MOLECULAR CLONING OF cDNA ENCODING HUMAN LANOSTEROL SYNTHASE

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A cDNA encoding human lanosterol synthase, the enzyme responsible for the backbone formation step in sterol biosynthesis, was cloned by extensive application of PCRs. Five degenerate oligonucleotide primers (139S, 440S, 528A, 575A and 712A) corresponding to the homologous amino acid sequences among the known 2,3-oxidosqualene cyclase (OSC) were designed. PCR with one pair (440S and 528A) of five primers yielded a 285-bp fragment. PCRs with the primers based on the obtained fragment and the degenerate primers (139S and 712A) gave longer fragments. Finally, full nucleotide sequence of cDNA was obtained by a "rapid amplification of cDNA ends" (RACE) method.

KEY WORDS lanosterol synthase; cDNA; human liver; PCR; 2,3-oxidosqualene; lanosterol; cyclase

Lanosterol synthase catalyzes the cyclization of 2,3-oxidosqualene to lanosterol, which is one of the most complex biosynthetic reactions found in nature³⁾ and is situated in the center of cholesterol biosynthesis of mammals. Control of cholesterol biosynthesis at a later stage, after HMG-CoA reductase, is preferable for development of cholesterol-lowering drugs since inhibition of HMG-CoA reductase blocks production of dolichol, ubiquinone and protein prenylations. In this context, sterol biosynthetic enzymes such as squalene synthase, squalene epoxidase and lanosterol synthase are promising targets for control of cholesterol biosynthesis. Among these enzymes, lanosterol synthase plays a crucial role in the regulation of intracellular cholesterol level because of its dual functions.^{4,5)}

We have purified lanosterol synthase to homogeneous protein from rat liver⁶⁾ and cloned its cDNA for the first time from a mammalian source by PCR with the primers based on amino acid sequences of the purified protein.⁷⁾ Human lanosterol synthase is more attractive than rat lanosterol synthase, since human organs, tissue and enzyme are the ultimate targets for medicinal and pharmaceutical purposes, though it is hard to obtain human liver for purification of enzyme protein. As a part of our continuing studies on steroid and cyclic triterpenoid biosynthesis, we cloned human liver lanosterol synthase gene, taking advantage of the homology found in four known OSCs. Alignment of OSC amino acid sequences of rat,⁷⁾ *Saccharomyces cerevisiae*,^{8,9)} *Candida albicans*¹⁰⁾ and *Arabidopsis thaliana*¹¹⁾ (Fig. 2) shows that there are plenty of homologous regions, of which the sequences DGGWGLH, KG(A/G)(F/W)PFST, DY(T/P)YVECT, DGSW(E/Y) GSWG, and FPI(W/K)ALG, located at 139-145, 440-447, 528-535, 575-583 and 712-718 in rat lanosterol synthase, were chosen for primer design.

Reverse transcribed (SuperscriptIITM, BRL) cDNA was prepared from human fetal liver poly(A⁺)RNA (CLONTECH, CL6521-1) and used as a template in the following PCR. Two of the above primers, 139S (5'-GAYGGIGGITGGGGIYTICA-3') and 440S (5'-AARGGIGCITGGCCITTYWSIAC-3'), were synthesized in the sense direction, and the other three, 528A (5'-GTRCAYTCIACRTAIGGRTAITC-3'), 575A (5'-CCCAISWICCITMCCAISWICCRTC-3') and 712A (5'-CCIARIGCCCADATIGGAA-3'), were synthesized in the anti-sense direction for corresponding amino acid sequences. Nested PCR, which was effective for the cloning of rat cDNA⁷⁾, was applied from the beginning. The first PCR product, obtained by using 139S and 575A primers, served as a template of the second PCR. But the second PCR with 440S and 528A primers gave no apparent amplified bands of the expected size when analyzed by agarose

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		GAGAGCACTGCAGCAGCA	-1
	ATGACGGAGGGCAGCTGTCTGCGCGCCGAGGGGGCCCTACAAGACCGAGCCCGCCACCGACCTCGGCGCGCTGGCGGACTCAACTGCGGAG	90	
1	M T E G G T C L R R R G G G G P Y K T E P A T D L G R W R L N C E		
	AGGGGCCCGGACAGCTGAGACTACCTGCAGGACGAGCGCGCGCGGAGCAGACCGGCTGGAAGCCTACGCCCTGGGGCTGGACACCC	180	
31	R G R Q T W T Y T L Q D E R A G R E Q T G L E A Y A L G L D T		
	AAGAATTACTTTAAGGACTTGCCTAAAGCCCAACCGCCTTTGAGGGGGCTCTGAACCGGATGACATTTTACGTGGGGCTGCAGGCTGAG	270	
61	K N Y F K D L P K A H T A F E G A L N G M T F Y V G L Q A E		
	GATGGGCACTGGACGGGTGATTATGTGTGGCCCACTTTTCCTGCTGCCAGGCCCTCCTGATCACTTGCCACGTGGCAGCATCCCTCTGCCA	360	
91	D G H W T G D Y G G P L F L L P G L L I T C H V A R I P L P		
	GCCGATACAGAGAAGAGATTGTGCGGTACCTGCGGTACGTGCAGCTCCCTGACGGTGGGTGGGGCTGCACATTGAGGATAAGTCCACC	450	
121	A G Y R E E I V R Y L R S V Q L P D G G W G L H I E D K S T		
	GTGTTTGGGACTCGGCTCAACTATGTGTCTCTCAGAATCTTGGGTGTTGGGCTGACGATCCTGACCTGGTACGAGCCCGGAACATTTCTT	540	
151	V F G T A L N Y V S L R I L G V G P D D P D L V R A R N I L		
	CACAAGAAAGTGGTGTCTGGCCATCCCTCTCGGGGAAGTTCTGTGGCTGGCTGTCTGTAATGTTTACAGCTGGGAAGGCCCTCAATACC	630	
181	H K K G G A V A I P S W G K F W L A V L N V Y S W E G L N T		
	CTGTTCCAGAGATGTGGCTGTTTCTCTGACTGGGACCGGACACCCCTCCACACTCTGGTGGCACTGCGCGCAGGTGTACCTGCCCATG	720	
211	L F P E M W L F P D W A P A H P S T L W C H C R Q V Y L P M		
	AGCTACTGCTACGCGGTTCCGGCTGAGTGGCGCGGAAGACCCGCTGGTCCAGAGCTCCCGCAGGAGCTCTATGTGGAGGACTTCGCCAGC	810	
241	S Y C Y A V R L S A A E D P L V Q S L R Q E L Y V E D F A S		
	ATTGACTGGCTGGCGCAGAGGAACAACGTGGCCCCGACGAGCTGTACAGCCGACAGCTGGCTGCTCCGCGTGGTATATGCGCTCTCCTC	900	
271	I D W L A Q R N N V A P D E L Y T P H S W L L R V V Y A L L		
	AACCTGTATGAGCAACCACAGTGGCCCACTGCGGCGAGGGGCGGTGCAGAACTGTATGAACACATTTGTGGCCGACGACCGATTACCC	990	
301	N L Y E H H H S A H L R Q R A V Q K L Y E H I V A D R F T		
	AAGAGCATCAGCATCGGCGCGATCTCGAAAACCATCAACATGCTTGTGCGCTGGTATGTGGACGGGGCCGCTCCACTGCTTCCAGGAG	1080	
331	K S I S I G P I S K T I N M L V R W Y V D G P A S T A F Q E		
	CATGCTCCAGAAATCCCGGACTATCTCTGGATGGGCTTGACGGCATGAAAATGCAGGGCACCACGGCTCAGAGATCTGGGACACCGCA	1170	
361	H V S R I P D Y L W M G L D G M K M Q G T N G S Q I W D T A		
	TTCCGCAATCCAGGCTCTGCTTGAAGCGGGCGGGCACCAGCGCCGAGTTTTCGTCCTGCTGCAGAAAGGCTCATGAGTTCCTGAGGCTC	1260	
391	F A I Q E A L L E A G G H H R P E F S S C L Q K A H E L P R		
	TCACAGGTCCCGAGATAACCCCTCCGACTACCAAGAGTACTACCGCCAGATGGCAGGGTGGCTTCTCCTTCAGTACGCTGGACTCGCGC	1350	
421	S Q V P D N P D Y Q K Y Y R Q M R K G G F S F S T L D C G		
	TGGATCGTTTCTGACTGCAGGCTGAGGCTTGAAGGTGTGCTGCTCTCTGCAGGAGAAGTGTCCCATGTTCACCGAGCACATCCCGAGA	1440	
451	W I V S D C T A E A L K A V L L L L Q E K C P H V T E H I P R		
	GAACGCTCTGCGATGCTGTGGCTGTGCTGCTGAACATGAGAAATCCAGATGGAGGGTTCGCCACCTATGAGACCAAGCGTGGGGGAC	1530	
481	R L C D A V A V L L N M R N P D G G F A T Y E T K R G G H		
	TTGCTGGAGCTGTGAACCCCTCGGAGGTCTTCGGGGACATCATGATTGACTACACCTATGTGGAGTGCACCTCAGCCGTGATGACGGG	1620	
511	L L E L L N P S E V F G D I M I D Y T Y V E C T S A V M Q A		
	CTTAAGTATTTCCACAAGCGTTTCCCGGAGCACAGGGCAGCGGAGATCCGGGAGACCCCTACGCGAGGGCTTAGAGTTTCTGTCGGCGGCAG	1710	
541	L K Y F H K R F P E H R A A E I R E T L T Q G L E F C R R Q		
	CAGAGGGCCGATGGCTCTGGGAAGGCTCCTGGGGAGTTTGTCTTACCTACGGCACCTGGTTTGGCTGGAGGCTTCGCGCTGTATGGGG	1800	
571	Q R A D G S W E G S W G C F T Y G T W F G L E A F A C M G		
	CAGACCTACCGAGATGGGACTGCTGTGCAGAGAGTCTCCGGGCTGTGACTTCTGCTGTCCCGCAGATGGCAGACGAGGCTGGGGG	1890	
601	Q T Y R D G T A C A E V S R A C D F L L S R Q M A D G G W G		
	GAGGACTTTGAGTCTGCGAGAGGCGGCTTATTTCAGAGTGCCCATCCAGATCCATAACACATGCTGGGCCATGATGGGCTGATG	1980	
631	E D F E S C E E R R Y L Q S A Q S Q I H N T C W A M M G G L M		
	GCCGTTCGGCATCTGACATCGAGGCCAGGAGAGGAGTCCGGTGTCTACTTGAGAAACAGCTCCCCAATGGCGACTGGCGCGAGAA	2070	
661	A V R H P D I E A Q E R G V R C L L E K Q L P N G D W P Q E		
	AACATTGTGGGGTCTTCAACAAGTCTGTGCCATCTCTACACGAGCTACAGGAACATCTTCCCATCTGGGGCTCGGCGCTCTCTCC	2160	
691	N I A G V F N K S C A I S Y T S Y R N I F P I W A L G R F S		
	CAGCTGTACCTGAGAGAGCCCTTGCTGGCCACCCCTGAGAACATGCTTACCTGCTGGGTGCGGTCTGTGCGTTCATGCGCTTCAAGTC	2250	
721	Q L Y P E R A L A G H P *		
	ACAGGACGACGAGATTCCCATTCCTGCCCCTCTTCGGTGTATTATACACAGGAGGACTTCAGTGTGATGATCCCTGCCTTCAGTCTCTCTT	2340	
	TAGAATACATCTGTGTCAATCCATGTTTATAGAGGAGTGTATTTTCTGTTCACGAGAGGAGCTTTTGTTCACATTTGGATCAC	2430	
	AATGCAGAGAGTCTGTTCTCCCTCCCGCTCGGCTTCTCGGTGCTGGGAGGGTGACCTGTCCAGATGACTCATCCCTGACATGCTCTTG	2520	
	ACAAAGGACACCAAGAGGAGATGGCAGCTGTACCGGTGACGCTCTGTCTGAGGGGATATTTGCCTCAGTGTGATTAATAATCAGT	2610	
	CATGAAGA	2619	

Fig. 1. Nucleotide and Deduced Amino Acid Sequences of Human Liver Lanosterol Synthase cDNA. Nucleotides are numbered from the deduced initiation code ATG, and amino acid residues are from corresponding methionine.

electrophoresis. However, the fragment of expected size(285-bp) was obtained when PCR was repeated twice using 440S and 528A primers. This fragment was subcloned into pT7Blue(R) and sequenced. The deduced amino acid sequence of this fragment showed 88% identity to that of rat lanosterol synthase, indicating it to be a part of cDNA of human lanosterol synthase. This fragment was extended toward the 5'- and 3'- ends by PCRs using primers based on the sequence of this 285-bp fragment, primers 139S and 712A. Finally, a full nucleotide sequence of cDNA was obtained by application of RACE method.¹²⁾ As shown in Fig. 1, the full nucleotide sequence revealed the presence of 2196-bp ORF that encodes a 732 amino acid polypeptide with a molecular mass of 83 kDa.¹³⁾ Based on the amino acid sequences of affinity-labeled peptide of rat lanosterol synthase, a possible catalytic function of the motif DDXX(D/E) corresponding to DCTAE around C-457 in rat lanosterol synthase has been proposed.¹⁴⁾ However, our previous finding in rat cDNA⁷⁾ and our present finding in human cDNA that there are no DDXX(D/E) indicate that some experimental mistakes occurred in their peptide sequencing. The deduced amino acid sequence of the human lanosterol synthase exhibits 83%, 40%, 38% and 42% identity to those of the lanosterol synthases of rat,⁷⁾ *S. cerevisiae*,^{8,9)} and *C. albicans*¹⁰⁾ and that of 2,3-oxidosqualene:cycloartenol cyclase of *A. thaliana*,¹¹⁾ respectively. Only one gap between the positions 40 and 41 in the human lanosterol synthase was required to make the maximum matching to rat enzyme. The role of this gap is obscure but will be clarified by molecular biological studies such as site-directed mutagenesis. The expression of this cDNA in *erg7* deficient yeast mutant is now in progress to obtain human enzyme protein in quantities for mechanistic studies and screenings for its specific inhibitor from natural products.

hOSC	(Human Liver)	MTEGTCRLRR	GGPYKTEPAT	DLGRW-RLN-	CERGRQWTWY	---LQ-DEB-	AGREQTGLE	A-----YA	55		
OSC1	(Rat Liver)	MTEGTCRLRR	GGPYKTEPAT	DLIRW-RLH-	NEIGRQSWTY	---YQABED-	PGREQTGLE	A-----HS	56		
ERG7	(<i>S. cerevisiae</i>)	MTEFYSDTI	GLPK-KTDE-	--RLW-RLRT	DELGRQSWY	---LTPQO--	AANDPPSTF	TQ-----	49		
CAN	(<i>C. albicans</i>)	M--YYSEBI-	GLP-KTDL-	--SRW-RLRS	DALGRQTHWY	---LSQSE--	CESBPQSTF	VQ-----	47		
CYC	(<i>A. thaliana</i>)	MWKLKIAEG-	GSP-----	---MLRLTN	NHVGRQWEF	DPNLGTHEDL	AAYVEARKSF	SDNRVQKHS	58		
hOSC		-----L---	GL-DTKNY	FKDLP--KA	HTAH--EGAL	-NGMTFYVGL	-Q-AEDGHWT	GDYGGPLFL	PGLLITCHVA	115	
rOSC		-----L---	GL-DTTSY	FKNLP--KA	QTAH--EGAL	-NCVTFYAKL	GDYGGPLFL	PGLLITCHIA		116	
ERG7		-----WL---	LQDKFEP	QPN-BERNKH	SPDESADAC	HNCASPF-KL	LQEPDSCIFP	CQYKGPYMT	IGYVAVNYIA	116	
CAN		-----WL---	ESPDFFP	SP--ESSDIH	TSG---EAA	RKCADPL-KL	LQL-DNGIFP	CQYKGPYMT	IGYVTANYYS	108	
CYC		ADLLMLRQFS	RENLI SPVLP	QVK-IEDTDD	VTEEMVETTL	KRGLDPYS-T	IQ-AEDGHWP	GDYGGPLFL	PGLLITLSIT	135	
hOSC		R---IPLPAG	YREEIVRYLR	SVQLP-DGGW	GLHIEDKSTV	FGTALNYSVL	RILGVGPDDP	D--LVRARNI	LHKKGGAVAL	189	
OSC1		H---IPLPAG	YREEIVRYLR	SVQLP-DGGW	GLHIEDKSTV	FGTALNYSVL	RILGVGPDDP	D--LVRARNI	LHKKGGAVAL	190	
ERG7		G---IPLPAG	YREEIVRYLR	SVQLP-DGGW	GLHIEDKSTV	FGTALNYSVL	RILGVGPDDP	D--LVRARNI	LHKKGGAVAL	191	
CAN		K---TEIPBEH	YRVEMIRYIV	NTAHFVDDGG	GLHSDVKSTC	FGTINNYVL	RULGMEDHDP	V--LWKARKT	LHRIGGAALK	183	
CYC		GALNTVLSQK	HQQEMRRLYLY	NHQNEDGGW	GLHIEGPTSM	FGSVLNNYVL	RULGEGENDG	DGDMEKGRDW	ILKMGGAATN	214	
hOSC		PSWGWFLAV	LNVSWEGLN	TLFPFEMWLP	DWFAHPSSTL	WCHCRQVYLP	MSYCYAVRLS	AEEDPLVQSL	ROELYVED--	269	
OSC1		PSWGWFLAV	LNVSWEGLN	TLFPFEMWLP	DWFAHPSSTL	WCHCRQVYLP	MSYCYAVRLS	AEEDPLVQSL	ROELYVED--	270	
ERG7		PSWGWFLAV	LNVSWEGLN	TLFPFEMWLP	DWFAHPSSTL	WCHCRQVYLP	MSYCYAVRLS	AEEDPLVQSL	ROELYVED--	268	
CAN		PSWGWFLAV	LNVSWEGLN	TLFPFEMWLP	DWFAHPSSTL	WCHCRQVYLP	MSYCYAVRLS	AEEDPLVQSL	ROELYVED--	263	
CYC		PSWGWFLAV	LNVSWEGLN	TLFPFEMWLP	DWFAHPSSTL	WCHCRQVYLP	MSYCYAVRLS	AEEDPLVQSL	ROELYVED--	291	
hOSC		-PASIDWIAQ	RNNVAP-DEL	YTPHSWLLRV	VYALLNLYE-	----HHHSAH	LRQRAVQKLY	EHIVADDRFT	KSISIGPISK	340	
OSC1		-FASIDWPAQ	RNNVAP-DEL	YTPHSWLLRV	VYALLNLYE-	----RPHSTS	LRQRAVQKLY	EHIVADDRFT	KSISIGPISK	341	
ERG7		PDDKINFSKN	RNTVCGVD-L	YYPHSTLNI	ANSIVVHYEK	YLRNRF----	YSLSKKRVY	DLTKTELONT	DSLGIAPVNO	343	
CAN		PYESIKFGNQ	RNNVCGVD-L	YYPHSTLNI	ANSIVVHYEK	-VRPKM----	LLNWNKRVY	DLTKTELONT	EYLCIAPVNO	337	
CYC		PYHEVNNBEA	RN-LCAKEDL	YYPHSTLNI	ANSIVVHYEK	PVLMRWPCAN	LRQRAVQKLY	EHIVADDRFT	KSISIGPISK	370	
hOSC		TNNMLVRWV	DGPASIAFOE	HVSRIEDYLW	MGLDGMKMQG	TNGSQIWDTA	FAIQALLEAG	GHRPPESSC	LQKAHEFLRL	420	
OSC1		TNNMLVRWV	DGPASIAFOE	HVSRIEDYLW	MGLDGMKMQG	TNGSQIWDTA	FAIQALLEAG	GHRPPESSC	LQKAHEFLRL	421	
ERG7		AFCALVTLLE	BCVDSFAFOR	LQYREKDLF	HCPGCMITVC	TNGSQIWDTA	FAIQALLEAG	GHRPPESSC	LQKAHEFLRL	423	
CAN		ANNMVVTCYH	RCSBSEAFKK	LQYREKDLF	HCPGCMITVC	TNGSQIWDTA	FAIQALLEAG	GHRPPESSC	LQKAHEFLRL	417	
CYC		VNNMLCCW-V	ELPNSAEKFL	HLPRTHDELW	LAEDGMKMQG	YNGSQIWDTA	FAIQALLEAG	GHRPPESSC	LQKAHEFLRL	447	
hOSC		SQVPDNEPDY	QKY-YRQMRK	GGFSESTLDC	GWIVSDCTAE	ALKAVILLQE	KCF-HVTEH-	IPRERIDAV	AVLLNMRNPD	497	
OSC1		SQVPDNEPDY	QKY-YRQMRK	GGFSESTLDC	GWIVSDCTAE	ALKAVILLQE	KCF-HVTEH-	IPRERIDAV	AVLLNMRNPD	498	
ERG7		AQDTECVPG	---SYDRKK	GAWGFSTKTQ	GYIVADCTAE	AKKAIIMVKN	SPVSEVHHM	ISSERLEFEG	DVLLNLQMG	500	
CAN		SOFTBNVDG	---SRDRRK	GAWGFSTKTQ	GYIVADCTAE	AKKAIIMVKN	HASFADIRDE	TKDENLQMG	EVLLQIONVG	494	
CYC		SQVLEDCPD	LNLYRHRISK	GAWGFSTADH	GWIVSDCTAE	GLKALLLSK	VPK-EIVGEP	IDAKELIYAV	NVITSLQND	526	
hOSC		---GGFATY	ETKRGGLLE	LLNPSEVFGD	IMIDYTYVEC	TSAMVQALRY	PHKRFPPHRA	AEIRETLNQG	LEFCRRQORA	573	
OSC1		---GGFATY	ETKRGGLLE	LLNPSEVFGD	IMIDYTYVEC	TSAMVQALRY	PHKRFPPHRA	AEIRETLNQG	LEFCRRQORA	574	
ERG7		SFEYGSFATY	EKIRAPLAME	TLNPAEVEFN	IMVEYTYVEC	TDSSVLGLAY	PHKRFPPHRA	AEIRETLNQG	LEFCRRQORA	579	
CAN		EWEYGSFATY	EKIRAPLAME	TLNPAEVEFN	IMVEYTYVEC	TDSSVLGLAY	PHKRFPPHRA	AEIRETLNQG	LEFCRRQORA	574	
CYC		---GGFATY	ETKRGGLLE	LLNPSEVFGD	IMIDYTYVEC	TSAMVQALRY	PHKRFPPHRA	AEIRETLNQG	LEFCRRQORA	602	
hOSC		-DGSWEGSWG	VCFTYGTWFG	LEAFACMGQT	YRQGTACAEV	SRACDFLLSR	QADGGGWGED	FESCEBERRY-	-LQSAQSQIH	650	
OSC1		-DGSWEGSWG	VCFTYGTWFG	LEAFACMGQT	YRQGTACAEV	SRACDFLLSR	QADGGGWGED	FESCEBERRY-	-LQSAQSQIH	651	
ERG7		-DGSWEGSWG	VCFTYGTWFG	LEAFACMGQT	YRQGTACAEV	SRACDFLLSR	QADGGGWGED	FESCEBERRY-	-LQSAQSQIH	653	
CAN		-DGSWEGSWG	VCFTYGTWFG	LEAFACMGQT	YRQGTACAEV	SRACDFLLSR	QADGGGWGED	FESCEBERRY-	-LQSAQSQIH	649	
CYC		-DGSWEGSWG	VCFTYGTWFG	LEAFACMGQT	YRQGTACAEV	SRACDFLLSR	QADGGGWGED	FESCEBERRY-	-LQSAQSQIH	678	
hOSC		NTCWAMGLM	AVRHP--DIE	AQERGVRCLL	EKQLPNGDWE	QENIAGVFNK	SCAISYTSYR	NIFPIWALGR	FSQLYPBRAL	AGHP	732
OSC1		NTCWAMGLM	AVRHP--DIE	AQERGVRCLL	EKQLPNGDWE	QENIAGVFNK	SCAISYTSYR	NIFPIWALGR	FSQLYPBRAL	AGHP	733
ERG7		QFAWALILL	PAEYB--NKE	VIDRGIDLLM	NROEESCEMK	FESVGEVFNH	SCAISYTSYR	NIFPIWALGR	FSQLYPBRAL	AGHP	731
CAN		QFAWALILL	PAEYB--NKE	VIDRGIDLLM	NROEESCEMK	FESVGEVFNH	SCAISYTSYR	NIFPIWALGR	FSQLYPBRAL	AGHP	728
CYC		NTAWAMLLAI	GAGQAEVDRK	PLHRAAFMLI	NAQMGNDSE	QOETMGVFNH	SCAISYTSYR	NIFPIWALGR	FSQLYPBRAL	AGHP	759

Fig. 2. Comparison of Amino Acid Sequence of Human Liver Lanosterol Synthase to Other OSCs. The deduced amino acid sequences of lanosterol synthase of rat(OSC1), *S. cerevisiae* (ERG7) and *C. albicans* (CAN) are from Refs. 7, 8 and 10, and that of 2,3-oxidosqualene: cycloartenol cyclase of *A. thaliana* (CYC) is from Ref. 11. Hyphens were inserted to maximize homology. Amino acid residues identical to that of human liver lanosterol synthase are boxed.

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