SciMedCentral

JSM Clinical Oncology and Research

Case Report

Tumor Profile and Neuropsychological Symptoms of a Family with Novel Pathogenic Variant in *NF1* Found by an RNA-Based Analysis

Minna Kankuri-Tammilehto*

Department of Clinical Genetics, Turku University Hospital, Finland

***Corresponding author**
Minna Kankuri-Tammilehto, Department of Clinical Genetics, Turku University Hospital, Finland, Email: mikanku@utu.fi

Submitted: 01 September 2021

Accepted: 09 November 2021

Published: 12 November 2021

ISSM: 2373-938X

Abstract

Neurofibromatosis 1 (NF1) is a hereditary monogenic disorder. Common symptoms are cafe au lait spots and / or axillary or inguinal freckles, and cutaneous neurofibromas. In a recent population-based study the cancer risk of NF1 patients was twice compared to average population. This is a case report of patients with variable disease in three generations with GIST and various neuropsychologic symptoms in family, and in which the pathogenic NF1 variant was identified first at the RNA level and then at the DNA level. The case report confirms that GIST tumor is a universal symptom in different NF1 PVs and good academic skills can be achieved even if neuropsychological symptoms are challenging.

INTRODUCTION

Neurofibromatosis 1 (NF1) is a hereditary monogenic disorder. Common symptoms are cafe au lait spots (hyperpigmented lesions that are flat coffee-colored skin lesions, borders may be smooth or irregular) and cutaneous neurofibromas (benign Schwann cell tumors affected nerve on or under the skin) (Table 1). NF1 results in variable expression with variable onset of diagnosis, variable severity of the disease and varying symptoms. *NF1* gene is a RASopathy gene and a tumor suppressor gene, in which more than 2000 pathogenic variants (PV) are known. Most of the germline pathogenic variants in NF1 patients are frameshift mutations that usually cause severe truncation of the gene product followed by splice-site mutations altering mRNA splicing and affecting the correct splicing [1]. Pathogenic variant in *NF1* gene is identified in approximately 95% of cases by using double characterization at the DNA and RNA levels [1]. This is a case report of patients with variable disease in three generations with different tumors and various neuropsychologic symptoms in family, and in which the pathogenic *NF1* variant was identified first at the RNA level and then at the DNA level. Compared to average population the cancer risk is double for NF1 patients based on a population-based series of more than 1400 patients over 25 years' follow-up [2]. Nowadays NF1 is attempted to be diagnosed and surveillance started as early as possible.

NF1 CASES IN THE FAMILY

Patient

When the patient was 9 years old, the doctor noted cafe au lait spots and axillary freckling and sent a referral to a clinical geneticist for further diagnostic examinations. The patient had no learning difficulties in academic skills, but she gets tired during the school day compared to her sibling, who does not have a NF1 diagnosis. There is a soft tissue lump on her neck, and there are freckles on her neck near this lump. MRI scan revealed the lump as the plexiform neurofibroma. The daughter has difficulties in executive function: starting and maintaining activities when the activities are not personally motivating, or the subject is difficult. During remote school (due to COVID-19), it has been particularly difficult to finish things.

Mother

The mother has more than 6 pieces of café au lait spots, as well as axillary freckles and skin freckles throughout her body. The mother has not had neurofibromatosis findings on the skin, or neurofibromatosis type pains or side differences. She does not have learning difficulties in academic skills except in mathematics. The mother has difficulties with visual-spatial performance. This causes challenges for example in finding her parked car in a parking lot. She has also been diagnosed with ADHD as an adult.

Mother's father

The mother's father was diagnosed with NF1 at the age of 48 based on his symptoms. He has café au lait sports and several skin neurofibromas, which have been removed a dozen times. He has had a plexiform neurofibroma in the right upper arm, which has been removed due to nerve symptoms in the upper limb. At the

Table 1: Revised NF1 diagnostic criteria proposed by International Consensus Group on Neurofibromatosis Diagnostic Criteria were published in August 2021 (Legius, 2021). Revised changes to the previous criteria (Legius, 2021) are shown in indented bullet (UPDATED:). Criteria proposals aim is to incorporate new clinical features and genetic testing and for better separation of NF1 from other diseases with spot symptoms.

A clinical diagnosis of NF1 is based on agreed criteria. The diagnosis can be considered certain if the patient has at least two of the following symptoms:
· At least 6 cafe au lait spots (flat coffee-colored skin lesions) with a size exceeding 5 mm before puberty or exceeding 15 mm after puberty
o UPDATED: At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
· Freckles in axillary or inguinal regions
o UPDATED: At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
· Neurofibroma (at least 2 regular or 1 plexiform)
· Optic glioma
· Lisch nodules of the iris (at least 2)
o UPDATED: or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging
· Skeletal development disorder such as sphenoid wing dysplasia or thinning of long bone cortex, with or without pseudarthrosis
· A first-degree relative (parent, child or sibling) has been diagnosed with NF1
o UPDATED: Parent has been diagnosed with NF1
· Genetic research has shown an NF1 genetic defect (pathogenic variant)

age of 74 years an MRI scan showed diffusion thickness of spinal nerves in the spinal canal. On the left side, a small thickening suitable for neurofibroma attached to the L4 nerve root. At C1-C2 level there are neurofibromas that spread extraspinal. In both brachial plexuses plexiform neurofibromas have been identified. The mother's father is not using pain medication. The symptoms have not progressed during surveillance of the last 5 years. The patient has numbness in the right arm. ENMG examination indicated a peripheral symptom that fits a conclusion that neurofibromas have affected nerve roots and distal nerves. Operational treatment has not been recommended. Regular magnetic control of the cervical spine is arranged. The father has been treated for GIST in 2008 when he was 65 years old. Three synchronous GISTs were removed from ileum, jejunum and stomach. All three GIST were primary and were low or very low risk tumors and were KIT positive.

The family's pathogenetic variant in NF1 gene and the method to found it

Clinical geneticist conducted a clinical examination of the 9-year-old girl, mother and mother's father. Based on a clinical examination of the 9-year-old patient and verified family medical history, the girl and the mother were diagnosed with NF1. The mother's father was diagnosed at 80's on the basis of his clinical picture. Gene tests were done from the patient's sample to identify the family's pathogenic variant. *NF1* gene sequencing, MLPA-analysis of copy number variation and neurofibromatosis next-generation sequencing (NGS) panel were unable to find a pathogenic variant. The pathogenic variant was observed at the RNA level. Sequence analysis of this patient's cultured lymphocyte cDNA sample using an RNA-based long-range PCR and next generation sequencing screening protocol identified aberrant inclusion of 86 base pairs (r.8113_8114ins8113+18113+85 p.(Ser2705SerfsTer3)). The addition of 86 base pairs causes a shift in the reading frame of the codons in the mRNA, which lead to the alteration in the amino acid sequence at protein translation. The variant was confirmed in the cDNA of the *NF1* gene, and is c.8113+86A>G. This is causative and clinically important heterozygous pathogenic variant (ACMG Class 5). No other variants of clinical relevance were detected in the *NF1* transcript.

DISCUSSION

This family's *NF1* PV was found by RNA/DNA method. This method was selected, because the double characterization of the pathogenic variant at the DNA and RNA levels has been shown to be highly effective in the detection of frameshift mutations and splice-site mutations [1]. RNA sequencing is routine used in NF1 molecular diagnosis, but it is not a routine in monogenic disorders mainly due to the problems with RNA stability and availability [3]. In *NF1* many of the identified splice-site mutations are located outside the canonical splicing sites and not be found by DNA analysis [3]. The combined RNA/DNA method plus deletion/duplication screening using MLPA increase PV detection sensibility up to approximately 97% [4]. The family was initially diagnosis as NF1 by clinical picture, until it was possible to confirm this via RNA / DNA method.

The family has been diagnosed NF1 in at least three generations, and, as far as we know, also most likely in a fourth generation in the patient's mothers' fathers' parent. This family case is typical in the sense that the *NF1* pathogenic variant has caused a variable phenotype and all relatives with the pathogenic variant have some NF1 symptoms. The mother has noticed neuropsychiatric challenges in her herself and in her daughter (patient). The patient and her mother's father both have plexiform neurofibroma. Plexiform neurofibromas develop within peripheral nerves and their perineurial sheaths, and can invade adjacent tissue by disrupting the perineurium, remaining non-metastatic and benign [5]. Plexiform neurofibromas may cause pain with an increased mortality risk due to the transformation to malignant tumor [5] (Table 2). In addition, in this family there has been a predisposition to NF1 related malignant tumors.

Regular surveillance is important for NF1 patients, because the patients have a greater risk for malignant tumors than general population. Crucial in surveillance is that the NF1 patients are

Table 2: Typical age of onset and penetrance of selected NF1 symptoms. (Legius 2021, Blanchard 2016, Heervä 2013, Elefteriou 2009, Pöyhönen 1997).

Symptom	Appearance	Penetrance
Long bone dysplasia such as anteriolateral tibial bowing and sphenoid wing dysplasia	Congenital	Less than 5 %
Diffuse plexiform neurofibromas of the face and neck	By the age of 1 year	Less than 5 %
Cafe au lait spots (flat coffee-colored skin lesions)	By the age of 5 years	More than 95 %
Freckles in axillary and inguinal regions	Approx. at the age of 6 years	Approx. 70 %
Optic glioma (most patient conditions can be managed conservatively)	By the age of 6 years	15-20 % to 5 % Penetrance starts to decline at the age of 10 spontaneously
Lisch nodules	At the age of elementary school	Approx. 95 %
Rapidly progressive form of scoliosis	Between ages six and ten years	Not available
Diffuse plexiform neurofibromas of other parts than face and neck	By adolescence	Approx. 50 %
Neurofibromas on or under skin from few to thousands	Adolescence	Approx. 95 % by adulthood
Osteoporosis, increased risk of fractures	Young adulthood	Approx. 30 %

Table 3: Increased cancer risk in NF1. (Petr 2018, Evans 2017, Gruber 2017, Uusitalo 2016, Agaimy 2012, Rodriguez 2008).

Cancer	Cancer risk	Typical onset
Malignant pheochromosytoma and paraganglioma	Less than 10 %	42 years
GIST (Gastrointestinal Stromal Tumors)	25 % years	average 49 years
MPNST (malignant peripheral nerve sheath tumor)	10-15 %	20 - 40 years
Diffusely infiltrating astrocytoma or other malignant CNS tumor	Rare	Not available
Breast cancer	10x	when under 40-years

aware of their cancer risk and other symptoms that should be paid attention to and informed to doctor. Increasing clinical knowledge and awareness on NF1 also helps the surveilling doctor to identify possible malignant tumors early allowing for better treatment. For these reasons it is important to arrange surveillance for all NF1 patients.

During surveillance removal of benign tumors that are painful or cosmetically harmful can be planned. It is also possible to discuss on neuropsychological symptoms and receive required support and rehabilitation. Blood pressure should be monitored annually due to the risk of increased diastolic blood pressure [6] and skin examination due to the risk of a rapid increase in the number and size of neurofibromas. NF1 patient´s assessments of quality of life are diminished in both children and adults [7].

Malignant tumor risk in NF1

Usually, NF1 tumors are benign. Still treatment of benign tumors can be challenging depending on their location as was the case in the patient's mother's father where they affected his quality of life. New information has been published on risk for malignant tumor in NF1 (Table 3). The risk of breast cancer in the average population of a Finnish woman is approximately 13%. The incidence of breast cancer in NF1 patients under the age of 40 is more than tenfold and in patients under 50 about five times greater than in average population [2,8]. Compared to the average population, breast cancers in NF1 patients are more often estrogen and progesterone receptor negative and HER2 gene amplification positive. NF1 patient´s breast cancers tend to be more advanced and may have an increased breast cancer related mortality [2,9]. In 2019 a surveillance guideline for NF1 women aged 30-50 years on annual breast magnetic resonance imaging (MRI) and mammogram was published in 2019 [10]. This recommendation has been given to the mother. After 50 years the breast cancer risk of NF1 women starts to decline towards the risk of average population [11]. In Finland there is a biannual mammography breast cancer screening for all women aged 50-69. There is no evidence in the benefit of risk-reducing mastectomy, but GIST tumor occurs more frequently in NF1 patients than in average population, and the tumor is located more often in the small intestine (duodenal, jejuno-ileal) [12]. NF1 patient`s GIST usually does not contain KIT or PDGFR mutations, which reduces the options for targeted treatment such as imatinib [13]. In this case the father was diagnosed with GIST at a later age (64 years) that the average onset age for NF1 patients (45 years). GIST tumor is a common malignant tumor in NF1 patients in all *NF1* PVs. Also, neuroendocrine tumors, particularly of the periampullary duodenum, are characteristic to NF1 [12]. Pheochromocytoma and paraganglioma in NF1 are usually benign, but often hormone producing causing significant morbidity and mortality excess catecholamine secretion and cardiovascular crises [14]. A combination of GIST and neuroendocrine tumors such as somatostatinoma raises a strong suspicion of NF1 [15].

Malignant peripheral nerve sheath tumor (MPNST) are

nerve-associated sarcomas, most of which arise in pre-existing plexiform neurofibromas of NF1 patient. MPNST is suspected when a rapidly growing and hardening plexiform neurofibroma related unexpected pain is identified, and unexplained neurological symptoms are observed. The incidence of MPNST in NF1 patients is more than a thousand times greater than in the general population [16,17]. In NF1 related MPNST the prognosis is worse than in sporadic MPNSTs, and NF1 related MPNSTs are quite aggressive and tend to metastasize, however the five-year survival has risen from 30 % to about 50% [18,19]. The best way to improve the prognosis is an early diagnosis as complete surgical resection is required to cure.

At least 15% of patients with NF1 develop optic pathway glioma, which are mainly benign grade I pilocytic astrocytoma [20]. Radiotherapy of benign gliomas of the optic nerve has been shown to increase the risk of second cancer in the treated area. For this reason, active treatment is recommended only in those rare cases when optic glioma behaves aggressively, and conservative treatment is not sufficient [21]. Because of this MRI of the head for screening purposes is not recommended for NF1 children [20], but at the age of 8 medical doctors can arrange the MRI imaging from the brain. High grade gliomas are rare [22].

Rhabdomyosarcoma, an uncommon malignant soft tissue sarcoma, in which urogenital system is usually involved [23], and juvenile myelomonocytic leukemia (JMML) [24], are rare or very rare in NF1 patients. There is insufficient data to recommend any routine screening for them [22].

NF1 patient's surveillance should be done in specialist centers familiar with their wide spectrum of symptoms and with multidisciplinary care. Imaging technological advances may improve the screening of hard to detect malignant tumors in NF1 patients [25,26]: whole-body screening for malignancy or malignant transformations for NF1 patients is a topic of current discussion but is not currently recommended.

Neuropsychological risks in NF1

Approximately half (40-60%) of NF1 patients have learning difficulties [27,28], which are seen also in elderly NF1 patients [29]. NF1 patients with learning disabilities have more depression, sensitivity to stress and uncertainty on NF1 symptoms [30]. Problems in visual- spatial skills and auditory long-term memory seem to be specific NF1 related deficits [31]. Deficits in attention, visual-spatial performance, and social competence, are most commonly seen in NF1 patients, but in addition problems with executive function, and memory are frequently seen [32]. In this case the families view is that neuropsychological difficulties clearly affect negatively everyday life.

Visual deficits are expansive and can be responsible for severe difficulties in everyday life, such as interpreting social cues and learning academic skills [33]. NF1 visual-spatial difficulties includes problems with perception and interpretation, difficulty in assessing spatial relationships and directions, problems with visual motoric coordination, and difficulty in perceiving parts of the whole. Deficits in visual spatial skills make it difficult to read map and learn routes, understand the mechanisms and operation of devices, and spatial reasoning of geometry. Spatial learning deficits may be an important target for cognitive interventions in children with NF1. Lovastatin administered once daily for 16 weeks was investigated but it did not improve visuospatial learning or attention in children, and it is not recommended for amelioration of cognitive deficits [34].

Auditory memory problems are possibly related to deficits in language use and comprehension, this support observations of problems in processing social information [31,35].

In general attention deficit hyperactivity disorder (ADHD) may influence motor performance, but recent research pointed that motor problems in NF1 seem to be independent from attention deficit [36]. At least 30% and maybe approximately 50% of children with NF1 fulfill ADHD or poor attention criteria, and ADHD was much more common in children with NF1 than in their siblings or parents [27,37,38].

Executive function is a set of mental skills and processes that allows an individual to function with focus and according to the situation [39]. Executive functions include planning, organization, abstract concept formation, acting according to plan, problem-solving, flexible thinking, inhibitory processes, tolerance to distractions, rule deduction, sustained attention, and working memory [32,39]. Evaluation of executive function is difficult in studies, often questionnaires are used [40], interviewing the subject and his/her inner circle and additional observational measures [32]. Problems with organizational skills are often mentioned in NF1 patients [41].

Children with NF1 seem to have more errors in working memory tasks compared to other children, although the reaction times does not differ between these two groups [35,37].

The mother says that she and her daughter have some of these difficulties. The mother has difficulties in visual observations, for example she does not remember people's faces well. Patients with NF1 have described to have difficulties in academic skills, but there have been no such difficulties in this family, except in mathematics in the mother. Patients with NF1 have more fatigue than population on average and this is also the case in this family.

The mother has an ADHD diagnosis. She says: "If the environment or external activity is not highly structured, it is difficult to act. In everyday life this has appeared as difficulties with cleaning and other household chores, especially finishing them. As younger when studying there were difficulties in larger projects. Now, as an adult, university studies seem to be going well again, but this requires strong scheduling, etc. structure, the making of which I myself have learned to do as an adult."

NF1 children who are diagnosed early can have well planned surveillance since early childhood, support learning at home and in enable earlier detection of emerging academic problems in school and efficiently react to them [42]. Neuropsychiatric examinations and support measures should be arranged as soon as they become necessary. However, arranging this support also for those who have been diagnosis as adults is justified [30,31].

Blood pressure and osteoporosis

NF1 is associated with increased blood pressure, especially due to renal artery stenosis or pheochromocytoma and therefore annual blood pressure monitoring is warranted [6]. In adults for

the risk of osteoporosis calcium and vitamin D -treatment should be considered and if required density boney measurements arranged [43].

CONCLUSION

In conclusion, the incidence of NF1 is about 1/2000 [44], so among rare diseases it can be categorized as a common rare disease. It is known that *NF1* PV may appear de novo, in which case there are no NF1 cases in the family's previous generations. It is known that some adult NF1 patients are not in surveillance because the patient has not been diagnosed due to mild symptoms. However, she or he may be at risk of malignant tumors and may have psychosocial problems for which surveillance and supportive treatment would be beneficial. A clinician should refer to a clinical geneticist if NF1 suitable symptoms are found even if treatment is provided for other diagnoses. If an adult patient has had two diagnosed neurofibromas on or under the skin even if she or he does not have other symptoms, diagnostic neurofibromatosis gene panel test [45] is warranted to be considered. Nowadays, a child patient is usually diagnosis early in life because almost all NF1 patients show up with cafe au lait spots by the age of 5 years. RNA/DNA method plus deletion/duplication screening using MLPA have enabled to diagnose molecular NF1 early in life. A child who meets one or more clinical criterion (Table 1) should have *NF1* molecular genetic testing offered to confirm if NF1 is the correct diagnosis, as a misdiagnosis most likely leads to incorrect surveillance. Co-existence of GIST and neuroendocrine tumor, such as somatostatin, should raise the possibility of NF1, and lead to diagnostic genetic testing.

Previously very few clear genotype-phenotype correlations have been observed [46]. Best known is NF1 microdeletion syndrome, where the whole *NF1* gene is deleted in the other allele and that causes a difficult disease with greater risk for malignant tumor, particularly MPNST risk, and severe cognitive problems compared to other PVs. A higher number of café au lait spots seem to associate with truncated mutations compared to missense mutations [4]. Up to now contradictory NF1 neuropsychological symptoms have been reported that may be caused by differences in genotype- phenotype. In a recent GWAS study potential modifier genes that might example NF1 phenotype variability have been observed, including potential genes in RAS pathway, myelination process of Schwann cells and cell cycle genes [47]. Phenotype variability according to neuropsychological factors are not explained only by hereditary PVs, but differences in cognitive skills are also affected by the environment where the child grows up [33,42]. This case report pointed that in the family with a novel splice-site mutation NF1 patients' experience is that neuropsychological symptoms influence significantly their everyday life. Tumor profile evaluation in this family confirmed previous observation that GIST tumor is universal symptom in different *NF1* PVs. In this family the GISTs were KIT-positive even though in most reported NF1 cases GISTs are KIT-negative. In future, more evaluation of tumor profile and neuropsychological factors affecting in different *NF1* PVs are warranted.

In near future, new targeted anti-cancer medication affecting the Ras-signaling pathway may also help NF1 patients. Anti-Ras inhibitors for cancer treatment are under evaluation in NF1 patients [48].

REFERENCES

1. Pros E, Gómez C, Martín T, Pere Fábregas, Eduard Serra, Conxi Lázaro. Nature and mRNA effect of 282 different NF1 point mutations: focus on splicing alterations. Hum Mutat. 2008; 29: E173-93.
2. Uusitalo E, Rantanen M, Kallionpää RA, Minna Pöyhönen, Jussi Leppävirta, Heli Ylä-Outinen, et al. Distinctive cancer associations in patients with neurofibromatosis type 1. J Clin Oncol. 2016; 34: 1978–86.
3. Abramowicz Anna, Gos Monika. Splicing mutations in human genetic disorders: examples, detection, and confirmation. J Appl Genet. 2018; 59: 253–268.
4. Sabbagh A, Pasmant E, Apolline I, Armelle Luscan, Magali Soares, Hélène Blanché, et al. NF1 Molecular Characterization and Neurofibromatosis Type I Genotype-Phenotype Correlation: The French Experience. Hum Mutat. 2013; 11: 1510-1518.
5. Prada CE, Rangwala F, Martin L, Anne M Lovell, Howard M Saal, et al. Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1. J Pediatr. 2012; 160, 461–467.
6. Cutruzzolà A, Irace C, Frazzetto M, Jolanda Sabatino, Rosa Gullace, Salvatore De Rosa, et al. Functional and morphological cardiovascular alterations associated with neurofibromatosis 1. Sci Rep. 2020; 10: 12070.
7. Vranceanu A-M, Merker VL, Park ER. Quality of life among children and adolescents with neurofibromatosis 1: a systematic review of the literature. J Neurooncol. 2015; 122: 219-28.
8. Suarez-Kelly LP, Yu L, Kline D, Eric B Schneider, Doreen M Agnese, et al. Increased breast cancer risk in women with neurofibromatosis type 1: a meta-analysis and systematic review of the literature. Hered Cancer Clin Pract. 2019; 17: 12.
9. Uusitalo E, Kallionpää R, Kurki S. Breast cancer in neurofibromatosis type 1: overrepresentation of unfavourable prognostic factors. Br J Cancer. 2017; 116: 211-217.
10. Daly MB, Pilarski R, Berry M, Saundra S Buys, Meagan Farmer. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017. J Natl Compr Canc Netw. 2017; 15: 9-20.
11. NCCN. Genetic/Familial High-Risk Assesment: Breast, Ovarian, and Pancreatic, Version, 2.2021.
12. Agaimy A, Vassos N, Croner R. Gastrointestinal manifestations of neurofibromatosis type 1 (Recklinghausen's disease): clinicopathological spectrum with pathogenetic considerations. Int J Clin Exp Pathol. 2012; 5: 852-62.
13. Miettinen M, Fetsch JF, Sobin LH, Jerzy Lasota. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol. 2006; 30: 90–6.
14. Petr E, Else T. Pheochromocytoma and Paraganglioma in Neurofibromatosis type 1: frequent surgeries and cardiovascular crises indicate the need for screening. Clin Diabetes Endocrinol. 2018; 4: 15.
15. Yamamoto R, Kato S, Maru T, Riki Ninomiya, Fumiaki Ozawa, Yoshifumi Beck, et al. The Coexistence of Somatostatinoma and Gastrointestinal Stromal Tumor in the Duodenum of a Patient with Von Recklinghausen's Disease. Intern Med. 2016; 55: 617-22.
16. Seminog OO, Goldacre MJ. Risk of benign tumours of nervous system, and of malignant neoplasms, in people with neurofibromatosis: population-based record-linkage study. Br J Cancer. 2013; 108: 193–8.
17. Tucker T, Wolkenstein P, Revuz J, J Zeller, J M Friedman. Association between benign and malignant peripheral nerve sheath tumors in

NF1. Neurology. 2005; 65: 205–211.

18. Stucky CC, Johnson KN, Gray RJ, Barbara A Pockaj, Idris T Ocal, Peter S Rose, et al. Malignant peripheral nerve sheath tumors (MPNST): the Mayo Clinic experience. Ann Surg Oncol. 2012; 19: 878–85.

19. Evans DG, Huson SM, Birch JM. Malignant peripheral nerve sheath tumours in inherited disease. Clin Sarcoma Res. 2012; 2: 17.

20. Listernick R, Ferner RE, Liu GT, David H Gutmann. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol. 2007; 61: 189–98.

21. Sharif S, Ferner R, Birch JM, James E Gillespie, H Rao Gattamaneni, Michael E Baser, et al. Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. J Clin Oncol. 2006; 24: 2570–5.

22. Evans DGR, Salvador H, Chang VY, et al. Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 1. Clin Cancer Res. 2017; 23: e46-e53.

23. Crucis A, Richer W, Brugières L, Christophe Bergeron, Aude Marie-Cardine, Jean-Louis Stephan, et al. Rhabdomyosarcomas in children with neurofibromatosis type I: A national historical cohort. Pediatr Blood Cancer. 2015; 62: 1733-8.

24. CA Stiller, J M Chessells, M Fitchett. Neurofibromatosis and childhood leukaemia/ lymphoma: a population-based UKCCSG study. Br J Cancer. 1994; 70: 969–972.

25. Dare AJ, Gupta AA, Thipphavong S, Markku Miettinen, Rebecca A Gladdy. Abdominal neoplastic manifestations of neurofibromatosis type 1. Neurooncol Adv. 2020; 2: i124-i133.

26. Ahlawat S, Blakeley J, Langmead S, Allan J Belzberg, Laura M Fayad, et al. Current status and recommendations for imaging in neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis. Skeletal Radiol. 2020; 49: 199-219.

27. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type1. Neurology. 2005; 65: 1037–44.

28. DeBella K., Szudek J, Friedman JM. Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000; 105: 608–614.

29. De Souza Costa D, De Paula JJ, De Rezende NA, Luiz Oswaldo Carneiro Rodrigues, Leandro Fernandes Malloy-Diniz, et al. Neuropsychological impairments in elderly Neurofibromatosis type 1 patients. Eur J Med Genet. 2014; 57: 216-9.

30. Granström S, Friedrich RE, Langenbruch AK. Influence of learning disabilities on the tumour predisposition syndrome NF1--survey from adult patients' perspective. Anticancer Res. 2014; 34: 3675-81.

31. Descheemaeker M-J, Plasschaert R, Frijns J-P. Neuropsychological profile in adults with neurofibromatosis type 1 compared to a control group. J Intellect Disabil Res. 2013; 57: 874-86.

32. Lehtonen A, Howie E, Trump D, Susan M Huson. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol. 2013; 55: 111-25.

33. Bulgheroni S, Taddei M, Saletti V, et al. Visuoperceptual Impairment in Children with NF1: From Early Visual Processing to Procedural Strategies. In Book Behavioural Neurology. Hindawi. 2019; 10.

34. Payne JM, Barton B, Ullrich NJ, Alan Cantor, Stephen J C Hearps, et al. Randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1. Neurology. 2016; 87: 2575–2584.

35. Huijbregts S, Swaab H, de Sonneville L. Cognitive and motor control in neurofibromatosis type I: influence of maturation and hyperactivity-inattention. Dev Neuropsychol. 2010; 35: 737–51.

36. Haas-Lude K, Heimgärtner M, Winter S, Victor-Felix Mautner, Ingeborg Krägeloh-Mann, Karen Lidzba, et al. Motor dysfunction in NF1: Mediated by attention deficit or inherent to the disorder? Eur J Paediatr Neurol. 2018; 22: 164-169.

37. Ullrich NJ, Ayr L, Leaffer E, Mira B Irons, Celiane Rey-Casserly. Pilot study of a novel computerized task to assess spatial learning in children and adolescents with neurofibromatosis type 1. J Child Neurol. 2010; 25: 1195-202.

38. Koth CW, Cutting LE, Denckla MB. The association ofneurofibromatosis type 1 and attention deficit hyperactivity disorder. Child Neuropsychol. 2000; 6: 185–94.

39. Denckla MB. Measurement of executive function. Kirjassa: Frames of reference for the assessment of learning disabilities. Lyon GR (ed.) 3. painos. Paul H. Brookes Publishing: Baltimore 2000.

40. Klenberg L, Jämsä S, Häyrinen T, Pekka Lahti-Nuuttila, Marit Korkman. The Attention and Executive Function Rating Inventory (ATTEX): Psychometric properties and clinical utility in diagnosing ADHD subtypes. Scand J Psychol. 2010; 51: 439- 48.

41. Payne JM, Hyman SL, Shores EA, North KN. Assessment of executive function and attention in children with neurofibromatosis type 1: relationships between cognitive measures and real-world behavior. Child Neuropsychol. 2011; 17: 313–29.

42. Biotteau M, Déjean S, Lelong S, Stéphanie Iannuzzi, Nathalie Faure-Marie, Pierre Castelnau, et al. Sporadic and Familial Variants in NF1: An Explanation of the Wide Variability in Neurocognitive Phenotype? Front Neurol. 2020; 11: 368.

43. Heervä E, Leinonen P, Kuorilehto T, Peltonen S, Pöyhönen M, Väänänen K, Peltonen J. Neurofibromatosis 1- related osteopenia often progresses to osteoporosis in 12 years. Calcif Tissue Int. 2013; 92: 23-7.

44. Kallionpää RA, Uusitalo E, Leppävirta J, Minna Pöyhönen, Sirkku Peltonen, Juha Peltonen, et al. Prevalence of neurofibromatosis type 1 in the Finnish population. Genet Med. 2017; 20: 1082–1086.

45. Couch FJ, Shimelis H, Hu C, Steven N Hart, Eric C Polley, Jie Na, et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. JAMA Oncol. 2017; 3: 1190-1196.

46. Shofty B, Constantini S, Ben-Shachar S. Advances in Molecular Diagnosis of Neurofibromatosis Type 1. Semin Pediatr Neurol. 2015; 22: 234-9.

47. Pacot L, Sabbagh A, Parfait B, et al. Modifier genes in NF1: results of the first Genome-Wide Association Study in 1333 patients. P24.041.D, e-poster presentation. Presented in Conference: The European Human Genetics Conference, Virtual Conference. 2021.

48. Chen K, Yalei Zhang Y, Ling Qian L, Peng Wang. Emerging strategies to target RAS signaling in human cancer therapy. J Hematol Oncol. 2021; 14: 116.

Cite this article

Kankuri-Tammilehto M (2021) Tumor Profile and Neuropsychological Symptoms of a Family with Novel Pathogenic Variant in NF1 Found by an RNA-Based Analysis. JSM Clin Oncol Res 9(1): 1068.