007). In 1910, Suzuki recorded the association of pheochromocytoma with neurofibromatosis type 1. He described a 60-year-old patient with a small chromaffin cell tumor of the right adrenal gland and cutaneous neurofibromas (Suzuki 1910). Since 1911, pheochromocytomas have been found to be a rare but persistent feature of neurofibromatosis type 1.

25.3 Epidemiology and Etiology

Neurofibromatosis type 1 is one of the most common autosomal dominant genetic disorders with an incidence ranging from 1:2,600 to 1:3,000 and complete penetrance (Lammert et al. 2005). Neoplastic proliferation of neural crest-derived cells is the predominant origin of tumor formation in NF1 and pheochromocytoma. In general, the term pheochromocytoma refers to endocrine-active, catecholamine-producing tumors of the adrenal gland and of the extra-adrenal, sympathetic paraganglia, whereas the term paraganglioma refers to endocrine-inactive tumors of parasympathetic paraganglia, mainly of the head and neck region (Neumann 2008). The incidence of pheochromocytomas is far lower than that of NF1 with approximately 2–8:1,000,000 (Beard et al. 1983). Between 25 % and 30 % of these tumors occur in the context of inherited cancer syndromes including NF1, multiple endocrine neoplasia type 2 (MEN2), von Hippel–Lindau disease (VHL), the pheochromocytoma/paraganglioma syndromes (PGL1–4), and the familial pheochromocytoma syndromes (Neumann et al. 2002; Karasek et al. 2010). In about 2–4 % of pheochromocytomas, NF1 constitutes the genetic basis of the disease (Bausch et al. 2006a, b; Mannelli et al. 2009). The estimated prevalence of pheochromocytomas in NF1 is 0.1–5.7 % (Walther et al. 1999).

25.4 Clinical Characteristics

Neurofibromatosis type 1 and pheochromocytoma are both characterized by a wide range of clinical signs and symptoms. NF1 is known for its extreme clinical variability among unrelated patients, among patients within the same family and

even within a single person at different times in life. Pheochromocytomas are referred to be "the great masquerader" owing to their variable clinical presentation. They are characterized by their excessive secretion of the catecholamines epinephrine, norepinephrine, and dopamine, resulting in about 24 % of patients in the classic triad of palpitation, headache, and sweating (Plouin et al. 1981; Mannelli et al. 1999). Severe catecholamine crises can be life-threatening due to the associated heart failure and arrhythmias. Even though the classic triad occurs in only 24 % of patients, almost all suffer from sustained or intermittent hypertension.

The hallmarks of NF1 are pigmentary abnormalities such as axillary or inguinal freckling, café au lait spots, neurofibromas or plexiform neurofibromas, optic gliomas, and Lisch nodules of the iris. About 50 % of the patients have learning disabilities and may develop skeletal abnormalities and vascular disease. Hypertension is a frequent finding and more common than in the general population (Lynch et al. 1972; Walther et al. 1999). In most cases, its origin is either unknown or caused by vasculopathies such as renal artery stenosis and coarctation of the aorta. Pheochromocytomas are a much less common cause with about 0.1–5.7 % in all NF1-affected patients but in 20–50 % of hypertensive NF1 patients (Lynch et al. 1972; Kalff et al. 1982; Walther et al. 1999).

25.5 Molecular Basis

Neurofibromatosis type 1 and the associated pheochromocytomas are caused by heterozygous, inactivating mutations of the *NF1* gene, a tumor suppressor gene, located on chromosome 17q11.2. Mutation analysis in patients with NF1 and pheochromocytoma has been performed rarely. The analysis is time consuming, complicated, and complex and remains a considerable challenge because of the large size of the gene and the low prevalence of pheochromocytomas in NF1 patients (0.1–5.7 %). The mutational spectrum in these patients has been found to be similar to that found in NF1 patients in general. More than 80 % of the mutations are either nonsense or frameshift mutations, likely to yield a truncated nonfunctional neurofibromin protein (Fig. 25.1). About 10 % are deletions or duplications which affect the length of one to >50 exons (Bausch et al. 2007) (Fig. 25.1). Whole gene deletions and large-scale rearrangements have not been described. Specific mutations associated with the development of pheochromocytomas have also not been identified.

In about 2–4 % of patients with pheochromocytomas, NF1 has been found to be the genetic background. So far, *NF1* mutation analysis is uncommon among patients with apparently sporadic pheochromocytomas. One study identified a pathogenic nucleotide substitution resulting in a missense mutation in a patient with benign, bilateral pheochromocytoma. The clinical reevaluation of the patient disclosed faint but characteristic features of neurofibromatosis type 1. Thus, the disease was not only identified by molecular genetic analysis but also by its typical clinical signs (Fig. 25.2) (Bausch et al. 2006a, b).

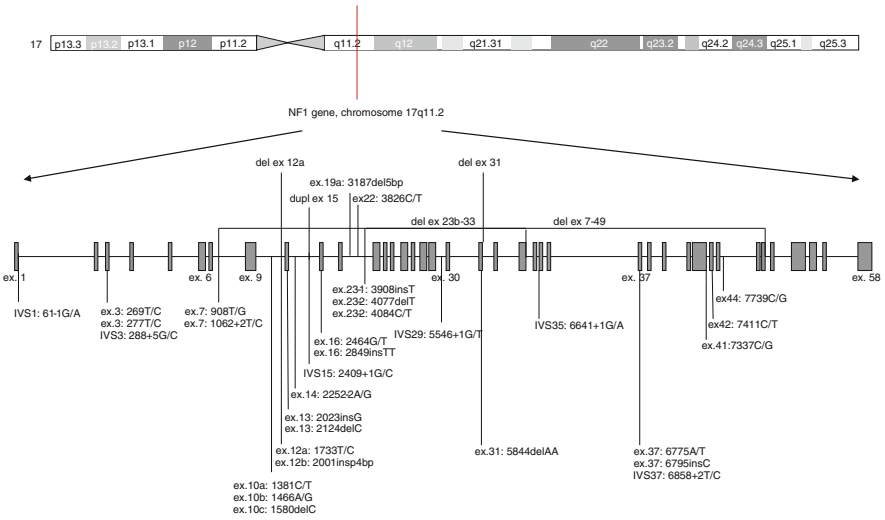

Fig. 25.1 Mutation spectrum in patients with NF1 and pheochromocytoma

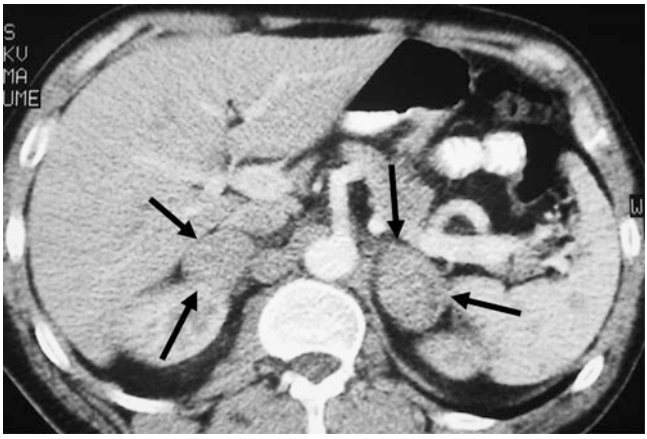

Fig. 25.2 CT scan of a bilateral pheochromocytoma

As the oldest known pheochromocytoma-associated syndrome, NF1 has to be seen in context with the different pheochromocytoma-associated syndromes, multiple endocrine neoplasia type 2 (MEN2), von Hippel–Lindau disease (VHL), the four pheochromocytoma/paraganglioma syndromes (PGL1, 2, 3, 4), and the familial pheochromocytoma syndromes, respectively. They are characterized by their clinical features and their molecular genetic basis. The *NF1* gene is only one of 10 tumor susceptibility genes associated with the pathogenesis of pheochromocytomas (Neumann et al. 2004; Benn and Robinson 2006; Mannelli et al. 2007; Bayley et al. 2010; Burnichon et al. 2010; Qin et al. 2010; Comino-Mendez et al. 2011)

(Table 25.1). Heterozygous, inactivating mutations of the *VHL* gene and of the genes encoding the SDH (succinate dehydrogenase) complex subunits (*SDHA*, *SDHB*, *SDHC*, *SDHD,* and *SDHAF2*) of the *MAX* gene and the *TMEM127* gene cause von Hippel–Lindau disease, the paraganglioma syndromes type 1, 2, 3, and 4, and the familial pheochromocytoma syndromes (Table 25.1). Activating, gain-of-function mutations in the *RET* proto-oncogene are responsible for MEN types 2A and 2B (Table 25.1). Their common pattern of inheritance is autosomal dominant with the exception of paraganglioma syndromes type 1 and 2 and the *MAX* gene associated familial pheochromocytoma syndrome which are autosomal dominant inherited disorders with maternal genomic imprinting, also known as a parent-of-origin effect. Tumors only develop if an individual inherits the mutation from the father (Hensen et al. 2004; Bayley et al. 2010; Comino-Mendez et al. 2011). In contrast to NF1, the molecular basis of these syndromes are genes that are smaller in size than the *NF1* gene and a clear genotype–phenotype correlation has been identified. Owing to the clear genotype–phenotype correlations in VHL, MEN2, and the paraganglioma syndromes and the consequent possibility of clinically significant risk stratification, mutation analysis is recommended and performed if one of these syndromes is suspected. The main phenotype of the familial pheochromocytoma syndromes caused by *TMEM127*, *MAX,* and *SDHA* gene mutations has, yet to be clearly defined, and genetic screening is therefore neither available nor recommended. The diagnosis of NF1 in current clinical and scientific work is still based on clinical criteria, although mutation analysis is possible. Molecular genetic analysis is usually not required for diagnosis and is complex and time-consuming owing to the large size of the gene and the lack of a distinct genotype–phenotype correlation.

25.6 Tumorigenesis

Mutations of *NF1*, a tumor suppressor gene, result predominantly in a loss of function of the protein product neurofibromin. Notably, pheochromocytoma tumorigenesis follows Knudson's "two-hit theory" put forward in 1971: loss of heterozygosity of the *NF1* gene due to a second somatic hit together with the loss of the remaining wild-type allele has been identified in pheochromocytomas (Knudson 1971; Bausch et al. 2007). Thus, the lack of neurofibromin expression seems causative for the development of these tumors. Neurofibromin is part of a family of GTPase-activating proteins (GAPs) that downregulate the cellular proto-oncogene p21–ras. p21–ras is important for cell growth and cell regulation via the activation of numerous different pathways such as stem cell factor (SCF)/c-kit signaling, mTOR, and MAP kinase pathways (Martin et al. 1990; Cichowski et al. 1999; Weiss et al. 1999). The loss of neurofibromin leads to the activation of p21–ras, which in turn stimulates cell proliferation. New insights into the tumorigenesis of hereditary pheochromocytomas were achieved via genome-wide expression studies. Based on their transcriptomes, hereditary pheochromocytomas/paragangliomas comprise two major subgroups (Burnichon et al. 2011). Tumors

Table 25.1 Molecular basis of hereditary pheochromocytoma-associated syndromes

	NF1	VHL	MEN2	PGL1	PGL2	PGL3	PGL4	Familial pheochromocytoma syndromes		
Mode of inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant + maternal imprinting	Autosomal dominant + maternal imprinting	Autosomal dominant	Autosomal dominant	Autosomal dominant		Autosomal dominant + maternal imprinting
Gene type	Tumor suppressor gene	Tumor suppressor gene	Proto-oncogene	Tumor suppressor gene	Tumor suppressor gene	Tumor suppressor gene	Tumor suppressor gene	Tumor suppressor gene		
Gene	*NF1*	*VHL*	*RET*	*SDHD*	*SDHAF2*	*SDHC*	*SDHB*	*TMEM127*	*SDHA*	*MAX*
Chromosome location	17q11.2	3p25.5	10q11.2	11q23	11q13.1	1q21	1p35-p36	2q11.2	5p15.33	14q23
Exons	60	3	21	4	4	6	8	4	15	5
Mutation type	Loss of function	Loss of function	Gain of function	Loss of function	Loss of function	Loss of function	Loss of function	Loss of function		

caused by *VHL* and *SDHx* mutations belong to group one or cluster one and are characterized by a hypoxic transcriptional signature indicating reduced oxidoreductase activity and increased hypoxia and angiogenesis. Tumors caused by mutations of the *RET*, *NF1,* and *TMEM127* genes belong to group two or cluster two and are characterized by the activation of p21–ras-mediated MAP kinase pathway leading to uncontrolled cell proliferation.

25.7 Clinical Characteristics of Pheochromocytoma in NF1

Pheochromocytomas occur sporadically or are part of an increasing number of familial cancer syndromes. Sporadic pheochromocytomas are mainly diagnosed between the age of 40 and 50 years and are characterized by the "rule of tens": 10 % are bilateral, adrenal tumors; 10 % are extra-adrenal tumors of thoracoabdominal, sympathetic paraganglia; and 10 % are malignant. The differentiation of benign and malignant pheochromocytomas is difficult owing to their identical histological and biochemical signs. The only reliable proofs of malignant pheochromocytomas are lymph node metastases and distant metastases (Tischler 2008).

Between 25 % and 30 % of pheochromocytomas are familial and associated with one of the classic pheochromocytoma syndromes such as NF1, VHL, MEN2, the paraganglioma syndromes, and the familial pheochromocytoma syndromes (Table 25.2). The prevalence is about 0.1–5.7 % in NF1, 10 % to 20 % in VHL, and 50 % in MEN2 (Walther et al. 1999; Dluhy 2002). As with NF1, these hereditary disorders present some striking additional clinical features (Table 25.2). Patients with von Hippel–Lindau disease develop retinal and cerebellar hemangioblastomas, clear cell renal carcinomas, and pancreatic islet cell tumors. MEN type 2A is associated with medullary thyroid carcinoma (MTC) and hyperparathyroidism; MEN type 2B is, in addition to MTC, associated with multiple mucosal neuromas and a Marfanoid constitution. Typical clinical features of paraganglioma syndromes type 1–4 are parasympathetic head and neck paragangliomas.

Paragangliomas, referred to as endocrine-inactive tumors of parasympathetic paraganglia mainly of the head and neck region, are not only associated with PGL syndromes type 1–4 but have a close connection to pheochromocytomas in general. Both tumors arise from neural crest-derived cells and hence share the same histopathologic origin. Nowadays they are usually regarded in the context of pheochromocytomas. Further, they are a striking clinical feature of pheochromocytoma-associated syndromes with a characteristic prevalence depending upon the underlying familial pheochromocytoma syndrome. The vast majority of head and neck paragangliomas are caused by mutations of the *SDHx* genes and hence are associated with paraganglioma syndromes type 1–4. The prevalence of these tumors among VHL patients is about 8 in 1,000. Only single cases were identified among MEN type 2 and NF1 patients (DeAngelis et al. 1987; Boedeker et al. 2009). In 1987, DeAngelis described a NF1 patient with pulmonary paragangliomas, a glomus jugulare tumor, and a pheochromocytoma.

Table 25.2 Clinical characteristics of hereditary pheochromocytoma-associated syndromes

	Sporadic	NF1	VHL	MEN2	PGL1	PGL2	PGL3	PGL4	Familial pheochromocytoma syndromes		
Gene	–	*NF1*	*VHL*	*RET*	*SDHD*	*SDHAF2*	*SDHC*	*SDHB*	*TMEM127*	*SDHA*	*MAX*
Prevalence of pheochromocytoma	100 %	0.1–5.7 %	10–20 %	50 %	34 %	0 %	Single case	37 %	100 %	Single case	100 %
Mean age at diagnosis of pheochromocytoma	40–50	43	16	34	26	23	41	34	43	–	–
Adrenal location	90 %	84–95 %	92 %	97 %	86 %	–	–	42 %	100 %	Single case	100 %
Bilateral location	10 %	5–15 %	55 %	65 %	48 %	–	–	12 %	35 %	–	67 %
Extra-adrenal location	10 %	6 %	17 %	3 %	57 %	–	Single case	58 %	–	Single case	–
Malignant pheochromocytoma	10 %	3–12 %	4 %	3 %	0 %	–	0 %	24 %	5 %	Single case	37 %
Head and neck paraganglioma	–	Single case	Rare	Single case	48 %	100 %	>90 %	6 %	Single case	Single case	–
Additional clinical features	–	Cafe au lait spots, axillary or inguinal freckling, neurofibromas, plexiform neurofibromas, optic gliomas, Lisch nodules	Hemangioblastomas of the eye and CNS, clear cell renal carcinomas, pancreatic islet cell tumors, endolymphatic sac tumors	Medullary thyroid carcinomas, type A: hyperparathyroidism, type B: multiple neuromas, marfanoid habitus	Gastrointestinal stromal tumors		Gastrointestinal stromal tumors	Renal cell carcinomas, Gastrointestinal stromal tumors			

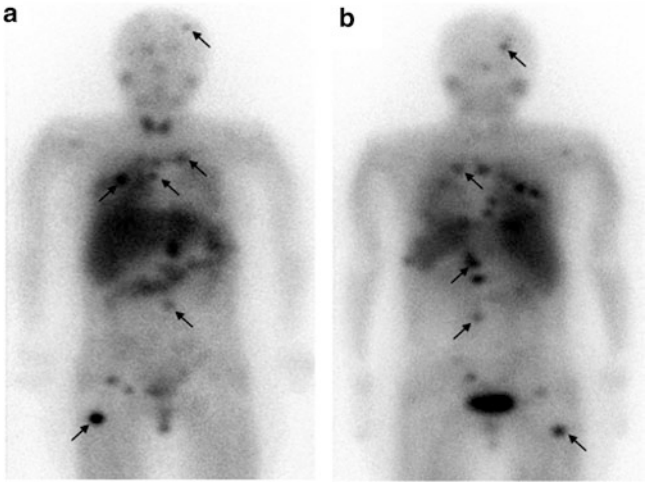

Fig. 25.3 MIBG scintigraphy of a malignant pheochromocytoma

Hereditary pheochromocytomas differ in their age at diagnosis, their tumor localization, and their malignant potential (Neumann et al. 2002; Bausch et al. 2006a, b) (Table 25.2). Compared to sporadic pheochromocytoma, the age at onset is lower, a bilateral and extra-adrenal tumor localization is more common, and a higher malignancy rate is evident. The age at onset is about 15 years younger than that in sporadic tumors. The youngest age at onset (16 years) is found in patients with von Hippel–Lindau disease. *MAX* mutation-associated pheochromocytomas are characterized by bilateral tumor development, identified in at least 67 % of patients. Familial pheochromocytomas are evident in more than 10 % located extra-adrenally with the highest rate of 58 % in patients affected by paraganglioma syndrome type 4 and the lowest rate of 3 % in patients affected by MEN type 2. The frequency of malignant transformation is high. *MAX* mutation-associated tumors and PGL 4-associated tumors show the highest malignancy potential with 37 % and 24 %, respectively. In contrast to these findings, NF1-associated pheochromocytomas share many features with sporadic pheochromocytomas (Walther et al. 1999; Bausch et al. 2006a, b). The mean age at diagnosis is relatively late with 43 years. 84 % to 95 % of them are localized in the adrenal gland with bilateral tumor growth in 5–15 % of patients. Extra-adrenal tumors have been found in up to 6 %; a malignant transformation has been identified in 3–12 % (Fig. 25.3), one of the highest rates among hereditary pheochromocytomas, but similar to those described in sporadic tumors.

25.8 Diagnostic Approach

The diagnosis of NF1 is based on clinical criteria developed by the NIH Consensus Conference in 1987 and updated in 1997 (Anonymous 1988; Gutmann et al. 1997). According to these criteria, at least two of the following clinical features must be

present in the absence of another diagnosis to make the diagnosis of NF1: (1) six or more café au lait spots >5 mm in diameter in prepubertal and >15 mm in diameter in postpubertal individuals, (2) two or more neurofibromas of any type or one plexiform neurofibroma, (3) axillary or inguinal freckling, and (4) optic glioma and two or more Lisch nodules. The diagnosis of pheochromocytoma is based on biochemical tests and imaging modalities. Pheochromocytomas are characterized by the excretion of the catecholamines, norepinephrine, epinephrine, and dopamine, and the predominant intratumoral metabolism of these catecholamines with the formation of metanephrine and normetanephrine. The measurement of 24-h urinary fractionated catecholamines and total metanephrines with a sensitivity of 90 % and the measurement of plasma-fractionated metanephrines with a sensitivity of 97 % are recommended as the first diagnostic step in pheochromocytomas. Biochemical testing should be followed by radiological evaluation. CT scan (computed tomography) and MRI (magnetic resonance imaging) are both sensitive (98–100 %) and quite specific (70 %). MIBG scintigraphy (metaiodobenzylguanidine scintigraphy) and 18-Fluor-DOPA PET (18-Fluor-DOPA positron emission tomography) are recommended in patients with strong clinical and biochemical evidence of pheochromocytoma but negative MRI and CT scan results and in patients with atypical tumor localization, multiple tumors, and malignant pheochromocytomas.

In 20–50 % of hypertensive NF1 patients, pheochromocytomas are causative for elevated blood pressure levels, which can be life-threatening with the possibility of a curative therapy. Owing to the clinical characteristics of pheochromocytomas in NF1, NF1 patients with hypertension and a mean age of 43 years should be screened for pheochromocytomas. The measurement of 24-h urinary fractionated catecholamines and total metanephrines and the measurement of plasma-fractionated metanephrines should be performed, followed by a CT scan or MRI. In the vast majority, the tumor is localized in the adrenal gland with a suspected malignancy rate of up to 12 %. A molecular genetic analysis of the *NF1* gene is possible but usually not required because of a lack of a relevant genotype–-phenotype correlation and high variability of the disease even within one family.

NF1 is associated with pheochromocytomas in only about 2–4 % of cases. The diagnosis of NF1 in both current clinical and scientific work is based on clinical findings, and patients with pheochromocytomas should be carefully examined for the striking and diagnostic features of the disease.

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