Mutations in *ichthyin* a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis

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We report the genomic localization by homozygosity mapping and the identification of a gene for a new form of non-syndromic autosomal recessive congenital ichthyosis. The phenotype usually presents as non-bullous congenital ichthyosiform erythroderma with fine whitish scaling on an erythrodermal background; larger brownish scales are present on the buttocks, neck and legs. A few patients presented a more generalized lamellar ichthyosis. Palmoplantar keratoderma was present in all cases, whereas only 60% of the patients were born as collodion babies. Six homozygous mutations including one nonsense and five missense mutations were identified in a new gene, *ichthyin*, on chromosome 5q33 in 23 patients from 14 consanguineous families from Algeria, Colombia, Syria and Turkey. *Ichthyin* encodes a protein with several transmembrane domains which belongs to a new family of proteins of unknown function localized in the plasma membrane (PFAM: DUF803), with homologies to both transporters and G-protein coupled receptors. This family includes *NIPA1*, in which a mutation was recently described in a dominant form of spastic paraplegia (SPG6). We propose that ichthyin and NIPA1 are membrane receptors for ligands (trioxilins A3 and B3) from the hepoxilin pathway.

INTRODUCTION

The clinically and genetically heterogeneous group of autosomal recessive congenital ichthyoses (ARCI) is characterized by generalized desquamation of the skin, usually with erythema (1–3). Most of the patients are born as collodion babies. The disease may progress to two main clinical forms, either lamellar ichthyosis (LI) or non-bullous congenital ichthyosiform erythroderma (NCIE). The estimated incidence is between 1 in 300 000 and 1 in 500 000 for both the forms. LI differs from NCIE in the characteristics of the scales, which are large, adherent, dark and pigmented, and in the absence of skin erythema. In NCIE, the scales are fine and white on an erythematous background, although they are larger and grayish on the limbs (3). Overlapping phenotypes have been described, and may depend on the age of the patient and the region of the body. LI is characterized histologically by ortho/hyperkeratosis and mild focal parakeratosis. Hyperkeratosis associated with an increase in stratum corneum thickness, a normal or prominent granular layer, and increased mitoses suggest a hyperproliferative epidermal defect in NCIE (3). Prominent dermal blood vessels and an upper lymphocytic infiltrate may explain the erythroderma. The terminal differentiation of the epidermis is disturbed in both the forms, leading to a reduced barrier function and defects in the stratum corneum lipid composition (2–5). LI is considered to be a retention ichthyosis, in comparison to NCIE, which is more a hyperproliferative disease (5,6).

ARCI has been shown to be genetically heterogeneous. Genes have been localized in five forms: LI1 (MIM 242300) on chromosome 14q11; LI2 (MIM 601277) on chromosome 2q33–35; LI3 (MIM 604777) on chromosome 19p12–q12; non-lamellar, non-erythrodermic congenital ichthyosis (NNCI) on chromosome 19p13.2–p13.1 (MIM 604781); and LI5 (MIM 606545), also known as NCIE1 (MIM 242100), on chromosome 17p13 (7–11). Four of these genes have been identified to date: transglutaminase 1 (*TGM1*) for LI1 (12,13), two lipoxygenases (*ALOXE3* and *ALOX12B*) for
RESULTS

Clinical and histological features and patient origins

We analyzed 14 families comprising 23 patients (12 females and 11 males) and 50 non-affected family members. Individuals for whom DNA was available are shown in Figure 1. All families are consanguineous from first cousin marriages, except two families in which the parents are second cousins (F1) or second cousins once removed (F14) (Table 1). Most families were from Mediterranean countries (eight from Algeria, four from Turkey and one from Syria), and one was from Colombia.

The majority of patients (60%) were born as collodion babies except for the patients from four Algerian families (F2, F4, F9 and F14) and two Turkish families (F6 and F8), who presented a clinical picture resembling NCI. They presented generalized ichthyosis with erythema, fine whitish scaling on the face and trunk, and larger brownish scaling on the neck, buttocks and legs. However, some of the families showed a more lamellar phenotype. Light microscopy of skin biopsies revealed typical histopathological features in the patients corresponding to their phenotype NCI or LI. Patients with NCI phenotype showed hyperkeratosis, thickening of the stratum corneum and moderate acanthosis and parakeratosis. We observed a normal or lightly prominent granular layer and a mild dermal perivascular lymphocytic infiltrate. In patients with lamellar phenotype, there was an important orthohyperkeratosis, moderate acanthosis, a normal or reduced granular layer, and a mild papillomatosis with dilatation of dermal capillaries. All the patients presented palmoplantar keratoderma, often yellowish with fissures, and some had clubbing of nails (Fig. 2).

Exclusion of candidate genes and identification of mutations in a novel gene ichthyin

Five genes were sequenced in the initial 2.3 Mb interval between the markers UT2159 and AFMb343xe9 (LOC91937, HAVCR1, HAVCR2, CRSP9 and MGC26988) and all seven known genes in the refined 1 Mb interval (CYFIP2, PRO133, ADAM19, SOX30, FLJ20546, FLJ38273 and ENTH). No mutations were found in the coding regions or the exon–intron boundaries of these 12 genes. Therefore, we started to analyze the human mRNAs and ESTs from the GenBank, between the markers AFMa083xb9 (DSS2112) and AFMb343xe9 (DSS2049). One mRNA (AK026158 and AF131815) was of particular interest, as it was highly expressed in epidermal tissues, including skin and keratinocytes. Sequencing of the corresponding gene revealed six different mutations in patients with ARCI.

Structure of the ichthyin gene and its cDNA

The longest mRNA (XM_351632) predicted by automatic analysis, corresponding to the ichthyin gene (LOC348938 DUF803.2), consists of a 3157 bp sequence and codes for a protein of 466 amino acids (XP_351633). This sequence was subsequently removed from the database and a new predicted sequence (XM_371777) of 3077 bp was proposed corresponding to a cDNA (AK026158 and FLJ22505) of 3094 bp, which codes for a protein of 404 amino acids. BLAST analysis between this mRNA and the BAC sequence AC008676 supported the existence of six exons as described in other public databases. We performed 5′-rapid amplification of cDNA ends (RACE) with five different primers and subcloned some of these 5′-RACE products, but we failed to identify any elongation of the 5′ end. The sequence was checked by...
overlapping RT–PCR, and the products were sequenced and compared with the sequences from public databases. BLAST analysis revealed one mouse (NM_172524) and one rat mRNA ortholog (XM_220330) showing homologies of 83 and 84% for the nucleotide sequence, and of 74 and 75% for the protein sequence, respectively. The mouse mRNA of 3299 bp is reported to be full-length, whereas the rat mRNA is only 1272 bp long. Multiple nucleotide alignments (http://prodes.toulouse.inra.fr/multalin/) of orthologs from human, mouse and rat showed also a highly conserved coding sequence with a homology of around 80%.

**Mutation analysis of the ichthyin gene**

Sequencing of the six exons and of the exon–intron boundaries of the *ichthyin* gene revealed six different homozygous mutations in the 14 consanguineous families (Table 1). One was a nonsense mutation and five were missense

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**Figure 1.** Pedigrees of families F1–F14. Mutations in *ichthyin*. Sequences are shown in two affected patients from families F4 and F10, in one parent and in one normal control.
mutations: 247C→T (R83X) and 239G→T (G80V) in exon 2; 341C→A (A114N) in exon 4; 437C→T (S146F) and 523C→G (H175N) in exon 5; and 703G→A (G235R) in exon 6. The mutations were all situated in parts of the gene that are highly conserved between mice, rats and humans. None of these sequence variations was found in 100 normal chromosomes from a Mediterranean control population.

Expression analysis

We analyzed tissue expression by *ichthyin*-specific RT–PCR with primer pairs RT_4 (Table 2) for a 1111 bp fragment using the RAPID-SCANTM gene expression panel and RNAs from cultured keratinocytes, fibroblasts, placenta and lymphocytes (data not shown). The *ichthyin* transcript was found to be expressed in most tissues tested; it was highly expressed in brain, lung, stomach, skin and leukocytes, and was present at a lower level in the other tissues except liver, thyroid and fetal brain, in which no expression was detectable. Strong expression of *ichthyin* transcripts was observed in cultured keratinocytes from normal skin biopsies; expression was weaker in cultured fibroblasts from the same skin biopsies, in placenta and in lymphocytes.

Sequence analysis of the *ichthyin* protein and identification of conserved residues

The sequence of 404 amino acids corresponds to a protein with a calculated molecular weight of 44 kDa. This sequence was submitted to the topology prediction programs for sequence signals, transmembrane (TM) domains and protein orientation available through the ExPaSy server (www. expasy.org), to the protein analyzing tools from the Biology WorkBench (http://biowb.sdsc.edu/) and to the homology searches through protein databases (http://www.ncbi.nlm.nih.gov). The protein is predicted to localize in the plasma membrane, but does not possess a signal sequence. The number of predicted TM domains was eight using the PSORTII program (http://psort.nibb.ac.jp/form2.html) and nine using the SMART program (http://smart.embl-heidelberg.de/); each of these domains consists of 22 amino acids. This structure defines a new family of proteins of unknown function (PFAM: DUF803). By the Dense Alignment Surface (DAS) method (http://www.sbc.su.se/~miklos/DAS/) (17), only seven TM domains were identified; one TM region (amino acids 162–168) was considered too small, as it consisted of only seven amino acids in humans and only three amino acids in the mouse ortholog. It was identified as a secondary hydrophilic TM helix using SOSUI analysis (http://sosui. proteome.bio.tuat.ac.jp/) owing to the absence of amphophilic side chains at the helix ends, which is one of the two arguments used (together with hydrophobicity) to define a TM domain (18). The BPROMPT (http://www.jenner.ac.uk/ BPROMPT/) program also predicted seven TM domains for *ichthyin*. Analysis using the ProtFun2.1 server (http://www. cbs.dtu.dk/services/ProtFun/) classifies *ichthyin* in functional and gene ontology categories under transport and binding activities.

A new family of proteins with several TM domains

BLAST analysis identified five human paralogs of *ichthyin* (listed later), of which the first three are the most closely related to *ichthyin*, with up to 57% homology. Four of these genes have the same basic structure and have 5–8 exons: (1) NIPA1 (Non-Imprinted in Prader–Willi/Angelman syndrome 1) or spastic paraplegia (SPG6) on chromosome 15q11.2; (2) NIPA2 (DUF803.0) also on chromosome 15q11.2; (3) LOC152519 (DUF803.3) on chromosome 4p12; (4) FLJ13955 (DUF803.1) on chromosome 8q22.2; and (5) dJ462023.2 (DUF803.4) on chromosome 1p36.12–p35.1. The FLJ13955 and dJ462023.2 genes are predicted to have 12 exons. Some of these sequences were annotated by automatic analysis pipelines such as GeneWise, Genscan and Gnomon, and could be either too long or incomplete, with the exception of NIPA1 and 2, which have been more extensively analyzed (19,20). Two transcripts were found for NIPA1, one of 2.2 kb and a larger one of 7.5 kb with a long 3’-untranslated region (UTR) which is present at low levels in most tissues, but at higher levels in neuronal tissues (19).

Fifty-two homologues were found in eukaryotes including *Caenorhabditis elegans*, *Drosophila*, mice and plants (IPR008521; http://ebi.ac.uk/interpro/). Weaker BLASTP homologies were also found with a hypothetical transport protein in *Pseudomonas denitrificans* (ORF6; SW:YCB6_PSEDE), and with a *C. elegans* chemoreceptor with seven TM domains of the sri family (WP:CE33629) (21).

Multiple amino acid alignment confirms both the high homology and the conservation of the positions of the TM regions of the six proteins of the family.

The phylogenetic tree (Tree Top, http://www.genebee.msu.su/services/phltre_reduced.html) of the multiple sequence alignments (CLUSTALW) of the six human DUF803 proteins and 347 human G-protein coupled receptor (GPCR) protein sequences from the GPCR database (GPCRDB, May 2003 release; http://www.gpcr.org/7tm/) identified DUF803 proteins as a branch between glutamate and frizzled/taste2 receptors (22).

The mutations identified in *ichthyin* include a nonsense mutation in the second exon, which would lead to the synthesis of a truncated protein. Four of the five missense mutations were situated inside one of the predicted TM

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domains, in the second (aa80), the third (aa146), the fourth (aa175) and the sixth (aa235). The fifth mutation (aa114) is located between the second and third TM domains.

Genotyping on chromosomes 15q11.2 and 8q22.2, and mutation analysis of NIPA2 and FLJ13955 in families in which other known loci had been excluded

Two of the ichthyin paralogs, NIPA2 and FLJ13955, have been described to be strongly expressed in keratinocytes (SAGE). In order to test linkage, the localizations containing these paralogs in a form of ARCI were genotyped in 65 consanguineous ichthyosis families (226 individuals including 103 affected family members). Potential linkage to chromosome 15q11.2 or 8q22.2 was suggested in 12 families, but when the two candidate genes were sequenced for the exons and the exon–intron boundaries, no mutations were found.

DISCUSSION

The identification of mutations in a new gene with several TM domains, in patients with ARCI is a landmark in the analysis
Figure 3. Patients' haplotypes and corresponding mutations. Loss of homozygosity is indicated by gray color. Inside the smallest segregating interval between markers a083xb9 and D5S378, mutations and common alleles are in red. The allele number is indicated as 0 when no genotyping result is available. Paternal and maternal alleles for each affected child are presented.
of this group of disorders, for which both low-incidence and wide clinical and genetic heterogeneity have made it difficult to develop a classification scheme using clinical (2,3,6), biochemical (5,6,23) and ultrastructural criteria (24). This supports a metabolic origin of ARCI, which had already been suspected after two genes from the lipoxygenase family (ALOX12B and ALOXE3) were found to be mutated in this disorder (14). This finding was extended by the identification of ALOXE3 as a hydroperoxide isomerase (25). Two other genes which are mutated in ichthyoses, CGI-58 or abhydro-lase 5 (ABHD5) (12,13,16) and the transporter ABCA12 (15), could belong to the hepxoxilin metabolic pathway, in which membrane arachidonic acid is transformed to hepxoxilin, trioxilin and derivatives of R-chirality (26,27). The phenotype of this ARCI caused by mutations in ichthyin is similar to that previously described for other ARCIs, in which the majority of patients present a NCIE phenotype. Not all ARCI patients are born as collodion babies; this was the case in nine of our patients, from four Algerian and two Turkish families.

As was the case for the five genes previously identified in ARCI and in Chanarin-Dorfman syndrome (12–16), homozygosity mapping turned out to be a powerful method for

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PCR conditions: I, as described in Materials and Methods; II, Tm 55 °C; III, Tm 59 °C using Hot Master Taq (Eppendorf); IV, Tm 59 °C, 100 ng of DNA; V, Tm 55 °C using Advantage GC genomic Polymerase Mix (Clontech); VI, Tm 55 °C, 100 ng of DNA; VII, RT–PCR as described in Materials and Methods; VIII, Tm 60 °C using Advantage GC genomic Polymerase Mix (Clontech); IX, Tm 55 °C using Advantage GC genomic Polymerase Mix (Clontech), 100 ng of DNA.
localization of the causative genes. The main difficulty in the present study was the identification of the gene, which necessitated the sequencing of all the genes present in the refined interval, and a search for new genes, which were suspected only by the presence of cDNAs.

A precise characterization of the structure of this novel gene by RT–PCR and 5’- and 3’-RACE was necessary. Moreover, we expected a classical protein of the large GPCRs family with seven TM domains.

The nine TM domains proposed for ichthyin by SMART, which, according to PFAM, define a new family of proteins, which has been designated as DUF803. The nine TM domains are not always found in other proteins of this family, or in the homologs in other species or by using other topology TM prediction programs. For example, only eight TM domains are predicted by SMART in the ichthyin homologue in mouse, with 406 amino acids, and a signal sequence of 30 amino acids. Other topology programs such as DAS or BPROMPT predict only seven TM domains for ichthyin as is the case for NIPA1 and NIPA2, and eight TM domains, instead of nine, for the three other proteins of the family. The eighth supplementary predicted TM domain is localized in the N-terminal portion of the protein, which normally contains the signal sequence. The difficulty in differentiating between a signal sequence and a TM domain (28,29), as well as the discrepancies in the number of TM domains found between topology prediction programs, are well known (30). With its 7–9 TM domains, ichthyin is clearly membrane-associated, but it is not yet possible to determine whether it is a GPCR (GPCRs have seven TM domains, and 10% of them have signal sequences), or whether it is localized in the plasma membrane or in one of the intracellular membrane systems. However, no sequences targeting internal membranes were detected. Even for the extensively studied proteins like presenilin 1, which was assumed to possess 10 hydrophobic regions, recent immunofluorescent studies with specific antibodies to the C- and N-tails led the authors to propose a new model with only seven TM domains (31).

The DUF803 family includes a group of membrane proteins of unknown function, recently revealed by the identification of a heterozygous mutations in NIPA1 (T45R) in two families (20), in one of the numerous types of autosomal dominant spastic paraplegia. Owing to the presence of several TM domains, this protein has been proposed to be a transporter or a receptor for an unknown ligand (19,20). A transporter of the ABC family, ABCA12, has already been found to be mutated in one form of ARCI (15). By analogy with the predicted function of ichthyin, NIPA1, which is a homolog, is proposed to be a receptor for the ligand from the hepoxilin pathway (trioxilin B3). The heterozygous mutation found in NIPA1 could correspond to a dominant negative mutation of this receptor, as observed for several GPCR proteins.

Two receptors for each ligand of the leukotriene pathway, and for LXA4 of the lipoxin pathway, which are parallel to the hepoxilin pathway, have been identified to date: LTB4R and LTB4R2 for LTB4; CYSLTR1 and CYSLTR2 for LTC4/LTD4/LTE4; and FPRL1 and 2 for LXA4 (32,33). NIPA2 is the gene with the closest homology to ichthyin. No mutations have been found in this gene in SPG6, at least in the families studied to date (20). We sequenced the paralogs of ichthyin, in the families with ichthyosis which are not linked to the seven loci identified to date, but found no mutations in NIPA2 (DUF803.0) and FLJ13955 (DUF803.1).

A stable hepoxilin analog, PBT-3, was found to selectively inhibit the binding of antagonists of the thromboxane α receptor (34), but there is no homology between the thromboxane α receptor and ichthyin.

The suspicion that ichthyin is a membrane receptor of the hepoxilin pathway offers strong opportunities to provide simple treatments to patients. This type of protein is easily accessible and it should be possible to synthesize both agonists and antagonists with high specificity and sensitivity in the ligand–receptor interactions. It should be noted that these applications could also be useful in the treatment of dry skin, which is far more frequent than ARCI.

**MATERIALS AND METHODS**

**Subjects and samples**

Four dermatologists (B. Bouadjar, M.-J. Rueda, A. Karaduman and M. Nourallah) recorded the clinical data and pedigree information of the families. Blood samples were collected from each participating family member after obtaining written informed consent. DNA extraction from peripheral blood leukocytes and establishment of cell lines were performed at the DNA bank of Génèthon using standard procedures.

**Genetic analysis**

Genotyping was carried out using 400 highly polymorphic microsatellite markers from the ABI panel (Linkage Mapping Set2, LMS2, Applied Biosystems) and a MegaBase capillary sequencer for the genome-wide scan. ABI 377 sequencers were used for fine mapping with publicly available microsatellites. Haplotypes were constructed assuming the most parsimonious linkage phase. Linkage programs were used on the basis of the assumption of autosomal recessive inheritance, full penetrance and a disease frequency of 1 in 500 000 in the general population. Pairwise LOD scores were calculated with the MLINK program of the LINKAGE 5.1 package (37) incorporating consanguineous loops into the pedigree files.

**Mutation screening**

Mutation analysis was performed in affected patients and in both parents in the 14 families, and in supplementary non-affected sibs in cases of missing parents. We designed intronic oligonucleotide primers flanking the exons for amplification and sequencing of the ichthyin gene (Table 2) using the Primer3 program (http://www-genome.wi.mit.edu/genome_software/other/primer3.html) (38). Sets of PCR conditions were used as indicated in Table 2. The touch-down PCR reaction was performed in a 45 μl volume containing 50 ng of genomic DNA (in 5 μl) with Hot Master™ Taq DNA polymerase (Eppendorf): initial denaturation step at 95 °C for 5 min, 6 cycles of amplification consisting of 40 s at 94 °C, 30 s 68 °C, and a 30 s elongation step at 72 °C, followed by 30 cycles of 40 s at 94 °C, 30 s at optimal annealing temperature, 30 s at
72°C, and a 5 min terminal elongation step. Aliquots of 1–2 µl of purified PCR products were added to 0.5 µl of sense or antisense primer (20 µM) and 2 µl of BigDye terminator mix (Applied Biosystems) in a 15 µl volume. The linear amplification consisted of an initial 5 min denaturation step at 96°C, 25 cycles of 10 s of denaturation at 96°C and a 4 min annealing–extension step at 56–60°C. The reaction products were purified and sequenced on an Applied Biosystems Sequencer 3700. The forward or reverse strands from all patients and controls were sequenced for the entire coding region and the exon–intron boundaries. The sequences were analyzed with the Phred Phrap program on Unix.

**Lymphoblastoid, keratinocyte and fibroblast cell cultures, and RNA extraction**

Lymphoblastoid cell lines were established using standard procedures. Total RNA from lymphocytes was extracted with the RNA-PLUS (Quantum-Applegate) kit following the manufacturer’s instructions. Human keratinocytes and fibroblasts were obtained from the skin removed during routine plastic surgery of a normal individual. The skin sample was processed for primary keratinocyte culture, and the cells were grown according to the standard procedure described by Invitrogen Life Technologies, using products from the same company in serum-free keratinocyte medium supplemented with bovine pituitary extract (25 µg/ml) and recombinant epidermal growth factor (0.1 ng/ml). For primary fibroblast culture we used Dulbecco’s Modified Eagle’s Medium with 10% fetal calf serum and 2% L-glutamine. Cultures were grown for two passages and were harvested when they reached 90% confluence. Total RNA was isolated using the QiAamp RNA Mini Protocol for isolation of total RNA from cultured cells (QIAGEN) following the manufacturer’s instructions. The mRNA was isolated following the Oligoex direct mRNA protocol as provided by the manufacturer (QIAGEN).

**5′-RACE and cloning of the amplification products**

5′-RACE was performed with Marathon-Ready cDNA from melanoma, placenta and stomach (Clontech) using the Advantage 2 Polymerase Mix (Clontech) following the manufacturer’s instructions. The PCR was run with AP1 primer and one of the five gene-specific antisense primers which we designed from the cDNA sequence, starting with an initial 5 min denaturation step at 96°C, 25 cycles of 10 s of denaturation at 96°C and a 4 min annealing–extension step at 56–60°C. The reaction products were purified and sequenced on an Applied Biosystems Sequencer 3700. The forward or reverse strands from all patients and controls were sequenced for the entire coding region and the exon–intron boundaries. The sequences were analyzed with the Phred Phrap program on Unix.

**RT–PCR and Rapid-Scan™ gene expression panel**

RT–PCR was performed using the RT–PCR kit (Life Technologies) with oligo-T primers to generate the first strand of cDNA. Amplification of cDNA from keratinocytes, fibroblasts, placenta and lymphocytes was performed with four primer pairs (Table 2) covering the entire coding region, the 3′- and 5′-UTR regions.

A gene expression panel including 24 human tissues was tested following the manufacturer’s instructions (Rapid-Span, OriGene Technologies) using primer pair RT_4 which is specific for the ichthyin transcript. Expression in keratinocytes, fibroblasts, placenta and lymphocytes was also tested.

**Accession numbers**

*Ichthyin.* LocusID LOC348938; mRNA XM_37177 (GI:42657191); AK026158 (GI:10438919); protein XP_351633 (37549911).

*Ichthyin orthologs.* Mouse: 9530066K23Rik, LocusID 214112; mouse mRNA NM_172524 (GI:27369725) identical to AK035561 (GI:26303753); mouse protein: NP_766112 (27369726); identical to BAC29107 (GI:26330754). Rat: LocusID LOC303070; mRNA XM_220330.2 (GI:34870677); XM_220330.1 (GI:27669704, record removed); rat XP_220330.2 (GI:34870678); XP_220330.1 (GI:27669704, record removed).

**Paralogs.** Chromosome 15q11.2 NIPA2 (non-imprinted in Prader–Willi/Angelman syndrome 2), LocusID 81614; mRNA NM_030922 or BC011775 (GI:33989168). Chromosome 8q22.2 FLJ13955. LocusID 79815; NM_024759 (GI:13376096) identical to AK024017 (GI:10436266); protein NP_079035 (GI:13376097) identical to BAB14779 (GI:10436267).

**Online Mendelian inheritance in man** (http://www.ncbi.nlm.nih.gov/Omim). Abhydrolase domain containing 5 (ABHD5), previously CGI58, Comparative Gene Identification 58 [CGI58; MIM 604780]; arachidonate lipoxygenase 3 [ALOX3; MIM 607206]; arachidonate 12-lipoxygenase, R type [ALOX12R; MIM 603741]; ATP-binding cassette, sub-family A, member 12 [ABCA12; MIM 607800]; Chanarin-Dorfman syndrome [CDS; MIM 275630]; cysteiny1 leukotriene receptor 1 [CYSLTR1; MIM 300201]; cysteiny1 leukotriene receptor 2 [CYSLTR2; MIM 605666]; ichthyosis non-lamellar and non-erythrodermic congenital [NNC; MIM 604781]; ichthyosis [LI; MIM 242300]; lamellar ichthyosis 1 [LI1; MIM 604777]; lamellar ichthyosis 2 [LI2; MIM 601277]; lamellar ichthyosis 3 [LI3; MIM 604777]; lamellar ichthyosis 5 [LI5; MIM 606545]; leukotriene B4 receptor [LTB4R; MIM 601531]; leukotriene B4 receptor 2 [LTB4R2; MIM 605773]; non-bullous ichthyosiform erythroderma [NCIE1, MIM 242100]; non-bullous ichthyosiform erythroderma [NCIE2, MIM 604780]; non-imprinted gene in Prader–Willi/Angelman syndrome chromosome region 1 [NIPA1; MIM 6008145]; non-imprinted gene in Prader–Willi/Angelman syndrome chromosome region 2 [NIPA2; MIM 6008146]; Presenilin 1 [PSEN1; MIM 104311]; transglutaminase 1 [TGMI; MIM 190195]; Spastic paraplegia 6, autosomal dominant [SPG6; MIM 600363].

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