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ORIGINAL ARTICLE

FINCA syndrome—Defining neurobehavioral phenotype in survivors into late childhood

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Abstract

Background: By 2021, 10 cases of fibrosis, neurodegeneration, and cerebral angiomatosis (FINCA, MIM #618278) syndrome have been reported, and five causative variants in the *NHLRC2* gene (*618277) have been identified. First reported patients presented with recurrent respiratory distress, leading to death before the age of 3. In the recent publication by Rapp, Van Dijck, and Laugwitz et al., six more patients were described. The authors underlined the possibility of survival beyond infancy and neurodevelopmental delay occurrence.

Methods: Our goal is to characterize further neurobehavioral phenotype of patients with the *NHLRC2* gene variants. Therefore, we describe three previously unreported patients with FINCA's clinical features who survived into late childhood and reviewed the neurobehavioral phenotype of all known cases.

Results: We identify the so far unfamiliar neurological features of FINCA syndrome and a novel variant in the *NHLRC2:* c.977G>T, p.(G326V) detected in one of the patients.

1 | INTRODUCTION

Fibrosis, neurodegeneration, and cerebral angiomatosis (FINCA) syndrome is a rare disease (OMIM #618278) with only 10 cases described until now from six families (Uusimaa et al. 2018; Brodsky et al., 2020, Rapp et al., 2021). The reported cases carry variants in NHL repeat containing two gene (*NHLRC2*) (Biterova et al., 2018). In the first report, released in 2018, three Finnish patients were described (Uusimaa et al., 2018). In the second one, published in 2020, one Ukrainian patient was reported (Brodsky et al., 2020). These reports were followed by a recent publication of Rapp et al. (2021), reporting on six additional patients from three families. Patients with FINCA have multi-organ symptoms, which can be manifested along with feeding problems, growth failure, chronic

diarrhea, malabsorption, recurrent bronchopulmonary infections, seizures, and lung fibrosis, leading to progressive respiratory failure in some, but not all patients. Patients described by the Finnish and Ukrainian group, and two patients described by Rapp et al. (2021) died before reaching the age of 3 **(**Uusimaa et al. 2018; Brodsky et al., 2020, Rapp et al., 2021**)**. The respiratory disorder in all patients was progressive or exacerbated during infections. The remaining four patients of Rapp et al. (2021) survived into late childhood. The oldest patient described so far is 14 years old (Rapp et al., 2021). The *NHLRC2* gene function remains generally uncharacterized (Nishi et al., 2017). NHLRC2 protein is present in several cell types and regions of the human brain. It participates in cellular organization and is responsible for regulating the cytoskeleton and vesicle transport (Paakkola et al., 2018). Thus, pathogenic variants in the *NHLRC2* gene could cause uncontrolled tissue fibrosis and, therefore, can induce the differentiation of fibroblasts to myofibroblasts (Paakkola et al., 2018). The vesicular trafficking dysfunction was the proposed cause of predisposition to neurodegeneration in FINCA disease (Hiltunen et al., 2020). Other researchers suggest *NHLRC2* plays an important role in regulating reactive oxygen species-induced apoptosis (Nishi et al., 2017). *NHLRC2* dysfunction has not been associated with any other human diseases (Uusimaa et al., 2018). We aim to describe clinical features of three previously unreported patients with clinical features of FINCA syndrome and to characterize further the neurological and psychological phenotype of patients with variants in the *NHLRC2* gene who survived into late childhood.

2 | MATERIALS AND METHODS

2.1 | Genetic study

A genetic study was performed using NGS-based whole-exome sequencing (WES). WES was performed only in probands. Venous blood samples were collected from the probands and their families. DNA was isolated using DNeasy Blood and Tissue Kit (Qiagen) following the manufacturer's recommendations. In patient 1 and patient 2, WES was performed with SureSelectXT Human kit All Exon v7 (Agilent, Agilent Technologies), while in patient 3, Twist Human Core Exome (Twist Bioscience) was used. Then paired-end sequenced (2x100bp) on HiSeq 1500 (Illumina). Bioinformatics analysis of raw WES data and variants prioritization were performed as previously described (Śmigiel et al., 2020). Prioritized *NHLRC2* variants: (g.113876631G>T, NM_198514.4:c.442G>T, p.(D148Y) and g.113884318G>T, NM_198514.4: c.977G>T, p.(G326V) were validated in the probands and their families by deep-amplicon sequencing (DAS) using Nextera XT Kit (Illumina) and sequenced on HiSeq 1500 (Illumina).

Runs of homozygosity (ROHs) were detected using the bcftools program as described previously (Narasimhan et al., 2016; Smigiel et al., 2018). The reference group consisted of WES data from 559 unrelated Polish subjects from a local database.

3 | RESULTS

3.1 | Genetic findings

WES results revealed a homozygous missense variant in the *NHLRC2* gene (g.113876631G>T, NM_198514.4:c.442G>T, p.(D148Y) in both patient 1 and 2. In addition, the DAS showed that in these cases, the variant was inherited from healthy parents and present in a heterozygous state in the healthy brother of patient 2. In patient 3, WES results revealed two missense variants in the *NHLRC2*. Heterozygous p.D148Y variant in the *NHLRC2* gene inherited from healthy mother, and heterozygous variant (g.113884318G>T, NM_198514.4: c.977G>T, p.(G326V) inherited from healthy father and present in healthy sister.

In the ClinVar database, the p.(D148Y) variant was predicted as "pathogenic" (https://www.ncbi.nlm.nih.gov/clinvar). According to ACMG classification, the p.(G326V) variant was classified as "Variant of Uncertain Significance" (Tavtigian et al., 2018). In GnomAD, the p.(D148Y) variant was reported with an allele frequency of 0.0004338, while the p.(G326V) variant was absent in both, the public database (GnomAD) and in-house database of more than 300 WES of Polish individuals (https://gnomad.broadinstitute.org, v3.1.1). Based on 10 pathogenic predictions from BayesDel_addAF, DANN, EIGEN, FATHMM-MKL, LIST-S2, M-CAP, MVP, MutationAssessor, MutationTaster, and SIFT versus two benign predictions from DEOGEN2 and PrimateAI, the p.(G326V) variant was classified as pathogenic. According to the CADD, the p.(G326V) variant has a score value of 29.2.

The list of all variants which were considered during WES analysis is shown in File S1. For the variant (g.4546230A>T, NM_032108.4, c.1724T>A, p.[L575*]) in the *SEMA6B* gene found in P11 we performed parental studies by Sanger sequencing which showed that the variant was maternally inherited.

The analysis of runs of homozygosity (ROH) showed no evidence for consanguinity of patients who were homozygous for the p.(D148Y) variant. The total ROH length for patient 1 and 2 was 40.96 and 27.02 Mb, respectively.

Comparison with reference population showed, for patient P11 and P12 respectively, that 98% and 70% of unrelated Poles had total ROH length equal or longer than the patients. We also analyzed in P11 and P12 SNV markers available from WES in the neighborhood of the *NHLRC2* gene in a search for a shared haplotype which could indicate a recent founder event. However, we found haplotype divergence (in either direction) already in the distance of <0.5 Mb from the causative *NHLRC2* variant (File S2). This indicates that the sharing of homozygous *NHLRC2* variant in patients P11 and P12 is not a consequence of patients being related. Furthermore, lack of conserved haplotype in proximity to *NHLRC2* argues against p.(D148Y) being present in Polish population due to a relatively recent founder effect.

3.2 | Clinical findings

General data and comparing the clinical symptoms with other published cases that survived beyond early childhood are presented in Table 1. Considering that 10 patients have been described so far by other authors, we attributed numbers P11-P13 to patients reported by us. None of the Polish patients has neither visual impairment, hepatomegaly, cardiomegaly, nor progressive respiratory insufficiency, which were present in other cases **((**Uusimaa et al. 2018; Brodsky et al., 2020, Rapp et al., 2021**)**. Three patients had recurrent infections, Proband P11 has frequent upper respiratory tract infections, Proband P12 experienced bronchopulmonary infections only during the first year of life. In Proband P13, recurrent severe bronchopulmonary infections and diarrhea are still the main clinical problem at 10 years. After a gastrointestinal infection at the age of 6 months, feeding problems started. From then on, persistent diarrhea also appeared, intensifying during infection periods with up to 20 stools a day. She was admitted more than 10 times a year to a hospital for enterocolitis or pneumonia. Twice she developed bilateral pneumonia with acute respiratory insufficiency. Finally, at the age of 5, infections became less frequent (1–2 times a year), diarrhea reacted well to treatment with oral cromoglicic acid (Nalcrom), which was administered as a "last chance drug", and because of suspicion of a partially allergic background of frequent stools, in the absence of severe eosinophilia and elevation of IgE. Two girls have epilepsy with focal and generalized seizures that are not frequent however, may lead to status epilepticus. Episodes morphology, interictal EEG, and reaction to pharmacotherapy are described in (Table 1).

We have recorded one previously undescribed neuroradiological finding in Proband P13. During a 10-year follow-up, subsequent MRI studies of the brain did not reveal any significant clinical deviations in this patient. However, at the age of 10, thickening of the skull bones was noted in a routine MRI study (Figure 1), suggesting bone marrow hyperplasia.

4 | DISCUSSION

We describe three Polish patients with rare FINCA syndrome. One of the cases is caused by compound heterozygous variants, the already described one (c.442G>T, p.(D148Y)) and a novel one (c.977G>T, p.(G326V)) in the *NHLRC2* gene. In two cases, the homozygous mutation c.442G>T, p.(D148Y) was found. The same variant was previously found in Ukrainian, Jordanian, Greek, and Belgian patients. Thus, our findings further support the presence of a hot spot variant in the *NHLRC2* gene.

Described by us, patients contribute to the 13 known cases of FINCA syndrome reported until now. Seven patients survived infancy. This gives the unique opportunity to observe the further development of patients with this syndrome. The clinical characteristics included intellectual disability with severely retarded speech expression, relatively preserved speech comprehension, and behavior problems. The last symptom combined aggression outbursts, attention deficit, and irritability. The presence of hand stereotypic movements, poor fine motor function, and severely impaired expression of speech inspired the initial diagnosis of the atypical Rett syndrome in two girls. Therefore, the *NHLRC2* gene should be considered causative for atypical Rett syndrome (without microcephaly) and included in next-generation sequencing panels for Rett syndrome and Rett-like syndromes. The video presenting typical Rett syndrome stereotypic hand movements occurring in Proband P13 is included in the supplement.

4.1 | Video-link

Analysis of proteomes of the Nhlrc2$^{FINCA/-}$ harboring the FINCA patient missense mutation p.(D148Y) exhibited the dysfunction in vesicular trafficking, compared to wildtype mice (Hiltunen et al., 2020). According to the authors it may be related to predisposition to neurodegeneration in FINCA disease (Hiltunen et al., 2020). Noteworthy, Sbardella et al. (2017) studied fibroblasts of patients with Rett syndrome and a mouse model of the syndrome and proposed that defective autophagy is also involved in the pathogenesis of Rett syndrome. Thus, it might partially explain clinical similarities in these two neurodegenerative syndromes.

Interestingly, all patients but one who survived beyond infancy were females. It may suggest a milder course of

TABLE 1 Clinical features of all known FINCA syndrome cases that survived into late childhood

Clinical and molecular data	Proband P3 (Rapp et al., 2021)	Proband P4 (Rapp et al., 2021)	Proband P5 (Rapp et al., 2021)	Proband P6 (Rapp et al., 2021)
Age of onset	0–2 months	2 weeks	After birth	12 months
Genetic mutation	Compound heterozygote, p.(D75V)/p.(D148Y)	Compound heterozygote, (p.D148Y)/ p.(P338L)	Homozygote c.442G>T, p.(D148Y)	Homozygote c.442G>T, p.(D148Y)
Nationality/Sex	Greek/F	Belgian/F	Jordanian/M	Jordanian/F
Age at last follow-up (years)	10	4	14	7
Current age				
Diarrhea	+	−	NDA	NDA
Transient liver dysfunction	+	+	−	−
Hematologic dysfunction	−	Macrocytic anemia, initially hemolysis	−	−
Recurrent infections	+	+	NDA	−
Progressive respiratory insufficiency	+/− (Oxygen 12–15 L/min until the age of 2)	+	+ (Improved over disease course)	−
Feeding problems	+	+	−	−
Motor milestones	Delayed walking	At the age of 4 unable to sit	Delayed walking	Delayed walking
Speech	Express simple needs (like thirst) verbally	At the age of 4 no language	Delay	Delay
Stereotypic movements of hands	NDA	NDA	NDA	NDA
Behavior phenotype	Irritability, no interest in toys or TV, easily distractible. Shows emotions	Irritability, poor eye contact	Irritability, poor eye contact, shy demeanor, normal sleeping pattern	Irritability, poor eye contact, social life and sleep pattern unremarkable
Gait	Walking with support since the age of 5	At the age of 4 unable to sit	NDA	NDA

Proband P11	Proband P12	Proband P13	Summary
After birth	9 months	3 months	
Homozygote c.442G>T,p.(D148Y)	Homozygote c.442G>T, p.(D148Y)	Compound heterozygote c.442G>T, p.(D148Y)/ c.977G>T, p.(G326V)	
Polish/F	Polish/F	Polish/F	
6	9	12	
7	10	13	
–	–	+	2/5
–	–	+	3/7
–	After birth, the patient developed prolonged hyperbilirubinemia with anemia	+ (Increased MCV, currently no anemia. Neonatal jaundice with anemia requiring transfusion)	3/7
+	+ (During infancy)	+++	5/6
–	–	–	3/7
–	–	+	3/7
Walking 16 mo	Head stabilization 3 mo., rolling 6 mo., sitting 9 mo., crawling 12 mo., walking 18 mo. No pincer grasp	Walking 4 years	
Single words since the age of 4	Poor gurgling, first words at the age of 2.5, disappeared before the age of 3. At the age of seven, she started to speak a few simple words again. At present she speaks 3 words, communicates non-verbally by gestures and facial expressions. She vocalizes, uses symbols for communication (PCS), shows good speech comprehension, follow even complicated commands	First words at the age of 9, uses several single words, shows better speech comprehension	
Clapping and waving, suggestive of Rett syndrome	Hand flapping and jumping	Squeezing hands, clapping, and putting hands into the mouth, suggestive of Rett syndrome	
Irritability, poor eye contact.	Frequent mood changes, periods of irritability with aggression, lack of distance in contacts with strangers, unable to control her strength while playing with other children - she squeezes them firmly, pinches. Sudden cry or anger outbursts. Requires attention of others. In large groups, easily distractible stops following commands. Short attention span. Prefers relations with adults, not with other children. She enjoys music	During infancy, she cried a lot at night. At the age of six, sudden outbursts of laughter or crying started and are still observed. A tendency to squeeze firmly and hold strongly other children. Irritability, frequent mood changes. Short attention span	
Unstable, wide-based ataxic gait	Walks independently, with bent knees, adducted thighs - poor stabilization of posture	Atactic, wide gait, with truncal instability, bent knees	

(Continues)

TABLE 1 (Continued)

Clinical and molecular data	Proband P3 (Rapp et al., 2021)	Proband P4 (Rapp et al., 2021)	Proband P5 (Rapp et al., 2021)	Proband P6 (Rapp et al., 2021)
Neurological examination	Dystonia	Dystonia, peripheral and axial hypotonia, hyperreflexia in lower limbs, dysmetria	Dystonia, truncal hypotonia, decreased muscular tonus, balance problems while sitted	Dystonia, truncal hypotonia, decreased muscular tonus, strabismus
Functioning	Limited fine motor skills at the age of 5, bladder and bowel movement control since the age of 9	NDA	Moderate intellectual disability, able to walk without balance problems	Mild intellectual disability
Epilepsy	One episode of seizures	–	–	–
EEG	NDA	NDA	NDA	NDA
Reaction to antiepileptic drugs	NDA	NDA	NDA	NDA
MRI findings	Normal	Thin corpus callosum, global cortical and subcortical atrophy	NDA	NDA
Other	–	Dilatation of ascending aorta	–	–

Abbreviations: F, female; LAMI, lamotrigine; LEV, levetiracetam; M, male; NDA, no data available; TOPA, topiramate; VAL, valproate.

the disease related to the female gender. This hypothesis needs further confirmation in larger groups of patients.

None of the patients' survived infancy did show cerebral angiomatosis. Furthermore, patients reported by us did not show signs of neurodegeneration on MRI studies throughout the follow-up period. Interestingly, diarrhea in P13 was temporally resolved with the use of cromoglycic acid. This treatment was introduced without evident biochemical markers of an allergic background of symptoms, as a "last chance" solution. Cromoglycic acid prevents mast cell activation and degranulation, and inhibits neutrophil chemotaxis. The potential relation of dysfunction in the *NHLRC2* gene and impairment of the function of mast cells and neutrophils should be further studied.

Proband P11	Proband P12	Proband P13	Summary
Axial hypotonia, convergent alternating strabismus	Axial hypotonia, normal reflexes, no pathological signs, fine position tremor in hands	Axial hypotonia, normal reflexes, no pathological signs	
NDA	Able to eat soup with a spoon, undress, clean her room. Unable to get dressed	Frequent episodes of inappropriate laughter, she speaks few single words, walk on her own, impulsive behavior	
–	Seizures with focal onset since the age of 4.5. After awakening, the first episode starts with gagging, eye deviation, after 8 minutes atonia, cyanosis, loss of consciousness. Similar episodes 1–2 times a year	First two focal seizures with secondary generalization occurred, VAL was introduced with good tolerance, next episode in the fifth year of life, three times status epilepticus. Episodes twice a year	3/7
4 years 8 mo.: in wakefulness, a record of disturbed spatial organization, high-voltage, with high superimposed fast activity at 14–18 Hz, up to 150 uV. Against this background single and groups of sharp waves up to 280 uV in right posterior temporo-occipital leads. During sleep, series of irregular sharp-and-slow-wave and spike–wave complexes at 3.5–4 Hz, up to 615 uV	6 years: bilaterally in the posterior temporo-parieto-occipital area numerous discharges of sharp waves and sharp-and-slow-wave complexes at 3 Hz, up to 800 uV 6 years 3 mo.: in the posterior area with a predominance of the right side, single and groups of sharp-and-slow-wave complexes, up to 700 uV. During sleep numerous generalized series of slow waves at 2–2.5 Hz and spike–wave complexes, up to 450 uV, with a predominance in the central areas	4 years: when awake, irregular alpha waves at 8–10 Hz, up to 180 uV in the posterior leads, with a predominance of fast beta activity in all leads. In posterior occipital-parietal–temporal leads, discharges of high-voltage sharp waves, spikes, and polyspikes, sometimes within a slow wave complex, up to 400–500 uV. During sleep, multiple generalized discharges in the form of sharp waves, polyspikes, and spike-and-slow-wave complexes	
–	After introduction of LEV, TOPA, LAMI worsening of behavior, all drugs were withdrawn by the parents	Good reaction to VAL, no reaction to LEV (was withdrawn)	
Normal	Venous anomaly in left cerebellar hemisphere	Thickening of bone marrow in skull bones, thin corpus callosum	
Hypothyroidism	Gilbert syndrome, cholelithiasis diagnosed at the age of 6	–	

The connection between FINCA syndrome and calvarial red bone marrow hyperplasia, to our knowledge, is unclear. This phenomenon appears in response to systemic stresses such as red blood cell disorders, iron deficiency anemia, or hemolytic disorders (Gomez et al., 2018). Additionally, phenytoin has a well-documented effect on osteoblast activation and secondary calvarial thickening (Lau et al., 1995). However, neither of the above diseases were diagnosed in the patient described by us, nor was phenytoin used. There was also a lack of any clinical data suggesting abnormal mineral homeostasis. Such connection perhaps could be clearer in the intra or inter-patient comparative radiologic interpretation based on imaging documentation over a longer time.

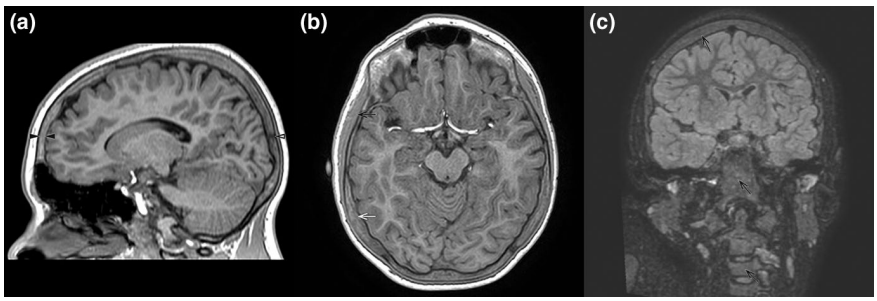

FIGURE 1 Head MRI (1.5 T) in a 10-year-old girl consistent with red marrow hyperplasia. (a) Sagittal T1WI revealed thickening of the diploic space of calvarial bones. Despite the cortical bone loss, the inner and outer tables of the calvarial bones are preserved (black arrowheads). The occipital bone separated with lambdoid suture (hollow arrowhead) is less widened due to the slighter residual bone marrow. (b) Axial T1WI indicates red bone marrow in the diploic space (white arrow) by presenting the same signal intensity as the temporal muscle (black arrow). (c) Coronal T2 FLAIR with fat saturation shows a similar signal intensity of calvarial, clival, and vertebral bone marrow (black arrows), without features of edema or fatty marrow transformation

ETHICAL COMPLIANCE

A retrospective review of the clinical and diagnostic findings in three cases of Polish patients with FINCA under our care was made. Acceptation of the Ethical Board of Poznan University of Medical Sciences was not needed, as the data were collected retrospectively. All patients` caregivers gave their informed consent for molecular studies before testing. Patient's P13 caregivers gave their informed consent for publication of the video material.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Magdalena Badura-Stronka and Robert Śmigiel; Methodology: Rafał Płoski, Małgorzata Rydzanicz, Magdalena Badura-Stronka, and Robert Śmigiel; Formal analysis and investigation: Magdalena Badura-Stronka, Robert Śmigiel, Karolina Rutkowska, Krystyna Szymańska, Adam Sebastian Hirschfeld, Michał Monkiewicz, Joanna Kosińska, and Ewelina Wolańska, Writing - original draft preparation: Magdalena Badura-Stronka, Robert Śmigiel, Adam Sebastian Hirschfeld, Rafał Płoski, and Michał Monkiewicz; Writing - review and editing: Anna Latos-Bieleńska; Rafał Płoski, Adam Sebastian Hirschfeld, and Magdalena Badura-Stronka; Supervision: Anna Latos-Bieleńska and Rafał Płoski.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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