INTRODUCTION

History

Neurofibromatosis type 1 (NF1), previously known as von Recklinghausen disease, is a common neurogenetic condition affecting 1:2500 people worldwide. NF1 probably existed in ancient times, with art and literature from the 3rd century BCE documenting descriptions consistent with the disease (Zanca, 1980). In 1849, an Irish surgeon named Robert W. Smith differentiated patients with traumatic neuromas from those with cases of multiple, idiopathic neuromas (Smith, 1849). However, it was not until 1882 that the disease entity was fully recognized: the German pathologist Frederick von Recklinghausen first published a classic monograph, in which he described the disease as well as the pathologic basis of neurofibromas (von Recklinghausen, 1882). Iris hamartomas, or Lisch nodules, were first described in patients with NF1 by the Austrian ophthalmologist Karl Lisch in 1937 (Lisch, 1937). Later, Frank Crowe and his colleagues (1956) were the first to recognize NF1 as a hereditary disease, affecting 50% of offspring. In 1964, Dr. Crowe then described skinfold freckling (Crowe, 1964). With the recognition that NF1 was a genetic condition, the US National Institutes of Health (NIH) convened a consensus development conference to establish consistent diagnostic criteria to enable the identification of people with NF1 (National Institutes of Health Consensus Development Conference, 1988). This landmark conference laid the foundations for the genetic analysis of families with NF1, culminating in the discovery of the NF1 gene in 1990 (Viskochil et al., 1990; Wallace et al., 1990).

Epidemiology

The prevalence of NF1 is approximately 1:2500 to 1:3500 in individuals, regardless of ethnic and racial background (Huson et al., 1989; Rasmussen and Friedman, 2000; Johnson et al., 2013). While NF1 is an autosomal dominant condition, only 50% of people have an affected family member with NF1 (familial cases). As such, 50% of patients will be the first person in their family with NF1, arising from a sporadic NF1 gene mutation (DeLuca et al., 2004; Evans et al., 2010). Life expectancy is reduced by 8–15 years relative to the general population, with malignancy constituting the major reason for death prior to the age of 30 (Rasmussen et al., 2001; Evans et al., 2011). With the establishment of an online worldwide registry for patients with NF1, new insights into the epidemiology of this common condition will likely emerge (Johnson et al., 2013).

CLINICAL MANIFESTATIONS

Hallmark signs and symptoms

The diagnostic criteria for NF1 were first established by the NIH Consensus Development panel in 1987 (National Institutes of Health Consensus Development Conference, 1988) and updated in 1997 (Gutmann et al., 1997). To make the diagnosis of NF1, two of the following clinical features are required:

- six or more café-au-lait macules with diameters greater than 5 mm in a prepubertal patient and greater than 15 mm in a postpubertal patient
- two or more neurofibromas or one plexiform neurofibroma
- skinfold (axillary or inguinal) freckling
- optic pathway tumor
- two or more iris hamartomas
- characteristic bony lesion
- first-degree relative with neurofibromatosis type 1.

In most cases, the diagnosis of NF1 can be made on clinical grounds; however, only in rare circumstances is it
necessary to pursue genetic testing. When employed, NF1 mutation analysis is 95% sensitive (Messiaen et al., 2000; Valero et al., 2011). The features that are typically evident from birth or early infancy include a positive family history and café-au-lait macules. Café-au-lait macules grow in size and number during the first 2 years of life (Fig. 4.1A). Skinfold freckling, most commonly observed in the axillary and inguinal regions, begins to appear in early childhood, most commonly between 5 and 8 years of age (Fig. 4.1B). Optic pathway gliomas develop almost entirely in the pediatric population, usually prior to the age of 7 years old, with a median age at presentation of 4 years (Listernick et al., 1994). Lisch nodules appear as a function of age, such that 30–50% harbor these iris hamartomas by age 6 years, and 92% are present by adulthood (Fig. 4.1C) (Nichols et al., 2003). Characteristic bony abnormalities, such as long bone pseudarthrosis and sphenoid wing dysplasia, when present, are seen in early infancy (Fig. 4.1D). Dermal neurofibromas typically appear in the peripubertal years, and increase in number over the ensuing years. Plexiform neurofibromas are considered congenital, but may not cause problems until later during development or in adulthood.

In addition to the classic features of NF1, people with NF1 are prone to developing aqueductal stenosis, pheochromocytoma, learning and intellectual disabilities, attention deficit, scoliosis, seizures, and vasculopathy as well as other types of tumors and malignancies (e.g., breast cancer and malignant brain tumors).

**Cutaneous manifestations**

Café-au-lait macules occur in at least 95% of patients with NF1 (Johnson et al., 2013). A child with NF1 usually has at least one café-au-lait macule present at birth, and there will be an increase in number of macules as well as size of the existing macules over the first 1–2 years of life (Nunley et al., 2009). These macules range in color from light to dark brown, depending on the background skin pigmentation. Typically, café-au-lait macules are homogeneous in color with smooth borders. Pathologic examination of these lesions reveals an increased number of macromelanosomes (Slater et al., 1986).

Skinfold freckling is present in 50% of children with NF1 by 10 years of age (Huson et al., 1988; DeBella et al., 2000). The freckles are typically 1–3 mm in diameter, and occur in symmetric clusters in the intertriginous areas of the axillary and inguinal regions as well as under the chin and breasts in women.

**Neurofibromas and malignant peripheral nerve sheath tumors**

Neurofibromas are the most common tumor type in NF1, affecting 40–60% of patients with NF1 (Friedman and Birch, 1997; McGaughran et al., 1999). Neurofibromas
are benign tumors of peripheral nerve sheath cells (WHO grade I) and can occur throughout the peripheral nervous system. Dermal neurofibromas arise from a single peripheral nerve, whereas plexiform neurofibromas arise from a bundle of fascicles or a larger nerve plexus (sacral or brachial plexus).

Cutaneous, localized neurofibromas appear on the surface and can be pedunculated, subcutaneous, or sessile (Fig. 4.2A). They may show slight overlying skin discoloration, sometimes initially appearing as raised erythematous areas. Dermal neurofibromas first appear around the time of puberty, and they typically increase in number with age. While these tumors are benign and do not transform into malignant cancers (Boyd et al., 2009; Jouhilahti et al., 2011), they are frequently associated with significant cosmetic impact or cause irritation because of rubbing or clothing irritation.

Between 30% and 50% of patients with NF1 have plexiform neurofibromas (Waggoner et al., 2000; Mautner et al., 2008). Plexiform neurofibromas are clinically distinct from localized neurofibromas in that they have potential for malignant transformation. Cutaneous plexiform neurofibromas are characterized by overlying skin hyperpigmentation and a thickened dermis, and have been described as “a bag of worms” on palpation (Fig. 4.2B). Internal plexiform neurofibromas can appear as extensive tumors on imaging studies (Fig. 4.2C). Plexiform neurofibromas are most likely congenital, and usually grow most rapidly during the first decade of life. Although the majority of plexiform neurofibromas remain benign, there is still considerable

Fig. 4.2. NF1-associated peripheral nerve sheath tumors. (A) Dermal neurofibromas on the arm of an adult with NF1. (B) Plexiform neurofibroma on the foot of an adult with NF1. (C) Internal plexiform neurofibroma in the abdomen/pelvis of an adult with NF1. (D) Neck plexiform neurofibroma in an adolescent with NF1. (E, F) Positron emission tomography reveals malignant peripheral nerve sheath tumors in the neck (E) and leg (F) of two different adults with NF1.
morbidity associated with them, including disfigurement and local invasion of neighboring structures (e.g., bone), leading to pain and bony deformities (stimulation of bone growth or bony erosion) as well as rare instances of internal organ, trachea, or vascular compression (Prada et al., 2012) (Fig. 4.2D).

Spinal neurofibromas may cause neurologic symptoms by compressing the spinal cord or spinal roots within the foraminal spaces. Symptoms may include pain, numbness, weakness, or bowel/bladder dysfunction. When arising from the nerve root, the tumor grows in a dumbbell-shaped pattern as it passes through the foramen.

On pathologic examination, neurofibromas consist of neoplastic Schwann cell progenitors growing within a microenvironment of non-neoplastic perineural cells, fibroblasts, mast cells, and collagen (Woodruff, 1999; Jouhilahti et al., 2011).

Although uncommon, new onset of pain or a neurologic deficit in a person with an NF1-associated plexiform neurofibroma should warrant prompt evaluation to exclude a malignant peripheral nerve sheath tumor (MPNST) (Korf, 1999; King et al., 2000). MPNSTs are high-grade spindle-cell sarcomas, found in 8–13% of patients with NF1. Unlike their sporadic counterparts, which typically appear in the 50s and 60s, the mean age at presentation of NF1-associated MPNST is in the mid-30s (Evans et al., 2002). Whereas 5–10% of plexiform neurofibromas transform into MPNSTs (Evans et al., 2002), these cancers can also arise \textit{de novo} in the absence of a known plexiform neurofibroma (Woodruff, 1999).

MRI is not adequate for detecting malignant transformation. For this reason, most clinicians employ 18-FDG-positron emission tomography (PET), which has been shown to be both a sensitive and specific diagnostic test (Mautner et al., 2007; Ferner et al., 2008; Derlin et al., 2013). Standard uptake values greater than 4.0 should raise suspicion for a malignancy (Fig. 4.2E, F). MPNST frequently metastasize, most commonly to the lungs and bone (Ducatman et al., 1986). Unfortunately, the prognosis for NF1-associated MPNST is poor, even after treatment, with overall survival typically less than 5 years (Porter et al., 2009).

**Brain tumors**

Within the central nervous system, the majority of tumors arising in pediatric patients with NF1 are World Health Organization (WHO) grade I pilocytic astrocytomas. The optic pathway glioma (OPG) is the most common brain tumor associated with NF1, with as many as 15–20% of children with NF1 harboring an optic pathway tumor (Lewis et al., 1984; Listernick et al., 1994). These tumors can occur anywhere along the optic pathway, including the optic nerves, chiasm, and postchiasmic tracts and radiations (Fig. 4.3A–C) (Listernick et al., 1989, 1994, 1995). Up to half of optic pathway gliomas become symptomatic, but typically only one-third of children with NF1-OPG require therapeutic intervention (Lewis et al., 1984; Listernick et al., 1994; Fisher et al., 2012; de Blank et al., 2013). The decision to treat should be based on increasing visual loss (Listernick et al., 1997, 2007; Avery et al., 2012). Other signs and symptoms may include color vision changes, subacute progressive proptosis, strabismus, papilledema, and optic nerve atrophy. When locally invasive into the hypothalamus, precocious puberty may ensue (Habiby et al., 1995).

Low-grade gliomas may also be found in the brainstem, and these tumors typically exhibit an indolent course (Pollack et al., 1996). The lifetime incidence of brainstem gliomas in NF1 is ~4%, with presentation typically before the age of 10 years (Molloy et al., 1995; Ullrich et al., 2007).

While rare, adults with NF1 have a 50-fold increased risk of developing malignant gliomas, typically glioblastoma (GBM) (Matsui et al., 1993; Gutmann et al., 2002). These cancers appear earlier in life than those observed in the general population; however, the clinical presentation, pathology, and outcomes are similar to sporadically occurring GBM.

**Other tumors**

Individuals with NF1 are also at risk for developing other cancers. Of these, pheochromocytomas occur with increased frequency in people with NF1 (0.1–13%) (Walther et al., 1999; Vlenterie et al., 2013). In addition, there is also an increased incidence of NF1-associated leukemia (juvenile chronic myeloid leukemia and myelodysplastic syndromes), gastrointestinal stromal tumors, rhabdomyosarcoma, and early-onset breast cancer (Matsui et al., 1993; Stiller et al., 1994; Side et al., 1997, 1998; Gutmann and Gurney, 1999; Sung et al., 2004; Sharif et al., 2007; Vlenterie et al., 2013).

**Neurologic manifestations**

In addition to tumor-related clinical problems, children with NF1 are also prone to exhibit learning disabilities, cognitive delays, and attention deficits. Compared to the general population, the mean IQ of children with NF1 is 85 (Hyman et al., 2005). However, mental retardation (IQ < 70) is rare in children with NF1. When examined across several studies, the frequency of learning disabilities in children with NF1 is estimated to be between 30% and 65% (North et al., 1997). The most commonly affected intellectual domains include verbal learning, visuospatial and visual perceptual processing.
In addition, children with NF1 have an increased prevalence of attention deficits (Mautner et al., 2002; Pride et al., 2012; Isenberg et al., 2013), sleep disturbances (Licis et al., 2013), motor delays (Soucy et al., 2012; Wessel et al., 2013), autism spectrum disorders (Garg et al., 2013; Walsh et al., 2013), and impaired social functioning (Huijbregts et al., 2010; Lehtonen et al., 2013), each of which can impact on overall scholastic performance.

Seizures occur in 4–9% of patients with NF1 (Riccardi, 1981; Kulkantrakorn and Geller, 1998; Hsieh et al., 2011). Relative to the general population, seizures in people with NF1 are more often focal and related to a brain tumor. Moreover, individuals with NF1 and seizures frequently require more aggressive therapy than those without NF1, and some patients with NF1-related epilepsy should be considered for surgery when appropriate (Ostendorf et al., 2013).

With the increase in availability of magnetic resonance imaging (MRI), benign abnormalities have been uncovered on neuroimaging of pediatric NF1 patients. More than half of all children with NF1 harbor T2-high signal intensity lesions on brain MRI (Gill et al., 2006). The most common locations are the brainstem, thalamus, cerebellum, and basal ganglia (Fig. 4.3D). These abnormalities are typically well-circumscribed and none-nhancing; the presence of mass effect (architectural distortion), diffuse parenchymal infiltration, or contrast enhancement should warrant further investigation for an underlying brain tumor. While the precise etiology of these lesions remains unknown, one study revealed that these abnormalities may represent vacuolar or spongiotic changes (DiPaolo et al., 1995). In most cases,
the lesions disappear by late adolescence or early adulthood (Gill et al., 2006).

Orthopedic manifestations

Tibial pseudarthrosis and sphenoid wing dysplasia are both relatively specific to children with NF1, and typically are detected in early infancy. Sphenoid wing dysplasia usually presents as an orbital abnormality. Orbital dysplasia may result from an associated plexiform neurofibroma.

Long bone dysplasia manifests as cortical thinning and bowing, which may lead to a pathologic fracture. Repetitive cycling of fracture with incomplete healing leads to the development of a pseudarthrosis ("false joint"). In certain situations, a pathologic fracture may indicate bony erosion from a plexiform neurofibroma, but also may be secondary to a nonossifying cyst or osteopenia, both of which occur more frequently in NF1 (Dulai et al., 2007; Stevenson et al., 2007; Brunetti-Pierri et al., 2008; Elefteriou et al., 2009; Petramala et al., 2012). Vertebral anomalies are also associated with NF1, and may appear as benign scalloping of the vertebral body. Scoliosis is common in NF1 and is most commonly lower cervical or upper thoracic. In rare instances, the scoliosis may be dystrophic, leading to significant disfigurement.

Vascular manifestations

The two most common vascular changes associated with NF1 are hypertension and vascular dysplasia. Most cases of NF1-associated hypertension are primary hypertension, but secondary causes include pheochromocytoma and renal vascular dysplasia (renal artery stenosis). NF1-associated vascular dysplasia more commonly affects arteries (Salyer and Salyer, 1974). Dysplasia of the intracranial vessels may cause moyamoya syndrome, which may lead to ischemic stroke (Cairns and North, 2008), whereas vascular dysplasia in adults typically causes hemorrhage and arterial dissection (Friedman et al., 2002). Cerebral vasculopathy has been associated with prior cranial radiation therapy in individuals with NF1.

Variants

Segmental NF1 is a clinical variant of NF1 in which only a single region of the body harbors the manifestations of NF1 (café-au-lait macules, skinfold freckling, neurofibromas). Segmental NF1 results from a somatic mutation in the NF1 gene during early embryonic development, leading to NF1 restricted to one portion of the child’s body. However, if the gonads are involved, a parent with segmental NF1 may have children with generalized, not segmental, NF1 (Ruggieri, 2001).

Genetics

Molecular basis

NF1 is an autosomal dominant disorder that exhibits complete penetrance. In this regard, there are no carriers of NF1. The NF1 gene is located on the long arm of chromosome 17 in humans, and forms an 11-13 kb mRNA containing at least 60 common and three alternatively spliced exons (Fig. 4.4A). The encoded protein, termed neurofibromin, is 220–250 kDa and is abundantly expressed in neurons, oligodendrocytes, and Schwann cells. Neurofibromin functions primarily as a GTPase-activating protein (GAP), and inhibits RAS activity by accelerating the conversion of GTP-bound active RAS to its inactive GDP-bound state (Buchberg et al., 1990; Xu et al., 1990; Basu et al., 1992; Cichowski and Jacks, 2001). As a proto-oncogene, RAS promotes cell division and proliferation (Pylayeva-Gupta et al., 2011). In NF1-associated tumors, loss of neurofibromin expression, due to bi-allelic NF1 gene inactivation, is associated with high levels of active RAS. Depending on the cell type, RAS hyperactivation leads to increased signaling through the RAS downstream pathway intermediates, AKT/mTOR and RAF/MEK (Fig. 4.4B) (Basu et al., 1992; DeClue et al., 1992; Gutmann et al., 1994; Bollag et al., 1996; Kimura et al., 2002; Dasgupta et al., 2005b; Jessen et al., 2013). Each of these RAS

Fig. 4.4. NF1 gene structure and function. (A) The structure of the NF1 gene product (neurofibromin) with the alternatively spliced exons (9a, 23a, 48a) labeled. The GRD denotes the GAP-related domain. (B) Neurofibromin negatively regulates RAS activity and downstream RAS effector (PI3K/AKT/ mTOR and RAF/MEK) signaling as well as positively controls cyclic AMP (cAMP) production. In NF1-deficient tumor cells, increased RAS function and reduced cAMP levels promote cell growth.
downstream effectors has been investigated as potential rational therapies for NFI-associated tumors. In addition, neurofibromin is also a positive regulator of intracellular cyclic AMP (cAMP) production (Tong et al., 2002; Dasgupta et al., 2003), which in neurons is responsible for maintaining neuronal viability in the setting of optic glioma (Brown et al., 2010).

Animal models

Over the past decade, numerous laboratories have developed accurate genetically engineered mouse (GEM) models of NFI-associated cognitive deficits (Silva et al., 1997; Costa et al., 2002; Li et al., 2005; Cui et al., 2008; Shilyansky et al., 2010), skeletal abnormalities (Wang et al., 2011; Zhang et al., 2011; El-Hoss et al., 2012; El Khassawna et al., 2012), optic glioma (Bajenaru et al., 2003; Dasgupta et al., 2005a; Zhu et al., 2005b), malignant glioma (Zhu et al., 2005a; Kwon et al., 2008), cutaneous neurofibroma (Zhu et al., 2002; Mayes et al., 2011; Wu et al., 2008), MPNST (Cichowski et al., 1999; Vogel et al., 1999), myeloid leukemia (Le et al., 2004), and pheochromocytoma (Tischler et al., 1995). These preclinical models have led to a better understanding of the cellular and molecular bases that underlie the clinical features in children and adults with NFI, and have generated several promising new treatments for NFI-associated tumors and cognitive problems (Gutmann et al., 2013; Lin and Gutmann, 2013).

MANAGEMENT AND TREATMENT

The mainstay of the management of NFI is anticipatory guidance. Genetic counseling as well as the evaluation of first-degree family members is important. At every office visit, monitoring for macrocephaly, growth failure, precocious puberty, hypertension, developmental delays, learning disabilities, and scoliosis should occur. At each age, there are different problems that may develop, necessitating a focused and age-appropriate evaluation for children and adults. Annual ophthalmologic examinations by an ophthalmologist expert in NFI should be performed until the age of 12 years to screen for optic pathway gliomas (Listernick et al., 2007).

Children with developmental delay should be referred for appropriate therapies. As such, a concern for intellectual disability or learning disabilities should prompt neuropsychological evaluation. When appropriate, treatment of ADHD with stimulant medications should be considered (Mautner et al., 2002). In all cases, the management of neurocognitive disabilities requires teacher engagement and educational adaptations as indicated.

Surveillance neuroimaging in asymptomatic patients as a screening test for optic glioma pathways is not recommended (King et al., 2003; Segal et al., 2010). However, the development of visual loss, or other concerning symptoms such as precocious puberty, should warrant prompt brain MRI. If an optic pathway glioma is identified on neuroimaging, repeat ophthalmologic examinations should be performed every 3 months for the first year (Listernick et al., 2007). A two-line decrement in visual acuity should prompt treatment, typically with carboplatin and vincristine. Of patients with NFI-associated OPG causing visual impairment who received chemotherapy, 32% had improved visual acuity on follow-up, 40% had stable visual acuity, and 28% had worsened visual acuity (Fisher et al., 2012). Surgery for optic pathway glioma is indicated only in cases of intraorbital tumor causing proptosis and a blind eye. Radiation is not employed, because of increased risk for secondary high-grade CNS gliomas (Sharif et al., 2006).

Cutaneous neurofibromas may be treated with surgery and, occasionally, with CO2 laser therapy or electrodesiccation (Levine et al., 2008). In certain instances, plexiform neurofibromas may benefit from surgical debulking, although there is a high risk of iatrogenic injury to associated nerves and surrounding soft tissue as well as hemorrhage due to the significant degree of tumor vascularity. Currently, there are several chemotherapeutic trials underway aimed at halting plexiform neurofibroma growth (Robertson et al., 2012).

The management of MPNSTs involves the coordinated involvement of surgical oncologists, medical oncologists, and radiation oncologists. Small biopsies are notoriously inaccurate for diagnosing MPNST: for this reason, when clinical symptoms or 18-FDG-PET imaging suggests the possibility of malignancy, open biopsy or wide surgical excision is recommended (Ducatman et al., 1986; Ferber and Gutmann, 2002). Treatment following surgical excision entails local radiation and chemotherapy. While radiation therapy delays the time to tumor recurrence, it does not improve long-term survival (Ferber and Gutmann, 2002). Chemotherapy for MPNST has sometimes entailed the use of doxorubicin and ifosfamide; however, there is no current effective chemotherapy for these cancers (Moretti et al., 2011). In addition to local recurrence, these malignancies are prone to metastasis to the lungs and bone. Even with treatment, most patients with NFI-associated MPNST die within 5 years of diagnosis (Porter et al., 2009).

RECENT ADVANCES

Advances from neuroimaging

One of the major areas of focus is the identification of prognostic factors that provide risk assessment for people with NFI-associated medical problems. Recent
evidence suggests that favorable radiographic outcomes after chemotherapy for NF1-OPG do not correlate with visual acuity outcomes; rather, the location of the tumor, irrespective of radiographic response, was the single most consistent prognostic indicator (Fisher et al., 2012). In this study, tumors in the post-chiasmal optic radiations were most likely to lead to visual loss.

Other studies have focused on anatomic and diffusion-based abnormalities. While optic nerve tortuosity is frequently observed in children with NF1 patients, this radiographic feature has little predictive value in identifying optic gliomas (Ji et al., 2013). Similarly, fractional anisotropy has been explored as an easily quantifiable prognostic indicator for vision loss in NF1-OPG (de Blank et al., 2013).

The future of precision medicine

In 2005, the US Department of Defense established the Neurofibromatosis Clinical Trials Consortium (NFCTC) in order to efficiently deploy resources to critically evaluate the most promising experimental agents in a nationwide testing cohort. These efforts are likely to lead to a therapeutic paradigm shift from the current model of varied treatments to one of targeted and informed use of biologically targeted agents.

With the availability of accurate preclinical mouse models, an efficient clinical trials consortium, and a detailed understanding of neurofibromin function, we are uniquely poised to develop treatments tailored to specific features and subgroups of people with NF1-associated medical problems. For example, rapamycin, which inhibits RAS-dependent mammalian target of rapamycin (mTOR) function, first shown to inhibit the growth of optic glioma in mice (Hegedus et al., 2008), is now in clinical trial for NF1-associated glioma. Similarly, imatinib, which targets the c-kit signaling pathway deregulated in mouse plexiform neurofibromas (Yang et al., 2008), has been investigated in early clinical trials for people with NF1-associated plexiform neurofibroma (Robertson et al., 2012). Finally, based on exciting findings in Nf1 mouse models of learning and memory defects (Li et al., 2005), lovastatin, a nonselective RAS inhibitor, has been evaluated in children with NF1-associated cognitive problems (Krab et al., 2008; van der Vaart et al., 2013). Additional promising agents are also now in human clinical trials.

Future therapies will also begin to consider cell type-specific growth control pathways downstream of RAS as well as the contribution of non-neoplastic cells present in the tumor microenvironment. As we envision the possibility of personalized treatments for NF1, it will be critical to employ various converging approaches, including registry-based epidemiologic data, NF1 genetic/genomic sequencing, and patient-derived cell types, to inform novel therapeutic strategies targeted against NF1-associated clinical problems arising in a specific individual with NF1.

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