LCAT Deficiency in Amerindian Populations: A Systematic Review With the Clinical and Genetic Description of Mexican Kindred

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Abstract

Background: LCAT deficiency is a rare disease, characterized by two distinct phenotypes, familial LCAT deficiency (FLD) and Fish Eye disease (FED). There is little knowledge of LCAT deficiency syndromes in Amerindian populations. We present the results of the first systematic review evaluating the ethnic distribution of LCAT deficiency, with particular emphasis on Latin America and discuss the case histories of three Mexican-Mestizo probands.

Methods: A systematic review was conducted following the PRISMA Statement in Pubmed and SciELO. Articles which described subjects with LCAT deficiency syndromes and an assessment of the ethnic group to which the subject pertained, were considered for analysis.

Results: In our region, 47 cases of LCAT deficiency have been published from six countries (Argentina (1 unclassified), Brazil (38 FLD), Chile (1 FLD), Columbia (1 FLD), Ecuador (1 FLD) and Mexico (4 FLD, 1 FED and 1 unclassified). In Mexico, one of the FLD probands' showed a novel mutation; this patient came from an isolated village in the south of Mexico, with little genetic admixture in this region.

The systematic review revealed 215 cases of LCAT deficiency (154 FLD, 41 FED and 20 unclassified) in at least 33 ethnic/racial groups (predominantly Caucasian). In addition, at least 138 different mutations in the LCAT gene have been identified. There was no association between genetic alteration and ethnicity. The mean age of diagnosis was 42 ± 16.5 years, with FED identified significantly later than FLD (55 ± 13.8 vs. 41 ± 14.7 years respectively). The prevalence of premature coronary heart disease was significantly greater in FED vs. FLD (p=0.00).

Conclusion: The systematic review shows that LCAT deficiency syndromes are clinically and genetically heterogeneous. We were unable to confirm any association between ethnicity and LCAT mutation. However, we were able to show a significantly greater risk of premature coronary artery disease in FED compared to FLD. In FLD, the emphasis should be in preventing progression of renal disease, while in FED, cardiovascular risk management should be the priority. The LCAT mutations discussed in this article are the only ones reported in the Mexican- Amerindian population.

Introduction

Lecithin cholesterol acyltransferase (LCAT) is a 67 kDa protein, predominantly expressed in the liver (1). It circulates in plasma bound to high density lipoproteins (HDL) but can also be found on apolipoprotein B100 containing particles (2, 3, 4). It catalyzes the transfer of an unsaturated fatty acid from lecithin to free cholesterol, producing lysolecithin and cholesteryl ester. This reaction occurs on immature HDL particles in the presence of apolipoprotein A-I (apo A-I), and corresponds to the alpha activity of the LCAT enzyme. When this reaction occurs on LDL or VLDL it is referred to as the beta activity. The net result is the formation of hydrophobic cholesterol ester, which is transferred to the lipoprotein core. In the case of HDL, this allows the conversion of discoidal pre-beta 1 particles to mature spherical alpha forms. In addition, the esterification of cholesterol on HDL increases the concentration gradient for free cholesterol between cell membranes and HDL, thus promoting the removal of cholesterol from cells (1, 2).

LCAT deficiency is a rare autosomal recessive disease (3, 4). Loss of LCAT function causes decreased maturation of HDL particles and increased HDL levels of unesterified cholesterol and phosphatidylcholine. There is no reliable estimate of the prevalence of the disease; in individuals with low HDL cholesterol (HDL-C) ranges, the estimated prevalence of LCAT deficiency is between 2–9% (5, 6, 7). The disease is characterized by two distinct phenotypes, familial LCAT deficiency (FLD) and Fish Eye disease (FED). In FLD, both the alpha and beta LCAT activity is lost, leading to extremely low plasma HDL-C (below the 5th percentile for the population), premature corneal opacification, hemolytic anemia, proteinuria and renal failure (8). In FED, only the alpha LCAT activity is lost, the beta activity is preserved, permitting cholesterol esterification on very low density lipoprotein (VLDL) and low density lipoprotein (LDL) but not on HDL-C (9). As a result, the HDL particles contain only 20% cholesteryl ester, as compared to 75 to 80% in control HDL. These individuals present with corneal opacities and low HDL-C levels, but are free of the renal consequences seen in complete LCAT deficiency. Calabresi et al., have suggested that FLD and FED are not two distinct syndromes, but the same disease showing differing levels of LCAT activity (10).

The clinical phenotype is only apparent in individuals who carry two mutant LCAT alleles (11). The LCAT gene consists of 6 exons, spans 4,200 base pairs and is located on chromosome 16 (16q22) (12). Of the reported mutations, the majority are associated with the FLD phenotype, with a significant number remaining unclassified (21.5%) (13).

Mutations in the *LCAT* gene have been recorded in multiple ethnic and racial groups. However, there is no description of LCAT deficiency in terms of ethnic distribution. In particular, there is sparse knowledge of LCAT deficiency syndromes in Latin America. The greater susceptibility of Hispanics for dyslipidemia (in particular phenotypes with low HDL cholesterol) is a well-documented phenomenon (14). Hispanic ethnicity results from the admixture of native Americans and Spaniards. Many Hispanics living in the USA and in Latin America have their origins in the Amerindian ethnic groups; these were the first residents of the North American continent. The Amerindians have suffered infections, wars and famine that have reshaped their environment, lifestyle and population size (15). As a consequence, it is likely that selection processes have occurred in this ethnic group.

In this article, we report the results of the first systematic review conducted to explore the distribution of LCAT disorders, particularly those associated with the Amerindian /Hispanic group. In addition describe the biochemical and genetic investigation of three previously unreported Mexican probands and their kindred with LCAT deficiency syndromes.

Methods For Systematic Review

A systematic search was conducted following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement in Pubmed and SciELO. Articles which described subjects with a confirmed mutation in the LCAT gene (based on genetic and clinical characteristics) and an assessment of the ethnic group to which the subject pertained, were considered for analysis. All epidemiological, cross-sectional, cohort, retrospective, longitudinal, observational, comparative, case-control and case-reports were considered which contained the following keywords or MeSH terms: Fish eye disease (FED),

Familial Lecithin cholesterol acyl transferase deficiency (FLD), LCAT enzyme deficiency (partial and total), LCAT gene mutation or polymorphism, homozygotes, compound heterozygotes, corneal opacities, corneal clouding, low high density cholesterol levels, anemia, renal failure, atherosclerosis. These terms were cross- referenced with the keywords and MeSH terms for ethnicity: minority groups, ethnic groups, African-Americans, Hispanic-Americans, American Native Continental Ancestry Group, Amerindian, Oceanic Ancestry Group, Black, Hispanic, Latino, Asian American, African American, Native American, Indian, Asian, and Pacific Islander. Articles written in English or Spanish were included. Data collection was carried out by four investigators, commenced in September 2018 and concluded in March 2020. The investigators took care to avoid double counting of cases. In addition, the reference lists of review articles and conference abstracts were also considered. Abstracts were independently assessed to identify eligible research reports. The commonest reasons for ineligibility were; insufficient information regarding either the LCAT gene mutation, clinical characteristics or no mention of ethnicity.

Methods For Biochemical And Genetic Analysis Of Lcat Probands

Biochemical measurements

Fasting blood samples were obtained from all three probands. These included full blood count, chemistry, a complete lipid profile, erythrocyte fragility studies (in FLD deficiency subjects), and 24 hour urine collection for determination of microalbuminuria and creatinine clearance. The lipid parameters were measured in the Institute's central laboratory. For total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglycerides and glucose measurements commercial enzymatic methods were used (Beckman Coulter). Apolipoprotein A1 and apolipoprotein B concentrations were measured using nephelometric methods (Beckman Coulter).

Measurement of LCAT activity

α-LCAT activity was measured by the method of Chen and Albers (16). Briefly: apoAI/phosphatidilcholine/^{3}H-cholesterol complexes were incubated with plasma in a shaking water bath for 1 hour al 37 °C (esterification was linear during this time). The reaction was stopped, and lipids were extracted. Esterified and unesterified cholesterol were separated by thin-layer chromatography, and the radioactivity was counted. LCAT specific activity was expressed as the nanograms of cholesterol esterified by 1 L of plasma in 1 hour (nmol/mL/h).

Measurement of PON-1 activity (patient 1 and kindred, patient 3)

PON1 activity was measured using phenylacetate as substrate (17). Initial rates of hydrolysis were determined spectrophotometrically at 270 nm. The assay mixture included 1 mM phenylacetate and 0.9 mM $CaCl_2$ in 20 mM Tris-HCl, pH 8.0, and 10 µL serum (diluted 1:40). The ε_{270} for the reaction was 1310 $M^{-1}cm^{-1}$. Arylesterase activity was expressed as the number of micromoles of phenylacetate hydrolyzed per minute per milliliter of serum. To determine the distribution of PON1 in lipoprotein fractions, 300 µL of plasma heparin was separated by size exclusion chromatography using a Bio-Prep SE1000/17 column coupled to a Bio-Rad Duo Flow system as previously described (18) with slight modifications. Briefly, protein elution was accomplished with 2 mM $CaCl_2$ in 20 mM Tris-HCl, pH 8.0, at a flow rate of 1 mL/min. Fractions of 0.5 mL were collected and PON1 activity was assessed after elution using 10 µL of each fraction. The column was calibrated with VLDL, LDL and HDL isolated by ultracentrifugation from a pool of 5 plasma samples obtained from 5 normolipemic volunteers. For the calibration, cholesterol was determined in the elution fractions by enzymatic colorimetric methods commercially available.

Mutational analysis

Genomic DNA was extracted from peripheral leucocytes using a Commercial Kit (Qiagen). The DNA was amplified using conventional polymerase chain reaction (PCR) to obtain the corresponding exons, including the exon-intron regions. The products of PCR were amplified using primers as follows: 1F, CACTCCCACACCAGATAA; 1R TTATGTCGGGGCTTATGC (332 pb) E2-3F, GGGGAGGGTAAGTGTGCTTT; E2-3R, GTGTGCAGGTACCCTGTGG (600 pb) E4-5F, TGTGGAGTACCTGGACAGCA; E4-5R, AGGATCAGCTTGGTCTCACC (584 pb) E6F, GAGCCTACACTCAGCAGGTTG; E6R, GTGGCTGGTGAGGAGTGAA (746 pb). This was carried out under the following conditions: 97 °C 7 min per cycle; 95 °C 30 s; 56 °C 30 s; 72 °C 2 min; 40 cycles; 72 °C 10 min per cycle; 4 °C hold. To amplify exon 6, the temperature for alignment was 58 °C. After purification, all DNA fragments were sequenced using forward and reverse primers. The sequencing was performed in an ABI prism 3100 genetic analyzer (Applied Biosystems). The reference sequence was obtained from the National Center for Biotechnology Information (NM_000229.1).

Statistical analysis

The distribution of categorical variables is reported as frequencies and percentages. Continuous data is described as mean and standard deviation or with median and interquartile range depending on the parametric or non- parametric distribution of variables. Statistical analyses was performed using Statistical Package for Social Science (SPSS Inc, Chicago, IL, and Version 21.0) and GraphPad Prism, version 7.0.

Results Of The Systematic Review

The PRISMA algorithm is shown in Fig. 1. Our research strategy retrieved a total of 3,373 publications. After removing any duplicate documents, 2,800 abstracts were reviewed. Of these, 2,153 articles were excluded, as they did not complete inclusion criteria. In total, 87 relevant articles/abstracts were reviewed in detail for eligibility. Of these, six publications were excluded due to incomplete information. Finally, 81 studies were included for the purposes of this article (Table 1, (19–100)).

Table 1
Systematic analysis of cases with LCAT deficiency

Ethnicity/ Country	REF	Study Type	Sample Size	Median Age	Gender	Phenotype	HDL-C (mg/dL)	Hemolytic Anemia	Proteinuria/ Albuminuria	eGFR <60 mL/min	LCAT Activity nmol/mL/h
Asian											
Japanese	19–32	Case report: 13 Review: 1	21	44	F:7 M:11 Unk: 3	FLD:18 FED:3	8.1	No:2 Yes:15 Unk: 4	No:3 Yes:13 Unk: 5	No:12 Yes:4 Unk: 5	7.91
Korean	33	Case report: 1	1	33	M:1	FLD:1	12	Yes:1	Yes:1	No:1	0.10
African											
Morrocan	34	Case report: 1	3	17,12,3	F:2 M:1	FLD:3	6	Yes:1 No: 2	Yes:3	No:3	0.39
Caucasian											
Australian	35	Case report: 1	1	63	F:1	FED:2	4	No:1	No:1	No:1	0.80
Austrian	36–37	Case report: 2	4	42	M:2 Unk:2	FLD:3 Unclassified: 1	11.75	No:1 Yes:3	Yes:4	Normal:1 Yes:1 Unk:2	0.08
British	38–40	Case report: 3	3	58	F:1 M:2	FLD:2 FED:1	3	No:2 Yes:1	No:2 Yes:1	Normal:3	0.47
Canadian	41–42	Case report: 2	7	38	F:2 M:5	FLD:3 FED:4	6.14	No:4 Yes:3	No:4 Yes:3	No:5 Yes:2	4.30

Ethnicity/ Country	REF	Study Type	Sample Size	Median Age	Gender	Phenotype	HDL-C (mg/dL)	Hemolytic Anemia	Proteinuria/ Albuminuria	eGFR <60 mL/min	LCAT Activity nmol/mL/h
Caucasian	43–44	Case report: 2	4	34	M: 4	FLD: 4	15	Yes:2 Unk:2	No:1 Yes:1 Unk:2	No:2 Unk:2	7.55
Danish	41	Case report:1	1	47	M:1	FLD:1	7	Yes:1	Yes:1	Yes:1	1.30
Dutch	45–49	Case report: 3 Review: 1	15	55	F:7 M:8	FED:10 Unclassified:5	12	No:10 Unk:5	No:10 Unk:5	No:10 Unk:5	41.71
Finnish	50–52	Case report: 2	4	44	F:1 M:3	FLD:4	8	Yes: 4	Yes: 2 No:2	No:4	
French	53–57 41	Case report: 3	9	43	F:6 M:3	FLD:5 FED:2	5.91	No:4 Yes:4 Unk:1	No:5 Yes:2 Unk:2	No:6 Yes:2 Unk:1	5.57
French Canadian	58	Case report: 1	2	25	M: 2	FLD: 2	6.5	Yes:2	Yes:1 No:1	No:2	4.00
Germany	59–62	Case report: 4	3	55	F: 1 M:2	FLD:2 FED: 1	4.33	Yes:1 No:2	Yes:1 No:2	No:2 Yes:1	0.51
Greek	63	Case report: 1	9	49	F:1 M:8	FLD:9	13	Yes:9	Yes:9	Yes:9	

Ethnicity/ Country	REF	Study Type	Sample Size	Median Age	Gender	Phenotype	HDL-C (mg/dL)	Hemolytic Anemia	Proteinuria/ Albuminuria	eGFR <60 mL/min	LCAT Activity nmol/mL/h
Italy	64–71, 41	Case report: 6 Review: 1	27	33	F: 2 M: 20 Unk:5	FLD: 18 FED:4 Unclassified:5	10	No: 4 Yes:16 Unk:7	No:7 Yes:13 Unk:7	No:7 Yes:11 Unk:9	8.96
Norwegian	72,73	Case report: 2	9	33	F:6 M:3	FLD:9	11	Yes:9	Yes:8 No:1	Yes:3 No:6	0.4, 1.3
Polish	74	Case report: 1	2	35	F:1 M:1	FLD:2	19	Yes:2	Yes:2	Yes:1 No:1	
Portuguese	75	Case report: 1	2	39	M:2	FLD:2	15	Yes:2	Yes:2	Yes:2	
Romanian	76	Case report:1	1	33	F:1	FLD:1	12	Yes:1	Yes:1	No:1	
Spanish	77–80	Case report: 3 Review: 1	12	51	F:3 M:2 Unk:7	FLD:3 FED:1 Unclassified:8	10.4	No:2 Unk:10	No:3 Yes:2 Unk:7	No:3 Yes:2 Unk:7	19.36
Swedish	81	Case report: 1	3	68	F:3	FED:3	7.3	No:3	No:3	No:3	2.40
Latin-American											

Ethnicity/ Country	REF	Study Type	Sample Size	Median Age	Gender	Phenotype	HDL-C (mg/dL)	Hemolytic Anemia	Proteinuria/ Albuminuria	eGFR <60 mL/min	LCAT Activity nmol/mL/h
Argentinian	82	Case report: 1	1	63	F:1	FED:1	4	No:1	No:1	No:1	2.40
Brazilian.	83,84	Review: 1 Abstract:1	38	38	F: 18 M: 20	FLD: 38	10	Yes: 25 No: 13	Unk:38	Yes: 7 Unk:31	
Chilean	85	Case report: 1	1	36	F:1	FLD:1	3	Yes:1	No:1	No:1	
Colombian	86	Case report: 1	1	33	M:1	FLD:1	4	Yes:1	Yes:1	Yes:1	
Ecuadorian	87	Case report: 1	1	60	F:1	FED:1	Unk:1	No:1	No:1	No:1	
Mexican Mestizo	88	Case report: 1	6 (191)	42	F:3 M:3	FLD:5 FED:1	8	No:1 Yes:5	No:1 Yes:5	Normal:1 Yes:5	3.33
Middle East/south asian											
Indian	89–91	Case report: 3	6	38	F:3 M:3	FLD:4 FED:2	13	Yes:4 No:2	Yes:4 No:2	No:2 Yes:4	28.00
Iranian	92	Case report: 1	8	28	F:5 M:3	FLD:8	28	No:8	No:8	Yes:8	
Lebanese	93	Case report and Review: 1	1	50	M:1	FLD:1	7	Yes:1	Yes:1	Yes:1	
Pakistani	94	Case report: 1	1	33	F:1	FLD:1	13	Yes:1	Yes:1	No:1	0.10
Turkish	95	Case report: 1	2	54	F:1 M:1	FED:2	12	No:2	No:2	No:2	
Mixed											
American	96–100	Case report: 5	6	33	F:2 M:3 Unk:1	FLD:2 FED:3 Unclassified:1	5.62	No:3 Yes:2 Unk:1	No:3 Yes:2 Unk:1	No:5 Unk:1	3.08

The systematic analysis retrieved 215 cases, of which 71.6% (n = 154) were FLD, 19.0% (n = 41) were FED and 9.3% (n = 20) were unclassified (Table 2). Most of the information was found in case reports (87.6%). The LCAT deficiency cases are from 33 countries, the majority of individuals are Caucasians and the commonest presenting feature was corneal opacity. There is a predominance of men (n = 116, 53.9%) and the mean age of individuals is 42 ± 16.5 years. The median concentration of HDL-C is 7 (4–12) mg/dl and median LCAT activity is 1.65 (0.0-7.1) nmol/ml/hr. A creatinine clearance < 60 ml/min was found in 30.2%, > 60 in 40.4% and unknown in the remaining cases. Albuminuria/ proteinuria was present in 39.1% and absent in 29.8% of cases. Anemia was reported in 53.9% and absent in 32.1%. Premature coronary artery disease was present in 7.4%, absent in 59.1% and not evaluated or unknown in the remaining cases.

Table 2
Systematic analysis: Characteristics of FLD and FED cases

		Total (215) Unclassified (n = 20, 9.3%)	FLD (n = 154, 71.6%)	FED (n = 41, 19.0%))	p
AGE (years)		42 ± 16.5	41 ± 14.7	55 ± 13.8	**0.02**
GENDER (n = 215 (Unknown = 18)	MALE	116 (53.9%)	93 (60.4%)	18 (43.9%)	0.17
	FEMALE	81 (37.7%)	57 (37.0%)	23 (56.1%)	
PREMATURE CHD (n = 177) (Unknown = 34)	YES	15 (6.9%)	2 (1.3%)	12 (29.2%)	0.00
	NO	128 (59.5%)	152 (98.7%)	29 (70.7%)	
HDL mg/dL		7 (4–12)	8.83	7.55	0.45
LCAT ACTIVITY nmol/mL/h (n = 78)		1.65 (0.0-7.1)	0.1 (0.0–2.1)	2.7 (0.8–7.0)	**0.01**
GFR < 60 (n = 184) (Unknown = 32)	YES	65 (30.2%)	62 (40.2%)	3 (7.3%)	**0.00**
	NO	87 (40.4%)	48 (31.1%)	38 (92.7%)	
PROTEINURIA/ MICROALBUMINURIA (n = 177) (Unknown = 29)	YES	84 (39.1%)	82 (53.2%)	1 (2.4%)	**0.00**
	NO	64 (29.8%)	24 (15.6%)	40 (97.6%)	
HEMOLYTIC ANEMIA (n = 215) (Unknown = 30)	YES	116 (53.9%)	115 (74.7%)	2 (4.9%)	**0.00**
	NO	69 (32.1%)	28 (18.2%)	20 (48.7%)	

On comparing the individuals with FLD and FED, certain differences are apparent. The FLD cases are significantly younger than the FED cases (41 ± 14.7 vs. 55 ± 13.8 years, p = 0.02, respectively). There was no difference in HDL-C levels between groups. However, LCAT activity was significantly lower in FLD compared to FED (0.1 (0.0–2.1) nmol/ml/hr vs. 2.7 (0.8–7.0), p = 0.01). Unsurprisingly, clinical features compatible with FLD are significantly more common in these cases (low creatinine clearance, albuminuria/proteinuria and anemia). Premature coronary artery disease was significantly more prevalent in FED compared with FLD (p = 0.00).

Mutational analysis:

A total of 138 mutations in the *LCAT* gene were recovered (136 in exons and 2 in introns) (supplementary table 1). Mutations have principally been published in Caucasians. Genetic alterations are present on all exons of the gene; there was no association between a particular exon and phenotype. No specific mutation was associated with an ethnic group. The number of mutations associated with FLD, FED and unclassified cases were 77, 38 and 23 respectively. The FLD phenotype was associated with exon 6 (n = 27), exon 5 (n = 13) and exon 1 (n = 13). In FED, exon 6 (n = 12), exon 4 (n = 10) and exon 1 (n = 8) appeared to have the greatest number of alterations. In unclassified cases, exon 6 was also the predominant site on the *LCAT* gene.

The ethnic distribution of the cases was reviewed with respect to location of LCAT mutation (supplementary table 1). Here exon 6 (n = 41) and exon 1 (n = 19) were the most common sites for LCAT mutations. There was a predominance of exon 6 mutations, in particular in Italians, Dutch and Japanese groups. In the Amerindian ethnic group, exon 1 appeared most common in Mexican-Mestizos whilst exon 6 predominated in Brazil and Chile.

Finally, the number of mutations per exon, adjusted for size of exon was examined (supplementary table 2). This avoids exon size bias; exon 6 is more than double the length of the others, perhaps explaining the greater number of mutations encountered. With this analysis, a fairer comparison between exons is possible. Exon 4 and exon 1 show the greatest density of mutations, with exons 5 and 6 showing the least number of alterations. There was no clear relationship between the alterations and the key positions for the enzymatic activity of the LCAT protein.

Characteristics of the Latin American cases:

In total, 47 cases of LCAT deficiency have been published from six Latin American countries (Argentina, Brazil, Chile, Columbia, Ecuador and Mexico) (Table 3). There are 38 FLD cases from Brazil (published in an abstract), one unclassified case from Argentina and 3 FLD cases from Chile, Columbia and Ecuador respectively. In Mexico, six cases (4 probands) have been encountered (4 FLD, 1 FED and 1 unclassified); one of which has previously been published (unclassified probable FED).

Table 3
Characteristics of Latin America population

Country	Exon mutation	Nucleotide change	Phenotype	Age	Gender	HDL-C mg/dL	LCAT act nmol/mL/h
Argentinean	Unknown	Unknown	Unclassified	63	F	4	2.4
Brazilian	Ex 5 Ex 6	c.679 A > T c.803 G > A c.893 C > T	38 FLD	38	18F, 20M	<10	-
Chilean	Ex 6 Ex 6	c.997G > A c.1210A > G	FLD	36	F	3	-
Colombian	-	-	FLD	33	M	4	-
Ecuadorian	-	-	FLD	60	F		-
Mexican Mestizo (1 proband and 2 other members of same family)	Ex 1	Trp8*	FLD	37	F	15	3.70
Mexican Mestizo	Ex 1 Ex 1	c.101dupC c.110C > T	FED	70	F	11	4.20
Mexican Mestizo	Ex 1	c.110C > T	FLD	34	M	2	2.10
Mexican Mestizo	Ex 4	c.490C > T	FLD	29	F	4	-
Total		**10**	**46**	**-**	**-**	**-**	**-**

The mean age of the cases was 45 years (in Brazil it was 38 years) and the cases were equally distributed between genders. The mean HDL-C level was 5.4 (in Brazil it was < 10 mg/dl) and LCAT activity was reported in only 4 individuals with a mean level of 3.1 nmol/ml/hr.

Molecular analysis of the Mexican- Mestizo patients revealed mutations in exon 1 (Trp8*, c.101dupC, c.110C > T) in 3 probands, and a homozygous alteration on exon 4 in 1 proband (c.490C > T). The Chilean case reported alterations on exon 6, c.1210A > G and c.997G > A. In Brazil, 38 cases have been encountered; the investigators report three pathogenic mutations in the LCAT gene, each corresponding to a distinct geographic disease cluster. Two mutations are on exon 6 (c.803 G > A and c.893 C > T) and one on exon 5 (c.679 A > T). Finally, molecular analysis was not carried out in Argentina, Columbia and Ecuador.

MEXICAN PROBANDS WITH LCAT DEFICIENCY SYNDROMES

1. PROBAND 1: Familial LCAT deficiency (FLD)

The proband was a 37-year old woman with bilateral corneal opacities (no deficit in visual acuity). She came from a small village in the state of Oaxaca, in south-west Mexico. She was the 6th of 10 children and her parents were apparently non-consanguineous. Only her paternal grandmother had eyes similar to hers. Of her 9 siblings, 2 brothers had corneal opacities and nephrotic syndrome. There was no history of cardiovascular disease in her family. We studied all available members of her family, including her parents and 5 of their 10 children.

She had a history of hyperlipidemia, arterial hypertension and nephrotic syndrome; a renal biopsy reported glomerulopathy characterized by mesangial proliferation, vacuolated macrophages and presence of intramembranous lipid deposits in glomerular capillaries. A recent carotid doppler ultrasound was normal with no alteration in carotid-intima thickness.

Biochemical analysis:

Laboratory results showed a normochromic, normocytic anemia (hemoglobin 9.2 g/dl (normal 13–15 g/dl)) and measurement of erythrocyte osmotic fragility confirmed the presence of brittle cells. There was evidence of renal failure with nephrotic syndrome (creatinine clearance 47 ml/min, and proteinuria of 5 g/24hrs). The lipid profile showed low HDL-C, hypertriglyceridemia and low levels of apolipoprotein A1 (Table 4). The LCAT activity was low (LCAT activity 0.4%, specific activity 3.7 nmol/ml/hr) and there was a reduction in paroxonase-1 activity (27.8, control = 100.77).

Table 4
Biochemical results of probands 1, 2 and 3 and their kindred

		TG	Total chol	HDL	LDL	Apo A1	Apo B	LCAT activit %	Specific LCAT Activity (nmol/ml/h)	PON-1 (Control 100.77) mU/ml/h
PROBAND 1	Father (II-1)	112	168	37	109	132	92.5	2.70	25.63	100.5
	Mother (II-2)	188	203	38	127	135	122	3.18	30.19	62.6
	Proband (37 yrs) (III-7)	**300**	**153**	**15**	**78**	**44**	**113**	**0.4**	**3.79**	**27.8**
	Brother1 (35 yrs) (III-2)	1076	222	**11**	—	**35.3**	52.1	**0.9**	**8.54**	**42.6**
	Brother2 (33 yrs) (III-1)	589	313	**17**	178	**47.2**	114	**0.5**	**4.74**	**53.0**
	Brother3 (22 yrs) (III-10)	117	161	26	112	91.6	102	2.42	22.98	97.0
	Sister (45 yrs) (III-5)	177	168	23	110	—	—	3.82	36.27	81.7
PROBAND 2	**Proband** (II-1)	**334**	**150**	**12**	**71**	**48.7**	**109**		**4.2**	
	Daughter 1 (III-1)	290	196	30	108	131	116		55	
	Daughter 2 (III-2)	191	157	25	94	123	108		52.7	
	Granddaughter (mother is daughter 1) (IV-1)	59	180	81	87	210	52.7			
	Grandson (mother is daughter 1) (IV-2)	450	240	48	102	169	121			
	Grandson (mother is daughter 2) (IV-4)	85	162	46	99	157	92.3			
PROBAND 3	**Proband (II-1)**	**186**	**117**	**4**	**59**				7.3	
	Father (II-1)	257	168							

Two brothers were affected (homozygotes) and heterozygote family members had half- normal HDL-C concentrations (Table 4). All three affected individuals showed some paroxonase-1 activity, whereas LCAT activity was virtually absent. The proband had a 72% reduction in PON-1 activity, while her affected brothers showed a 47% and 57% reduction respectively. The 2 remaining siblings and both parents had low LCAT activity (2.4–3.8%) and higher paroxonase activity compared to the affected individuals. On separation of the lipoproteins by exclusion chromatography, the paroxonase-1 activity was essentially on HDL, with little activity on LDL.

Mutational analysis:

A novel mutation was encountered in this proband. This was a nucleotide replacement resulting in a stop codon at position 8 on exon 1 of the *LCAT* gene (in the leader sequence). Tryptophan (TGG) was replaced by Ambar stop (TAG). This is reported as Trp8* or Trp-17* (*indicates stop codon) in the nucleotide sequence. The parents were heterozygous for the mutation and the proband and both her affected brothers were homozygous. The family pedigree is shown in the supplementary Fig. 1.

2. PROBAND 2: Fish Eye Disease (FED)

The 70 year old proband from Mexico City, had bilateral corneal opacities and a history of myocardial infarction. The subject's father and mother had suffered from coronary artery disease (her father died at age 66, her mother died at age 70). The only other family members with similar eyes were her father, paternal grandmother and one male sibling who died soon after birth. None of her 8 siblings were alive. Both her children and 5 grandchildren had normal corneas and no health issues. We studied the proband, her two daughters and 4 of her grandchildren.

The proband had type 2 diabetes mellitus (no known complications), mixed hyperlipidemia, and arterial hypertension (history of atrial fibrillation and left ventricular hypertrophy). The coronary heart disease was characterized by occlusion of 3 coronary vessels (left coronary: trunk, circumflex and right coronary); she had been treated with two medicated stents.

Biochemical analysis:

The lipid profile showed an HDL-C level of 11 mg/dl (Table 4). The remaining laboratory results included; glucose 102 mg/dl, creatinine 0.87 mg/dl, hemoglobin 12.1 g/dl. The proband had no evidence of anemia or renal disease.

No other family member had a clinical or biochemical phenotype compatible with FED. The proband and her daughters had HDL cholesterol levels < 40 mg/dl, while all the grandchildren had normal HDL-C levels. The proband had low levels of apolipoprotein A1; her daughters had levels intermediate between hers and those of her grandchildren. The proband had extremely low LCAT activity (LCAT specific activity 4.2 nmol/ml/hr) and both daughters had relatively normal LCAT activity (55.0 and 52.7 nmol/ml/hr respectively, Control = 78.7)

Mutational analysis:

Two mutations were found on exon 1:

1. On one allele, there was an insertion of cysteine (reported as c.101dupC) at codon 34. This mutation resulted in a stop codon 7 codons later. The proband was heterozygote for this mutation.
2. On the other allele, the alteration was c.110C > T. When this allele is translated, threonine is substituted by methionine (ACG-ATG Thr37Met) (missense mutation) at position 37 of the protein. The proband was heterozygote for this mutation.

The proband is compound heterozygote for both mutations. The family pedigree is shown in Supplementary Fig. 1. Daughter 1 is heterozygote for the second mutation (c.110C > T at codon 37), while daughter 2 is heterozygote for the first mutation (c.101dupC at codon 34). Analysis of the apoA1 gene and its promotor region was also carried out in the proband, no alterations were found.

The family pedigree is shown in supplementary Fig. 1.

PROBAND 3 (Familial LCAT Deficiency).

The proband was a 29-year-old woman from Monterrey, with bilateral corneal opacities resembling premature corneal arcus. She had an FLD phenotype with extremely low levels of HDL-C, anemia and kidney disease (glomerulopathy). There was no clinical or biochemical evidence of FLD or FED in her parents or sibling. There was no family history of premature cardiovascular disease. She had attended consultations with several specialists, had undergone three kidney biopsies and one bone marrow aspiration; despite this she had not been diagnosed.

Biochemical analysis.

The proband had an HDL-C level of 4 mg/dl (Table 4). The laboratory profile showed: glucose 101 mg/dl, creatinine 1.12 mg/dL, hemoglobin 12.9 g/dL and 24-hour urinary protein 2307 mg/day. The proband had extremely low LCAT activity (7.3 nmol/ml/hr, LCAT specific activity in control 145.34 nmol/ml/hr) and a 60% reduction in PON-1 activity compared with controls.

Mutational analysis:

The genetic alteration was a point mutation in exon 4 of the LCAT gene, i.e., a G to A substitution on codon 140 converting Arginine to Histidine. The family pedigree is shown in supplementary Fig. 1.

Discussion

FLD and FED are rare LCAT deficiency syndromes with differing clinical manifestations. In this article, we discuss the results of the first systematic analysis evaluating the ethnic distribution of LCAT deficiency, with particular emphasis on Latin America, and we present the case histories of three Mexican-Mestizo probands.

The systematic review retrieved 215 published cases of which 71.6% were reported as FLD, 19% as FED and 9.3% were unclassified. This number is significantly greater than that reported in the current literature (101). The majority of probands have been published in case reports, often with incomplete clinical or genetic information. It is evident that this disease continues to be encountered at a late age, with corneal opacifications being the principal reason for consultation. Furthermore, FED is diagnosed significantly later than FLD, probably due to the more severe clinical phenotype of the later warranting earlier medical attention. Timely diagnosis of this disease is needed for the application of preventive strategies and the use of newer therapies.

The biochemical features of the cases showed that LCAT enzyme activity was significantly lower in FLD compared to FED. Low HDL-C levels are a characteristic feature of this disease, however, there was no difference in concentrations between the phenotypes. Indeed, FLD and FED can have similar lipid profiles, suggesting any variability in parameters is unrelated to LCAT function. Pavanello et al. have commented that the severity of the hypoalphalipoproteinemia varies widely among carriers of different LCAT genotypes (101). Furthermore, carriers of one mutant LCAT allele show an intermediate biochemical phenotype between homozygous carriers and controls, suggesting that the disease, which is reported as recessive, is indeed co-dominant for the biochemical phenotype. This was also confirmed in the relatives of the Mexican-Mestizo probands.

The clinical features of the cases showed a clear difference between FED and FLD, with renal disease and anemia prevalent in the later. However, not all the FLD cases showed significant proteinuria or a reduction in eGFR; this suggests that the rate of progression of renal failure may well be variable. Lamiquiz-Moneo et al. state that this clinical variability is likely to be related to the biochemical phenotype rather than to the inherited mutation (80). In addition, 9.3% of cases had an unclassified clinical phenotype; the authors could not confirm either familial LCAT deficiency (FLD) or fish eye disease (FED). Some authors

have commented that the clinical manifestations of patients with LCAT gene mutations may vary even among members of the same family carrying identical mutations (41). Therefore, it is evident that LCAT deficiency syndromes show both biochemical and clinical heterogeneity.

An important finding of this systematic review was the significantly greater prevalence of premature CHD in FED patients compared to FLD patients. The cardiovascular risk associated with LCAT deficiency syndromes has been a matter of debate for a number of years. A severe deficiency of HDL-C in LCAT deficient carriers would be expected to increase their risk of developing coronary heart disease (83). Oldoni et al., have compared carotid intima media thickness between 33 heterozygous FLD subjects and 41 heterozygous FED subjects (102). Carriers of FLD mutations exhibited less carotid atherosclerosis, whereas those with FED mutations presented with more subclinical atherosclerosis. The authors proposed that this discrepancy was related to the capacity of LCAT to esterify cholesterol on apolipoprotein B–containing lipoproteins- this capacity is lost in FLD, but is unaffected in FED. In a study of Italian FLD families, the inheritance of a mutated LCAT genotype had a remarkable gene-dose dependent effect in reducing carotid IMT, whereas a subgroup of these carriers also showed normal flow-mediated dilation (65, 83, 103). A Mendelian randomization study in 54,500 subjects concluded that common genetic variation in *LCAT* resulting in decreased HDL-C levels, did not associate with an increased risk of ischemic cardiovascular disease (104). Low HDL-C levels robustly associated with increased risk of myocardial infarction (MI), but genetically decreased HDL cholesterol did not. This may suggest that isolated low HDL cholesterol levels do not cause MI; the inverse relation between HDL-C and CHD observed in epidemiological studies may not be causal.

The molecular defects associated with LCAT deficiency syndromes show heterogeneity. In total, 138 LCAT mutations were encountered with no particular exon dominating in a particular ethnicity. Again this number is greater than that reported in the literature (101). There was no association between clinical phenotype and genetic alteration, this may be due to the low number of cases worldwide. Exon 6 was the predominant site for both FLD and FED; however, after adjusting for exon size, exon 1 and 4 showed the greatest concentration of mutations. At present, it is impossible to predict the phenotype (FLD or FED) associated with the LCAT mutations (101).

With regards to ethnicity, at least 33 different groups are represented, of which Caucasians are most common. The predominance of Caucasian and Asian cases may reflect better health awareness and access to health care compared with developing regions. Remarkably, only one case has been found in the African sub-continent. Cases are more likely to be found in affluent countries, but also in countries hosting research groups with interest and resources to investigate this disease. In Latin American few cases have been published (82–88). At present, only six countries have reported probands with LCAT deficiency, and genetic evaluation has only been carried out in three countries. Of these, Brazil reports three mutations causing FLD each associated with a distinct geographical region. In Mexico, the first FLD proband, came from an isolated village in the south of Mexico, there is little genetic admixture in this region. The indigenous heritage of this patient may have been responsible for disease susceptibility. The mutations reported in Brazil and Chile are on exon 5 and 6. In Mexico, exon 1 mutations predominate (3 probands), with only 1 case from the north of the country showing a homozygous exon 4 alteration.

The first Mexican- Mestizo proband (FLD phenotype) showed an alteration located in the leader sequence (a stop codon at position 8 in exon 1 of the LCAT gene), thus normal protein synthesis is abolished. In accordance with the genetic results, the laboratory results confirmed low HDL-C concentrations and very low specific LCAT activity. Both parents and 2 siblings were heterozygotes and presented with intermediate low HDL-C levels (< 40 mg/dl) and low specific LCAT activity (22–36%). To our knowledge, this particular mutation is novel, only one other mutation in this region of the gene has been reported: Calabresi et al. mention a subject with a Thr-13Met mutation and an FLD phenotype (64).

On interesting finding was that the proband continued to show paroxonase- 1 activity. This was essentially on HDL, even though the number of particles was extremely low and despite a clear lack of LCAT activity. The proband had 27% activity, while her affected siblings had approximately 50% activity. The heterozygote family members had essentially normal paroxonase-1 (PON-1) activity. This enzyme prevents the conversion of LDL cholesterol into a more atherogenic particle (105). Preserved PON-1 activity has been reported in other HDL deficiency states, and in vitro experiments with LCAT deficient plasma suggest an apparent maintenance of cholesterol efflux (94, 106, 107). Although HDL cholesterol levels were reduced by 93%, there was only a 50% reduction in reverse cholesterol transport (RCT). This suggests that RCT is conserved even in the presence of complete LCAT deficiency, supporting the differential cardiovascular risk between phenotypes.

The second Mexican- Mestizo proband (FED) had two distinct *LCAT* mutations, one on each allele (compound heterozygote). One of the alterations was a frameshift mutation (c.101dupC) on exon 1; the other mutation was a missense mutation (c.110C > T) on the same exon. Both mutations have previously been reported in the literature (25, 26, 27).

Argyropoulos et al. have reported an FLD Caucasian proband who was compound heterozygote with a missense mutation identical to that in our proband (c.110C > T on exon 1) (44). Posadas-Sanchez et al. have reported the presence of the same missense mutation (c.110C > T) on both alleles (homozygote) in an unrelated Mexican subject with an unclassified LCAT deficiency syndrome (probable FED) (88). The 34- year old Mexican man had type 2 diabetes, premature coronary artery disease, corneal opacities, normal renal function and extremely low levels of HDL cholesterol (2 mg/dl). The investigators reported an increase in the number of small HDL particles in the proband. In addition, the HDL-C particles had a reduced ability to promote cholesterol efflux (PON-1 activity was low). Finally, Bujo et al. have published the presence of the homozygous c.101dupC mutation on exon 1 in a Japanese subject. This resulted in a truncated 16 amino-acid non -functional LCAT protein and an FLD phenotype (20).

Predicting the effect of the co- existence of these mutations (one on each allele) on LCAT function and structure is not straightforward. The majority of mutations are not located in sites involved in the catalytic function of the enzyme; the affected sites are probably involved in maintaining protein stability and structure. The mature LCAT protein contains 416 amino acids and a leader sequence (67 kDa) (108, 109). The enzyme is thought to undergo post-translational glycosylation which appears to be essential for the conformational stability of the protein (110). In addition, LCAT has two disulfide bridges between Cyst50-Cys74 and Cys313-Cys356; the first bridge partially covers the active site of LCAT, forms part of the lid region and is thought to enable the enzyme to bind to lipid surfaces. Hence, in this patient, the genetic alterations may interfere with the nearby lid structure or produce a conformational change

when the mature protein is folded, resulting in enzyme- substrate interference. The frameshift mutation is a more detrimental alteration; however, clinical expression of which would only be apparent in homozygotes. Hence, the predominant phenotype in our subject is FED.

The third Mexican-Mestizo proband (FLD), had a point mutation on exon 4 of the *LCAT* gene, i.e., a G to A substitution on codon 140 converting Arginine to Histidine. This mutation has been reported previously in an Austrian kindred who were also homozygous for this modification (37). It appears that this domain (where Arg140 resides) is crucial for an enzymatically active LCAT protein, mutations in this region possibly affect tertiary structure.

In Latin America, persons with LCAT deficiency syndromes face unique challenges. The medical community is unaware of this condition; our third proband had attended consultations with several specialists, had undergone three kidney biopsies and one bone marrow aspiration; despite this, she had not been diagnosed. Additionally, many centers do not have the infrastructure to carry out the biochemical or genetic studies necessary to confirm this condition. Current management of FLD is preventative and involves lipid lowering therapy, ACE inhibitors, diuretics and steroids, in order to delay progression to end-stage renal disease: for many in Latin America, these medications will be an out of pocket expense. Furthermore, in this region, access to further treatment with peritoneal dialysis or hemodialysis is variable. This is related to fragmented health care coverage and socioeconomic inequality. Although, provision of renal replacement therapy (RRT) has increased in all Latin American countries over the past 20 years, universal access is available in only a few countries (Argentina, Brazil, Chile, Cuba, Uruguay, Venezuela, and Colombia) (111). Kidney transplantation may offer a temporary cure, but reoccurrence of nephropathy is inevitable and occurs within a few years (112). Currently, trials are underway with human recombinant LCAT enzyme and there is the possibility of gene therapy in the future (113). However, such products maybe subsequently unavailable and/or unaffordable (cost is much greater than average monthly income) to most of the Latin American population (114).

Earlier identification and adequate follow up of patients is urgently needed; the implementation of models of care and national disease registries can aid in this process. Recently, the Norwegian National Advisory Unit on Rare Disorders has been asked to establish a worldwide contact registry on FLD; this will allow the integration of efforts throughout the world to tackle the health burden and improve care for this condition (83).

We must acknowledge the strengths and limitations of this work. This is the first systematic review of LCAT deficiency syndromes; this work highlights the major knowledge gaps in this disease. The overall number of cases and mutations is far greater than currently thought. In Latin America, the limited number of cases may have influenced our findings and further work is necessary in order to confirm whether isolated geographical regions may have ethnicity specific mutations. Measurements of free cholesterol and cholesteryl ester, as well as cholesterol esterification rate to complete the biochemical characterization of the Mexican probands and their families would have been desirable, this was limited by the death of two of the probands, and the geographical location of the last proband.

In conclusion, the systematic review shows that LCAT deficiency syndromes are diagnosed late; with FLD cases identified significantly earlier than FED. Furthermore, we confirm that this condition is clinically and genetically heterogeneous. We were unable to confirm any association between ethnicity and LCAT mutation. However, we were able to show a significantly greater risk of premature coronary artery disease in FED compared to FLD. This finding is important, it suggests that management should be tailored according to the LCAT deficiency profile. In FLD patients, the priority is to mitigate progression to end stage kidney disease; in contrast, in FED patients, management of cardiovascular risk may well be paramount. Finally, the LCAT mutations discussed in this article are the only ones reported in the Mexican- Amerindian population. We report a novel mutation associated with FLD, in a Mexico-Mestizo woman, suggesting the influence of Amerindian ancestry.

Abbreviations

TC = total cholesterol, PON-1 = paroxonase-1, FLD: familial LCAT deficiency, FED: Fish Eye disease, LCAT: Lecithin–cholesterol acyltransferase, HDL: high density lipoproteins, LDL: low density lipoprotein, VLDL: very low density lipoprotein, apo A-I: apolipoprotein A-I, apo A-II: apolipoprotein A-II,

Declarations

Ethics approval and consent to participate: this study received approval from the Research and Ethics Committee at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

Consent for publication: not applicable

Availability of data and materials: all data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Figures

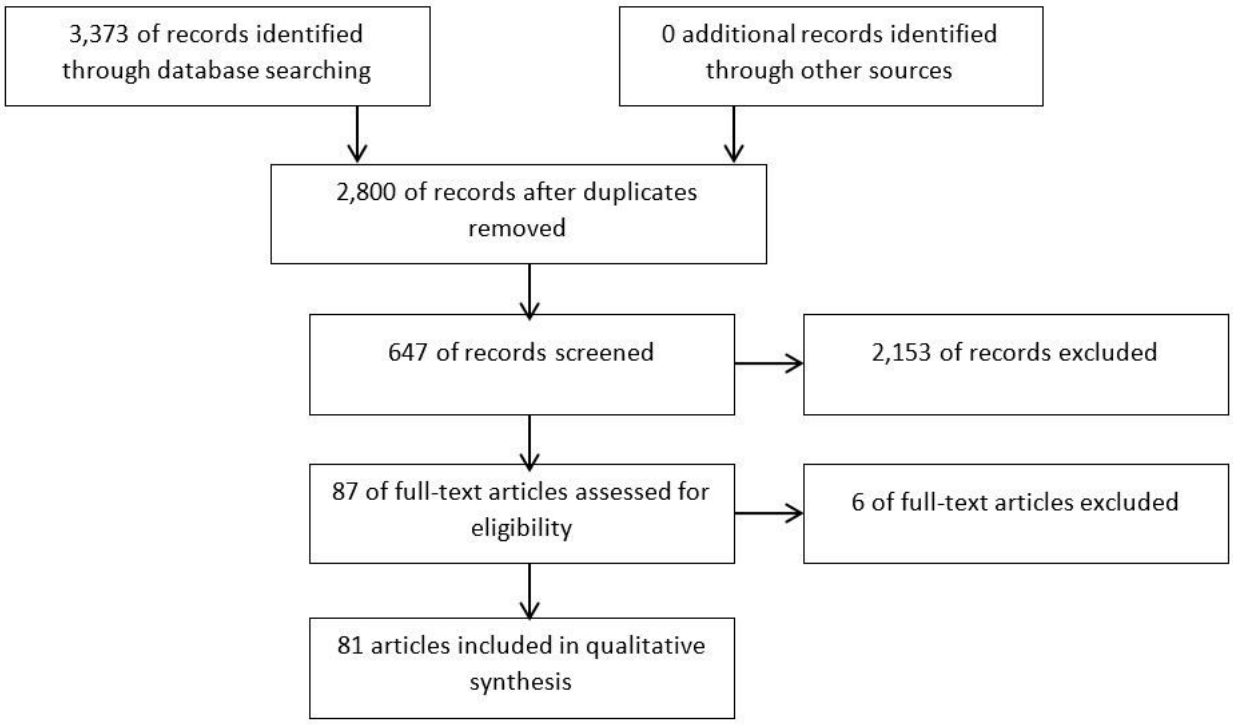

Figure 1

Systematic review

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