Case Report
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# Co-occurrence of both maternally inherited neurofibromatosis type 1 and Lesch-Nyhan disease in a child with severe neurodevelopmental impairment

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Lesch-Nyhan disease (LND) is a rare X-linked recessive inherited purine metabolic disorder that accompanies neurodevelopmental problems. Neurofibromatosis type 1 (NF1) is a relatively common autosomal dominant inherited genetic disorder characterized by tumors in various systems. Some children with NF1 also accompanies neurodevelopmental problems. Here, we describe a 5-year-old boy with a maternally inherited pathogenic variant in *NF1* and hypoxanthine-guanine phosphoribosyltransferase (*HPRT*). He was referred for severe neurodevelopmental impairment and hyperuricemia. His mother was diagnosed with NF1 and the patient was also suspected of having NF1 because of cafe au lait macules. He had dystonia, rigidity, cognitive deficit, and speech/language impairment. Serum and urine uric acid concentrations were elevated. He had more severe neurodevelopmental delay than patients with only NF1, so his clinical symptoms could not be fully understood by the disease alone. To find the cause of his neurologic symptoms and hyperuricemia, the patient and his mother underwent a whole-exome sequencing test. As a result, the pathogenic variant c.151C>T (p.Arg51Ter) in *HPRT1* was identified as hemizygote in the patient and heterozygote in his mother. The pathogenic variant c.7682C>G (p.Ser2561Ter) in *NF-1* was identified as heterozygotes in both of them. Although the clinical symptoms of both diseases were overlapping and complicated, genetic testing was helpful for accurate diagnosis and treatment. Therefore, we suggest to consider preemptive genetic evaluation if there are symptoms not sufficiently explained by known existing diseases. And it is considered valuable to review this rare case to understand the clinical course and possible synergic effects of these diseases.

**Key words:** Neurofibromatosis 1, Lesch-Nyhan disease, Developmental disabilities, *Hypoxanthine phosphoribosyltransferase*.

## Introduction

Lesch-Nyhan disease (LND) is a rare X-linked recessive genetic disorder associated with purine metabolism dysfunction [1]. It was first described at Johns Hopkins Hospital in 1964 by Lesch and Nyhan [2]. The prevalence is estimated at 1/380,000 live births in Canada and 1/235,000 in Spain, respectively [3]. It presents severe dystonia, gout, intellectual disability, short stature, attention deficit, and self-mutilation [4,5].

On the other hand, neurofibromatosis type 1 (NF1) is a relatively common autosomal dominant genetic disorder. It is a multisystem disorder which attributes to the development of

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benign or malignant tumors in various systems, mainly in the nervous system [6]. Most commonly associated tumors include optic glioma, glioblastoma, gastrointestinal stromal tumor, leukemia, pheochromocytoma, breast cancer, and rhabdomyosarcoma [6]. It was first described by German pathologist Friedrich von Recklinghausen in 1882 [6]. About 1 in 2,500-3,000 people worldwide, irrespective of ethnicity or sex, are affected by the disease [6]. Patients with NF1 can manifest cognitive impairments including language and memory, behavioral problems, attention deficits, and problems with executive functions, and motor skills [7].

Here we report a rare case of a patient who has inherited two genetic mutations from his mother that leads to co-existing two diseases from these mutations.

This study was approved by the Institutional Review Board (IRB) of Soonchunhyang University Bucheon Hospital (IRB no. SCHBC 2022-05-006). The patient's parents provided written informed consent for the publication of this case report including patient information.

## Case

A 5-year-old boy was referred to our hospital for hyperuricemia and severe neurodevelopmental impairment. He was born at 39 weeks of gestation and birth weight of 3,140 g via spontaneous vaginal delivery without perinatal problems. His father and older brother were healthy without any diseases. His mother was diagnosed with NF1 but had no intellectual disabilities (Fig. 1). Because he had typical multiple café au lait macules like his mother, he was clinically suspected of NF1. Additionally, he also showed head lagging even after 8 months after birth. He was then diagnosed with NF1 by genetic testing. He underwent regular physical and occupational rehabilitation. When he was 2 years old, hyperuricemia was observed and he started taking allopurinol continuously.

When he was 5 years old, he visited our hospital for accurate evaluation and treatment of hyperuricemia and severe developmental impairment. He was 120.9 cm in height (>97 percentile in the Korean national growth chart) and 13 kg in weight (<3 percentile). He showed multiple café au lait macules scattered on his whole body but there was no visible neurofibroma on his skin, unlike his mother. He was able to crawl on his stomach and stand still for a while with his arms supported. Also, he showed neurologic symptoms such as dystonia, rigidity, and involuntary movement.

His laboratory test result showed that he has significantly elevated serum uric acid levels despite continuous treatment. He also showed punctate high echogenic foci of the left kidney and right upper pole kidney, mainly in the renal sinus and medullary portion, which suggests nephrocalcinosis in kidney ultrasonography. The patient and his mother underwent a whole-exome sequencing (WES) to determine the exact cause of his neurologic symptoms and hyperuricemia. As a result, the variant c.151C>T (p.Arg51Ter) in hypoxanthine-guanine phosphoribosyltransferase (*HPRT1*) was identified as hemizygote in the patient and heterozygote in his mother. The variant c.7682C>G (p.Ser2561Ter) in *NF-1* was identified as heterozygotes in both of them (Figs. 2 and 3). These variants are classified as 'pathogenic variants' according to recent American College of Medical Genetics and Genomics guidelines.

At 5 years old, he had the first seizure in about an hour and took levetiracetam orally for about a year. After that, there were no seizures and the electroencephalogram was normal, so he stopped taking an anticonvulsant. Also, he underwent brain

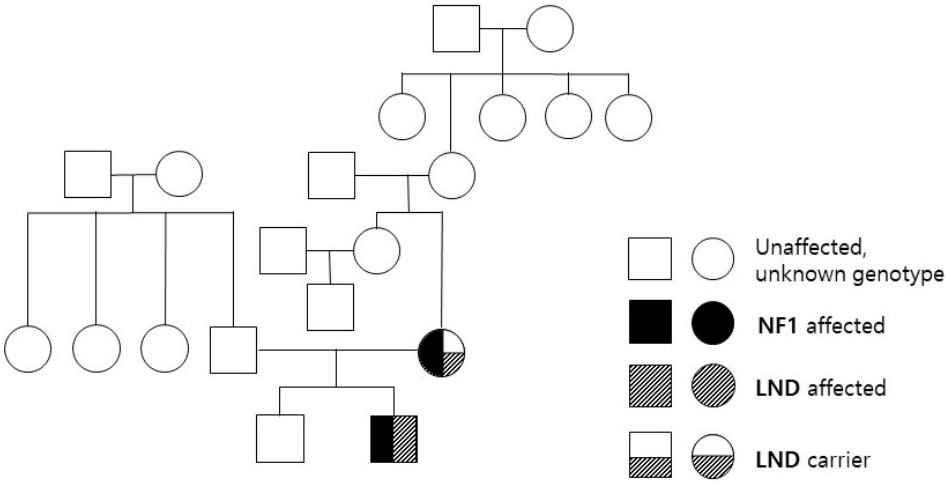


**Fig. 1.** Pedigree. The patient and his mother have the same genetic mutation. The patient was NF1 and LND affected simultaneously. His mother was NF1 affected and LND carrier as LND is an X-linked recessive disorder. NF1, neurofibromatosis type 1; LND, Lesch-Nyhan disease.

magnetic resonance imaging. Mild aneurysmal change in the right distal internal carotid artery and multiple subtle T2 high-signal intensity scattered lesions including pons, bilateral basal ganglia, thalamus, and cerebellar white matters were found, which were suspected to be related to NF1. An ophthalmologic examination was performed for NF1-related ocular signs, but there were no abnormal findings.

At 7 years old, his developmental delay was evaluated by Korean Developmental Screening Test for Infants & Children (K-DST), which is designed to assess gross motor skills, fine motor skills, cognitive development, social development, and language development. He obtained the lowest grades in every area in K-DST for his age. He could only stand still for a limited time and not walk alone without support. He could only speak a few words like "Mama" or "Papa". Recently, he started to grind his teeth occasionally, but he has not yet shown typical self-mutilation.

Now, he continues to take sodium bicarbonate and allopurinol. His serum uric acid levels are well within the normal range so far. Also, he is doing more comprehensive rehabilitation including occupational, physical, cognitive, and Vojta rehabilitation.

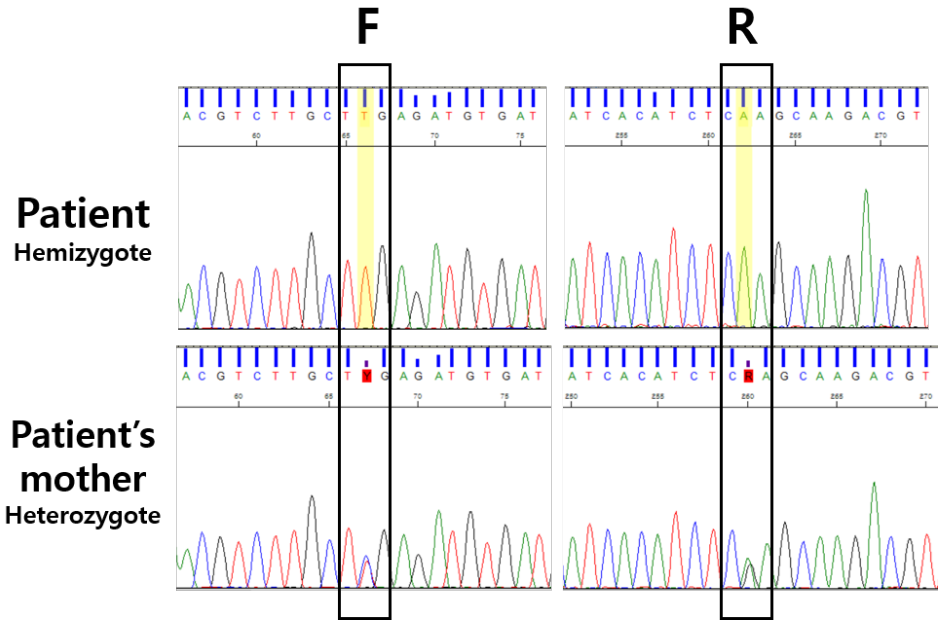


**Fig. 2.** A pathogenic variant c.151C>T (p.Arg51Ter) in *HPRT1* was identified as hemizygote in the patient and heterozygote in his mother, which is causative for LND. *HPRT1*, hypoxanthine-guanine phosphoribosyltransferase; LND, Lesch-Nyhan disease.

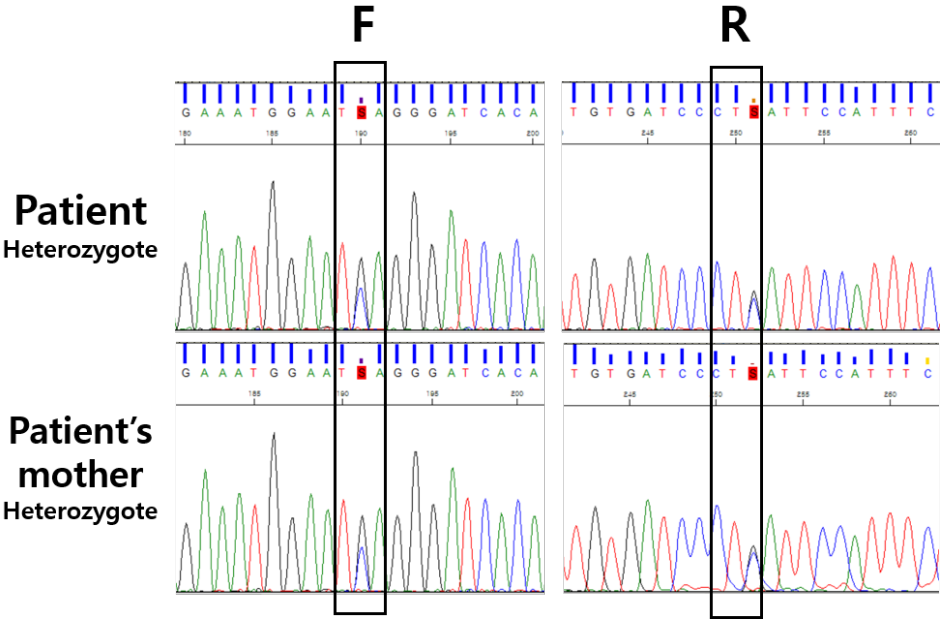


**Fig. 3.** A pathogenic variant c.7682C>G (p.Ser2561Ter) in *NF1* was identified as heterozygotes in the patient and his mother, which is causative for NF1. NF1, neurofibromatosis type 1.

## Discussion

LND is a rare X-linked recessive genetic disorder associated with dysfunction of purine metabolism [1]. Clinical manifestations of LND include severe dystonia, gout, intellectual disability, short stature, attention deficit, and self-mutilation [4,5]. *HPRT1*, located on the chromosome locus Xq26.2-q26.3, is an important enzyme in the purine salvage pathway and its mutation is causative for LND [8]. The enzyme converts guanine and hypoxanthine into guanosine monophosphate and inosine monophosphate. It remains to be unveiled how deficits in hypoxanthine and guanine recycling can lead to such a profound neurological impairment but are thought to relate to dysfunction of basal ganglia circuits [9].

Patients with LND usually have normal prenatal and perinatal histories. The most common initial findings during the first year of life are delayed motor skills and hypotonia. Children with LND fail to achieve normal milestones such as sitting, crawling, and walking. Within the first few years of life, abnormal movements emerge, especially severe action dystonia which resembles dyskinetic or athetoid cerebral palsy. Most patients with LND have neurodevelopmental impairment whose severity usually ranges from mild to moderate, rarely severe [10].

The most typical and remarkable symptom that makes clinicians suspicious of LND is self-mutilation. Self-mutilation in LND patient usually begin to manifest after 1 year of age, especially perioral self-mutilation as their teeth come in. The behavior continues and can lead to the partial or total destruction of perioral tissue, and amputation of fingers, toes, and tongue [11]. In this case, the patient did not show this symptom until the age of 5, so the diagnosis of LND was delayed.

LND has a defect in the purine salvage pathway, so patients have elevated uric acid levels in their serums. It is commonly treated using allopurinol to mitigate uric acid overproduction but it seems ineffective in neurobehavioral symptoms. In one study, a prenatally diagnosed LND patient who was administered allopurinol upon birth and never had elevated uric acid levels still developed neurobehavioral impairment, while it is effective in treating gout and liver failure [12]. Since its first description in 1964, several therapeutics, including dopaminergic agents, deep brain stimulation, and S-adenosylmethionine, have been tried for the treatment of LND. Although some progress has been made, many LND patients and their families still do not receive effective treatment today [12].

While the mutations are widely distributed throughout the *HPRT1*, there are some isolated hot spots where the same mutation occurs multiple times in unrelated patients. In this case, the patient has c.151C>T on the *HPRT1*, which is known as one of the most commonly found isolated hot spots in LND. It is classified as a nonsense mutation that results in the conversion of a codon encoding arginine to a stop signal (p.R51), leading to premature termination of protein translation. It is known to be associated with the classic form of LND, which manifests a more severe form of clinical phenotype, as they are not likely to permit some residual enzyme function, unlike other milder phenotypes [13].

NF1 is a relatively common autosomal dominant genetic disorder. It is a multisystem disorder which attributes to the development of benign or malignant tumors in various systems, mainly in the nervous system. Clinical manifestations in NF1 are extremely variable including cognitive impairments, behavioral problems, attention deficits, and problems with motor function, executive function, and language, specific dermatological findings such as Café au lait macules, skinfold freckling, and Lisch nodules. Many NF1 patients develop only cutaneous manifestations and Lisch nodules. The frequency of other complications tends to increase with age. Although NF1 patients have nearly normal intelligence in general, behavioral problems and learning disabilities are commonly seen in 50-80%. Intellectual disability is seen in 6-7%, which is about twice that in the general population [14,15]. Features of autism spectrum disorder occur in up to 30% of children with NF1 [14]. Germline mutation of the *NF1* tumor suppressor gene, located on chromosome 17q11.2, is known to cause NF1 [16]. The gene encodes tumor suppressor protein named neurofibromin, which is expressed in many kinds of cells including neurons, astrocytes, and oligodendrocytes. Its defects can affect abnormal cell proliferation and survival [17]. Although cognitive abnormalities are thought to be related to alterations in neurofibromin production, the causes of neurocognitive deficits are not fully explained yet.

NF1 has extreme clinical variability, not only between unrelated individuals and among affected individuals within a single family but even within a single person at different ages in life. The detection of mutations in the *NF1* is complex due to the large size of the gene (>350 kb), the presence of pseudogenes, the lack of hot spots, and a high mutation rate [18]. Only a few clear genotype-phenotype correlations have been observed between known pathogenic *NF1* alleles and consistent clinical phenotypes [19]. In this case, the patient showed c.7682C>G single-nucleotide nonsense mutation. It is known to be pathogenic but its genotype-phenotype correlation is not known until now.

Treatment is individualized on the clinical symptoms of the patient. Dermatologic findings such as Café-au-lait macules, skinfold freckling, and Lisch nodules have no malignant potential that dermatological camouflage is useful for cosmetic purposes. Tumorous lesions can vary and treatment should be individualized according to the characteristics of the tumor. Surgical removal, radiation therapy, and chemotherapy can be an option. There is no established pharmacological method to improve neurodevelopmental impairment in NF1 patients. Recent research on lovastatin showed the beneficial effects of this medication on some cognitive functions related to learning and memory by acting on synaptic plasticity. Methylphenidate has shown benefits by decreasing attention-deficit-hyperactivity-disorder symptoms [6]. But these drugs need further study to prove their clinical effectiveness and long-term safety when used in NF1 patients.

Due to the rarity of LND, cases of patients with LND who also have NF1 simultaneously have not yet been widely reported and their association has also not been unveiled. So here we report a rare case of a patient who has inherited two genetic mutations from his mother and has co-existing two diseases from these mutations. In this case, we speculate that these two mutations may have occurred by chance in the patient's mother without any correlation as their causative genes are located differently.

The patient showed severe neurodevelopmental impairment. We suppose that this severe intellectual disorder may be affected by the co-occurrence of these two diseases. As clinical symptoms of these two diseases seem to be overlapped clinically and manifest in a mixed form, his neurodevelopmental problems are not well distinguished in their origin. As it is not well known how these diseases affect clinical courses of each other, further study is needed. We believe that it is worthwhile tracking the clinical course of this rare case to understand the clinical course in the special situation that these two different diseases co-exist simultaneously and their possible synergistic effect on impairing patients' neurodevelopment.

In this case, hyperuricemia and severe developmental delay, which is not well explained by the only presence of NF1, made us do further evaluation including WES, and it led to the discovery of a new disease that was previously unknown. It helped us to understand the patient much better and to individualize treatment for the patient. From this point, we suppose that in the complicated mixture of symptoms in the patient of a rare genetic disease, unpredicted symptoms that are not well explained by the only presence of a previously known disease can sometimes justify the need for further evaluation. So we suggest considering a preemptive genetic evaluation if there are symptoms that are not fully explained by known, existing diseases as in this case.

## Authors' Contributions

Conception and design: JHY. Acquisition of data: YLS. Analysis and interpretation of data: YLS, GHS. Drafting the article: JHY, YHH, YLS. Critical revision of the article: JHY, YLS. Final approval of the version to be published: all authors.

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