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Genetic and Metabolic Diseases

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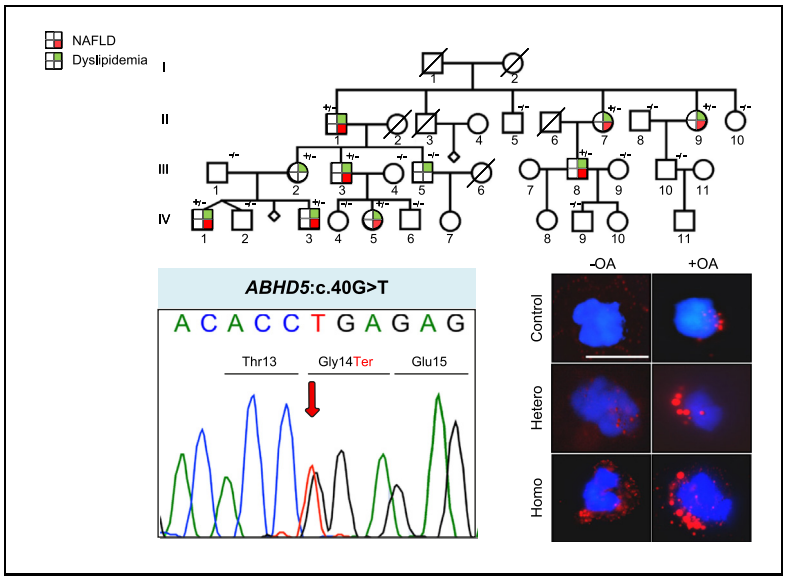
Inherited non-alcoholic fatty liver disease and dyslipidemia due to monoallelic *ABHD5* mutations

Graphical abstract



Highlights

- Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world.
- We identified monoallelic *ABHD5* mutations in 7 families with NAFLD.
- *ABHD5* is involved in neutral lipid metabolism, highlighting the role of lipid disorders in NAFLD.

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Lay summary

Non-alcoholic fatty liver disease (NAFLD) is a common multifactorial disorder with a strong genetic component. Inherited forms of NAFLD have been suspected but, their molecular pathogenesis has not been disclosed. Here we report a heritable form of NAFLD with clinical expression after 40 years of age, associated with monoallelic *ABHD5* mutations.

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Inherited non-alcoholic fatty liver disease and dyslipidemia due to monoallelic *ABHD5* mutations

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Background & Aims: Non-alcoholic fatty liver disease (NAFLD) is a multifactorial condition and the most common liver disease worldwide, affecting more than one-third of the population. So far there have been no reports on mendelian inheritance in families with NAFLD.

Methods: We performed whole-exome or targeted next-generation sequencing on patients with autosomal dominant NAFLD.

Results: We report a heritable form of NAFLD and/or dyslipidemia due to monoallelic *ABHD5* mutations, with complete clinical expression after the fourth decade of life, in 7 unrelated multiplex families encompassing 39 affected individuals. The prevalence of *ABHD5*-associated NAFLD was estimated to be 1 in 1,137 individuals in a normal population.

Conclusion: We associate a Mendelian form of NAFLD and/or dyslipidemia with monoallelic *ABHD5* mutations.

Lay summary: Non-alcoholic fatty liver disease (NAFLD) is a common multifactorial disorder with a strong genetic component. Inherited forms of NAFLD have been suspected but, their molecular pathogenesis has not been disclosed. Here we report a heritable form of NAFLD with clinical expression after 40 years of age, associated with monoallelic *ABHD5* mutations.

Keywords: Non-alcoholic fatty liver disease; *ABHD5*; CGI-58; Mendelian; NAFLD; Familial aggregation; Dyslipidemia; Inheritance.
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Introduction

Non-alcoholic fatty liver disease (NAFLD) is an increasingly common disorder that is strongly associated with the metabolic syndrome, and which may progress from simple steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, hepatic failure, and hepatocellular carcinoma. NAFLD is a major health issue worldwide and is associated with significant morbidity and mortality. The prevalence of this condition reaches 12–18% in the European countries and 27–38% in the US.[1,2] NAFLD is a multifactorial disease and up to 50% of its relative risk has been attributed to genetic susceptibility, with evidence coming from familial aggregation, twin studies, and differential ethnic predisposition.[3] Genome-wide association studies identified a number of variants that are associated with NAFLD, but in most cases the odds ratios were relatively small. However, in large-scale population studies, variants in the *PNPLA3*, *TM6SF2*, *LYPLAL1*, and *GCKR* genes were associated with elevated liver fat levels.[4] The existence of inherited forms of NAFLD has been suspected, but neither a specific causal gene or a susceptibility locus has been identified.[5] We hypothesized that genetic alterations might account for some cases of NAFLD, especially those that exhibit Mendelian inheritance.

Patients and methods

After obtaining written informed consent to perform genomic studies, we performed whole-exome sequencing (WES) or targeted next-generation sequencing (NGS) of genomic DNA from NAFLD cases in 7 unrelated multiplex families (Fig. 1A; Supplementary materials and methods).

Results

In a large non-consanguineous family of Italian ancestry (Family 1-F1; Fig. 1A), 9 affected members were diagnosed with NAFLD and/or dyslipidemia, based on blood chemical analyses and liver ultrasound findings (Table 1). In subjects F1, III-3 and II-1 with

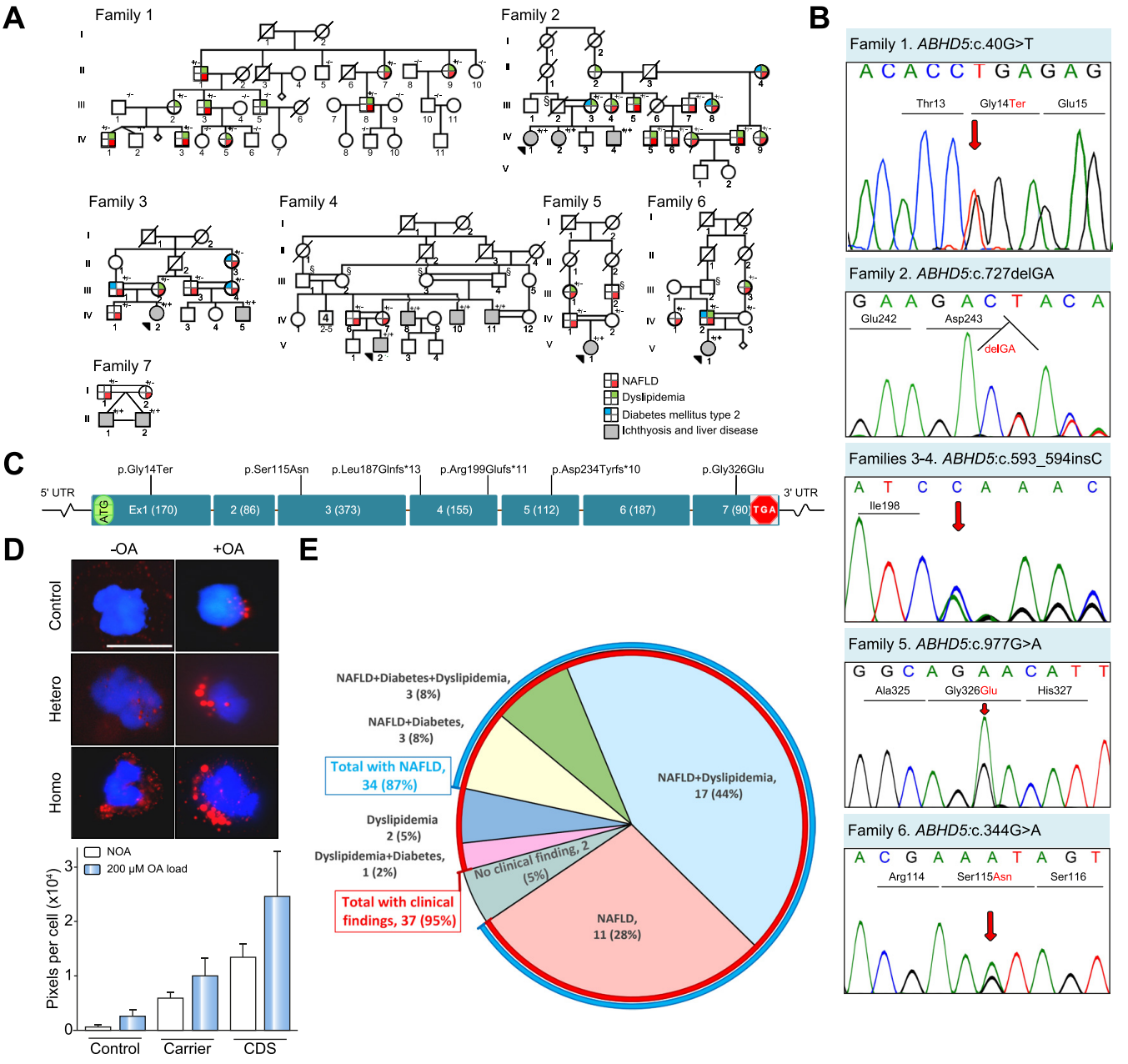

Fig. 1. Pedigree structures and clinical findings in NAFLD families with *ABHD5* mutations. (A) Family 1 is of Italian ancestry with a monoallelic mutation in *ABHD5*. Note the lack of consanguinity in this family. Families 2–7 of Iranian ancestry show extensive consanguinity. Heterozygous carriers (+/−) show evidence of NAFLD and/or dyslipidemia and type 2 diabetes mellitus, and patients with bi-allelic mutations (+/+) manifest with CDS with neonatal ichthyosis and NAFLD. Individuals marked with § are presumed obligatory carriers of the mutation. For the presence of clinical manifestations in individuals tested, see the color code. (B) Sanger sequencing of mutations in Families 1–6. The mutation of Family 7, *ABHD5*:c.560_578 del19 was published previously.[17] (C) Positions of the distinct mutations along the *ABHD5* consisting of 7 exons drawn to scale; the introns are not in scale. (D) Presence of lipid droplets (red) in leukocytes from a control (upper panels), a heterozygous carrier (middle panel), and a homozygous individual (lower panel) after incubation without (-OA, left) or with (+OA, right) 200 µM OA. The lipid content was quantitated by assay of pixel density of Oil red O and DAPI stained cells (bar graph). The values represent the mean ± SD of 105–125 cells for each sample. (E) Relative distribution of clinical findings and their combinations in 39 *ABHD5* carriers. Note that 35 individuals had NAFLD (87%, blue line) while 37 had clinical findings (95%, red line). CDS, Chanarin-Dorfman syndrome; NAFLD, non-alcoholic fatty liver disease; OA, oleic acid; UTR, untranslated region.

NAFLD, WES was performed and bioinformatics analysis identified a heterozygous nonsense mutation (c.40G>T; p.Gly14Ter) in exon 1 of *ABHD5* (OMIM #604780), confirmed by Sanger sequencing (Fig. 1B). Segregation analysis of the pedigree revealed that all 9 affected patients carry the same *ABHD5* mutation, while 13 members without evidence of NAFLD have a wild-type *ABHD5* genotype, among which only 1 patient (F1, III-5) presented with dyslipidemia. Jordans' bodies (abnormal lipid droplets [LDs] accumulation)[6] were evident in leukocytes from *ABHD5* mutation carriers after *in vitro* oleic acid loading (Fig. 1D). None of the tested individuals demonstrated homozygosity for the *ABHD5* mutation. Thus, these findings suggested that monoallelic mutations in *ABHD5* predispose individuals to NAFLD.

While individuals with NAFLD in Family 1 presented with a monoallelic loss-of-function *ABHD5* mutation that predisposed

Table 1. Clinical manifestations, and genotypes of individuals with monoallelic *ABHD5* mutations.

No.	Patient	Phenotype	Age (yrs)	Gender	Levels of Ch, TG (mg/dl)	Liver enzymes levels	NAFLD grades[+]	FIB-4 score	Weight (kg)	Height (m)	BMI	Other diseases
Family 1: c.40G>T, p.G14*												
1	II:1[*]	NAFLD, DL	76	M	TG:284 CH:248	High	1 to 2		64	1.78	20.2	
2	II:7	NAFLD, DL	67	F	TG:256 CH:235	High	2		76	1.71	26.0	Hypertension, heart arrhythmia
3	II:9	NAFLD, DL	64	F	TG:188–212, Ch:210–244	High	1		55	1.63	20.7	
4	III:2	DL	51	F	TG:179 CH:255	Moderately raised	–		63	1.59	24.9	
5	III:3	NAFLD, DL	48	M	TG:287–324, Ch:237–269	High	2		82	1.75	26.8	Hypertension
6	III:8	NAFLD, DL	42	M	TG:195 CH:230	High	2		57	1.65	20.9	
7	IV:1	NAFLD, DL	26	M	TG:171–188, Ch: 218–240	High	1		59	1.74	19.5	Left varicocele (grade II)
8	IV:3	NAFLD, DL	23	M	TG:165, Ch:215	Moderately raised	1		61	1.58	24.4	
9	IV:5	NAFLD, DL	21	F	TG:155–171, Ch:205–226	Moderately raised	0 to 1		66	1.79	20.6	Pollen allergy, chronic fatigue
Family 2: c.727delGA, p.D243Y*fs10												
10	II-2	DL	77	F	TG:235 Ch:249	Normal	–	2.54	45	1.55	18.7	
11	II-4	NAFLD, DL, DM	57	F	LDL:190 Ch:285	Normal	1		60	1.63	22.6	Skin cancer
12	III-3	DL, DM	46	F	TG:224 Ch:231	Normal	– (S0)		60	1.6	23.4	
13	III-4	NAFLD, DL	38	F	TG: 457, CH:259	High	1 to 2	0.87	60	1.6	23.4	Hypothyroidism
14	III-5	NAFLD, DL	44	M	Ch:240	Normal	1		70	1.9	19.4	
15	III-7	NAFLD	59	M	Normal	Normal	1	0.82	73	1.78	23	
16	III-8	NAFLD, DL, DM	47	F	Ch:285	Normal	1		90	1.58	36.1	Focal nodular hyperplasia
17	IV-5	NAFLD, DL	32	M	Ch:254	High	1	0.77	89	1.8	27.5	
18	IV-6	NAFLD	29	M	Normal	High	1	0.74	85	1.81	25.9	
19	IV-7	NAFLD, DL	28	F	LDL:108	Normal	1		63	1.6	24.6	
20	IV-8	NAFLD, DL	40	M	LDL:126	Normal	2		80	1.83	23.9	
21	IV-9	NAFLD, DL	42	F	LDL:117	Normal	1		72	1.65	26.4	Hypertension, Infertility
Family 3: c.593_594insC, p.R199Qfs*11												
22	II-3	NAFLD, DM	70	F	Normal	Normal	1		62	1.65	22.8	
23	III-1	NAFLD, DM	57	M	Normal	Normal	1		80	1.85	23.4	
24	III-2	NAFLD, DL	48	F	Ch:230	Normal	1	0.81	68	1.74	22.5	
25	III-3	NAFLD	57	M	Normal	Normal	2	0.88	74	1.7	25.6	
26	III-4	NAFLD, DM	47	F	Normal	Normal	1		85	1.65	31.2	Hypothyroidism
27	IV-1	NAFLD	31	M	Normal	High	1	0.24	100	1.89	28	Immune thrombocytopenic purpura
Family 4: c.593_594insC, p.R199Qfs*11												
28	IV-6	NAFLD	36	M	Normal	Normal	1 (S2)	0.88	100	1.9	27.7	
29	IV-7	NAFLD	38	F	Normal	Normal	– (S2)	0.52	60	1.56	24.7	
Family 5: c.977G>A, p.G326E												
30	III-1	NAFLD, DL	59	F	LDL: 136 (<130) Ch:224	Normal	1 (S2)	1.11	85	1.7	31.2	Hypothyroidism
31	IV-1	NAFLD	36	M	Normal	Normal	– (S2)		80	1.83	23.9	
32	IV-2	Normal	29	F	Normal	Normal	0 to 1 (S2)		73	1.68	25.9	
33	III-2	NAFLD	64	M	Normal	n.a.	(S3)		100	1.78	31.6	
Family 6: c.344G>A, p.S115N												
34	III-3	NAFLD, DL	60	F	Ch:218	Normal	1	1.79	63	1.6	24.6	(Atorvastatin 20 mg/day)
35	IV-1	NAFLD	35	F	Normal	Normal	2		75	1.7	26	

Table 1 (*continued*)

No.	Patient	Phenotype	Age (yrs)	Gender	Levels of Ch, TG (mg/dl)	Liver enzymes levels	NAFLD grades[+]	FIB-4 score	Weight (kg)	Height (m)	BMI	Other diseases
36	IV-2	NAFLD, DL, DM	43	M	TG:356	High	1 (S3)	0.94	76	1.73	25.4	
37	IV-3	Normal	40	F	Normal	Normal	–	1.41	60	1.6	23.4	
Family 7: c.560_578 delTTGCTGATCAAGACAGACC												
38	I-1	NAFLD	26	F	Normal	Normal	1		68	1.62	25.91	
39	I-2	NAFLD	28	M	Normal	Normal	1		72	1.75	23.5	

BMI, body mass index; Ch, cholesterol; DL, dyslipidemia; DM, diabetes mellitus; LDL, low-density lipoproteins; n.a., not available; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride.

[*] No more than 1 glass of wine or beer twice a day, during lunch and dinner (no alcohol intake outside meals).

[+] The values were obtained by ultrasound, while those in parenthesis were acquired by FiboScan.

them to liver disease with no apparent multisystemic involvement, biallelic mutations in the same gene encoding for the LD-binding protein CGI-58 have been reported in patients with Chanarin-Dorfman syndrome (CDS; OMIM #275630). This rare autosomal recessive neutral lipid storage disorder is characterized by an excessive accumulation of LDs in multiple tissues and is more frequent in Mediterranean, Middle Eastern and Indian inbred populations.[7,8] The clinical hallmark of CDS is congenital generalized dry and scaly skin (ichthyosis). Further clinical features include hepatomegaly with late fatty degeneration of the liver, myopathy, cataracts and/or ectropion, progressive hearing loss, developmental delay, and cognitive impairment.[9] Vacuolated leukocytes are present in patients and are occasionally identified in non-ichthyotic carriers.

To explore the potential presence of NAFLD in heterozygous carriers of *ABHD5* mutations in CDS families, we investigated 6 independent, highly consanguineous Iranian families with ichthyosis suggestive of CDS (Fig. 1a: F2–F7) by a 38-gene targeted NGS panel for hereditary ichthyoses including *ABHD5*.[10,11] In all 6 families, comprising 13 patients with ichthyosis and liver disease, CDS was confirmed by the identification of 5 distinct biallelic *ABHD5* mutations (Fig. 1B, C). We next genotyped non-CDS family members who were either proven or obligate heterozygous carriers of the *ABHD5* mutation, did not consume alcohol, and provided their informed consent to the study. We found that 28 of the 30 (see Fig. 1A, E) Iranian participants had features of NAFLD, dyslipidemia, or type 2 diabetes, as ascertained by blood chemical analyses, hepatic ultrasound findings, and FibroScan® (transient elastography) (Table 1). The age of the 2 individuals without clinical findings (F5, IV-2, and F6, IV-3), who did not display features of NAFLD, was 29 and 40 years, respectively. Calculation of Fibrosis-4 scores in 14 individuals from whom necessary data were available, revealed scores ranging from 0.24 to 2.54, and 2 of them were above the lower cut-off value, 1.45, indicating risk for advanced fibrosis.[12]

Overall, 37 out of 39 ascertained *ABHD5* mutation carriers showed evidence of NAFLD and/or dyslipidemia (Fig. 1E; estimated penetrance: 95%), and 15 of those with NAFLD could be graded as ≤2 and 2 of them ≥3 (Table 1). All individuals >40 years of age with monoallelic mutations showed evidence of liver involvement and/or dyslipidemia. The youngest *ABHD5* carrier (F1, IV-5; 21 years of age) showed only initial signs of NAFLD, suggesting an age-dependent development of this inherited form of NAFLD, with complete clinical expression after the fourth decade of life. Interestingly, the 2 individuals without NAFLD are carriers of missense *ABHD5* mutations (p.Ser115Asn and p.Gly326Glu) which, in contrast to nonsense or frameshift mutations, could retain some residual activity that may contribute to reduced penetrance or delayed onset in families 5 and 6. Liver histopathology was not available because of local Institutional Review Boards' refusal to approve liver biopsy from patients with monoallelic mutations. However, patients with CDS and biallelic mutations have previously been shown to have liver fibrosis in biopsy[13]. In our series, FibroScan of 6 patients with biallelic *ABHD5* mutations revealed evidence of fibrosis in 3 of them: In 1 patient who was 17 years of age (Family 6, V-1), the F score was F4, indicating cirrhosis, and in 2 other patients who were 10 and 30 years of age (Family 2, IV-1 and IV-4, respectively), the F score F3 implied moderate fibrosis. Three patients had an F score of F0/1, all of whom were relatively young (3–20 years of age).

In an attempt to estimate the frequency of potentially NAFLD-causing *ABHD5* deleterious alleles, we analyzed *ABHD5* variants from 188,951 unrelated individuals of diverse ethnic backgrounds reported in the Exome Aggregation Consortium (ExAC), Genome Aggregation (gnomAD) and Greater Middle East Variome Project (GME) databases (Fig. S1).[14] The reported 1,149 variants in *ABHDs* were annotated (ANNOVAR software), with exclusion of synonymous, intronic, 3′ and 5′ UTR variants, and removal of those predicted to be benign by *in silico* analysis. The surviving 77 variants (Fig. S1) were present in a total of 167 individuals, predicting a prevalence of *ABHD5*-associated NAFLD in the general population of 1 in 1,131 individuals, a figure that is <0.001 if the genetic penetrance is assumed to be 95%.

Discussion

The specific metabolic and cellular mechanism(s) leading to NAFLD are still under investigation, but there is strong evidence that increased hepatic deposition of triglycerides resulting from an imbalance in lipid storage and lipolysis or secretion plays an important role in the establishment and progression of NAFLD to NASH and its inflammatory, organ-failure and neoplastic sequelae.[15] CGI-58, the protein encoded by *ABHD5*, is a highly conserved regulator of adipose triglyceride lipase and is involved in lipid metabolism, tumor progression, viral replication, and skin barrier formation. While the latter role requires at least 1 functional *ABHD5* allele as evidenced by the autosomal recessive mode of inheritance of CDS, the hypothesis of a haploinsufficiency effect on LD homeostasis in the liver, with incomplete penetrance and progressive, age-dependent expressivity of dysfunctional *ABHD5* variants, is consistent with our clinical, chemical, and genetic observations and previous animal studies. Specifically, *ABHD5* complete knockout mice die shortly after birth due to a skin barrier defect that closely resembles ichthyosis in patients with CDS, while a liver-specific *ABHD5* knockout mouse shows steatohepatitis and fibrosis.[16]

In conclusion, our findings disclose the existence of a rare heritable form of NAFLD associated with monoallelic mutations

in, *ABHD5*, involved in neutral lipid metabolism, and highlight the importance of further studies on the role of LD disorders in the liver pathology.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
LY, HV, RC and JU: Study concept and design, manuscript preparation; LY, AHS, SP, SS, PM, DA, SZ, KP: Patient recruitment and characterization, data acquisition and analysis; MAL: Data analysis and conceptual advise. All authors provided input and critical revision to the manuscript and approved the final version.

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Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.026.

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