

## Neurofibromatosis type 1, from gene mutation to clinical presentation

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### ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant disease with a prevalence of about 1/3000. The clinical diagnosis of NF1 is based on the presence of two or more of the following criteria: six or more café au lait spots, >2 neurofibromas of any type, freckling in the axillary or inguinal region, optic glioma, a distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis, and a first degree relative with NF1.

We report a 7-year-old male with multiple café au lait spots diagnosed with Neurofibromatosis in Kigali-Rwanda by using next-generation sequencing and copy number variation analysis, the patient presented with painless nodular skin lesions that first developed 4 years earlier. Skin nodules initially appeared on the anterior chest wall and progressed to the posterior chest wall extending to the axilla region. His medical history and that of his family were unremarkable. To our knowledge, this is the first case to be diagnosed using this technology; The disease has numerous complications. The mutation rate for NF1-gene is high; 50% of all cases of NF1 are from new mutations. The gene protein product- neurofibromin plays an important role in tumor genesis as a tumor-suppressor gene.

Combining both clinical findings and molecular genetic evaluation to identify disease-causing mutations is paramount in confirming the diagnosis. Patient care is best done in a multidisciplinary setting approach for proper patient satisfaction and better prediction of future prognosis.

**Keywords:** Neurofibromatosis, Gene Mutation, Clinical Presentation, Café Au Lait Spots, Neurofibromas, Case Report

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## INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder with an incidence of approximately 1:3000 individuals [1]. There are several clinically and genetically distinct forms of neurofibromatosis, neurofibromatosis type 1, neurofibromatosis type 2-related schwannomatosis (NF2, formerly neurofibromatosis type 2), and schwannomatosis related to genetic variants other than NF2. NF1, previously known as von Recklinghausen disease, is the most common type caused by de novo mutations occurring primarily in paternally derived chromosomes [2]. The hallmarks of NF1 are multiple café-au-lait macules and neurofibromas. The condition is called "segmental NF1" when clinical features are limited to one area of the body due to somatic mosaicism of a pathogenic variant in the neurofibromin 1 (NF1) gene [3]. Neurofibromatosis type 1 (NF1) is due to pathogenic variants in the NF1 gene located at chromosome 17q11 [4]. The protein product, neurofibromin, belongs to a family of guanosine triphosphate hydrolase (GTPase)-activating proteins (GAPs) that stimulate intrinsic GTPase activity in the ras p21 family (21 kD rat sarcoma viral oncogene homologs). Ras activates a number of signaling pathways that include the stem cell factor (SCF)/c-kit signaling mammalian (mechanistic) target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways [5]. Its penetrance, or the likelihood that the individual carrying the variant will manifest the disorder, is complete. NF1 is highly variable in its expression; however, the severity and specific manifestations of the disorder vary among affected individuals within the same family and from one family to another [6]. Somatic mutation or loss of heterozygosity at the NF1 locus, in

combination with a germline NF1 mutation, leads to complete loss of neurofibromin expression that is seen in NF1 lesions such as pseudoarthrosis and neurofibromas, NF1, therefore, functions as a tumor suppressor gene [7].

Haploinsufficiency (heterozygosity for a pathogenic variant with an intact second allele) may account for some aspects of the phenotype, such as neurocognitive problems. Segmental NF1 is caused by somatic mosaicism due to a postzygotic mutation in the NF1 gene. This results in some cells having two fully functional NF1 genes and other cells containing a pathogenic variant in one copy of the NF1 gene. Thus, persons with segmental NF1 do not have an affected parent [8]. When an adult with localized NF1 who has mosaicism within both somatic and gonadal tissues transmits the mutation to a child, the child will carry the NF1 mutation in all cells and will not have segmental manifestations. Rare individuals have been described who have only germline mosaicism without apparent somatic features [9]. This case report presents the first case of NF1 to be diagnosed using next-generation sequencing and copy number variation analysis (CNV) technology.

## CASE PRESENTATION

A 7-year-old male with multiple café au lait spots presented with painless nodular skin lesions that first developed 4 years earlier. Skin nodules initially appeared on the anterior chest wall and progressed to the posterior chest wall extending to axilla regions (Figure 1). His medical history and that of his family were unremarkable. A blood sample was drawn from a peripheral vein and sent to Lancet Laboratory for testing using next-generation sequencing and copy number variation analysis (CNV) technology,



**Figure 1:** Multiple café au lait spots, and skin nodules

and a heterozygous pathogenic variant was identified in the NF1 gene. The genetic diagnosis of autosomal dominant neurofibromatosis type I was confirmed, and no further clinically relevant variants were detected. The patient was referred to the dermatology department for further review after genetic counseling to the patient and the family in general. As a long-term follow-up, the patient will have at least one annual visit to check different parameters but not limited to examining skin for new neurofibromas, signs of plexiform neurofibromas, blood pressure for signs of hypertension, evaluating growth measurements including height, weight, and head circumference.

## DISCUSSION

The typical order of appearance of NF1 clinical manifestations is café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules (iris hamartomas), and neurofibromas [10]. The number of café-au-lait macules then stabilizes over time. Up to 15 percent of the general population has one to three café-au-lait macules; however, six or more café-au-lait macules are highly suggestive of NF1 [11]. Lisch nodules are raised, tan-colored hamartomas of the iris and represent a specific finding for NF1. They do not affect vision in any manner. Lisch nodules are useful in establishing a diagnosis of NF1 in a child and determining whether a parent is affected. These lesions are detected in fewer than 10 percent of affected children younger than six years of age but are seen in greater than 90 percent of adults [12]. Persons with NF1 develop both benign and malignant tumors at increased frequency throughout life [13]. Optic pathway glioma and other gliomas are the predominant types of intracranial neoplasms, and malignant peripheral nerve sheath tumors are the most common non-central nervous system malignancy [14]. Neurofibromas are benign peripheral nerve sheath tumors composed of a mixture of Schwann cells, fibroblasts, perineurial cells, and mast cells [15]. In the Schwann cells, loss of both NF1 alleles occurs, indicating that this is the primary tumor cell of the neurofibroma [16]. Children with tumors involving the optic chiasm occasionally present with either premature or delayed puberty caused by hypothalamic involvement [17]. Detecting precocious puberty early in patients with NF1 is important because it may indicate the presence of a clinically significant

optic pathway glioma, although abnormal puberty can occur in the absence of optic pathway glioma. Treatment can minimize the complications of accelerated linear bone growth and premature development of secondary sexual characteristics. One of the earliest signs of precocious puberty is accelerated linear growth, highlighting the importance of maintaining accurate growth charts using standards for children with NF1 [18]. Patients with NF1 are also at an increased risk of developing gastrointestinal stromal tumors, which are soft tissue tumors that arise within the stromal compartment of the gastrointestinal tract [19]. In NF1, gastrointestinal stromal tumors frequently occur in the small intestine (more than 70 percent), are often multiple, and have a different molecular pathology from sporadic gastrointestinal stromal tumors in persons who do not have NF1 [20]. Neurologic disorders include cognitive deficits, learning disabilities, headaches, and seizures. Gross and fine motor developmental delays are also seen, and macrocephaly is a common feature. Dural ectasia along the spine can result in symptoms such as pain resulting from nerve root compression [21]. Seizures are approximately twice as common in patients with NF1 compared with the general population, with a prevalence of approximately 4 to 6 percent [22]. Hypertension is frequently found in adults with NF1 and may develop during childhood. In most cases, hypertension is considered primary (essential), but vascular lesions producing renovascular hypertension are more frequent in patients with NF1. Thus, evaluation for renal artery stenosis should be initiated in children with NF1 and hypertension [23]. Although renovascular lesions can be detected in patients who are still normotensive, the frequency with which such patients develop hypertension is unknown. Renal tubular and glomerular dysfunction may also occur with increased frequency compared with healthy controls [24]. Pheochromocytoma is a much less common cause of hypertension in NF1, although consideration of this possibility in a hypertensive person with NF1 is important, given the potential morbidity [25]. Malignant peripheral nerve sheath tumors are the most common complication and magnetic resonance imaging is the preferred modality for investigation. Adults should also be monitored for osteoporosis and scoliosis. Given the diverse manifestations, neurocognitive problems, and risk of disfigurement and even

death, it is not surprising that persons with NF1 report a decreased quality of life, as affected adults and children may experience problems with self-image, anxiety and chronic pain [26].

## CONCLUSION

Combining both clinical findings and molecular genetic evaluation to identify disease-causing mutations is paramount in confirming the NF1 diagnosis. The patient's care is best done in a multidisciplinary setting approach for proper patient satisfaction and the best prediction of future prognosis.

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