Received: 25 March 2021 | Revised: 11 June 2021 | Accepted: 21 June 2021

DOI: 10.1111/cge.14016

SHORT REPORT

CLINICAL GENETICS WILEY

Expanding the phenotypic spectrum of FINCA (fibrosis, neurodegeneration, and cerebral angiomatosis) syndrome beyond infancy

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Funding information
Bundesministerium für Bildung und Forschung, Grant/Award Number: project "HCQ4Surfdefect" under E-Rare-3; chILD-EU, Grant/Award Number: FP7 305653; Deutsche Forschungsgemeinschaft, Grant/Award Numbers: 418081722, 433158657, Gr 970/9-1; Deutscher Akademischer Austauschdienst, Grant/Award Number: German-Arab Transformation Program ID 57166498

Abstract

Fibrosis, neurodegeneration, and cerebral angiomatosis (FINCA, MIM#618278) is a rare clinical condition caused by bi-allelic variants in *NHL repeat containing protein 2* (*NHLRC2*, MIM*618277). Pulmonary disease may be the presenting sign and the few patients reported so far, all deceased in early infancy. Exome sequencing was performed on patients with childhood interstitial lung disease (chILD) and additional neurological features. The chILD-EU register database and an in-house database were searched for patients with *NHLRC2* variants and clinical features overlapping FINCA syndrome. Six patients from three families were identified with bi-allelic variants in *NHLRC2*. Two of these children died before the age of two while four others survived until childhood. Interstitial lung disease was pronounced in almost all patients during infancy and stabilized over the course of the disease with neurodevelopmental delay (NDD) evolving as the key clinical finding. We expand the phenotype of FINCA

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syndrome to a multisystem disorder with variable severity. FINCA syndrome should also be considered in patients beyond infancy with NDD and a history of distinct interstitial lung disease. Managing patients in registers for rare diseases helps identifying new diagnostic entities and advancing care for these patients.

KEYWORDS
cerebropulmonary disease, childhood interstitial lung disease, cholesterol pneumonia, FINCA, lung fibrosis, lipoid pneumonitis, multi-organ disease, NHLRC2

1 | INTRODUCTION

The kids-lung register, accessible via the European Management Platform for Childhood Interstitial Lung Disease (www.childeu.net), collects patients with childhood onset interstitial lung disease (chILD).[1] More than 300 different conditions, all rare, sometimes with known genetic cause like the surfactant dysfunction disorders, but mostly of unknown etiology, can be distinguished.[2]

In 2004, an infant boy was referred to the register, because of suspected surfactant dysfunction disorder. He died at the age of two before identifying the cause of disease. In a recently funded project exome sequencing was performed to identify the underlying genetic etiology in undiagnosed chILD. Resuming investigations in the case above identified bi-allelic missense variants in *NHL repeat containing protein 2* (*NHLRC2*, MIM*618277) in two sisters of the index patient. One girl died early after a similar history of lung disease, the other survived her initial respiratory impairment and severe neurodevelopmental delay (NDD) became overt over the further course of the disease.

Bi-allelic variants in *NHLRC2* have been associated with a rare autosomal recessive multi-organ disease called FINCA syndrome (fibrosis, neurodegeneration, and cerebral angiomatosis; MIM#618278), first mentioned in 2018.[3] Up to now, only four patients have been described. They all died before the age of three.[3,4] To further define the phenotypic spectrum of FINCA syndrome, we searched the chILD-EU database and an in-house database (Tuebingen) for *NHLRC2* variants. We here report two novel, disease causing variants in *NHLRC2* and detail the disease course of six previously unreported cases of FINCA syndrome. Our observations confirm previous reports on the pulmonary pathology but expand the phenotypic spectrum towards a milder disease course with NDD evolving as main characteristic.

2 | METHODS

The probands and their families gave their written informed consent to participate in the child-EU consultation and diagnosis program and for genetic analysis. This study was approved by the Ethics Committees of the University of Munich, Germany (EK111-13, EK20-329), the University Hospital Leuven, Belgium (s65013), the University of Tübingen, Germany (594/2015BO1) and Philadelphia University Amman, Jordan. Clinical data were retrieved from patient records.

Exome sequencing was performed on genomic DNA samples as previously described.[5] In brief, coding regions were enriched using SureSelectXT™ Human All Exon kit (AGILENT®, v6/7) for subsequent sequencing as paired-end reads on an Illumina® platform (NextSeq500™, HiSeq2500, NovaSeq6000). Generated sequences were processed using open-source tools for adapter trimming, mapping, variant calling, and variant annotation (family 1: Burrows-Wheeler Aligner (BWA v.0.7.15), Genome Analysis ToolKit (GATK v.3.8), Variant Effect Predictor (Ensemble VEP 89); family 2 and 3 see pipeline Github documentation; https://github.com/imgag/ngs-bits/tree/master/doc/GSvar).

Prioritization of likely clinically relevant variants included the exclusion of variants with minor allele frequency > 0.01% (GnomAD https://gnomad.broadinstitute.org/; 15 000 in-house exomes). Variant classification was done according to the guidelines of the American college of Medical Genetics and Genomics.[6]

3 | RESULTS

3.1 | Genetic variant interpretation

Variant filtering under the assumption of autosomal recessive inheritance prioritized compound heterozygous or homozygous *NHLRC2* (NM_198514) variants in all three families. We did not observe additional changes in established disease genes (OMIM phenotype key 3) that we considered as the likely explanation of the patients' disease presentations. Of note, the previously reported[3,4] pathogenic missense variant c.442G > T, p.(Asp148Tyr) was detected in all individuals. In family 1 and 2 the variant was identified in compound heterozygosity with two different rare missense variants, c.224A > T, p.(Asp75Val) and c.1013C > T, p.(Pro338Leu), respectively. In family 3 the variant c.442G > T was detected in homozygous state. None of the variants was observed in a homozygous state in previously mentioned databases. All *NHLRC2* variants identified alter evolutionarily highly conserved amino acid residues and are predicted to be damaging by different in silico algorithms (Figure 1). Together with the peculiar clinical presentation resembling previous FINCA syndrome patients we considered the identified *NHLRC2* variants as the likely disease-causing defect explaining our patients' disease phenotypes.

Despite the considerably allele frequency of the c.422G > T variant in GnomAD (0.0004316, accessed June 2021), the variant was listed exclusively in heterozygous state.

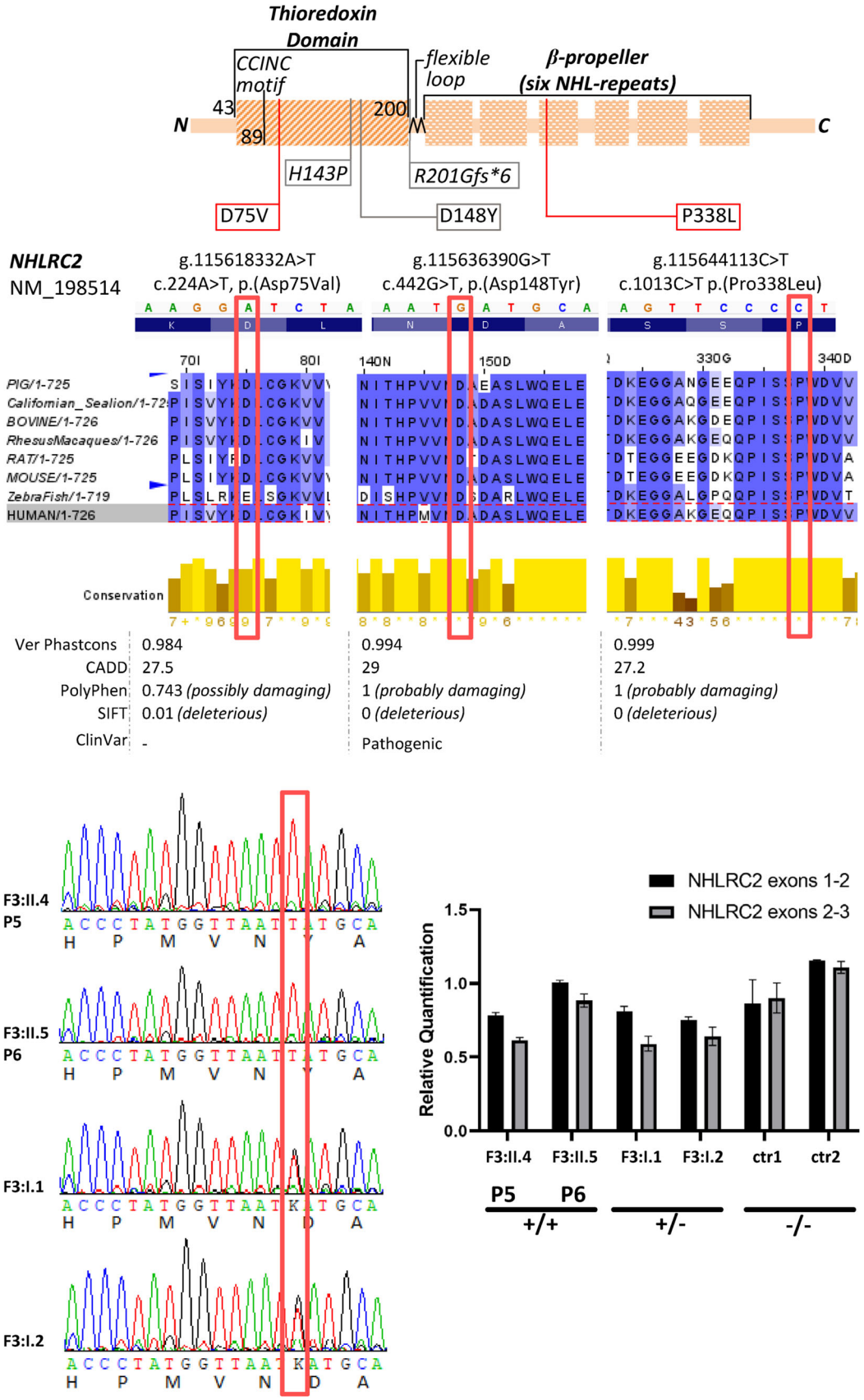

FIGURE 1 Identified *NHLRC2* variants in relation to the genomic position, the coding region, and affected amino acid within the protein structure with its two domains indicated. Further information regarding the conservation and prediction is provided by https://cadd.gs.washington.edu/. Novel variants identified in our patients (red rectangles), previous reported variants (gray rectangles). Sanger analysis and relative quantification of *NHLRC2* expression in homozygous individuals (+/+) and heterozygous carriers (+/−) of the c.422G > T variant compared to controls (−/−) [Colour figure can be viewed at wileyonlinelibrary.com]

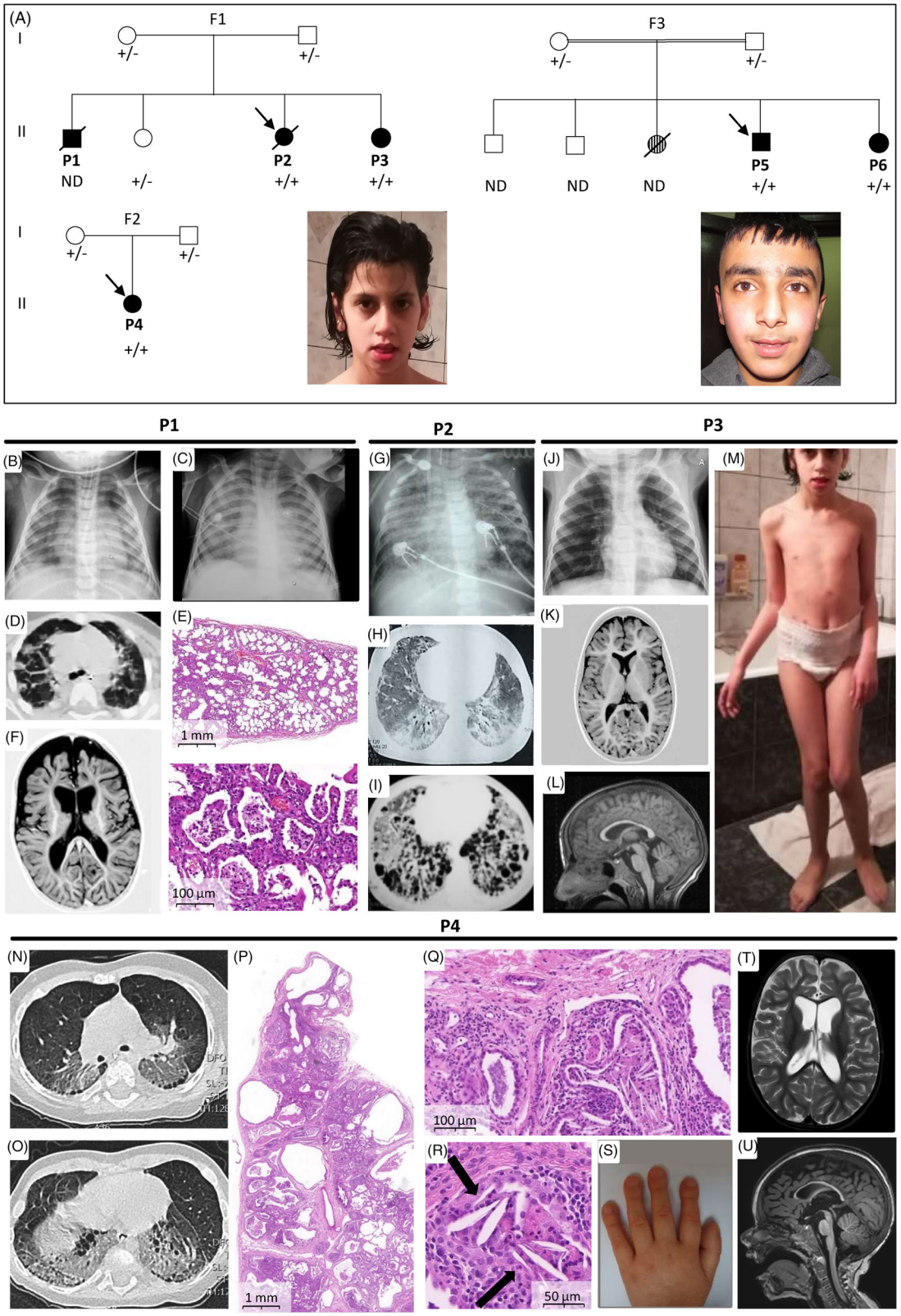

FIGURE 2 Legend on next page.

3.2 | Probands disease course

We present detailed case histories in the supplement. Briefly, probands **P1** and **P2**, born to a Greek family (Figure 2(A),F1), had a similar clinical history with recurrent respiratory distress since infancy with interstitial changes on chest CT imaging (Figure 2(D),(H),(I)) leading to the suspicion of surfactant dysfunction. In addition, they had an involvement of several other organ systems, including the immune system, central nervous system, liver, and gastro-intestinal tract (Table 1). Both children died early before the age of two. The family's fourth child, proband **P3**, suffered from episodes of severe respiratory distress in the first years of life. Beyond the age of two the pulmonary situation stabilized and she did not require oxygen supplementation or hospitalizations, while NDD became the leading clinical feature. At the age of five she exhibited very limited fine and gross motor skills. She was able to walk with support and to express rudimentary needs verbally. A cerebral MRI at the age of five was unremarkable (Figure 2 (K),(L)).

Proband P4 (Figure 2(A),F2), a Belgian girl, was frequently hospitalized because of respiratory distress and persistent hypoxia since day 12 of life, without an infectious etiology. Lung CT scan at the age of 9 months showed bilateral ground-glass opacifications (GGO), emphysema and multiple subpleural cysts (Figure 2(N),(O)). Lung histology revealed nonspecific interstitial pneumonitis (NSIP) and cholesterol pneumonitis (Figure 2(P)–(R)). Since the age of three her pulmonary situation stabilized. She exhibited NDD from the age of 2 months, starting with truncal hypotonia in combination with peripheral hypertonia and hyperreflexia in the lower limbs. At last examination at the age of four, she had not achieved any language development or ability to sit. Brain MRI revealed a thin corpus callosum and global cortical and subcortical atrophy at the age of 22 months (Figure 2(T),(U)).

Probands **P5** and **P6** were born of consanguineous Jordanian parents (Figure 2(A),F3). Their older sister died at the age of 11 due to kidney failure. At the age of 6 months, **P5** suffered from dyspnea and exhibited hypoxia. Over the disease course the respiratory problems improved while NDD became more evident. At last examination at the age of 14, he presented intellectual disability, irritability and muscular hypotonia. His sister **P6** never suffered from respiratory distress and showed a milder course of similar clinical features at her last examination at the age of seven.

3.3 | Review of known FINCA cases

Nine of 10 children with FINCA syndrome, including this study, had interstitial lung disease that became clinically apparent during infancy in combination with NDD in all and variable multisystem involvement[3,4] (Table **1**). The clinical course of their respiratory disorder was often progressive and aggravated by infectious or non-infectious exacerbations (8/10). All children had neurologic findings, including global developmental delay (9/10), axial hypotonia (9/10), and dystonia (10/10). When available, MRI identified global cerebral atrophy (6/7) and aberrant angiomatosis (3/7) as an inconsistent finding. Most children had gastrointestinal problems identified by episodic diarrhea (8/8), and failure to thrive (7/10). Several other organs were affected, including the liver (5/10), the immune system (5/8), and rather rarely the cardiovascular system (3/10).

4 | DISCUSSION

NHLRC2 has been implicated in the mediation of fibroblast differentiation,[7] regulation of reactive oxygen species generation,[8] cellular apoptosis, and T-cell homeostasis.[9] However, the exact function of NHLRC2 and how its dysfunction might cause this specific multi-organ phenotype is currently unknown. Its broad expression in multiple tissues (https://www.gtexportal.org/home/gene/NHLRC2), indeed, is consistent with the wide range of affected organs.

FIGURE 2 (A) Pedigrees demonstrate carrier status of investigated families; index patients of the exome sequencing (arrows). Photo of P3 (age 10 years) and P5 (age 14 years): Typical facial features are rather discreet and include prominent, unruly eyebrows, long palpebral fissures, a long philtrum, and a bulbous nasal tip. P1: (B) Chest X-ray (age 7 months) shows irregular opacifications, (C) progressing ground-glass opacifications (GGO), patchy consolidations (age 19 months) and (D) corresponding CT imaging. (E) (HE, ×20): Lung biopsy with enlarged and simplified airspaces. Mildly widened alveolar septa with scattered lymphocytes, plasma cells and macrophages, few neutrophils and eosinophils. Insert (HE, ×200): DIP-pattern. (F) MRI with generalized brain atrophy, dilatation of the temporal ventricles (age 9 months). P2: (G) Chest X-ray (age 4 months) showed bilateral GGO and consolidation. (H) CT imaging (age 6 months) patchy GGO, mosaic pattern, bronchiectasis, interstitial and alveolar markings, (I) at 9 months cystic lesions in areas of previous consolidations. P3: (J) X-ray (age 2 years) hyperinflated lungs. MRI (age 5 years)(K) axial inversion recovery image, (L) sagittal T1-weighted images with normal myelination. (M) Walking and balancing difficulties at age 10 years. P4: (N,O) CT images at age 9 months GGO, paraseptal and centrilobular emphysema, cystic lesions. (P,Q,R) Lung biopsy with cystic lesions, dominant nonspecific interstitial pneumonitis (NSIP) pattern, cholesterol pneumonitis (age 9 months). (P) (HE, ×20): Lung with simplified, cystically dilated airspaces containing macrophages, cholesterol granulomas, variable inflammatory exudates. (Q) (HE, ×100): enlarged, simplified airspaces with macrophages, giant cells containing cholesterol clefts, surrounded by moderate chronic inflammatory infiltrates and fibrosis. (R) (HE, ×200): cholesterol clefts (arrows) in macrophages and giant cells, hyperplasia of type-II-pneumocytes, chronic interstitial inflammatory infiltrates, fibrosis constituting cholesterol pneumonitis. (S) Digital clubbing (age 3.8 years). (T,U) Axial T_2-weighted and sagittal T_1-weighted images with thin corpus callosum, generalized brain atrophy (age 22 months). ND, not determined [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Comparative phenotype and genotype description of known *NHLRC2* cases

Individual (Family)	Proband P1 (F1:III.1)	Proband P2 (F1:III.2)	Proband P3 (F1:III.4)	Proband P4 (F2:II.1)	Proband P5 (F3:II.4)	Proband P6 (F3:II.5)	Proband P7 (Fam.A,1)[3]	Proband P8 (Fam.A,2)[3]	Proband P9 (Fam.B)[3]	Proband P10[4]
Variant in *NHLRC2*	N/A	**p.D75V, p.D148Y**		**p.D148Y, p.P338L**	**p.D148Y, D148Y**		**p.D148Y, p.Arg201GlyfsTer6**			**p.H143P, p.D148Y**
Onset and disease course										
Sex	male	female	female	female	male	female	male	male	male	male
Origin	Greek	Greek	Greek	Belgian	Jordanian	Jordanian	Finish	Finish	Finish	Ukrainian
Neonatal period	full term, uneventful	full term, uneventful	full term, jaundice	full term, uneventful	full term (NICU for 22 days)	full term, uneventful	full term, uneventful	full term, uneventful	late preterm, uneventful	full term, jaundice, bilateral pneumonia
Age at disease onset (months)	7	5	0–2	0.5	0	12	2	2	0–2	0
Overall progressive disease course	+	+	stable	sick-better	sick-better	stable	+	+	+	stable until viral infection (27 mo)
Age at death (months)	22	17	Alive (10 yrs)	Alive (4 yrs)	Alive (14 yrs)	Alive (7 yrs)	21	13	14	29
Respiratory findings										
Progressive respiratory course	+	+	+/−, oxygen (12 to 15 L/min) <2 yrs	+/−, oxygen <4 yrs	+, improved over disease course	−	+	+	+	+/−
Resp. exacerbations (+/− infection)	+	+	+	+	N/A	−	+	+	+	+
Lung histology/ cytology	DIP with diffuse alveolar damage	Pulmonary alveolar proteinosis	N/A	Cholesterol Pneumonitis, NSIP	N/A	N/A	Granuloma-like, hyaline material, myo-fibroblasts	Granuloma-like, hyaline material, myo-fibroblasts	Granuloma-like, hyaline material, myo-fibroblasts	Fibrosis (not further specified)
Chest CT imaging	GGO and patchy consolidations	GGO and patchy consolidations	−	perihilar interstitial GGO and subpleural cyst formation	N/A	N/A	Overflation, perihilar interstitial opacities, diffuse infiltrations, atelectasis	Overflation, perihilar interstitial opacities, diffuse infiltrations, atelectasis	Overflation, perihilar interstitial opacities, diffuse infiltrations, atelectasis	bilat. Consolidation /atelectasis, air bronchograms, compressed trachea, pectus excavatum
Neurologic findings										
Irritability	+	+	+	+/−	+	+	+	+	+	+/−
Axial hypotonia	+	+	−	+	+	+	+	+	+	+
Dystonia	+/−	+/−	+	+	+/−	+/−	+	+	+	+
Developmental delay	+	+/−	+	+	+	+	+	+	+	+

TABLE 1 (Continued)

Individual (Family)	Proband P1 (F1:III.1)	Proband P2 (F1:III.2)	Proband P3 (F1:III.4)	Proband P4 (F2:II.1)	Proband P5 (F3:II.4)	Proband P6 (F3:II.5)	Proband P7 (Fam.A,1)[3]	Proband P8 (Fam.A,2)[3]	Proband P9 (Fam.B)[3]	Proband P10[4]
Feeding problems	+	+	+	+	−	−	+	+	+	+
Failure to thrive	+	+	−	+	−	−	+	+	+	+
Poor visual contact/ decreased vision, strabism	+	+	+	+/−[a]	+/−	+	+	+	+	−
Seizures	+	during intubation in hospital	during intubation in hospital	−	−	−	+	−	+	+
Brain atrophy	+	N/A	−	+	N/A	N/A	+	+	+	+
Angiomatosis	− (10 mo)	N/A	− (5 yrs)	− (22 mo)	N/A	N/A	increased angiomatosis-like leptomeningeal	prominent congested leptomeningeal and superficial brain parenchymal vasculature	vascular congestion, angiectasia	− (18 mo)
MRI additional findings	−	N/A	−	Thin corpus callosum	N/A	N/A	Thin corpus callosum	Thin corpus callosum	Thin corpus callosum Increased signal intensity of globus pallidum	Thin corpus callosum
Gastrointestinal findings										
Episodic Diarrhea	+	+	+	-	N/A	N/A	+	+	+	until age 8 mo: +
Other										
Hepatomegaly	+	−	−	−	−	−	+	+	+	+
Transient liver dysfunction	−	−	+, jaundice, bilirubin up to-2.5 mg/dl), chololithiasis, cholecystectomy	2 yrs: +, during severe viral infection	−	−	+	+	−	2 yrs: +, during severe viral infection
Cardiovascular abnormality	−	−	−	Dilatation of ascend. aorta (13.5 mm, +7.6 SD)	−	−	Cardiomegaly	−	−	Cardiomegaly with biventricular hypertrophy
Immune system	IgG deficiency	IgG deficiency	−	until age 10 mo: + (low level IgG)	N/A	N/A	N/A	Enlarged thymus	IgG deficiency	IgG deficiency
Blood forming organs	temporary pancytopenia	−	−	Macrocytic anemia, only initially hemolysis	−	−	Hemolytic anemia	Hemolytic anemia	Hemolytic anemia	Hemolytic anemia

Abbreviations: DIP, desquamative interstitial pneumonia; GGO, ground glass opacities; mo, months; N/A, not available; NSIP, nonspecific interstitial pneumonia; yrs, years.

Note: Overview of the clinical features of all known cases with FINCA syndrome. P7-P9 from Finland[3]; P10 from Ukraine.[4]

[a]Abnormal electroretinogram (ERG) and visual evoked potential (VEP), clinical impression of presence of sight.

Structurally, the protein contains a thioredoxin-like domain and a β-propeller domain. The highly conserved active site within the thioredoxin-like domain, the CCINC motif (residue 89–93), is characteristic for oxidoreductases and is involved in thiol-disulfide exchange reactions. Multiple β-sheets form the six blades of the β-propeller, built by six NHL-repeats (Figure 1). The β-propeller builds a solvent channel and acts as a protein–protein-interaction module, similar as in other oxidoreductases. The flexible loop between the two domains enables the intramolecular association between the active site and the solvent channel.[10]

The c.422G > T variant was identified in all previously reported cases, four children of three unrelated families (probands P7-P10).[3,4] Functional studies confirmed the pathogenicity of this variant resulting in reduced NHLRC2 protein levels compared to healthy controls.[10] Notably, probands P5 and P6 are the only individuals with homozygote p.(Asp148Tyr) variant reported. These subjects exhibit a milder phenotype with intellectual disability and no other organ involvement; in particular, proband P6 did not suffer from respiratory distress. NHLRC2 RNA expression was not altered compared to heterozygous family members and controls (methods in the supplement, Figure 1). Unfortunately, due to lack of material, we could not assess changes on the protein level. One could hypothesize that the residual protein expression due to the homozygous c.422G > T variant leads to an alleviated phenotype.

The second variant identified (c.224A > T) is located closely to the active site. Its structure, mainly based on hydrogen-bonds will probably be disturbed by the replacement to hydrophobic valine. The third variant identified (c.1013C > T) affects the highly conserved proline, which is located prior to every individual β-sheet. Moreover, the adjacent amino acid Asp340 is important for hydrogen-bond formation with water and the backbone of the β-propeller-blades.[10] Thus, we suppose an impaired function of the solvent channel by the identified substitution.

Up to now, the clinical definition of FINCA disease was referring to case reports of only four patients with poor survival. The phenotype was primarily characterized by severe and lethal lung fibrosis, neurodegeneration and cerebral angiomatosis. Our cases expand the spectrum of identified histologic pulmonary patterns of early interstitial lung disease. Histologically, some patients exhibited interstitial fibrosis and granuloma-like lesions, others desquamative interstitial pneumonia (DIP), pulmonary alveolar proteinosis, NSIP or cholesterol pneumonia. CT findings included GGO, cystic lesions, and patchy opacities.

Hence, the disease courses of the four patients who survived until childhood and are currently still stable is of great interest, as the spontaneous stabilization of such severe pulmonary phenotypes is rare and came unexpected. Meanwhile NDD became apparent over time including behavioral issues like irritability and short attention span. The hypothesis that NDD is the key clinical finding of FINCA phenotype was strengthened by the FINCA mouse model ($Nhlrc2^{D148Y/-}$), mimicking the genotype described in the Finish probands (P7-P9,Table 1).[11] Contrary to the human FINCA phenotype, those mice did not develop a severe, early onset multiorgan disease. An altered protein expression in murine neuronal precursor cells (NPCs) compared to wildtype was noticed. The authors assume that an impaired autophagy of mutated Nhlrc2 RNA and vesicular trafficking might result in NDD.[11]

Our findings contribute to the phenotypic expansion of FINCA syndrome. We suggest that FINCA syndrome should be considered in individuals of all age groups who present with primary NDD and a history of chILD that improved over time. Registers for rare diseases, like chILD-EU, are useful to identify rare disease entities and to improve the diagnostic yield based on phenotypic similarity or shared mutational patterns. As a benefit, the professional exchange of information and expertise helps to improve management and eventually treatment of these patients with ultra-rare diseases.

ACKNOWLEDGEMENTS

We thank all probands and families for their kind contributions and participation in the study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

These first authors contributed equally: Christina K Rapp, Ine Van Dijck, Lucia Laugwitz; Patient's Clinical Care and Follow up: George Briassoulis, Stavroula Ilia, Stefanie Hornung, Rebecca Buchert, Linda Sofan, Tawfiq Froukh, Peter Witters, Daisy Rymen; Conceptualization: Christina K Rapp, Matthias Griese; Data curation: Christina K Rapp, Lucia Laugwitz, Tobias B Haack, Birgit Kammer, Simone Reu, Rebecca Buchert, Linda Sofan; Funding Acquisition: Matthias Griese Tobias B Haack; Project Administration: Christina K Rapp, Matthias Griese; Writing–original draft: Christina K Rapp, Ine Van Dijck, Matthias Griese; Writing–review & editing: Christina K Rapp, Ine Van Dijck, Lucia Laugwitz, Mieke Boon, Peter Witters, Tobias B Haack, Marijke Proesmans, Matthias Griese.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14016.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Rapp CK, Van Dijck I, Laugwitz L, et al. Expanding the phenotypic spectrum of FINCA (fibrosis, neurodegeneration, and cerebral angiomatosis) syndrome beyond infancy. *Clinical Genetics*. 2021;100(4):453-461. https://doi.org/10.1111/cge.14016