The LOXL2 Gene Encodes a New Lysyl Oxidase-like Protein and Is Expressed at High Levels in Reproductive Tissues*

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We have reported in this paper the complete cDNA sequence, gene structure, and tissue-specific expression of LOXL2, a new amine oxidase and a member of an emerging family of human lysyl oxidases. The predicted amino acid sequence, from several overlapping cDNA clones isolated from placenta and spleen cDNA libraries, shared extensive sequence homology with the conserved copper-binding and catalytic domains of both lysyl oxidase (LOX) and the lysyl oxidase-like (LOXL) protein. These conserved domains are encoded by five consecutive exons within the LOX, LOXL, and LOXL2 genes that also maintained exon-intron structure conservation. In contrast, six exons encoding the amino-terminal domains diverged both in sequence and structure. Exon 1 of the LOXL2 gene does not encode a signal sequence that is present in LOX and LOXL, suggesting a different processing and intracellular localization for this new protein. Expression of the LOXL2 gene was detected in almost all tissues with the highest steady state mRNA levels in the reproductive tissues, placenta, uterus and prostate. In situ hybridization identified placental syncytial and cytotrophoblasts responsible for the synthesis of LOXL2 mRNA and demonstrated a spatial and temporal expression pattern unique to the LOXL2 gene.

Lysyl oxidase is a copper-dependent amine oxidase that belongs to a heterogeneous family of enzymes that oxidize primary amine substrates to reactive aldehydes. This enzyme family is subdivided into two main classes on the basis of the chemical nature of the co-factors associated with these amine oxidases. Flavine adenine dinucleotide is the co-factor of monamine oxidase and of an intracellular form of polyamine oxidases. Flavine adenine dinucleotide is the co-factor of monamine oxidase and of an intracellular form of polyamine oxidases. Dia mine oxidase, monoamine-metabolizing semi-carbazide-sensitive amine oxidase, and lysyl oxidase belong to this latter subfamily of amine oxidases (1–3).

Most of the studies on lysyl oxidase have focused on the specific cross-linking activity and catalytic mechanism of action of this enzyme on the extracellular matrix substrates, collagen and elastin. Lysyl oxidase participates in the critical post-translational modification essential to the biogenesis of connective tissue by deaminating the side chains of lysine residues in these proteins, thus catalyzing the covalent cross-linking of several fibrillar collagen types and the formation of desmosine and isodesmosine cross-links in elastin (4, 5).

Recently, multiple novel biological functions have been attributed to lysyl oxidase (6, 7) that have suggested that other intracellular and intranuclear substrates may be involved in these multiple functions (8, 9). The range of these novel activities of lysyl oxidase cover a spectrum of biological functions from developmental regulation (10) to tumor suppression (7, 11–14) and cell growth control (15, 16). An attractive hypothesis to explain how a single protein can fulfill these different functions is that a family of several different lysyl oxidases may exist that individually function to perform these roles.

Over the past few years, we and others have described two lysyl oxidase-related proteins that fulfill all the requirements of being functional copper-dependent, but genetically distinct, lysyl oxidases that could potentially serve as the basis for a family of proteins present in a variety of cellular and tissue locations, each with an unique function.

The first of these LOX1-related proteins was called LOXL or lysyl oxidase-like (17, 18). A comparison of the cDNA sequence of LOXL and LOX confirmed a significant homology within the carboxyl-terminal end of these proteins. This homology included a striking conservation of the copper binding site, the catalytic domain, and the carbonyl co-factor binding site. This domain conservation was also reflected in conservation of exon size and exon-intron boundaries in five of the seven exons in both of the LOX and LOXL genes encoding these conserved domains (18, 19). We have also mapped this LOXL gene to chromosome 15q23 (20), and the LOX gene was previously mapped to chromosome 5q23.3 (21, 22). We have, moreover, localized the LOXL protein to sites of de novo fibrosis in the liver and showed co-regulated expression of the LOXL gene with the colIII1 gene and the LOX gene with the gene encoding pro-a1(I) collagen. These results suggested different functions for LOX and LOXL (23).

We now report the detailed structural and expression analysis of a new member of the lysyl oxidase gene family encoding a protein we have referred to as LOXL2. The unique temporal and spatial tissue-specific expression pattern in reproductive tissues and the possible intracellular localization of LOXL2 indicate a role for LOXL2 that is distinctly different from either LOX or LOXL.

The abbreviations used are: LOX, lysyl oxidase; LOXL, lysyl oxidase-like; PCR, polymerase chain reaction; kb, kilobase(s); bp, base pair(s); UTR, untranslated region; PAC, bacteriophage P1-derived vector.

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**Isolation of LOXL2 cDNA Clones**—DNA sequence obtained from Human Genome Sciences (Applied Biosystems) expressed sequence tag clone HSSAE08RB provided information for the design of PCR primers, and we have used these primers to screen a human spleen cDNA library (cDNA Isolation Service, Life Technologies, Inc.). A human placenta library (Stratagene, La Jolla, CA) was also screened using a LOXL2-specific PCR-amplified cDNA probe. The primers used to generate this probe were LOXL2-34 (5'-CTG CTG CGA CTG AGA GGC G 3') and LOXL2-35 (5' GAA GGC GTT GCT GGC GAA TC 3'). The probe was random primer-labeled, and filters with plaque plaques were hybridized overnight at 42 °C, followed by four washes for 30 min each at room temperature in 2 x SSC, 0.1% SDS, and two washes for 30 min at 50 °C in 0.2 x SSC and 0.1% SDS. Positive plaques were purified, and the insert size was determined and sequenced.

**LOXL2 Genomic Sequencing**—Two overlapping PAC clones, 17459 and 17460 (Genome Systems, Inc., St. Louis, MO), containing the LOXL2 gene were used as templates for DNA sequencing using the Thermo Sequenase radiolabeled terminator cycle sequencing kit (Amersham Pharmacia Biotech). Oligonucleotides were designed based on LOXL2 cDNA sequences and synthesized by Genosys Biotechnologies Inc. (The Woodlands, TX) and Life Technologies, Inc. Sequencing reactions were performed using 32.5 fm PAC DNA in a reaction mixture containing the following reagents: 2 μM each dATP, dGTP, dTTP, ddCTP, and each primer. Each reaction was terminated, and aliquots were loaded on a 6% denaturing polyacrylamide gel. Following electrophoresis, gels were exposed for 2 days at −80 °C.

**Intron-Exon Size Determination**—Exons were determined by genomic sequencing from PAC clones 17459 and 17460. Intron sizes were determined using sets of primers that corresponded to 5' and 3' end sequences of previously identified exons of the LOXL2 cDNA and DNA from PAC clone 17459 and PAC clone 17460. Polymerase chain reactions were performed using the GeneAmp kit (Perkin-Elmer) with the following parameters: initial denaturation at 94 °C for 3 min was followed by 30 cycles of denaturation at 94 °C for 30 s, annealing at primer-specific temperatures (between 52 and 66 °C) for 30 s, and extension at 72 °C for 1 min with a final extension at 72 °C for 7 min. PCR reactions were performed using 80 ng of DNA in 25 μl of reaction mixture containing final concentrations of the following reagents: PCR buffer from Perkin-Elmer containing 1.5 mM MgCl₂, 0.2 mM each of dGTP, dATP, dTTP, and dCTP, and 0.625 unit of Taq polymerase. Amplified products were electrophoresed on 1% agarose gels, and size-separated DNA fragments were visualized by ethidium bromide staining.

**Primer Extension**—Primer extension was performed on 5 μg of total RNA from human placenta. 32P-Labeled antisense primers LOXL2-2 (5'-CTG CTG CGA GTT GCT GGC G 3') and LOXL2-18 (5'-CAC GAA CAG 3') were annealed, and extension reactions were performed for 50 min at 42 °C with 200 IU of SuperScript II transcriptase (Life Technologies, Inc.) and terminated for 15 min at 70 °C. These extension products were treated with RNase A for 30 min at 37 °C, extracted with phenol, precipitated, re-dissolved, and subjected to electrophoresis through an 8% denaturing polyacrylamide gel. A sequencing reaction performed on PAC clone 17460 using primers LOXL2-2 or LOXL2-18 was loaded on the same gel. Extension reactions lacking either RNA or primers were used as controls.

**Northern Blot Analysis**—Two-μg aliquots of size-separated poly(A)+ RNA obtained from adult heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, prostate, testis, uterus, small intestine, colon, and peripheral blood leukocyte were present in the two Multiple Tissue Northern blots were probed with 32P-labeled cDNA fragments. Each Multiple Tissue Northern blot was probed with 32P-labeled cDNA: 48 h after electrophoresis in a 2.0-kb β-actin cDNA probe (to confirm the presence of the tissue Northern blots. The specificity of hybridized RNA fragments used in these incubations was 5 x 10⁶ dpm/μg.

**In Situ Hybridization**—Placentas with attached fetal membranes and decidua were obtained from a patient after elective pregnancy termination at 14 weeks of gestation and from patients after elective cesarean section at term from Kapiolani Medical Center (Honolulu, HI).

**RESULTS**

**LOXL2 cDNA Isolation and Sequence Analysis**—A search of the Human Genome Sciences Inc. protein data base identified three expressed sequence tag clones with homology to lysyl oxidase. DNA sequence analysis of one of these clones, HSSAE08RB, demonstrated a 45% homology to lysyl oxidase (LOX) and 48% homology to the lysyl oxidase-like (LOXL) cDNA. PCR-derived DNA fragments prepared using this expressed sequence tag sequence information were used to identify 16 cDNA clones from a human spleen cDNA library and an additional 8 clones from a human placenta library. DNA sequencing and alignment of these clones resulted in a full-length DNA sequence encoding LOXL2. An open reading frame of 1191 bp was identified that clearly demonstrated sequence homology within this LOXL2 cDNA to both LOX and LOXL cDNAs.

Conservation of the nucleotide and deduced amino acid sequence within the carboxyl-terminal end of LOXL2, LOX, and LOXL included the copper-binding domain (WEWHSC-HQQHYH) in LOX and LOXL and WIWHDCHRYIH in LOXL2 with the four histidines that supply the nitrogen ligands for the copper coordination complex specific for lysyl oxidase proteins (26). The active site in LOX (DIDCGWWIDTDVXGPYN) and in LOXL2 (DIDCGWWIDTDVPPGGY) contains, in each, a Tyr residue (Y) at the COOH-terminal end, which is known to participate together with a Lys residue in the formation of the quinone co-factor that is present in these proteins. Ten cysteines characteristic of LOX and LOXL were similarly conserved in LOXL2 (4). A growth factor and cytokine receptor domain present in the LOX and LOXL proteins was also identified within the LOXL2-derived amino acid sequence domain. This domain is conserved with the consensus sequence C-X₂-C-X₁₀–₁₅-C-X₂-C-X₁₀–₁₅ (where X is a defined number of any amino acids) that is a proposed ligand-binding domain for a number of receptors for cytokines and growth hormones (18, 27). Three repeats of the scavenger receptor cysteine-rich domain were also present at amino acids 13–125, 149–250, and 258–368 in the derived LOXL2 sequence (25, 28).

The hydrophobic profile of the LOXL2 protein was determined and compared with that of the LOX and LOXL proteins using the MacMolly analysis program. Unlike other lysyl oxidases, LOXL2 had no obvious evidence for a hydrophobic signal sequence.

Three major transcription initiation sites were noted within 3'-UTR domains in the 20 LOXL2 cDNA clones that we have analyzed. The first termination site was 690 bp 3' of the termination codon, the second site was 740 bp, and the final transcription termination site was 900 bp 3' of the termination site. These DXRNA all had 3'UTRs differing slightly in size but were detected by Northern analysis as a single mRNA species of 3.6 kb. A less abundant mRNA species of 4.9 kb that was detected in Northern blots of heart, liver, and pancreas RNA samples using LOXL2 cDNA as a probe raises the possibility that an additional, but less frequently used, transcription termination signal may exist further 3' of those we have al-
Structure of the LOXL2 Gene—Two overlapping PAC clones, PAC 17459 and PAC 17460, that were isolated using LOXL2-specific PCR primers, served as templates for sequencing the exon-intron boundaries, complete exons, and to determine intron sizes using PCR and extra long PCR reactions. Most exon-intron boundaries of the LOXL2 gene show the consensus sequence (C/T)AG-exon-GT(A/G). The sizes of the 11 exons of the LOXL2 gene ranged from 112 to 940 bp. Although the LOXL2 gene has 11 exons, five consecutive exons (exons 6–10), which encode the copper-binding and catalytic domains, revealed 84% sequence similarity, and exon sizes were very similar to the corresponding exons of the LOX and LOXL genes (18, 19). All the other exons in the LOXL2 gene are divergent in both sequence and size.

The sizes of the introns were the following from intron 1 to intron 10, respectively, with the exception of intron 6 that could not be amplified by these methods and is most probably larger in size: 2.0, 0.4, 0.53, 2.15, 2.7, 0.61, 1.22, 3.0, and 0.75 kb. The structure of the LOXL2 gene and the exact sizes of each exon and intron was very similar to the corresponding exons and introns of the LOX and LOXL genes.

The LOXL2 Promoter—An 830-bp region of the 5′-flanking sequence of the human LOXL2 gene that included the first exon and the first intron was analyzed using the DNA sequence analysis program GCG (Genetics Computer Group, Madison, WI) and the TF sites database to identify potential transcription factor binding sites. A large number of potential transcription factor binding sites were detected within the 5′-flanking region of the LOXL2 gene and the first exon and the first intron, including 10 AP-2 sites and two SP1 sites. The LOXL2 gene promoter domain contains no significant TATA or CAAT box sequences. There is a single AP-1 site (TGAAATCA) at position −522. There are four CAP/CRP-lac sites (ACACTTT) at positions −459 and −816, within the first exon at −130 and within the first intron (AAAGTGT). There is a single MRE site at −716 (TGCCAC), two MAP sites (GGAAGA) at −400 and −55, a single GAGA site (AAGAGAG) at −716, one GR-teruglobin (AGAAGGA) at −442, four GR-MT sites (TTGTCTT) at −879, −506, −53, and one within the first exon at −113. A zeste-white (CACTCA) at position −490 and a JCV (GAGGTGGGG) at −856 were also present within this promoter domain of the human LOXL2 gene. The DNA sequence of the promoter region of the LOXL2 gene and the major transcription factor binding site consensus sequences are shown in Fig. 2.

Transcription Initiation Sites—Transcription initiation sites of the LOXL2 gene were determined by primer extension analysis using total RNA from human placenta. The sizes of these fragments identified two transcription initiation sites at positions −95 and −100 and two additional but less abundant sites at −54 and −110.

LOXL2 and the Lysyl Oxidase-related cDNA—Recently, a lysyl oxidase-related cDNA was reported (25). This cDNA (WS9-14) contained a 3′ sequence homologous to sequences within our LOXL2 cDNA. This region of homology started from bp 780 of the WS9-14 sequence and was identical to LOXL2 cDNA sequence with the following differences: at bp 278 of the LOXL2 sequence there is an A, while at the corresponding position at bp 1131 of WS9-14 there is a T; at bp 433 a G in LOXL2 and an A in WS9-14; at 1350 an A in LOXL2 and a C in WS9-14; at 1631 a C in LOXL2 and a G in WS9-14; at 1715 an additional C in LOXL2; at 1779 a T in LOXL2 and a C in WS9-14. Several of these changes result in amino acid differences between LOXL2 and WS9-14. A number of additional sequence differences in the 3′-UTR were found between WS9-14 and LOXL2. The LOXL2 cDNA, however, has no sequence homology whatsoever to the most 5′ 780 bp of WS9-14. The significance and origin of this 780-bp part of the WS9-14 sequence is unclear. Our analysis of the LOXL2 gene has confirmed that the cDNA sequence we have identified is encoded within 11 exons. The most 5′ of our cDNA is found at the 5′ end of exon 1 and primer extension, and promoter analysis has demonstrated that transcription initiation begins within this region. From these studies, it is clear that the most 5′ sequence of our LOXL2 cDNA is derived from the most 5′ exonic sequences of the LOXL2 gene.

The most 5′ 780-bp sequences of the WS9-14 mRNA were generated by two independent PCR extension and 5′ rapid amplification of cDNA ends reactions, and the authors of this work (25) had not confirmed these results by corresponding cDNA sequences. We were unable to isolate any cDNA or genomic clones that would contain identical or homologous sequences to this domain of WS9-14. Therefore the origin of the WS9-14 mRNA is unclear; it is possible that this 5′ part of the WS9-14 cDNA is a PCR product unrelated to the rest of the mRNA. It is certainly unlikely to be a transcript derived from the LOXL2 gene that we have mapped to chromosome 8p21.3 (29).

Tissue-specific Expression of the LOXL2 Gene—Northern blot analysis of the LOXL2 mRNA detected a 3.6-kb band in all tissues with the exception of blood leukocytes. An additional,
A much less abundant mRNA of 4.9 kb was also detected in heart, liver, and pancreas. The steady state levels of the LOXL2 mRNA were quantitated in all tissues relative to β-actin mRNA. The expression of the LOXL2 mRNA was significantly higher in placenta, prostate, uterus, and pancreas (ratios between 2 and 3) compared with lower expression in brain, lung, skeletal muscle, thymus, and kidney (ratios below 0.5). The results of these experiments are presented in Fig. 3.

**LOXL2 Expression in the Placenta**—As placenta showed the highest level of LOXL2 mRNA, we have further analyzed placental tissues and fetal membranes to identify the cells in these tissues that are responsible for the synthesis of the LOXL2 mRNA. Placental villi and fetal membrane sections from 14 weeks of gestation and at term were used for in situ hybridizations using a LOXL2-specific 60-mer oligonucleotide probe. There was no hybridization signal detected with this LOXL2-specific oligonucleotide probe with any of the cells in fetal membranes under these conditions. A weak signal was detected at 14 weeks gestation in the placental villi that was significantly increased in intensity in the villi of the term placenta (Fig. 4). Positive autoradiographic signals were associated with the syncytiotrophoblasts, which are clearly responsible for the synthesis of this abundant LOXL2 mRNA in placental tissue.

**DISCUSSION**

Based on the significant sequence homology and similarity in gene structure of the lysyl oxidases, it is likely that at least parts of the lysyl oxidase genes share a common ancestor. There is a closer evolutionary relationship between LOX and LOXL than between these two lysyl oxidases and LOXL2. It is likely that at least parts of the LOX, LOXL, and LOXL2 genes share a common ancestor, as the exons encoding the functional domains of the mature protein have remained closely homologous both in sequence and in size. In contrast, exons encoding the 5'- and 3'-untranslated regions and the amino-terminal domains of these proteins have diverged significantly, not only in sequence but also in gene structure.
FIG. 3. Tissue-specific expression of the LOXL2 gene. Multiple tissue Northern blots containing 2 μg of poly(A)^+ RNA from several human tissues were hybridized to ^32P-labeled LOXL2 cDNA probe and β-actin probe (A and C). The quantitation of the LOXL2 mRNA in each tissue is also presented (B and D).

FIG. 4. In situ hybridization analysis of LOXL2 mRNA distribution in term placental tissue. Placental tissue sections were obtained and prepared for in situ hybridization analysis as described previously (24). An ^35S-labeled LOXL2-specific oligomer was incubated with pretreated and prehybridized placenta tissue sections. Following post-hybridization washes and autoradiography, counterstained tissue sections were visualized by dark field light microscopy. A, a section of placental villi counterstained with toluidine blue viewed by regular light microscopy, demonstrating the syncytiotrophoblasts. B, a dark field image of a consecutive section showing the placental tissue after incubation with a radiolabeled LOXL2 oligomer. C, a dark field image using an LOXL2 sense oligomer. D, a diagram illustrating the structure and position of the syncytium in placental villous tissue.
The LOXL2 mRNA was detected in almost all human tissues analyzed with highest expression in several reproductive tissues, such as placenta, prostate, and uterus. Although both LOX and LOXL genes are expressed in placenta, the LOX gene shows highest expression in heart and lung, while the highest LOXL mRNA levels were noted in heart, skeletal muscle, and kidney (18). The results of in situ hybridizations confirmed abundant LOXL2 mRNA levels in the placenta and have identified the syncytiotrophoblasts as responsible for this high expression of the LOXL2 gene.

These findings support an earlier description of a protein that had been identified in the placenta with LOX activity but which was, however, different from LOX in its amino acid composition (30). Moreover, while LOX has been shown to be present in the amnion, one of the components that makes up the fetal membranes (31), we did not detect any LOXL2 mRNA in the fetal membranes using these conditions for the in situ hybridization that readily detected its expression in the placenta. Clearly, therefore, LOX and LOXL2 are expressed in very different locations within reproductive tissues. The highest steady state level of LOX mRNA was reported at 12 weeks of gestation, both in amnion and placenta (31, 32). Thereafter, we have observed increasing levels of LOXL2 mRNA between 14 and 40 weeks gestation in placenta, suggesting not only a different spatial but also a different temporal activity of the LOXL2 gene.

There is an additional and quite significant difference between LOXL2 and all the other lysyl oxidases. Comparison of hydropathy profiles of LOX, LOXL, and LOXL2 revealed that the LOXL2 protein, strikingly, had no evidence for the hydrophobic signal sequence necessary for extracellular transport that has been noted in all the other lysyl oxidases. This result suggested that the LOXL2 protein may be processed and transported through an intracellular pathway that is different from the processing of the other members of the lysyl oxidase family (33). This prediction is supported by our immunohistochemical observations using a LOXL2-specific antibody that localized LOXL2 intra- as well as extracellularly. 2

In summary, we have identified LOXL2 as a new member of the lysyl oxidase gene family. Although its precise processing and localization are not known, based on the presence of the copper-binding and catalytic domains, it is very likely that this protein will have a catalytic function either extra- or intracellularly.

A possible intracellular localization of LOXL2 coincides with recent reports of novel intracellular and intranuclear lysyl oxidases. However, it was not clear from these studies how the 32-kDa active and secreted form of lysyl oxidase could also have an intranuclear location (8, 9). A LOX-dependent alteration of chromatin structure has also been observed (34). This raises the possibility that LOX, or more likely an intracellular

2 C. Jourdan-Le Saux, H. Tronecker, L. Bogie, G. D. Bryant-Greenwood, C. D. Boyd, and K. Csiszar, unpublished observation.

LOXL2, may directly or indirectly exert effects on nuclear components (5, 8). An intracellular form of LOX was also found in association with fine, filamentous structure in the cytoplasm of fibroblasts, consistent with this form of LOX being a cytoskeletal protein (9). Based on the significant sequence homology and the intracellular localization of LOXL2, it is possible that this new protein is responsible for these reported intracellular and intranuclear catalytic functions and for at least some of the developmental and growth regulatory functions previously attributed to lysyl oxidase (LOX) (10, 15).

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