Molecular Genetics and Genomics
https://doi.org/10.1007/s00438-020-01663-z

ORIGINAL ARTICLE

Mutation in *ALOX12B* likely cause of POI and also ichthyosis in a large Iranian pedigree

Afagh Alavi[1] · Faezeh Darki[2] · Mohammad Masoud Rahimi Bidgoli[1] · Davood Zare-Abdollahi[1] · Ashraf Moini[3] · Mostafa M. Shahshahani[4] · Judith Fischer[5] · Elahe Elahi[2]

Received: 23 December 2019 / Accepted: 29 February 2020
© Springer-Verlag GmbH Germany, part of Springer Nature 2020

Abstract

Premature ovarian insufficiency (POI) is a clinically and etiologically heterogeneous disorder characterized by menstrual irregularities and elevated levels of FSH before age of 40 years. Genetic anomalies are among the recognized causes of POI. Here, we aimed to identify the genetic cause of POI in an inbred pedigree with nine POI and two ichthyosis-affected members. Inheritance of POI and ichthyosis were, respectively, dominant and recessive. Reproduction-related information and measurements of relevant hormones were obtained. Genetic studies included homozygosity mapping, linkage analysis, exome sequencing, and screening of candidate variants. A mutation within *ALOX12B*, which is a known ichthyosis causing gene, was identified as cause of ichthyosis. *ALOX12B* encodes a protein involved in steroidogenesis and lipid metabolism. Considering the importance of steroidogenesis in reproduction functions, the possibility that the *ALOX12B* mutation is also cause of POI was considered. Screenings showed that the mutation segregated with POI status. Linkage analysis with respect to POI identified a single strongly linked locus (LOD > 3) that includes *ALOX12B*. Exome sequencing on POI-affected females identified the mutation in *ALOX12B* and also a sequence variation in *SPNS2* within the linked locus. A possible contribution of the *SPNS2* variation to POI was not strictly ruled out, but various data presented in the text including reported association of variations in related gene *ALOX12* with menopause-age and role of *ALOX12B* in atretic bovine follicle formation argue in favor of *ALOX12B*. It is, therefore, concluded that the mutation in *ALOX12B* is the likely cause of POI in the pedigree.

Keywords Premature ovarian insufficiency (POI) · *ALOX12B* · Lipoxygenases · Steroidogenesis · Ichthyosis

Communicated by Stefan Hohmann.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00438-020-01663-z) contains supplementary material, which is available to authorized users.

✉ Elahe Elahi
elaheelahi@ut.ac.ir; elahe.elahi@gmail.com

[1] Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

[2] School of Biology, University College of Science, University of Tehran, Tehran, Iran

[3] Department of Gynecology and Obstetrics, Roointan Arash Women's Health Research and Educational Hospital, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

[5] Institute of Human Genetics, Medical Center—University of Freiburg, Freiburg, Germany

Abbreviations

POI	Primary ovarian insufficiency
FSH	Follicle stimulating hormone
StAR	Steroidogenic acute regulatory protein
ALOX12B	12(R)-Lipoxygenase (12R-LOX)
ARCI	Autosomal recessive congenital ichthyosis
LH	Luteinizing hormone
AMH	Anti-Müllerian hormone
SNP	Single-nucleotide polymorphisms
LOD	Logarithm of the odds
NCIE	Nonbullous congenital ichthyosiform erythroderma
PCR	Polymerase chain reaction

Introduction

Premature ovarian insufficiency (POI) is a clinically and etiologically heterogeneous disorder characterized by menstrual irregularities (amenorrhea or oligomenorrhea)

Published online: 06 April 2020

before the age of 40 years (Chapman et al. 2015; Qin et al. 2015a, b; Tucker et al. 2016; Huhtaniemi et al. 2018; Jiao et al. 2018; Venturella et al. 2019; Yatsenko and Rajkovic 2019). Elevated levels of gonadotropins, particularly follicle stimulating hormone (FSH), are confirmatory diagnostic measurements. POI is estimated to affect one percent of women of reproductive age (Coulam et al. 1986; Qin et al. 2015a, b; Tucker et al. 2016). Recognized causes of POI include iatrogenic causes such as surgery, radiation, or chemotherapy, metabolic and storage diseases, infections, autoimmune disorders, and genetic factors (Goswami and Conway 2007; Chapman et al. 2015; Qin et al. 2015a, b; Tucker et al. 2016; Yatsenko and Rajkovic 2019). The latter are estimated to account for approximately 20–25% of the cases. A genetic component for POI was originally suggested by familial clustering and later substantiated by identification of over 60 causative and many susceptibility genes (Table S1) (Tucker et al. 2019). Each of several of these genes was first identified in studies on a single pedigree (de Vries 2014; Wang 2014; AlAsiri et al. 2015; Qin et al. 2015a, b). Many POI cases are idiopathic and it is believed that multiple genetic defects, some in yet unidentified genes, may contribute to the etiology of these cases (Chapman et al. 2015). Genetic forms of POI show variable patterns of inheritance. Not unexpectedly, some genes whose protein products affect steroidogenesis are among known POI-causing genes. These include *CYP17A1*, *CYP19A1*, and *STAR* (Conte et al. 1994; Miura et al. 1996; Bose et al. 1997). The first two are involved in estrogen production, and the protein steroidogenic acute regulatory protein (StAR) encoded by *STAR* is responsible for transport of cholesterol into mitochondria of theca cells for conversion into steroids.

Ichthyosis that is characterized by abnormal skin scaling over the whole body is also a heterogeneous disorder (Williams and Elias 1985; Takeichi and Akiyama 2016). Like POI, ichthyosis can very adversely affect quality of life. Nearly all forms of ichthyosis have a genetic basis, and approximately 40 causative genes have till now been identified (Schmuth et al. 2013; Youssefian et al. 2017). Ichthyosis presents with variable patterns of inheritance, including autosomal recessive inheritance. Autosomal recessive congenital ichthyosis (ARCI) itself comprises various types which together have a prevalence of approximately 1/100 000 or less in various Western populations (Pigg et al. 1998; Oji and Traupe 2006; Hernández-Martín et al. 2012; Youssefian et al. 2017). As the lipid barrier of the skin malfunctions in ichthyosis, it is also not surprising that the products of several known ARCI causing genes have lipid-related functions. These include *ALOX12B* coding 12(R)-lipoxygenase (12R-LOX), *ALOXE3* coding lipoxygenase-3, and *FATP4* coding fatty acid transport protein (Jobard et al. 2002; Eckl et al. 2005; Klar et al. 2009).

Here, we present a family that has both POI and ichthyosis-affected members, and report results of genetic analysis that suggest both anomalies may be caused by mutated *ALOX12B* alleles.

Materials and methods

This research was performed in accordance with the Declaration of Helsinki and with approval of the ethics board of the University of Tehran. Participants or their guardians consented to participate after being informed of the nature of the research.

Subjects

The subjects of this study are members of a highly inbred Iranian pedigree (IA-105) that includes individuals affected with ARCI and/or reproductive anomalies that may justify diagnosis of POI (Fig. 1) (Alavi, Shahshahani et al. 2012). Ichthyosis was initially diagnosed in two individuals (V-32 and VI-4) based on standard criteria by several dermatologists experienced in keratinization diseases. The affected individuals exhibited generalized scaling and mild erythroderma; one had been born as a collodion baby (Fig. 2, Table 1).

Some members of the pedigree who were contemplating marriage were concerned about the possibility of giving birth to ARCI affected children. Conversations with these individuals made apparent that several female members of pedigree IA-105 had reproduction-related problems (Fig. 1, Table 2). Reliable information on reproduction-related features of individuals of generations I–III, all of whom are deceased, is not available. However, information on 16 females and 13 males distributed in three generations (IV–VI) of pedigree IA-105 was gathered by interviews. None of the interviewed males claimed reproduction-related anomalies, and none agreed to undergo clinical examination or laboratory testing. Present age of 7 interviewed females of generation IV ranged between 58 and 68 years. Although documentation of hormone levels in these older females was not available, there were indications of reproduction-related anomalies in five as miscarriages and/or curettages were experienced by three and menstrual irregularities were reported by all five (Table 2). Age at menopause, defined as age at which natural menstruation ceases, was early (between 30 and 35 years) in these females. Menstrual irregularities and early menopause are consistent with POI diagnosis. Steroid treatment-induced menstruation continued for a few years, and menstruation rapidly stopped after termination of the treatment. Age at menopause in the two unaffected females of generation IV (IV-6 and IV-8) who had not been given steroid hormones were 55 and 45 years.

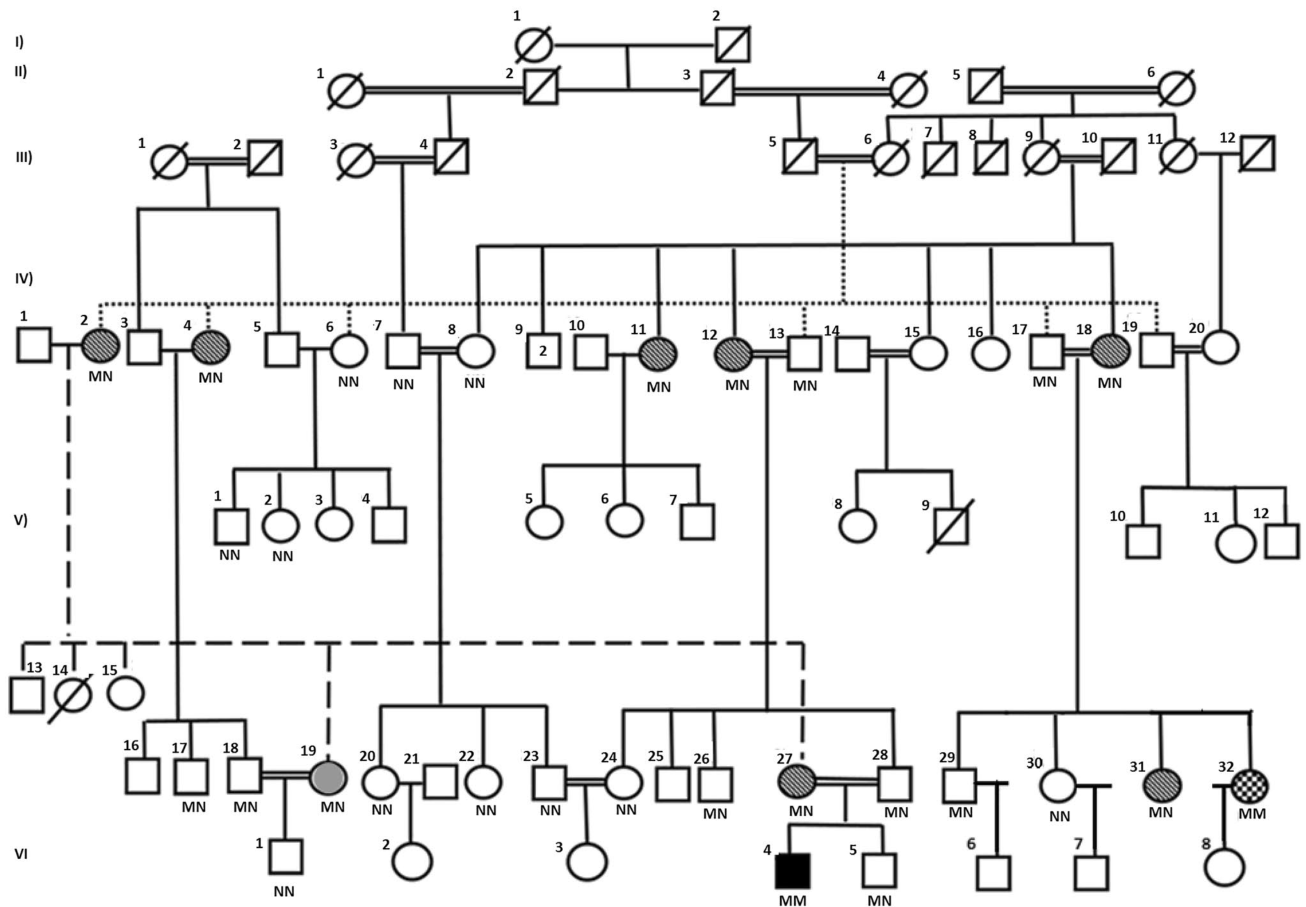


Fig. 1 Pedigree IA-105 with POI and ichthyosis-affected members. Phenotypes of individuals of generations I and II are unknown. Generations IV–VI: circle with crossed lines, POI-affected, filled circle, asymptomatic POI status likely due to young age (see "Subjects" within "Methods" section), filled square, ichthyosis-affected; circle with alternate filled and unfilled squares, POI and ichthyosis-affected, unfilled circle, unfilled square: presently clinically normal. The *ALOX12B* genotypes of individuals screened with respect to p.Arg442Gln mutation are presented: N, normal allele; M, mutant allele

Nine females of generation V were interviewed (Table 2). Their present ages range from 27 to 49 years. Three of the females, V-27, V-31, and V-32, reported having had menstruation-related problems. Individual V-27 had ceased to menstruate since the age of 32. Nevertheless, she unexpectedly became pregnant at the age of 39 years and, subsequently, gave birth to an apparently healthy child. Her hormone levels during pregnancy were normal. Spontaneous pregnancy in women with POI has often been reported and has been estimated to occur in approximately 5% of affected females (Bidet et al. 2011; Fritz 2012; Calik-Ksepka et al. 2018). Individual V-31 had normal menstruation till the age of 28 years, after which she experienced excessive bleeding. At the age of 32 years, she was diagnosed with POI. Prior to initiation of estrogen and progesterone therapy, her serum FSH and luteinizing hormone (LH) levels had reached, respectively, 73 mIU/ml and 29.3 mIU/ml and the anti-Müllerian hormone (AMH) level was decreased to < 0.2 ng/ml. V-31, who remained unmarried, stopped steroid medication after 8 years and no longer menstruates. Individual V-32, who is the ichthyosis-affected sister of V-31, similarly but yet more severely experienced bleeding from the early age of 25 and was diagnosed with POI at age of 28 years. After hormone-induced ovulation and in vitro fertilization with her husband's sperms, her embryo was implanted into the uterus of a surrogate carrier. FSH, LH, and AMH levels of V-32 prior to start of hormone treatment were, respectively, 87 mIU/ml, 19.3 mIU/ml, and < 0.1 ng/ml. Karyotyping and mutation screening of the *FMR1* gene have been performed for individuals V-27, V-31, and V-32. *FMR1* encodes fragile X mental retardation 1 protein. Chromosome abnormalities (Turner's syndrome) and premutation in *FMR1* are the most common causes of POI (Goswami and Conway 2005). Their karyotypes were normal and a premutation status in *FMR1* was not observed in the DNA of these individuals (Supplementary Fig. S1). The remaining six females of generation V (V-2, V-19, V-20,

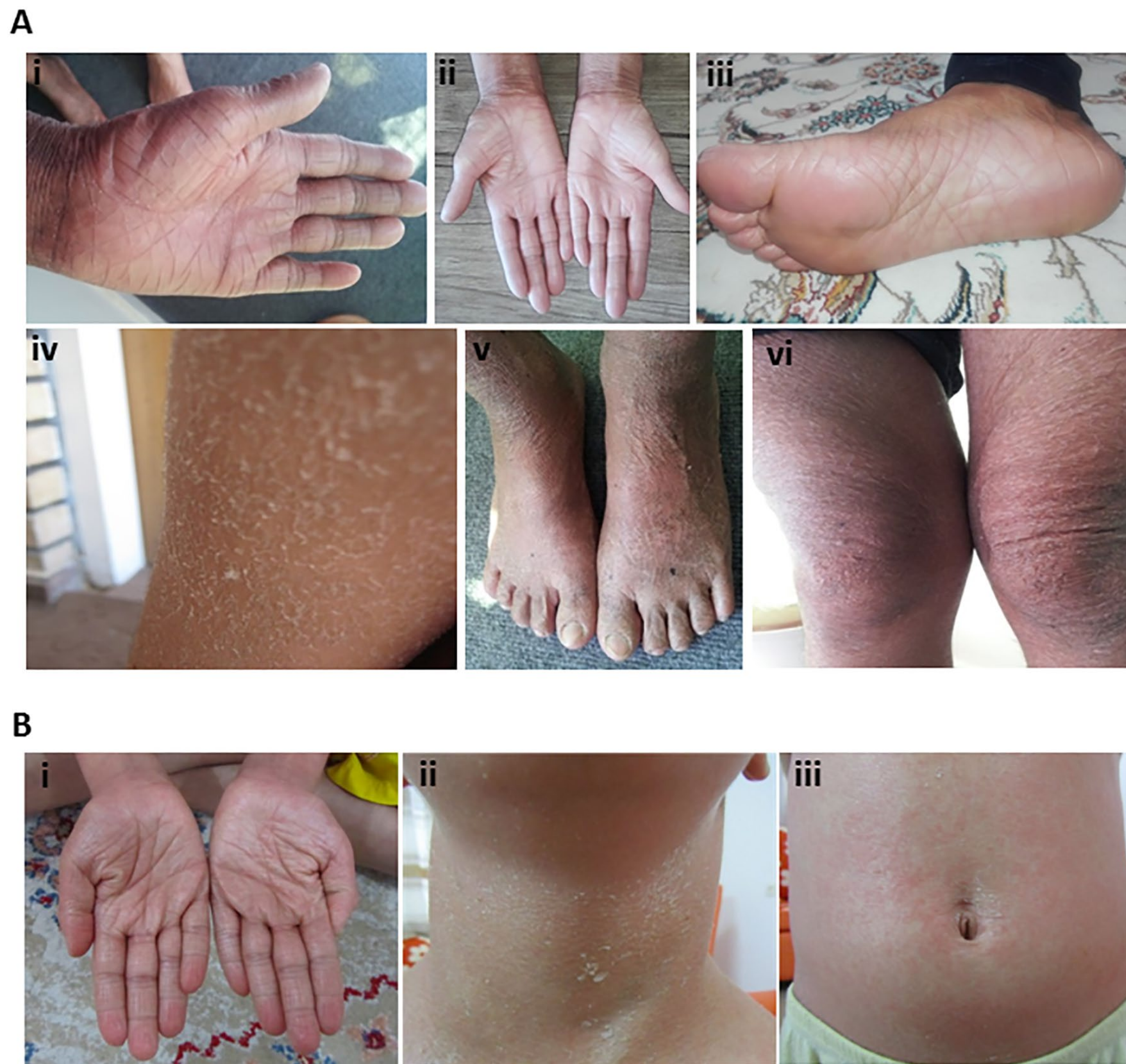


Fig. 2 Clinical manifestations in autosomal recessive congenital ichthyosis in two affected members of IA-105. A. Patient IV-32. B. Patient VI-4. Photographs show hyperlinearity in hands and feet (**a**: *i*, *ii*, *iii*; **b**: *i*), scaling (**a**: *iv*, *v*; **b**: *ii*), and erythroderma (**a**: *vi*; **b**: *iii*)

V-22, V-24, and V-30) did not report reproduction-related anomalies. Five, including the oldest (V-30, 49 years) presently menstruate normally. The somewhat high FSH level (27 mIU/ml) of individual V-30 at the age of 40 years may at least partially be due to severe stress that she was experiencing at that time due to marital problems (Schliep, Mumford et al. 2015). V-19 is a 32-year-old woman and the sixth female of generation V without reproduction problems; she is presently breast feeding and not menstruating. Two females of generation VI (VI-2 and VI-3) who are 13 and 15 years old menstruate normally. VI-8 is only 2 years old.

We considered the possibility that POI in the pedigree may have a genetic basis and may be related to presence of ichthyosis in the same pedigree.

Genetic analysis

DNA was isolated from peripheral blood cells of available pedigree members by standard protocols. Initially, genome-wide single-nucleotide polymorphisms (SNP) genotyping on two ichthyosis-affected (V-32 and VI-4) and three ichthyosis unaffected pedigree members (V-29, V-30, and V-31) was performed using the HumanCytoSNP-12v1-0_L BeadChips (www.illumina.com). These chips allow genotyping of approximately 300,000 tag SNPs distributed throughout the human genome. Call rates for SNPs on these chips are generally > 95%. Data analysis was done as earlier reported (Alavi et al. 2012; Suri et al. 2018). Briefly, homozygous regions common to the two affected individuals with a minimum physical length of 1 Mb and absent in the non-affected

Table 1 Phenotypic features of ARCI affected patients of pedigree IA-105

Patient ID	Present age (years)	Sex	Collodion baby	Scaling features	Erythroderma	Keratoderma	Yellowish keratoderma	Ectropion	Alopecia	Heat intolerance	Hyperlinearity[a]	Clubbing of nails	Photophobia	Lacrimation
V-32	35	F	+	Fine white scales/whole body	+	+	–	–	–	+	+	+	+	+
V1-4	18	M	–	Fine white scales/whole body	+	+	–	–	–	+	+	+	–	–

F female, *M* male

[a]In palms and soles

individuals were sought using the Homozygosity Detector tool within the GenomeStudio program (Illumina). The SNP chip data output was subsequently exported to Microsoft Excel software and homozygous regions were confirmed within the EXCLUDER spreadsheet. Additionally, the SNP genotyping data were used to perform a parametric linkage analysis and to obtain a logarithm of the odds (LOD) score using MERLIN under an autosomal recessive model of ichthyosis inheritance (Abecasis et al. 2001). The exons and bordering intronic sequences of candidate ichthyosis causing genes within a locus that was identified by both homozygosity mapping and linkage analysis were screened for mutations by direct DNA sequencing using the Sanger dideoxy-nucleotide termination protocol, and potential disease-causing mutations were subsequently assessed for segregation with disease status in the pedigree. The candidate ichthyosis causing mutation ultimately identified was also screened by an allele-specific PCR protocol in 300 ethnically matched control individuals. In this protocol, two PCR reactions are performed on the DNA of each individual. One primer is common to both reactions, but the second primer differs in the two reactions. The second primer in one reaction is designed to amplify only the wild-type sequence, and the second primer in the other reaction is designed to allow amplification of only the mutated sequence. The results of the two PCR reactions allow genotype assessment with respect to the candidate mutation site.

With respect to POI in IA-105, in light of potential involvement of steroid/lipid-related anomalies in both POI and ichthyosis, initially the mutation that was identified as cause of ichthyosis was screened by direct sequencing in nine POI-affected and seven POI unaffected females of the pedigree to assess possible segregation with POI status. Subsequently, genome-wide SNP genotyping was performed as described above on six additional members of IA-105 (IV-2, IV-6, IV-8, IV-12, IV-18, and V-27) who were not among the five individuals who had been earlier genotyped. In all, genotyping data on nine females, six of whom were POI-affected, became available. Homozygosity mapping was performed essentially as described above on the data pertaining to the six POI-affected individuals (IV-2, IV-12, IV-18, V-27, V-31, and V-32) to assess the possibility of recessive inheritance of POI in pedigree IA-105. A more stringent criterion was applied as shared homozygous regions with a minimum physical length of 0.5 Mb were sought. Subsequently, parametric linkage analysis for POI that included the SNP genotyping data of all 11 IA-105 members was performed using Merlin under an autosomal dominant model. Finally, whole-exome sequencing (WES) was performed on the DNA of two (IV-18 and V-31) POI-affected members of the pedigree, neither of whom was affected with ichthyosis. Exons were enriched using the SureSelect V6-Post kit and sequencing

Table 2 Clinical and genetic data on females of pedigree IA-105

Individual ID	*ALOX12B* genotype*	*SPNS2* genotype**	Present age (years)	Age at last pregnancy (years)	Age (years) at menarche	Age (years) at menopause#	Menstrual disorders (%)	Comments	Estrogen replacement therapy (at ages)	Histerectomy (age)	Hormone measurements					
											FSH (mIU/ml)	LH (mIU/ml)	Estradiole (pg/ml)	AMH ng/ml	POI diagnosis (%)	Ichthyosis diagnosis (%)
IV-2	NM	NM	68	36	13	30	+	2 miscarriages; 2 curettages due to heavy bleeding	Yes (30–47 years)	No	9.4	3.8			+	
IV-4	NM	NM	61	28	13	35	+	2 miscarriages	Yes (35–47 years)	No					+	
IV-6	NN	NN	63	35	14	55			No	No						
IV-8	NN	NN	63	36	13	45			No	No						
IV-11	NM	NM	58	26	14	30	+	Heavy bleeding since age of 30 years	Yes (30–40 years)	No					+	
IV-12	NM	NM	66	33	13	31	+	Heavy bleeding since age of 30 years	Yes (31–41 years)	Yes (41 years)					+	
IV-18	NM	NM	68	33	13	32	+	7 curettages; heavy bleeding since age of 30 years	Yes (32–41 years)	Yes (41 years)					+	
V-2	NN	NN	39	36	13				No	No						
V-19	NM	NM	32	29	12		+	Became pregnant immediately upon receipt of genotyping data; presently breast feeding	No	No					X	
V-20	NN	NN	42	25	12				No	No	9.3$^{\Delta}$	3.7$^{\Delta}$				
V-22	NN	NN	27		11				No	No						
V-24	NN	NN	40	25	11				No	No						

Table 2 (continued)

Individual ID	*ALOX12B* genotype*	*SPNS2 genotype***	Present age (years)	Age at last pregnancy (years)	Age (years) at menarche	Age (years) at menopause#	Menstrual disorders (%)	Comments	Estrogen replacement therapy (at ages)	Histerectomy (age)	Hormone measurements				POI diagnosis (%)	Ichthyosis diagnosis (%)
											FSH (mIU/ml)	LH (mIU/ml)	Estradiole (pg/ml)	AMH ng/ml		
V-27	NM	NM	40		14	32	+	Had ceased to menstruate since age of 32 years; became spontaneously pregnant at age of 39 years	No	No	6.1^	3.2^	0.8^		+	
V-30	NN	NN	49	30	11				No	No	27[&]	6.5[&]		2[&]		
V-31	NM	NM	45		14	32	+	Heavy bleeding since age of 28 years	Yes (32–40 years)	No	73[@]	29.3[@]	31[@]	< 0.2[@]	+	
V-32	MM	NM	35	31	12	28	+	Heavy bleeding since age of 25 years	Yes (32-present)	No	87[@]	19.3[@]		< 0.1[@]	+	+

X see discussion on status of V-19 in "Results" section, *N* wild-type allele, *M* mutated allele, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *AMH* anti-Müllerian hormone

*Genotype of p.Arg442Gln-causing mutation in *ALOX12B*

**Genotype of p.Thr226Met causing mutation in *SPNS2*

^Measurements during recent pregnancy

[#]Reported for those who have reached menapause;

[$]Blanks indicate measurements not available

[Δ]At age of 41 years

[&]At age of 40 years

[@]Measurements at ages of 32 years. (V-31) and 29 (V-32) before start of hormone treatment

[%]Indicated (+) only when the disorder or disease has been diagnosed

was done using the Illumina HiSeq 4000 system (Illumina). Sequence alignment was performed against human reference genome GRCH37/hg19, and variant callings were done using ENSEMBL Variant Effect Predictor (https://asia.ensembl.org/Tools/VEP) and wANNOVAR (https://wannovar.wglab.org/). Initial filtering was done by removing sequence variations with a MAF of > 0.01 in the dbSNP database and the Trans-Omics for Precision Medicine program (https://www.ncbi.nlm.nih.gov/), the 1000 Genomes database (www.1000genomes.org), the NHLBI Exome Sequencing Project (https://evs.gs.washington.edu/EVS/), the Exome Aggregation Consortium database (https://exac.broadinstitute.org/), the Genome Aggregation Database (https://genomad.inbroadinstitute.org/), or Iranome database (https://iranome.com/). Variations that did not affect amino acid change or splicing were also filtered out. Among the remaining variations, those that were present in the DNA of both POI-affected individuals IV-18 and V-31 and also positioned within the locus identified by linkage analysis were considered candidate POI-causing mutations in IA-105. Sequence variations outside the locus, but within previously reported POI genes were also identified. Candidate disease-causing variations within the linked locus and within previously identified POI-causing genes were screened for segregation with disease status by direct sequencing. Multiple in silico bioinformatics tools, including SIFT (https://sift.jcvi.org/) and PolyPhen-2 (https://genetics.bwh.harvard.edu/pph2/) that are most commonly used, were employed to predict the functional consequences of segregating sequence variations that caused amino acid changes. These tools are largely based on sequence homology and physical properties of amino acids. The Combined Annotation-Dependent Depletion tool (CADD; https://cadd.gs.washington.edu/info) scores the deleteriousness of mutations based on over 63 distinct annotations.

Table 3 summarizes the genetic analyses performed on different individuals of pedigree IA-105. Sequence of primers used in various PCR amplifications or sequencing reactions are available upon request.

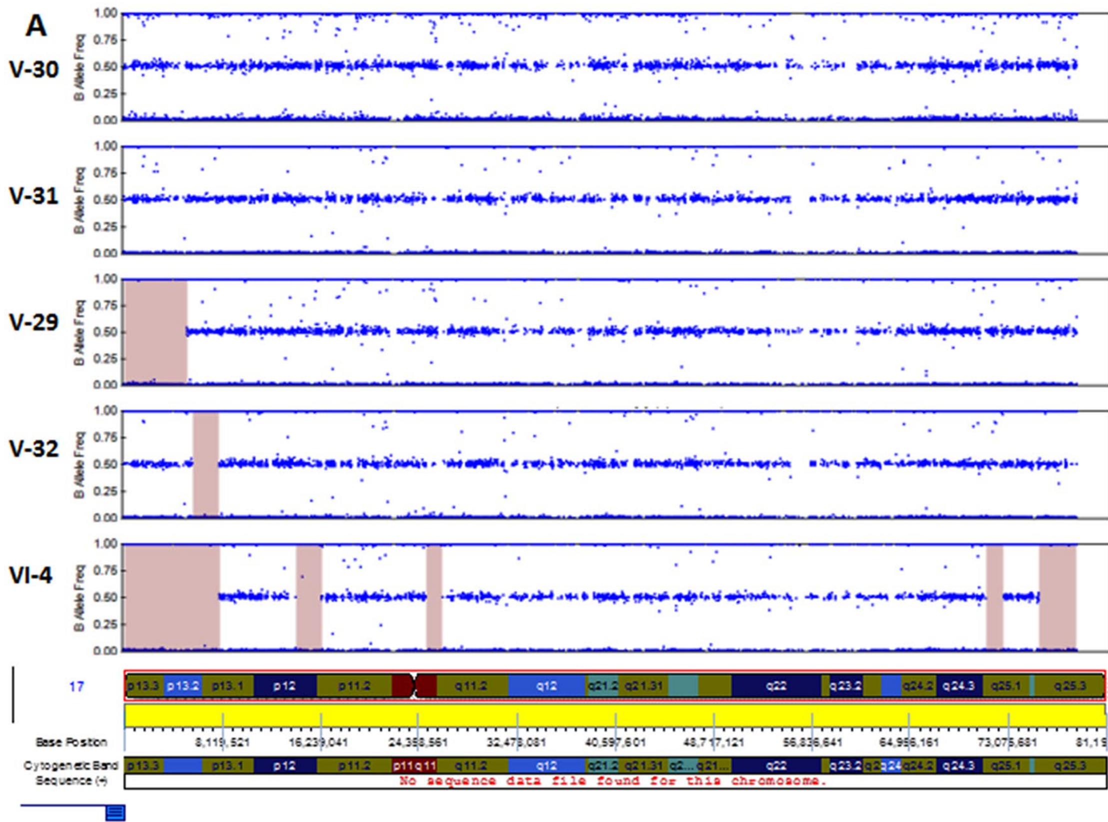
Fig. 3 Localization of ichthyosis causing gene by SNP genotyping to chromosome locus 17p13.1 in pedigree IA-105. **a** Homozygosity mapping shows that the two ichthyosis-affected individuals (bottom two samples) are homozygous (homozygosity shown as bookmarks) in the region bordered by rs888327 (5,778,528 bp) and rs9892725 (7,987,516 bp) on chromosome 17. The three unaffected individuals (top three samples) are not homozygous in this region. Similarly, only the ichthyosis-affected individuals were homozygous for two other loci on chromosomes 2q24.2 and 16q23 (not shown; see text). **b** LOD plot of locus on chromosome 17p13.1 pertaining to ichthyosis obtained under recessive model based on genotypes of two affected and three unaffected pedigree members

Results

The Homozygosity Detector tool of the GenomeStudio program identified three genomic regions that were homozygous in both ichthyosis-affected individuals of pedigree IA-105, but not homozygous in any of the three unaffected individuals genotyped (Fig. 3a). The homozygous regions were on chromosomes 2q24.2 [~4,3 Mb delimited by markers rs6756623 (158,574,077) and rs2909450 (162,867,791)], 16q23 [~4,2 Mb delimited by markers rs1983093 (79,024,344) and rs10514587 (83,256,377)], and 17p13.1 [~2.2 Mb delimited by markers, rs888327 (5,778,528) and rs9892725 (7,987,516)]. The loci with the maximum LOD scores (~3.0) identified by linkage analysis overlapped with regions identified by homozygosity mapping (Fig. 3b). The locus on chromosome 17p13.1 was considered the best candidate locus, because it included the previously identified ARCI-associated gene *ALOX12B* (7,975,954–7,991,021 bp; NC_000017, NM_001139; NP_001130) (Jobard et al. 2002). *ALOXE3*, another ARCI-associated gene (7,999,218–8,022,365 bp; NC_000017.10, NM_001165960.1; NP_001159432.1), was positioned adjacent to this locus (Jobard et al. 2002). The loci on chromosomes 2 and 16 did not include known ichthyosis causing genes. Screening of the exons and bordering intronic sequences of *ALOX12B* and *ALOXE3* by sequencing identified c.G1325A in *ALOX12B* that causes p.Arg442Gln as the candidate ichthyosis causing mutation (Table 4). It was observed in the homozygous state in both

Table 3 Summary of genetic analyses on members of pedigree IA-105

Genotyping of c.1325 G > A in *ALOX12B* by Sanger sequencing	Whole genome SNP genotyping for homozygosity mapping and linkage analysis for ichthyosis	Whole genome SNP genotyping for homozygosity mapping and linkage analysis for POI	Whole exome sequencing
IV2, IV-4, IV-6, IV-7, IV-8, IV-11, IV-12, IV-13, IV-17, IV-18, V-1, V-2, V-17, V-18, V-19, V-20, V-22, V-23, V-24, V-26, V-27, V-28, V-29, V-30, V-31, V-32, VI-4, VI-5	V-29, V-30, V-31, V-32, VI-4	IV-2, IV-6, IV-8, IV-12, IV-18, V-27, V-29, V-30, V-31, V-32, VI-4	IV-18, V-31


A
V-30
V-31
V-29
V-32
VI-4
B Allele Freq
1.00
0.75
0.50
0.25
0.00
17
Base Position
Cytogenetic Band
Sequence (+)
No sequence data file found for this chromosome.

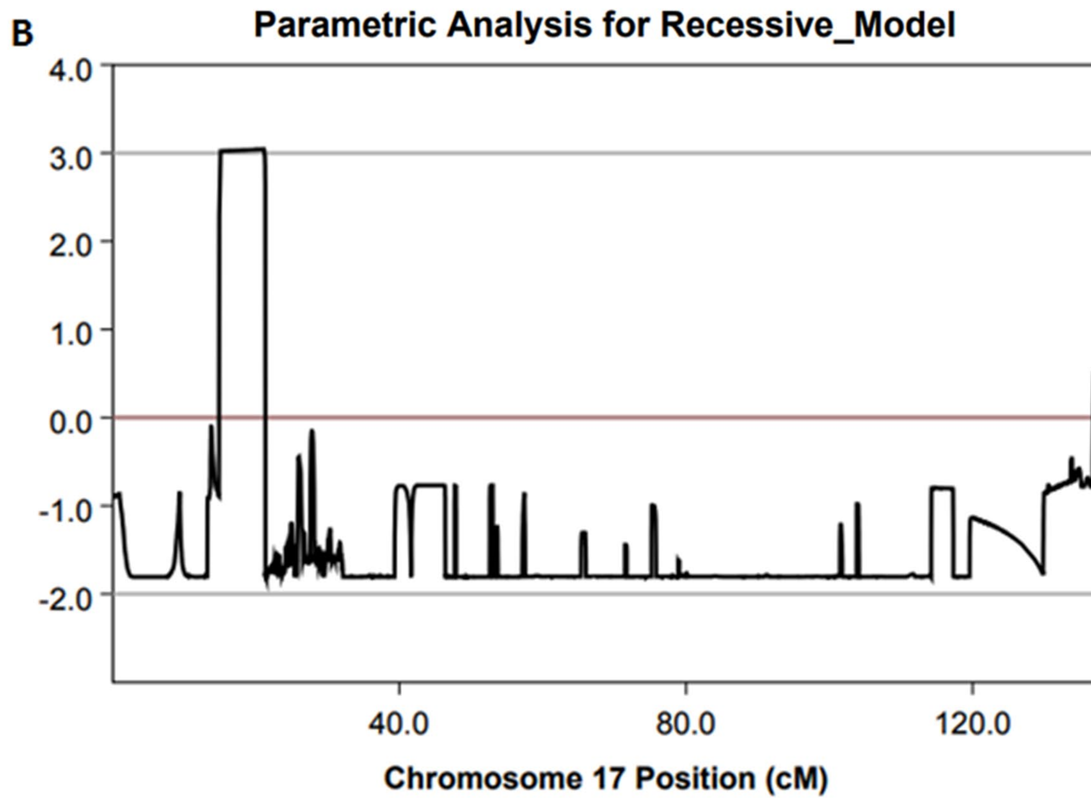

B
Parametric Analysis for Recessive_Model
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
40.0
80.0
120.0
Chromosome 17 Position (cM)

Table 4 Genotypes pertaining to c.G1325A in *ALOX12B* that causes p.Arg442Gln in members of IA-105 pedigree

Individual	*ALOX12B*	Ichthyosis	POI
ID	Genotype	Status	Status
V32	MM	+	+
VI-4	MM	+	Male
IV	MN	−	+
IV-4	MN	−	+
IV-6	NN	−	−
IV-8	NN	−	−
IV-11	MN	−	+
IV-12	MN	−	+
IV-18	MN	−	+
V-2	NN	−	−
V-19	MN	−	+
V-20	NN	−	−
V-22	NN	−	−
V-24	NN	−	−
V-27	MN	−	+
V-30	NN	−	−

N normal allele, *M* mutant allele

+ affected, − not affected

affected individuals. Subsequent segregation analysis in 14 additional available members of the pedigree showed that only the ichthyosis-affected individuals carried the mutation in the homozygous state, thus confirming segregation with ichthyosis status (Fig. 1 and Table 4). The variation was not observed in the DNA of 300 control individuals. Arginine at position 442 in the human 12(R)-lipoxygenase protein encoded by *ALOX12B* is evolutionarily well conserved among various human lipoxygenases and also among 12(R)-lipoxygenases of various species (Table 5). Finally, the same p.Arg442Gln-causing variation was earlier reported as one of two mutations in *ALOX12B* in a Japanese ichthyosis-affected individual (Akiyama et al. 2010). These findings evidence that c.G1325A in *ALOX12B* in the homozygous state is cause of ichthyosis in affected members of IA-105, and that nonbullous congenital ichthyosiform erythroderma (NCIE) is the form of ichthyosis that presents in the pedigree (Jobard et al. 2002).

With respect to POI, sequencing revealed that the c.G1325A mutation in *ALOX12B*, which in the homozygous state had been identified as cause of ichthyosis, was present in the heterozygous state in all five POI designated females of generation IV (IV-2, IV-4, IV-11, IV-12, and IV-18) of pedigree IA-105 (Fig. 1, Table 4). Two females (IV-6 and IV-8) of this generation who were not POI-affected did not carry the mutated allele. In generation V, POI designated individuals V-27 and V-31 were heterozygous carriers of the mutation, and V-32, who is ichthyosis and POI-affected, was homozygous for the mutation. Of six females of generation V who did not report reproduction-related anomalies, five (V-2, V-20, V-22, V-24, and V-30) were homozygous for the wild-type sequence, but one (V-19) was a heterozygous carrier. The latter was 28 years old when our results on

Table 5 Conservation during evolutionary of arginine at positions corresponding to amino acid 442 of ALOX12B in orthologous protein of various species and in various human lipoxygenases

ALOX12B of different species				Sequence ID[a]	Human ALOX family members				Sequence ID[a]
HUMAN	RYTVQINSIG	**R**	AVLLNEGG	O75342	ALOX12B	RYTVQINSIG	**R**	AVLLNEGGL	O75342
CHIMPANZEE	RYTVQINSIG	**R**	AVLLNEGG	H2QC68	ALOXE3	RYTLQVNTIA	**R**	ATLLNPEGL	Q9BYJ1
MACACA MULATTA	RYTVQINSIG	**R**	AVLLNEGG	F6WGW5	ALOX15	RYTLEINVRA	**R**	TGLVSDMGI	P16050
BABOON	RYTVQINSIG	**R**	AVLLNEGG	A0A096P2T3	ALOX5	RFTIAINTKA	**R**	EQLICECGL	P09917
GIANT PANDA	RYTIQINSIG	**R**	ALLLNEGG	G1L7R9					
BOVIN	RYTIQINSIG	**R**	AVLLNEGG	F1MXD8					
HORSE	RYTIQINSIG	**R**	ALLLNEGG	F6PXL3					
SHEEP	RYTIQINSIG	**R**	AVLLNEGG	W5QBJ9					
PIG	RYTIQINSIG	**R**	AILLNEGG	F1SSY8					
Dog	RYTIQINSIG	**R**	ALLLNEGG	E2RS35					
CAT	RYTIQINSIG	**R**	ALLLNEGG	M3WM43					
RABIT	RYTVQINSIG	**R**	ALLLNEGG	G1TMI8					
MOUSE	RYNVQINSIG	**R**	ALLLNKGG	O70582					
RAT	RYNVQINSIG	**R**	ALLLNKGG	Q2KMM4					
OPOSSUM	RFTIQINSIG	**R**	ALLLNEGG	F7FZA5					
BAT	RYTIQINSIG	**R**	AILLNEGG	G1PAF4					
XENOPUS LAEVIS	RYTLEINTLA	R	QTLIGPDG	Q5FWK8					

[a]Sequence IDs from UniProt (https://www.uniprot.org/)

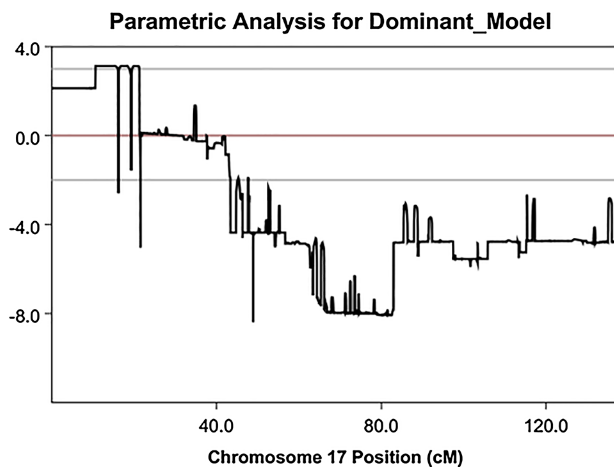


Fig. 4 Localization of POI-causing gene by SNP genotyping to chromosome locus 17p13.1 in pedigree IA-105. LOD plot pertaining to POI obtained under dominant model based on genotypes of 11 pedigree members

ALOX12B sequencing in pedigree IA-105 became available; she was the youngest female of generation V who was found to carry a mutated allele. She was informed of her genotype, and given the potential association being observed between the c.G1325A mutation and POI, quickly became pregnant to avoid potential onset of problems. She is now breast feeding and not menstruating. All generation V females with a normal genotype presently have normal menstruation. The three females of generation VI were not genotyped.

The findings described above show segregation of the p.Arg442Gln-causing mutation in *ALOX12B* with POI status among 16 females of pedigree AI-105. Despite segregation in this large number of individuals, the possibility of POI being associated with mutations in other genes was considered. Additional whole-genome SNP genotypings were performed and ultimately data on 11 IA-105 members became available. Call rates for the SNPs for the individuals were reported to range between 0.969 and 0.998, signifying high-quality genotyping (Table S2). Initial analysis of the data pertaining to six POI-affected individuals by homozygosity mapping confirmed that POI inheritance in AI-105 is not recessive; a shared homozygous region of ≥ 0.5 Mb among these individuals was not found (Table S3). Linkage analysis using the data pertaining to all 11 individuals under a dominant inheritance model showed a maximum LOD score (3.1) associated with a region on chromosome 17p13.1 that includes *ALOX12B*; 1.5 was the maximum LOD score associated with any region elsewhere in the genome (Fig. 4, Fig. S2). The linked region expanded approximately 4.2 Mb delimited by proximal and distal markers, respectively, rs1516801 (3,822,278 bp) and rs2304906 (7,983,681 bp). This result is consistent with the proposal that the POI-causing mutation is positioned within 17p13.1.

Exome sequencing on the genome of two POI-affected individuals (IV-18 and V-31) was done to ascertain whether the c.G1325A in *ALOX12B* is the only candidate causative mutation within the POI linked locus. The specifications of the exome data reflect high-quality sequencing; 95.3 or 94.6% of target sequences had coverage of more than 10X, and 90.6 or 86.7% had coverage of more than 20X (Table S4). The filtering protocol applied identified 331 sequence variations common to the two individuals (Table S5). Two of these, c.G1325A in *ALOX12B* and c.C677T in *SPNS2* that causes p.Thr226Met, were positioned within the linked locus on chromosome 17. *SPNS2* encodes sphingosine-1-phosphate transporter SPNS2. The *ALOX12B* and *SPNS2* variations are separated by approximately 3.5 Mb. The variation (rs202089427) in *SPNS2* has previously been reported at low frequencies (≤ 0.001) in various databases. Screening of the *SPNS2* variation among females of IA-105 showed that, like the *ALOX12B* mutation, it segregated with POI status; all nine affected individuals carried the mutation and six unaffected individuals were homozygous for the wild-type allele. Nevertheless, while acknowledging that the contribution of the *SPNS2* variation was not critically ruled out, the variation in *ALOX12B* was favored as the more likely POI-associated mutation. The *SPNS2* variation was assessed as non-damaging by nine of eleven predictor softwares (CAAD score = 24.9), whereas ten of the softwares assessed that the *ALOX12B* variation is damaging (CAAD score = 33.0) (Table 6). More importantly, functions attributed to the protein encoded by *ALOX12B* (see "Discussion") strongly support its potential contribution to POI etiology.

The exome sequence data allowed interrogation of possible contribution of known POI-causing genes to POI status in affected females of IA-105. Indeed, sequence variations in two POI genes, *MCM9* (NM_017696) encoding minichromosome maintenance complex component 9 (c.A2448C that causes p.Glu816Asp; rs116048760) and *EIF4ENIF1* (NM_019843) that encodes a translational factor (c.C1612T that causes p.Pro363Ser; rs142530811) were observed in the DNA of both individuals. Both mutations were present in the heterozygous state. Homozygous *MCM9* mutations have been reported in a few POI families and heterozygous carriers were reported to be unaffected (Wood-Trageser et al. 2014; Fauchereau et al. 2016; Yatsenko and Rajkovic 2019). Direct sequencing evidenced that the *MCM9* mutation did not segregate with POI status in IA-105; POI unaffected individual IV-8 carried the mutation and affected individuals IV-4 and IV-12 were homozygous for the wild-type allele (Table S6). Similarly, the sequence variation in *EIF4ENIF1* did not segregate as unaffected individual V-30 carried the mutated allele and affected individual IV-4 was homozygous for the wild-type allele (Table S6).

Table 6 Bioinformatics-based predictions by various softwares on functional effects of ALOX12B and SPNS2 variations observed in the IA-105 pedigree

Variation	Prediction tool											
	SIFT	Polyphen 2		LRT	Mutation taster	Mutation assessor	FATHMM	PROVEAN	Meta SVM	MetaLR	M-CAP	CADD
		HDIV	HVAR									
p.Arg442Gln in ALOX12B	D	D	D	D	D	M	D	D	D	D	D	33
p.Thr226Met in SPNS2	T	B	B	N	D	N	T	N	T	T	D	24.9

All predictions were reported by wANNOVAR (https://wannovar.wglab.org/index.php)

D damaging, *M* medium, *T* tolerated, *B* benign, *N* neutral

Based on the composite results of the various analyses, it was surmised that the c.G1325A mutation in *ALOX12B* likely makes a significant contribution to POI status in affected members of pedigree IA-105. Throughout the analysis presented, it has been presumed that the genetic cause of POI is the same in the nine affected members of IA-105. This sort of assumption is common and usually justified in genetic studies on pedigrees. Nevertheless, it is possible that sequence variations in other genes present in some of the POI individuals may also contribute to POI presentations in those individuals.

Discussion

The data presented suggest that the same p.Arg442Gln-causing mutation in *ALOX12B* may be cause of both ichthyosis and POI in pedigree IA-105. Whereas the mutation clearly causes the NCIE form of ichthyosis in the homozygous state, it causes POI in a dominant fashion (Jobard et al. 2002).The contribution of *ALOX12B* to POI in the pedigree was assessed by extensive genetic analysis on a large number of affected females that included mutation screening, linkage analysis, and exome sequencing. 12R-LOX is involved in arachidonic acid metabolism and catalyzes conversion of arachidonic acid to 12(R)-hydroxyeicosatetraenoic acid (Krieg and Fürstenberger 2014). With respect to ichthyosis, it is to be noted that 12R-LOX is involved in the processing of ω-hydroxyceramides that are essential components of water sealing lipid structures in the stratum corneum (Krieg and Fürstenberger 2014). With respect to POI, steroid hormones including progesterone, estrogen, and testosterone are present in the extended metabolic pathway that includes *ALOX12B* and arachidonic acid (Krieg and Fürstenberger 2014). Furthermore, as arachidonic acid affects *STAR* gene and protein expression, *ALOX12B* indirectly affects StAR activity; StAR is involved in the early and rate-limiting stages of steroid synthesis (Cooke et al. 1991; Romanelli et al. 1995; Wang et al. 2000,2003; Stocco et al. 2005). It is interesting that the skin which is the target of ichthyosis is now considered an organ capable steroidogenesis (Nikolakis et al. 2016). It has been shown that *STAR* and other genes of steroidogenesis pathways are expressed in keratinocytes (Gingras et al. 2003; Inoue et al. 2012; Anuka et al. 2013). It is intriguing to consider the possibility that defects in hormone synthesis by the skin caused by an *ALOX12B* mutation may contribute to POI anomalies (Feingold and Elias 1988; Paus 2016).

In addition to biochemical and physiologic considerations, existing genetic data also support the possibility that *ALOX12B* mutations may have roles in POI. Association between SNP markers within *ALOX12* and age

at menopause that has been reported in two studies suggests that lipoxygenase activities affect menopause (Liu et al. 2010; Xiao et al. 2012). *ALOX12* is a member of the lipoxygenase family of genes and the catalytic activity of its encoded protein is the same as 12R-LOX except that the products are enantiomers. Finally, *ALOX12B* was among differentially expressed genes identified in a recent comparison of the transcriptome of healthy and atretic bovine follicles (Hatzirodos et al. 2014). To the best of our knowledge, data on *ALOX12B* expression in human embryonic stages are not available. However, several databases report its expression at the RNA level in various reproduction-related tissues including the cervix, vagina, ovary, uterus, breast, prostate, and testes (https://www.proteinatlas.org/ENSG00000179477-ALOX12B/tissue; https://www.genecards.org/cgi-bin/carddisp.pl?gene=ALOX12B#expression; https://genecards.weizmann.ac.il/v3/cgi-bin/carddisp.pl?gene=ALOX12B#protein_expression).

The substantial information in the literature described above lends support to proposed existence of a role for *ALOX12B* in POI. For further substantiation and also for quantitative assessment of contribution of *ALOX12B* mutations to POI etiology, mutation screenings of the gene or exome sequencing of POI cohorts need to be performed. POI in NCIE pedigrees whose ichthyosis status is known to be caused by mutations in *ALOX12B* should also be critically assessed. POI incidence and inheritance in such pedigrees may be overlooked unless intentionally investigated. Parents of ichthyosis diagnosed offspring concentrate on and are most attentive to the severe disease of their offspring, and they may even wish to avoid additional pregnancies. In addition to this, it is to be noted that POI presentations in affected members of IA-105 were not severe as evidenced by fertility in the majority of its affected females. It may be that *ALOX12B* mutations generally promote mild POI. Finally, it is of important that the functional consequences of *ALOX12B* mutations be assessed in molecular and cellular studies and also in animal models.

Acknowledgements We would like to thank the patients and their family members for participating in the study, and we acknowledge the Iran National Science Foundation (INSF) and Iran's National Elites Foundation for funding the research. We also acknowledge Dr. PauliinaDamdimopoulou (Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden) and Dr. JuhaKere (Department of Biosciences and Nutrition, Karolinska Institute and Center for Innovative Medicine, Stockholm, Sweden and Department of Medical Genetics, Haartman Institute and Research Programs Unit, Molecular Neurology, University of Helsinki, Helsinki, Finland) for discussions and for making possible for FD a tenure focused on reproductive biology at Karolinska Institute and for supervising her during the tenure.

Author contributions AA: analysis of homozygosity mapping, SNP linkage, and exome sequencing data, mutation screening of *ALOX12B* in ichthyosis proband, *ALOX12B* segregation analysis pertaining to ichthyosis, contribution to design of research and writing of manuscript; FD: *ALOX12B* segregation analysis pertaining to POI, extensive literature search on *ALOX12B*; MMRB: *SPNS2* segregation analysis pertaining to POI, DZA: karyotyping; AM: POI diagnosis; MMS: ichthyosis diagnosis; JF: mutation screening of *ALOX12B* and *ALOXE3* in ichthyosis proband; EE: designed and supervised the research and wrote the manuscript.

Funding This study was funded by the Iran National Science Foundation (INSF) (Grant No. 96008134) and by Iran's National Elites Foundation.

Compliance with ethical standards

Conflict of interest Afagh Alavi, Faezeh Darki, Mohammad Masoud Rahimi Bidgoli, Davood Zare-Abdollahi, Ashraf Moini, Mostafa M Shahshahani, Judith Fischer, and Elahe Elahi declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human and animal participants This research was performed with compliance with ethical standards. All procedures that involved human participants were performed in accordance with the ethical standards of the research committee of the University of Tehran and with compliance to the 1964 Helsinki declaration and its later amendments.

References

Abecasis GR, Cherny SS, Cookson WO, Cardon LR (2001) Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. Nat Genet 30(1):97

Akiyama M, Sakai K, Yanagi T, Tabata N, Yamada M, Shimizu H (2010) Partially disturbed lamellar granule secretion in mild congenital ichthyosiform erythroderma with ALOX12B mutations. Br J Dermatol 163(1):201–204

AlAsiri S, Basit S, Wood-Trageser MA, Yatsenko SA, Jeffries EP, Surti U, Ketterer DM, Afzal S, Ramzan K, Faiyaz-Ul Haque M, Jiang H, Trakselis MA, Rajkovic A (2015) Exome sequencing reveals MCM8 mutation underlies ovarian failure and chromosomal instability. J Clin Investig 125(1):258–262. https://doi.org/10.1172/JCI78473

Alavi A, Shahshahani MM, Klotzle B, Fan JB, Ronaghi M, Elahi E (2012) Manifestation of diffuse yellowish keratoderma on the palms and soles in autosomal recessive congenital ichthyosis patients may be indicative of mutations in NIPAL4. J Dermatol 39(4):375–381

Anuka E, Gal M, Stocco DM, Orly J (2013) Expression and roles of steroidogenic acute regulatory (StAR) protein in 'non-classical', extra-adrenal and extra-gonadal cells and tissues. Mol Cell Endocrinol 371(1–2):47–61

Bidet M, Bachelot A, Bissauge E, Golmard JL, Gricourt S, Dulon J, Coussieu C, Badachi Y, Touraine P (2011) Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. J Clin Endocrinol Metab 96(12):3864–3872

Bose HS, Pescovitz OH, Miller WL (1997) Spontaneous feminization in a 46, XX female patient with congenital lipoid adrenal hyperplasia due to a homozygous frameshift mutation in the steroidogenic acute regulatory protein. J Clin Endocrinol Metab 82(5):1511–1515

Calik-Ksepka A, Grymowicz M, Bronkiewicz W, Urban A, Mierzejewski K, Rudnicka E, Smolarczyk R (2018) Spontaneous pregnancy in a patient with premature ovarian insufficiency: case report. Prz Menopauzalny 17(3):139–140
Chapman C, Cree L, Shelling AN (2015) The genetics of premature ovarian failure: current perspectives. Int J Women's Health 7:799
Conte FA, Grumbach MM, Ito Y, Fisher CR, Simpson ER (1994) A syndrome of female pseudohermaphrodism, hypergonadotropic hypogonadism, and multicystic ovaries associated with missense mutations in the gene encoding aromatase (P450arom). J Clin Endocrinol Metab 78(6):1287–1292
Cooke B, Dirami G, Chaudry L, Choi MS, Abayasekara DR, Phipp L (1991) Release of arachidonic acid and the effects of corticosteroids on steroidogenesis in rat testis Leydig cells. J Steroid Biochem Mol Biol 40(1–3):465–471
Coulam CB, Adamson SC, Annegers JF (1986) Incidence of premature ovarian failure. Obstet Gynecol 67(4):604–606
de Vries L, Behar DM, Smirin-Yosef P, Lagovsky I, Tzur S, Basel-Vanagaite L (2014) Exome sequencing reveals SYCE1 mutation associated with autosomal recessive primary ovarian insufficiency. J Clin Endocrinol Metab 99(10):E2129–E2132. https://doi.org/10.1210/jc.2014-1268
Eckl KM, Krieg P, Küster W, Traupe H, André F, Wittstruck N, Fürstenberger G, Hennies HC (2005) Mutation spectrum and functional analysis of epidermis-type lipoxygenases in patients with autosomal recessive congenital ichthyosis. Hum Mutat 26(4):351–361
Fauchereau F, Shalev S, Chervinsky E, Beck-Fruchter R, Legois B, Fellous M, Caburet S, Veitia RA (2016) A non-sense MCM9 mutation in a familial case of primary ovarian insufficiency. Clin Genet 89(5):603–607
Feingold KR, Elias PM (1988) Endocrine-skin interactions: Cutaneous manifestations of adrenal disease, pheochromocytomas, carcinoid syndrome, sex hormone excess and deficiency, polyglandular autoimmune syndromes, multiple endocrine neoplasia syndromes, and other miscellaneous disorders. J Am Acad Dermatol 19(1):1–20
Fritz MA, Speroff L (2012) Clinical gynecologic endocrinology and infertility. Lippincott Williams & Wilkins, Philadelphia
Gingras S, Turgeon C, Brochu N, Soucy P, Labrie F, Simard J (2003) Characterization and modulation of sex steroid metabolizing activity in normal human keratinocytes in primary culture and HaCaT cells. J Steroid Biochem Mol Biol 87(2–3):167–179
Goswami D, Conway GS (2005) Premature ovarian failure. Hum Reprod Update 11(4):391–410
Goswami D, Conway GS (2007) Premature ovarian failure. Horm Res 68(4):196–202
Hatzirodos N, Hummitzsch K, Irving-Rodgers HF, Harland ML, Morris SE, Rodgers RJ (2014) Transcriptome profiling of granulosa cells from bovine ovarian follicles during atresia. BMC Genom 15(1):40
Hernández-Martín A, Garcia-Doval I, Aranegui B, de Unamuno P, Rodríguez-Pazos L, González-Enseñat MA, Vicente A, Martín-Santiago A, Garcia-Bravo B, Feito M, Baselga E, Círia S, de Lucas R, Ginarte M, González-Sarmiento R, Torrelo A (2012) Prevalence of autosomal recessive congenital ichthyosis: a population-based study using the capture-recapture method in Spain. J Am Acad Dermatol 67(2):240–244
Huhtaniemi I, Hovatta O, La Marca A, Livera G, Monniaux D, Persani L, Heddar A, Jarzabek K, Laisk-Podar T, Salumets A, Tapanainen JS, Veitia RA, Visser JA, Wieacker P, Wolczynski S, Misrahi M (2018) Advances in the molecular pathophysiology, genetics, and treatment of primary ovarian insufficiency. Trends Endocrinol Metab 29(6):400–419
Inoue T, Miki Y, Abe K, Hatori M, Hosaka M, Kariya Y, Kakuo S, Fujimura T, Hachiya A, Honma S, Aiba S, Sasano H (2012) Sex steroid synthesis in human skin in situ: the roles of aromatase and steroidogenic acute regulatory protein in the homeostasis of human skin. Mol Cell Endocrinol 362(1–2):19–28
Jiao X, Ke H, Qin Y, Chen ZJ (2018) Molecular genetics of premature ovarian insufficiency. Trends Endocrinol Metab 29(11):795–807
Jobard F, Lefèvre C, Karaduman A, Blanchet-Bardon C, Emre S, Weissenbach J, Ozgüc M, Lathrop M, Prud'homme JF, Fischer J (2002) Lipoxygenase-3 (ALOXE3) and 12 (R)-lipoxygenase (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13 1. Hum Mol Genet 11(1):107–113
Klar J, Schweiger M, Zimmerman R, Zechner R, Li H, Törmä H, Vahlquist A, Bouadjar B, Dahl N, Fischer J (2009) Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome. Am J Hum Genet 85(2):248–253
Krieg P, Fürstenberger G (1841) (2014) The role of lipoxygenases in epidermis. Biochem Biophys Acta 3:390–400
Liu P, Lu Y, Recker RR, Deng HW, Dvornyk V (2010) ALOX12 gene is associated with the onset of natural menopause in white women. Menopause (New York, NY) 17(1):152
Miura K, Yasuda K, Yanase T, Yamakita N, Sasano H, Nawata H, Inoue M, Fukaya T, Shizuta Y (1996) Mutation of cytochrome P-45017 alpha gene (CYP17) in a Japanese patient previously reported as having glucocorticoid-responsive hyperaldosteronism: with a review of Japanese patients with mutations of CYP17. J Clin Endocrinol Metab 81(10):3797–3801
Nikolakis G, Stratakis CA, Kanaki T, Slominski A, Zouboulis CC (2016) Skin steroidogenesis in health and disease. Rev Endocr Metab Disord 17(3):247–258
Oji V, Traupe H (2006) Ichthyoses: differential diagnosis and molecular genetics. Eur J Dermatol 16(4):349–359
Paus R (2016) The Skin and endocrine disorders. Rook's textbook of dermatology, 9th edn. Wiley, New York, pp 1–30
Pigg M, Gedde-Dahl T Jr, Cox D, Hausser I, Anton-Lamprecht I, Dahl N (1998) Strong founder effect for a transglutaminase 1 gene mutation in lamellar ichthyosis and congenital ichthyosiform erythroderma from Norway. Eur J Hum Genet 6(6):589
Qin Y, Guo T, Li G, Tang TS, Zhao S, Jiao X, Gong J, Gao F, Guo C, Simpson JL, Chen ZJ (2015a) CSB-PGBD3 mutations cause premature ovarian failure. PLoS Genet 11(7):e1005419. https://doi.org/10.1371/journal.pgen.1005419
Qin Y, Jiao X, Simpson JL, Chen ZJ (2015b) Genetics of primary ovarian insufficiency: new developments and opportunities. Hum Reprod Update 21(6):787–808
Romanelli F, Valenca M, Conte D, Isidori A, Negro-Vilar A (1995) Arachidonic acid and its metabolites effects on testosterone production by rat Leydig cells. J Endocrinol Invest 18(3):186–193
Schliep KC, Mumford SL, Vladutiu CJ, Ahrens KA, Perkins NJ, Sjaarda LA, Kissell KA, Prasad A, Wactawski-Wende J, Schisterman EF (2015) Perceived stress, reproductive hormones, and ovulatory function: a prospective cohort study. Epidemiology (Cambridge, Mass) 26(2):177
Schmuth M, Martinz V, Janecke AR, Fauth C, Schossig A, Zschocke J, Gruber R (2013) Inherited ichthyoses/generalized Mendelian disorders of cornification. Eur J Hum Genet 21(2):123
Stocco DM, Wang X, Jo Y, Manna PR (2005) Multiple signaling pathways regulating steroidogenesis and steroidogenic acute regulatory protein expression: more complicated than we thought. Mol Endocrinol 19(11):2647–2659
Suri F, Yazdani S, Chapi M, Safari I, Rasooli P, Daftarian N, Jafarinasab MR, Ghasemi Firouzabadi S, Alehabib E, Darvish H, Klotzle B, Fan JB, Turk C, Elahi E (2018) COL18A1 is a candidate eye iridocorneal angle-closure gene in humans. Hum Mol Genet 27(21):3772–3786. https://doi.org/10.1093/hmg/ddy256

Takeichi T, Akiyama M (2016) Inherited ichthyosis: non-syndromic forms. J Dermatol 43(3):242–251

Tucker EJ, Grover SR, Bachelot A, Touraine P, Sinclair AH (2016) Premature ovarian insufficiency: new perspectives on genetic cause and phenotypic spectrum. Endocr Rev 37(6):609–635

Tucker EJ, Jaillard S, Sinclair AH (2019) Genetics and genomics of primary ovarian insufficiency. Human reproductive and prenatal genetics. Elsevier, New York, pp 427–445

Venturella R, De Vivo V, Carlea A, D'Alessandro P, Saccone G, Arduino B, Improda FP, Lico D, Rania E, De Marco C, Viglietto G, Zullo F (2019) The genetics of non-syndromic primary ovarian insufficiency: a systematic review. Int J Fertil Steril 13(3):161

Wang J, Zhang W, Jiang H, Wu BL, Collaboration POI (2014) Mutations in HFM1 in recessive primary ovarian insufficiency. N Engl J Med 370(10):972–974

Wang X, Walsh LP, Reinhart AJ, Stocco DM (2000) The role of arachidonic acid in steroidogenesis and steroidogenic acute regulatory (StAR) gene and protein expression. J Biol Chem 275(26):20204–20209

Wang XJ, Dyson MT, Jo Y, Eubank DW, Stocco DM (2003) Involvement of 5-lipoxygenase metabolites of arachidonic acid in cyclic AMP-stimulated steroidogenesis and steroidogenic acute regulatory protein gene expression. J Steroid Biochem Mol Biol 85(2–5):159–166

Williams ML, Elias PM (1985) Heterogeneity in autosomal recessive ichthyosis: clinical and biochemical differentiation of lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. Arch Dermatol 121(4):477–488

Wood-Trageser MA, Gurbuz F, Yatsenko SA, Jeffries EP, Kotan LD, Surti U, Ketterer DM, Matic J, Chipkin J, Jiang H, Trakselis MA, Topaloglu AK, Rajkovic A (2014) MCM9 mutations are associated with ovarian failure, short stature, and chromosomal instability. Am J Hum Genet 95(6):754–762

Xiao W, Ke Y, He J, Zhang H, Yu J, Hu W, Gu J, Yue H, Wang C, Hu Y, Li M, Fu W, Liu Y, Zhang Z (2012) Association of ALOX12 and ALOX15 gene polymorphisms with age at menarche and natural menopause in Chinese women. Menopause 19(9):1029–1036

Yatsenko SA, Rajkovic A (2019) Genetics of human female infertility. Biol Reprod 101(3):549–566

Youssefian L, Vahidnezhad H, Saeidian AH, Sotoudeh S, Mahmoudi H, Daneshpazhooh M, Aghazadeh N, Adams R, Ghanadan A, Zeinali S, Fortina P, Uitto J (2017) Autosomal recessive congenital ichthyosis: CERS3 mutations identified by a next generation sequencing panel targeting ichthyosis genes. Eur J Hum Genet 25(11):1282–1285

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.