Cholesteryl Ester Transfer Protein Expressed in Lecithin: Cholesterol Acyltransferase-Deficient Mice. *Arterioscler. Thromb. Vasc. Biol.* (2002) 22: 1347-1353

164. Y Wada, A Sugiyama, T Yamamoto, M Naito, N Noguchi, S Yokoyama, M Tsujita, Y Kawabe, M Kobayashi, A Izumi, T Khoro, T Tanaka, H Taniguchi, H Koyama, K Hirano, S Yamashita, Y Matsuzawa, E Niki, T Hamakubo T Kodama. Lipid accumulation in smooth muscle cells under LDL loading is independent of the LDL receptor pathway and enhanced by hypoxic conditions. *Arterioscler. Thromb. Vasc. Biol.* (2002) 22: 1712-1719

165. J Ito, Y Nagayasu, S Ueno S Yokoyama. Apolipoprotein-Mediated Cellular Lipid Release Requires Replenishment of Sphingomyelin in a Phosphatidylcholine-Specific Phospholipase C-Dependent Manner. *J. Biol.* Chem. (2002) 277: 44709-44714.

166. Y Yamauchi, S Abe-Dohmae S Yokoyama. Differential Regulation of Apolipoprotein A-I/ATP binding Cassette Transporter A1-mediated Cholesterol and Phospholipid release. *Biochim. Biophys. Acta* (2002) 1585: 1-10.

167. A Goto, K Sasai, S Suzuki, T Fukutomi, S Ito, T Matsushita, M Okamoto, T Suzuki, M Itoh, K Okumura-Noji, S Yokoyama. Plasma Concentrations of LPL and LCAT are in Putative Association with Female Sex and Alcohol That are Independent Negative Risk Factors For Coronary Atherosclerosis in Japanese. *Clin. Chim. Acta* (2002) 329, 69-76.

168. Toyota T, Oikawa S, the Beraprost Sodium Study Group: Effects of beraprost Sodium (Dorner) in patients with diabetes mellitus complicated by chronic arterial obstruction. Angiology 53(1)7-13, 2002

169. Saito T, Ishigaki Y, Oikawa S, Yamamoto T: Etiological significance of apolipoprotein E mutations in lipoprotein glomerulopathy. Trends Cardiovasc Med 12(2) 63-67, 2002

170. Nagashima T, Oikawa S, Hirayama Y, Tokita Y, Sekikawa A, Ishigaki Y, Yamada R, Miyazawa T: Increase of serum phosphatidylcholine hydroperoxide dependent on glycemic control in type 2 diabetic patients. Diab Res Clin Pract 56(1)19-25, 2002

171. Tanaka S, Tanabe Y, Tamura H, Ishii S, Shuto Y, Kamegai J, Sugihara H, Kobayashi M, Wakabayashi I, Murano T, Shirai K, Oikawa S: Chylomicronemia caused by lipoprotein lipase gene mutation related to a hyper-response of insulin secretion to glucose. Int Med. 41: 300-303, 2002

172. Shuto Y, Shibasaki T, Otagiri A, Kuriyama H, Ohata H, Tamura H, Kamegai J, Sugihara H, Oikawa S, Wakabayashi I: Hypothalamic growth hormone secretagogue receptor regulates growth hormone secretion, feeding, and adipposity. J Clin Invest 109(11): 1429-1436, 2002.

173. Tamura H, Kamegai J, Shimizu T, Ishii S, Sugihara H, Oikawa S: Ghrelin stimulates GH but not food intake in arcuate nucleus ablated rats. Endocrinology 143(9)3268-3275, 2002

174. Ishii S, Kamegai J, Tamura H, Shimizu T, Sugihara H, Oikawa S: Role of ghrelin in streptozotocin-induced diabetic hyperphagia. Endocrinology 143(12): 4934-4937, 2002

175. Kotake H, Sekikawa A, Tokita Y, Ishigaki Y, Oikawa S: Effect of HMG-CoA reductase inhibitor on plasma cholesteryl ester transfer protein activvity in primary hypercholesterolemia: Comparison among CETP/Taq1B genotype subgroups. J Atheroscler Thromb 9(5): 207-212, 2002

176. Eto M, Saito M, Nakata H et al : Type III

hyperlipoproteinemia with apolipoprotein E2/2 genotype in japan. Clinical Genetics 61:416-422, 2002

177. Matsuzaki M, Hiramori K, Imaizumi T, Kitabatake A, Hishida H, Nomura M, Fujii T, Sakuma I, Fukami K, Honda T, Ogawa H, Yamagishi M.Intravascular ultrasound evaluation of coronary plaque regression by low density lipoprotein-apheresis in familial hypercholesterolemia: the Low Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial (LACMART). *J Am Coll Cardiol.* 2002 Jul 17;40(2):220-227.

178. Takahashi T, Yano M, Minami J, Haraguchi T, Koga N, Higashi K, Kobori S. Sarpogrelate hydrochloride, a serotonin2A receptor antagonist, reduces albuminuria in diabetic patients with early-stage diabetic nephropathy. *Diabetes Res Clin Pract.* 2002 Nov;58(2):123-9.

H. 知的財産権の出願、登録状況

特になし。

厚生労働科学研究費補助金難治性疾患克服研究事業
研究課題：原発性高脂血症に関する調査研究
課題番号：H14-難治-11

研究目的

１）高脂血症の診断指針と病態解析におけるゲノム解析の有用性の検討
２）ハイリスク高脂血症の診断と病態および発症要因に関する研究
３）小児高脂血症におけるFCHLおよびFHの診断法の確立
４）動脈硬化発症におけるHDLに関する研究
５）高脂血症に関する各種検査法の実態調査

研究成果の概要

１）日本人の高脂血症起因遺伝子異常、家族性高コレステロール血症（FH）、2000年調査解析のゲノムデータベースの作成を終了し公表した。一般住民のSNPs解析の中間解析を公表した。
２）家族性複合型高脂血症（FCHL）の診断基準に沿って実際に同定された症例の解析から、その有用性と今後検討する必要性のある項目が明確化された。
３）小児FHの診断基準(案)が作成された。小児のFCHLの診断基準が新たに必要なことが明らかになった。
４）低HDL血症の治療による心筋梗塞の予防効果のシミュレーションから、心筋梗塞の 予防期待値はLDL低下を上回ることが明らかになった。
５）LDL-コレステロール測定のための各々の直接法の比較から、標準化の問題点が明確に なった。

これらの研究成果の一部は、日本動脈硬化学会英文誌に発表され、遺伝子解析 に関わるデータベースは学会ホームページから閲覧可能となる。

高脂血症の診断指針と病態解析におけるゲノム解析の有用性の検討
－日本人の高脂血症起因遺伝子異常－

・原発性高脂血症調査研究班（北班）で実施された全国レベルの症例調査の結果を基礎に、平成15年末までに学会・論文等で公表された遺伝子変異を調査蒐集し、遺伝子ごとに集計された。

・日本人原発性高脂血症及び関連疾患の原因遺伝子変異として、現在までに15遺伝子、195変異が報告された。

・日本動脈硬化学会英文誌に公表された（*J Atheroscler Thromb.* 2004;11:131-45.）。本データベースは学会ホームページにリンクされる。

・原発性高脂血症起因遺伝子データベースが一般臨床現場からアクセス可能になり、高脂血症診療におけるゲノム解析情報を組み入れることを可能にする。

表1．日本人で報告されたLDL受容体遺伝子異常

Exon/in	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
intron 1	AS-1G→C		G→C at AS-1	3' splice signal	class 1	Murayama T	Hum Mutat 11: 467-481, 1998
exon 2	W23X	Nanao	G→A at 132	Trp→Stop at 23	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 2	C25Y †		G→A at 137	Cys→Tyr at 25	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 2	D26N		G→A at 139	Asp→Asn at 26	NP	Yamt M	Nucl Acid Res 26: 248-252, 1998
exons2-3	Ins1-Ins3 del		deletion of Skb	deletion of exons2, 3	class 3	Yamakawa K	Hum Genet 82: 317-321, 1989
exons2-3	Ins1-Ins3 del		deletion of 1kb	deletion of exons2, 3	NP	Kajinami K	J Biochem (Tokyo) 113: 372-376, 1993
exons2-3	Ins1-Ins3 del	Tenaru-2	deletion of 10kb	deletion of exons2, 3	class 3	Kajinami K	Circulation(Suppl) 95: II-276, 1997
exons2-4	Ins1-Ins4 del	Kanagawa-1	deletion of 12kb	deletion of exons2-4	NP	Kajinami K	J Intern Med 227: 247-250, 1990
exon 3	C242		T→A at 223	Cys→Tyr at 54	class 2	Ezu M	Jpn Heart J 39: 785-796, 1998
exon 3	253delG †		deletion of G at 253	frameshift	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 3	C246 †		G→T at 244	Cys→Phe at 61	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 3	C246Z		C→A at 285	Cys→Stop at 74	class 1	Hamasima T	J Hum Genet 44: 256-258, 1999
exon 3	C248 † §		T→G at 286	Cys→Gly at 74	NP	Miyake Y	Dermatological Sc 16: 195, 1998
exon 3	C248 †		G→T at 288	Cys→Phe at 74	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	327insC †		insertion of C at 327	premature stop at codon 152	NP	Hoeks P.	Ann Clin Biochem 39(Pt6): 526-530, 2002
exon 4	P343H	Fukuoka	G→A at 344	Arg→His at 64	NP	Yamt M	Nucl Acid Res 26: 248-252, 1998
exon 4	355delTp †		deletion of CCCGAAGT at 355	premature stop at codon 163	NP	Hutton H	Hum Mutat 14: 87, 1999
exon 4	C360G †		T→G at 361	Cys→Gly at 100	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	D389T †		T→A at 358	Ser→Thr at 109	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	396insC †		insertion of C at 389	frameshift	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	E419K	Philippines	G→A at 415	Glu→Lys at 119	class 2B	Hobbs HH	Hum Mutat 1: 445-466, 1992
exon 4	C434R †		T→C at 490	Cys→Arg at 134	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	C434F †		T→C at 491	Cys→Arg at 139	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	C434F †		T→C at 500	Cys→Arg at 163	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	V465M †		G→A at 565	Val→Met at 168	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	C481R †		G→C at 411	Cys→Ser at 123	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 4	E207K † §		G→A at 425	Glu→Lys at 207	NP	Miyake Y	Dermatological Sc 16: 195, 1998
exon 5	D234N †	Niha	G→A at 296	Asp→Asn at 245	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 5	D241 †		A→G at 297	Asp→Gly at 245	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 6	D283Y	Tsuruga	G→T at 391	Asp→Tyr at 280	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 7	C317R	Wakayama	T→A at 1012	Cys→Ser at 317	class 2	Hamasima T	J Intern Med 235: 163-165, 1994
exon 7	C317R	Oda	T→C at 1012	Cys→Arg at 317	NP	Yamt M	Nucl Acid Res 26: 248-252, 1998
exon 7	P320X †		C→T at 1048	Arg→Stop at 329	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exons7-14	Ins-Ins14 del	Osaka-2	deletion of 12kb	deletion of exons8-14	class 5	Miyake Y	J Biol Chem 264: 19784-19789, 1989
exons7-14	Ex7-Ins14 del	Okayama	deletion of 18kb	deletion of exons8-14	NP	Kajinami K	J Intern Med 227: 247-250, 1990
exon 8	376insT †		insertion of T at 1021	frameshift	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 8	D384N	Kanagawa	G→C at 1056	Asp→His at 335	NP	Yamt M	Nucl Acid Res 26: 248-252, 1998
exon 8	111*del9bp, ins19p		deletion of 9bp, insertion of 19p from 1115	Gly Gly Gly Tyr→Ala Leu Asn Ser from 353	NP	Yamakawa K	Hum Genet 82: 317-321, 1989
exon 8	C394Y		G→A at 1133	Cys→Tyr at 358	class 5	Hamasima T	J Hum Genet 43: 253-254, 1998
exon 8	1050insC † §		insertion of C at 1050	frameshift	NP	Miyake Y	Dermatological Sc 16: 211, 1997
exon 9	F503L		T→A at 1067	Phe→Leu at 372	NP	Yamt M	Nucl Acid Res 26: 248-252, 1998
exon 9	1124insCbp		insertion of 5bp at 1124	frameshift after Arg395	NP	Hutton H	Hum Mutat 14: 87, 1999
exon 9	P550W §	Mieruka	C→T at 1246	Arg→Trp at 395	defective	Yagi K	Dermatological Sc 22: 195, 2000
exon 9	E567K †		G→A at 1252	Glu→Lys at 397	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 9	V468M	Afrikaner-2	G→A at 1285	Val→Met at 402	NP	Yamt M	Nucl Acid Res 26: 248-252, 1998
exon 9	A481T †		G→A at 1291	Ala→Thr at 410	NP	Hutton H	Hum Mutat 14: 87, 1999
exon 9	D482H	Osaka-3	G→C at 1297	Asp→His at 412	class 2	Miyake Y	Eur J Biochem 219: 1-7, 1994
exon 13	A627E §		C→A at 1532	Ala→Glu at 429	class 2B	Miyake Y	Dermatological Sc 16: 195, 1997
exon 13	V503M †		G→A at 1567	Val→Met at 502	class 2A	Ye W	Atherosclerosis 165: 335-342, 2002
intron 10	1567-1 G→AAt		G→A at 1567-1	3' splice signal	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 11	W512X †		G→A at 1599	Trp→Stop at 512	NP	Hutton H	Hum Mutat 14: 87, 1999
exon 11	1657insC †		insertion of C at 1657	premature stop at codon 559	NP	Hutton H	Hum Mutat 14: 87, 1999
exon 11	L547V †		C→G at 1702	Leu→Val at 547	NP	Hutton H	Hum Mutat 14: 87, 1999
intron 11	1705+1 G→C		G→C at 1705+1	5' splice signal	class 1	Miyake Y	Int Symposium Lipoprotein Metabolism&Atherogenesis, Kyoto
exon 13	S756Z §		C→G at 1757	Ser→Stop at 565	NP	Miyake Y	Dermatological Sc 16: 195, 1997
exon 12	1727insG		insertion of G at 1723	frameshift	class 1	Hamasima T	J Hum Genet 43: 255-256, 1998
exon 12	P574Q		C→A at 1754	Arg→Gln at 574	NP	Yamt M	Nucl Acid Res 26: 248-252, 1998
exon 12	P587S		C→T at 1822	Pro→Ser at 587	class 2	Hamasima T	J Hum Genet 43: 255-256, 1998
intron 12	1845+2 T→C	Nagata	T→C at 1845+2	5' splice signal	class 1	Matsumura T	Eur J Biochem 232: 709-716, 1995
exon 13	1913delT		deletion of T at 1913	frameshift	class 1	Hamasima T	J Hum Genet 43: 256-258, 1998
exon 13	1867delATC †		deletion of ATC at 1867-1869	deletion of Ile at 602	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 13	L621S †		T→G at 1925	Leu→Ser at 621	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 14	G655D †		G→A at 2026	Gly→Ser at 655	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 14	2035insT †		insertion of T at 2035	premature stop at codon 696	NP	Hutton H	Hum Mutat 14: 87, 1999
exon 14	P664L	Kanazawa-2	C→T at 2054	Pro→Leu at 664	class 2B	Soutar AK	Proc Natl Acad Sci USA 86: 4186-4190, 1989
exon 14	2055delG †		deletion of G at 2055	frameshift	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 14	E693K †		G→A at 2149	Glu→Lys at 693	NP	Hutton H	Hum Mutat 14: 87, 1999
exon 15	Ins14-Ins15 del	Tenaru-1	deletion of 6kb	deletion of exon 15	NP	Kajinami K	Arterioscler 8: 187-192, 1988
exon 15	2159delCA	Mukawa	deletion of CA at 2159 or 2291	frameshift after Thr713	NP	Tadaro J	Eur J Clin Invest 28: 712-719, 1998
exon 15	Q716X §	Yokote	C→T at 2215	Gln→Stop at 718	NP	Higashikata T	Dermatological Sc 25: 847, 1994
exons15-16	Ins14-Ins16 del		deletion of 5.5kb	deletion of exons15, 16	NP	Yamakawa K	Hum Genet 82: 317-321, 1989
intron 15	2312-3 C→AAt		C→A at 2312-3	3' splice signal	NP	Ye W	Atherosclerosis 165: 335-342, 2002
exon 16	1955delT		deletion of T at 1955	frameshift after Asp630	NP		
exons16-17	Ins15-Ins17 del		deletion of 6kb	deletion of exons16, 17	NP	Yamakawa K	Hum Genet 82: 317-321, 1989
exons16-18	Ins15-Ex18 del	Osaka-1	deletion of 7.9kb	deletion of exons16-18	class 4B	Miyake Y	Proc Natl Acad Sci USA 79: 5151-5155, 1982
exon 17	2412insG §		insertion of G after 2412	frameshift after Gly784	NP	Miyake Y	Dermatological Sc 22: 146, 1999
exon 17	K790X		A→T at 2431	Lys→Stop at 790	class 1, 4	Murayama T	Arterioscler Thromb Vasc Biol 15: 1783-1785, 1995

†：Mutation reported after the closing of registration to the Research Committee in 1998

高脂血症の診断指針と病態解析におけるゲノム解析の有用性の検討

―全国レベルの症例調査における家族性高コレステロール血症の集計―

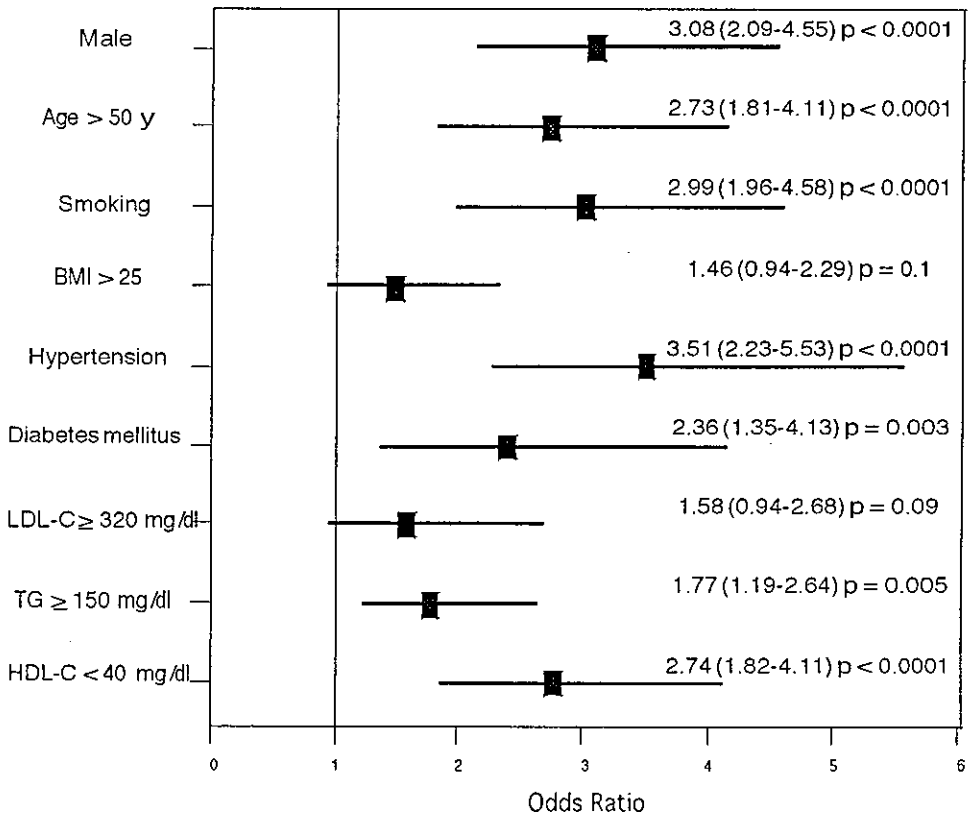
・全国レベルの症例調査のデータベースから、家族性高コレステロール血症の病態が集計された。

・家族性高コレステロール血症ホモ接合体19症例、ヘテロ接合体641症例が登録された。

・日本動脈硬化学会英文誌に公表された（*J Atheroscler Thromb.* 2004;11:146-51）。本データベースは学会ホームページにリンクされる。

・原発性高脂血症起因遺伝子データベースが一般臨床現場からアクセス可能になり、家族性高コレステロール血症の診療における病態およびゲノム解析情報を組み入れることを可能にする。

図　FHにおける冠動脈疾患危険因子のオッズ比



高脂血症の診断指針と病態解析におけるゲノム解析の有用性の検討
ー2000年調査解析ー

・1960年より10年ごとに行われている西暦2000年の日本人の血清脂質調査の解析が集計された。約１万２千人の血清脂質調査のなかでインフォームドコンセントにより同意を得た2267名の遺伝子解析が行われ血清脂質との関連が解析された。

・ 脂質関連因子の変異である遺伝子多型と血中コレステロール、中性脂肪値との相関が明らかになった。

・ 日本動脈硬化学会英文誌に公表される（*J Atheroscler Thromb.* 2005 in press）。本データベースは学会ホームページにリンクされる。

	野生型	ヘテロ	ホモ
CETP 1452GA	99.5%	0.5%	0.0%
CETP D442G	92.6%	7.3%	0.1%
LPL S447X	78.0%	20.7%	1.3%
	B1/B1	**B1/B2**	**B2/B2**
CETP Taq1B	35.8%	48.4%	15.8%
	C/C	**C/C**	**T/T**
HTGL 514CT	24.9%	50.4%	24.7%
MTHFR C667T	32.7%	49.0%	18.3%
	C/C	**C/G**	**C/G**
ApoCIII Sst	42.0%	45.8%	12.2%

日本人の脂質代謝異常の起因遺伝子のデータベースの作成

― 動脈硬化発症に関する多様性の原因である遺伝子異常の重積に関する一般住民のSNPs解析 ―

・高脂血症を有する一般住民におけるゲノムワイドおよび脂質関連SNPs解析を実施した。

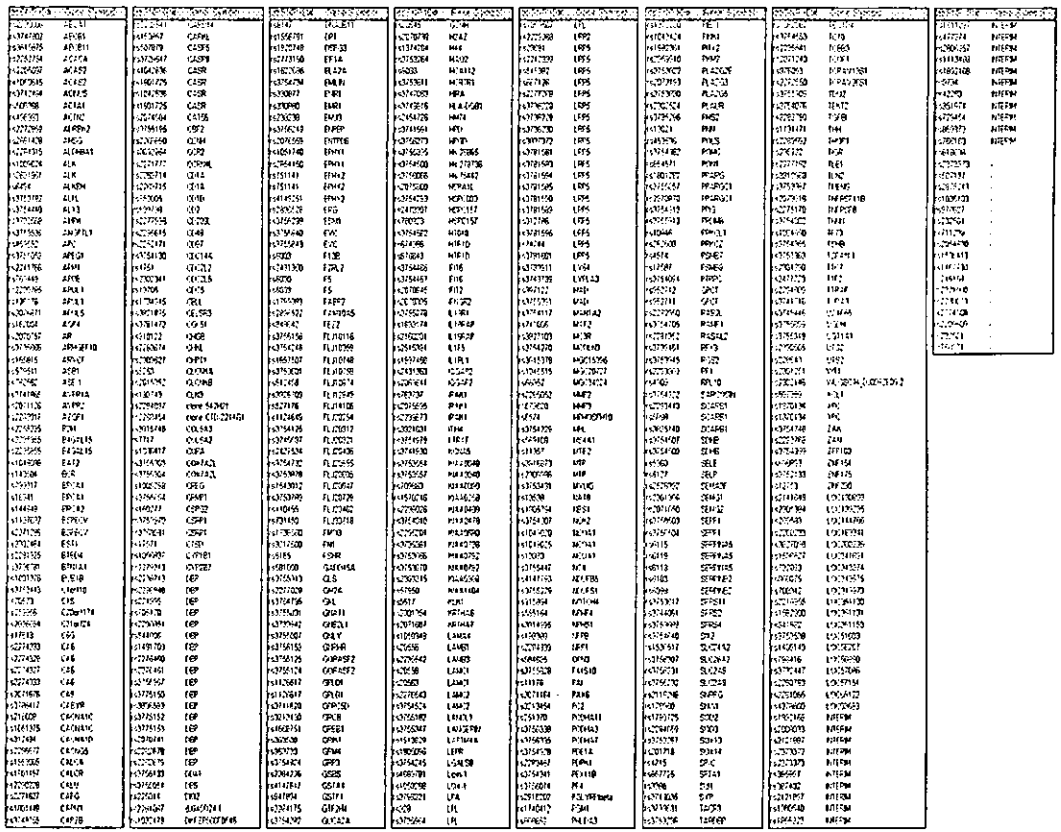
・1100検体の登録、547SNPsのタイピングを終了した。362検体、413SNPsの中間集計結果を公表した。

・動脈硬化進展度と6種類、LDL-コレステロールと6種類、HDLコレステロールと5種類、中性脂肪と5種類の関連SNPsが同定された。

・動脈硬化進展度へのSNPsと危険因子の寄与度を明らかにした。

・研究成果は英文誌に公表され（*J Hum Genet.* 2003;48:305-8、2003;48:447-50、2004;49:24-8）、本データベースは日本動脈硬化学会ホームページにリンクされる。

表　ゲノムワイドおよび脂質関連SNPsの一覧



ハイリスク高脂血症の診断と病態および発症要因に関する研究
ー　家族性複合型高脂血症(FCHL) の診断と病態　ー

・家族性複合型高脂血症(FCHL)と診断された100症例の臨床像が解析された。

・異なった地区におけるFCHLの症例解析から、血清脂質、アポ蛋白の特徴が明らかになった。

・ FCHLのアポB高値およびsmall dense LDLの存在の特異性を検討する必要がある。

・新FCHLの診断基準に沿った症例と家族歴から診断された症例の病態の比較が今後必要である。

・診断基準の普及により、冠動脈疾患の基礎疾患として最も頻度の高い高脂血症であるFCHLの治療体制の確立が可能になる。

表 1　FCHLの臨床像の比較

	千葉大学	金沢大学	
年齢	60±8 歳	52±2.8 歳	(p<0.001)
BMI	24.9±3.3 kg/m^2	24.3±2.8 kg/m^2	(ns)
TC	230±31mg/dl	235±35mg/dl	(ns)
TG	255±131mg/dl	200±115mg/dl	(<0.05)
LDL-C	138±31mg/dl	160±38mg/dl	(<0.05)
HDL-C	46±12 mg/dl	44±14mg/dl	(ns)
Apo A-I	133±22 mg/dl	122±29 mg/dl	(<0.05)
Apo A-II	31±5.5 mg/dl	35±7.8 mg/dl	(<0.05)
Apo B	136±23 mg/dl	135±30 mg/dl	(ns)
Apo CII	5.7±2.2 mg/dl	6.7±2.9 mg/dl	(<0.05)
Apo CIII	14±4.9 mg/dl	14±5.5 mg/dl	(ns)
Apo E	6.5±2.1 mg/dl	5.7±1.8 mg/dl	(<0.05)

小児高脂血症におけるFCHLおよびFHの診断法の確立

・幼児FHスクリ-ニング結果及び日本人学童の総コレステロ-ル(TC)値から家族性高コレステロール血症（FH)の診断基準(案)を作成した。

1. 血清総コレステロール値220 mg/dl以上でIIaまたはIIbの表現型を示す。

2. 第1度近親者にFH確診例がみられる。

3. LDL受容体の分析により受容体活性低下ないし異常が認められる。

１，２を満たした場合FHと診断する。 ３は努力目標とする。

・この診断基準案の妥当性を全国アンケ-ト調査により評価する必要がある。

・本診断基準の確定により、小児におけるFHの診断が可能になり早期からの動脈硬化性疾患の予防のためのフォローアップ体制が確立できる。

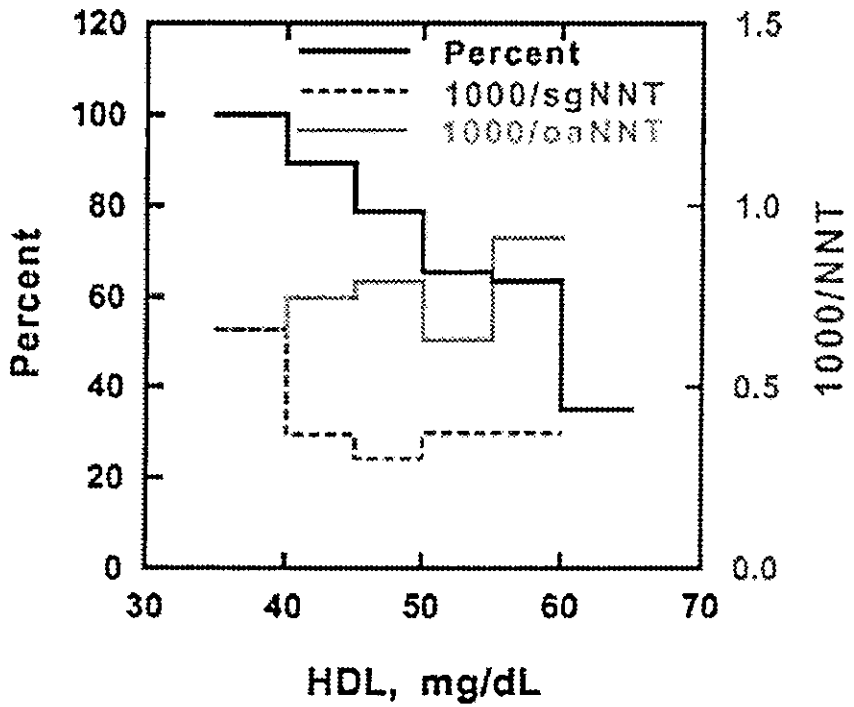
動脈硬化発症におけるHDLに関する研究

・ 1990 年の本研究班による日本人の年齢別・性別のLDL、HDLの濃度分布と1995年の国勢調査による年齢・性別人口、及びJ-LIT による性別のLDL、HDL依存心筋梗塞発症率から、それぞれの低下・上昇による発症予防のNNTを計算し、治療効率のシミュレーションを試みた。

・ LDL低下による予防効率は目標が160 mg/dL より高ければHDLに勝るがそれ以下では急速に低下する。これに比べ、HDL上昇による予防効率は目標値に関わらず一定であった。その結果、LDL低下による心筋梗塞の最大達成率は40 %、HDL上昇によるそれは65 % と試算された。

・ HDL増加をひき起こす治療は効果的であり今後の動脈硬化治療のターゲットとなる。

図　HDL低下による冠動脈疾患予防の治療効率



高脂血症に関する各種検査法の実態調査

・我が国における動脈硬化学会による動脈硬化性疾患診療ガイドラインにおいてカテゴリー別にLDL-コレステロール治療目標値が設定され、日常臨床における測定の重要性が認識されている。

・ LDL-C測定には、Friedewald式における計測に加え、直接法による測定が普及し、これらの標準化と有用性の検討が必要である。

・同一脂質異常検体を、異なる直接法により測定した結果、各々、LDL-C値の差異のあることが明らかになった。測定方法によることが考えられ、LDL-C値に関わる標準化が必要であることが明らかになった。

・様々な症例の検体を用いた測定結果を比較検討することにより検討をすすめる必要がある。

表1 対象血清の血清脂質

No.	T-CHO	TG	HDL	Midband の有無	LDL			
					計算式	第一	協和	和光
A-1	249	310	49	±	138	148	156.7	161.2
A-2	225	155	55	+	139	135	161.9	153.2
A-3	195	143	53	±	113.4	117	123.5	121.3
A-4	283	71	71	-	197.8	182	197.4	193.7
A-5	247	89	60	-	169.2	164	168.9	172.1
A-6	202	77	43	±	143.6	137	144.2	140.1
A-7	220	392	39	+	102.6	128	128.1	131.8
B-1	181	253	29	+	101.4	95	104	104.7
B-2	227	108	53	+	152.4	142	144.8	144.6
B-3	354	284	39	+	258.2	240	287.2	282.6
B-4	181	280	57	-	68	89	88.7	102.2
B-5	227	248	39	+	138.4	144	159.2	169.5
B-6	282	582	37	+	128.6	107	139.2	140.5
平均					142.35	140.6	154.14	155.19

II.研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ito M, Bujo H, Takahashi K, Arai T, Tanaka I, Saito Y.	Implantation of primary cultured adipocytes secreting insulin modifies plasma glucose levels in diabetic mice.	Diabetologia	in press		2005
Miyazawa-Hoshimoto S, Takahashi K, Bujo H, Hashimoto N, Yagui K, Saito	The roles of degree of fat deposition and its localization on VEGF expression in adipocytes	Am J Physiol Endocrinol Metab.	in press		2005
Seki N, Bujo H, Jiang M, Shibasaki M, Takahashi K, Hashimoto N, Saito Y	A potent activator of PPARalpha and gamma reduces the vascular cell recruitment and inhibits the intimal thickning in hypercholesterolemic rabbits	Atherosclerosis.	178	1-7	2005
Kitagawa Y, Bujo H, Takahashi K, Shibasaki M, Ishikawa K, Yagui K, Hashimoto N, Noda K, Nakamura T, Yano S, Saito Y	mpaired glucose tolerance is accompanied by decreased insulin sensitivity in tissues of mice implanted with cells that overexpress resistin.	Diabetologia	47	1847-55	2004
Bujo H, Takahashi K, Saito Y, Maruyama T, Yamashita S, Matsuzawa Y, Ishibashi S, Shionoiri F, Yamada N, Kita T. Research Committeon Primary Hyperlipidemia of the Ministry of Health, Labour, and Welfare of Japan.	Clinical features of familial hypercholesterolemia in Japan in a database from 1996-1998 by the research committee of the ministry of health, labour and welfare of Japan	J Atheroscler Thromb.	94	146-51	2004
Zhu Y, Bujo H, Yamazaki H, Ohwaki K, Jiang M, Hirayama S, Kanaki T, Shibasaki M, Takahashi K, Schneider WJ, Saito Y	LR11, an LDL Receptor Gene Family Member, Is a Novel Regulator of Smooth Muscle Cell Migration	Circ Res	94	752-8	2004
Yamazaki K, Bujo H, Taira K, Itou N, Shibasaki M, Takahashi K, Saito Y	Increased circulating malondialdehyde-modified LDL in the patients with familial combined hyperlipidemia and its relation with the hepatic lipase activity	Atherosclerosi	172	181-7	2004
Tanaga K, Bujo H, Zhu Y, Kanaki T, Hirayama S, Takahashi K, Inoue M, Mikami K, Schneider WJ, Saito Y	LRP1B attenuates the migration of smooth muscle cells by reducing membrane localization of urokinase and PDGF receptors	Arterioscler Thromb Vasc Biol	24	1422-8	2004
Fujita Y, Ezura Y, Emi M, Sato K, Takada D, Iino Y, Katayama Y, Takahashi K, Kamimura K, Bujo H, Saito Y	Hypercholesterolemia associated with splice-junction variation of inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4) gene	J Hum Genet	49	24-8	2004
Shibasaki M, Bujo H, Kobayashi H, Takahashi K, Saito Y	Statins as a possible distribution modulator of bone marrow-derived smooth muscle cells in plaques? Statins as a possible distribution modulator of bone marrow-derived smooth muscle cells in plaques?	Atherosclerosis	176	427-8	2004
Yoshida Y, Hashimoto N, Tokuyama Y, Kitagawa H, Takahashi K, Yagui K, Kanatsuka A, Bujo H, Higurashi M, Miyazawa S, Yoshida S, Saito Y	Effects of weight loss in obese subjects with normal fasting plasma glucose or impaired glucose tolerance on insulin release and insulin resistance according to a minimal model analysis	Metabolism	53	1095-100	2004

Scherzer CR, Offe K, Gearing M, Rees HD, Fang G, Heilman CJ, Schaller C, Bujo H, Levey AI, Lah JJ.	Loss of apolipoprotein E receptor LR1 1 in Alzheimer disease	Arch Neurol	61	1200-5	2004
Li Y, Bujo H, Takahashi K, Shi basaki M, Zhu Y, Yoshida Y, O tsuka Y, Hashimoto N, Saito Y.	Visceral fat: higher responsiveness of fat mass and gene expression to cal orie restriction than subcutaneous fat.	Exp Biol Med (Maywood)	228	1118-23	2003
Miyazawa-Hoshimoto S, Takaha shi K, Bujo H, Hashimoto N, S aito Y.	Elevated serum vascular endothelial g rowth factor is associated with viscera l fat accumulation in human obese su bjects.	Diabetologia.	461	483-8	2003
Ono S, Ezura Y, Emi M, Fujita Y, Takada D, Sato K, Ishigami T, Umemura S, Takahashi K, Kamimura K, Bujo H, Saito Y.	A promoter SNP (-1323T>C) in G-sub strate gene (GSBS) correlates with hy percholesterolemia.	J Hum Genet	48	447-50	2003
Shibasaki M, Takahashi K, Itou T, Bujo H, Saito Y.	A PPAR agonist improves TNF-alpha-i nduced insulin resistance of adipose t issue in mice.	Biochem Biophys Res Commun.	309	419-24	2003
Fujita Y, Ezura Y, Emi M, Ono S, Takada D, Takahashi K, U emura K, Iino Y, Katayama Y, Bujo H, Saito Y.	Hypertriglyceridemia associated with a mino acid variation Asn985Tyr of the RP1 gene.	J Hum Genet.	48	305-8	2003
Gutekunst CA, Torre ER, Shen g Z, Yi H, Coleman SH, Riedel IB, Bujo H.	Stigmoid bodies contain type I recept or proteins SorLA/LR11 and sortilin: n ew perspectives on their function.	J Histochem Cytochem.	51	841-52.	2003
Shibasaki M, Takahashi K, Itou T, Miyazawa S, Ito M, Kobaya shi J, Bujo H, Saito Y.	Alterations of insulin sensitivity by the implantation of 3T3-L1 cells in nude mice. A role for TNF-alpha?	Diabetologia	45	518-26	2002
Zhu Y, Bujo H, Yamazaki H, Hi rayama S, Kanaki T, Takahashi K, Shibasaki M, Schneider W J, Saito Y.	Enhanced expression of the LDL rece ptor family member LR11 increases migration of smooth muscle cells in vi tro.	Circulation.	105	1830-6	2002
Tanaga K, Bujo H, Inoue M, Mi kami K, Kotani K, Takahashi K, Kanno T, Saito Y.	Increased circulating malondialdehyde-modified LDL levels in patients with c oronary artery diseases and their ass ociation with peak sizes of LDL partic les.	Arterioscler Thromb Vasc Biol.	2	62-66	2002
Ishii I, Satoh H, Kawachi H, Jin gami H, Matsuoka N, Ohmori S, Bujo H, Yamamoto T, Saito Y, Kitada M.	Intimal smooth muscle cells up-regulat e beta-very low density lipoprotein-me diated cholesterol accumulation by en hancing beta-very low density lipoprot ein uptake and decreasing cholesterol efflux.	Biochim Biophys Acta.	1585	30-8	2002
Matsumoto F, Bujo H, Kuramoc hi D, Saito K, Shibasaki M, Ta kahashi K, Yoshimoto S, Ichino se M, Saito Y.	Effects of nutrition on the cell survival and gene expression of transplanted fat tissues in mice.	Biochem Biophys Res Commun.	295	630-5	2002
Kanaki T, Bujo H, Mori S, Yanj uan Z, Takahashi K, Yokote K, Morisaki N, Saito Y.	Functional analysis of aortic endotheli al cells expressing mutant PDGF rece ptors with respect to expression of m atrix metalloproteinase-3.	Biochem Biophys Res Commun.	294	231-7	2002

Kobayashi J, Okamoto H, Otabe M, Bujo H, Saito Y.	Effect of HDL, from Japanese white rabbit administered a new cholesteryl ester transfer protein inhibitor JTT-705, on cholesteryl ester accumulation induced by acetylated low density lipoprotein in J774 macrophage.	Atherosclerosis.	162	131-5	2002
Taira K, Bujo H, Kobayashi J, Takahashi K, Miyazaki A, Saito Y.	Positive family history for coronary heart disease and 'midband lipoproteins' are potential risk factors of carotid atherosclerosis in familial hypercholesterolemia.	Atherosclerosis.	160	391-7	2002
H Arai, A Yamamoto, Y Matsuzawa, Y Saito, N Yamada, S Oikawa, H Mabuchi, T Teramoto, J Sasaki, N Nakaya, H Itakura, Y Ishikawa, Y Ouchi, H Horibe, and T Kita	Serum Lipid Survey and its Recent Trend in the General Japanese Population in 2000	J Arteriosclerosis Thrombosis	in press		
H Arai, A Yamamoto, Y Matsuzawa, Y Saito, N Yamada, S Oikawa, H Mabuchi, T Teramoto, J Sasaki, N Nakaya, H Itakura, Y Ishikawa, Y Ouchi, H Horibe, T Egashira, Hi Hattori, T Kita	Common haplotypes in four genes influence genetic variance of triglyceride and HDL-cholesterol in the general Japanese population		submitted		
Horiuchi H, Kita T, Mabuchi H, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H; J-LIT Study Group. Primary cardiovascular events and serum lipid levels in elderly Japanese with hypercholesterolemia undergoing 6-year simvastatin treatment	a subanalysis of the Japan lipid intervention trial	J Am Geriatr Soc	52	1981-7	2004
Wada T, Ishine M, Sakagami T, Okumiya K, Fujisawa M, Murakami S, Otsuka K, Yano S, Kita T, Matsubayashi K.	Depression in Japanese community-dwelling elderly—prevalence and association with ADL and QOL.	Arch Gerontol Geriatr	39	15-23	2004
Horiuchi H, Matsuzawa Yuji, Mabuchi H, Itakura H, Sasaki J, Yokoyama M, Ishikawa Y, Yokoyama S, Mori S, Ohrui T, Akisita M, Hayashi T, Yamane K, Egusa G, and Kita T	Strategy for treating elderly Japanese with hypercholesterolemia	GGI	4	151-156	2004
Maruyama T, Yamashita S, Matsuzawa Y, et al: Mutations in Japanese subjects with primary hyperlipidemia	Results from the Research Committee of the Ministry of Health and Welfare of Japan since 1996	J Atheroscler Thromb	11	131-145	2004
Nagano M, Yamashita S, Hirano K, et al	Molecular mechanisms of cholesteryl ester transfer protein deficiency in Japanese	J Atherscler Thromb	11	110-121	2004

Okazaki M, Usui S, Yamashita S	Measurement of serum lipoprotein sub classes by an HPLC method. Lipoproteins and Vascular Diseases Division Newsletter "The Fats of Life"	American Association for Clinical Chemistry	18	64-68	2004
Chan DC, Watts GF, Ng TW, Yamashita S, et al	Adiponectin and other adipocytokines as predictors of markers of triglyceride-rich lipoprotein metabolism	Clin Chem	51	578-585	2005
Okazaki M, Usui S, Ishigami M, et al	Identification of unique lipoprotein sub classes for visceral obesity by component analysis of cholesterol profile in high-performance liquid chromatography	Arterioscler Thromb Vasc Bio	in press		
Yamashita S, Kuwasako T, Janabi M, et al	Physiological and pathological roles of a multi-ligand receptor CD36 in atherogenesis; Insights from CD36-deficient patients	Mol Cell Biochem	in press		
Nakagawa-Toyama Y, Hirano K, Tsujii, K, et al	Human scavenger receptor class B type I is expressed with cell-specific fashion in both initial and terminal site of reverse cholesterol transport	Atherosclerosis	in press		
Mabuchi H, Higashikata T, Nohara A, Lu H, Yu WX, Nozue T, Noji Y, Katsuda S, Kawashiri MA, Inazu A, Kobayashi J, Koizumi J	Cutoff Point Separating Affected and Unaffected Familial Hypercholesterolemic Patients Validated by LDL-receptor Gene Mutants	J Atheroscler Thromb	12(1)	35-40	2005
Todo Y, Kobayashi J, Higashikata T, Kawashiri M, Nohara A, Inazu A, Koizumi J, Mabuchi H	Detailed analysis of serum lipids and lipoproteins from Japanese type III hyperlipoproteinemia with apolipoprotein E2/2 phenotype	Clin Chim Acta	348(1-2)	35-40	2005
Kobayashi J, Sasaki T, Watanabe M	The relationship of abdominal fat mass assessed by helical or conventional computed tomography to serum leptin concentration	J Atheroscler Throm	11(3)	173-9	2004
Murase Y, Asano A, Kobayashi J, Yamaaki N, Mabuchi H	Impact of adiposity on carotid atherosclerosis in Japanese males with metabolic syndrome	J Intern Med	257(3)	311-2.	2005
Liang H, Yagi K, Asano A, Kobayashi J, Mabuchi H	Association between CTLA-4 +49 A/G Polymorphism and Type 1B Diabetes in Japanese Population	Endocrin	25	105-10	2004
Shimizu M, Ino H, Yasuda T, Fujino N, Uchiyama K, Mabuchi T, Konno T, Kaneda T, Fujita T, Masuta E, Katoh M, Funada A, Mabuchi H	Gene mutations in adult Japanese patients with dilated cardiomyopathy	Circ J.	69(2)	150-3	2005
Inoue M, Shimizu M, Ino H, Yamaguchi M, Terai H, Fujino N, Sakata K, Funada A, Tatami R, Ishise S, Kanaya H, Mabuchi H.	Differentiation between patients with takotsubo cardiomyopathy and those with anterior acute myocardial infarction	Circ J	69(1)	89-94	2005

Mabuchi H, Haba T, Tatami R, Miyamoto S, Sakai Y, Wakasugi T, Watanabe A, Koizumi J, Takeda R.	Effects of an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme a reductase on serum lipoproteins and ubiquinone-10 levels in patients with familial hypercholesterolemia. 1981	Atheroscler Suppl	5	51-5	2004
Mabuchi H	Penicillin for hypercholesterolemia	Atheroscler Suppl	5(3)	23	2004
Kobayashi J	Pre-heparin lipoprotein lipase mass	J Atheroscler Thromb	11(1)	1-5	2004
Yagi K, Kobayashi J, Yasue S, Yamaguchi M, Shiobara S, Mabuchi H	Four unrelated cases with Takayasu arteritis and CD36 deficiency: possible link between these disorders	J Intern Med	255(6)	688-9	2004
Murase Y, Yagi K, Kobayashi J, Nohara A, Asano A, Koizumi K, and Mabuchi H	Association of coronary artery ectasia with plasma insulin levels in Japanese men of heterozygous familial hypercholesterolemia with the low-density lipoprotein receptor gene mutation K790X	Clin Chim Acta	in press		
Lu H, Higashikata T, Inazu A, Nohara A, Yu W, Shimizu M, Mabuchi H.	Association of estrogen receptor-alpha gene polymorphisms with coronary artery disease in patients with familial hypercholesterolemia.	Arterioscler Thromb Vasc Biol.	22(5)	817-823	2002
Noji Y, Higashikata T, Inazu A, Nohara A, Ueda K, Miyamoto S, Kajinami K, Takegoshi T, Koizumi J, Mabuchi H.	Long-term treatment with pitavastatin (NK-104), a new HMG-CoA reductase inhibitor, of patients with heterozygous familial hypercholesterolemia.	Atherosclerosis.	163(1)	157-164	2002
Guo Z, Inazu A, Yu W, Suzumura T, Okamoto M, Nohara A, Higashikata T, Sano R, Wakasugi K, Hayakawa T, Yoshida K, Suehiro T, Schmitz G, Mabuchi H.	Double deletions and missense mutations in the first nucleotide-binding fold of the ATP-binding cassette transporter A1 (ABCA1) gene in Japanese patients with Tangier disease.	J Hum Get	47(6)	325-329	2002
Yu W, Nohara A, Higashikata T, Lu H, Inazu A, Mabuchi H.	Molecular genetic analysis of familial hypercholesterolemia: spectrum and regional difference of LDL receptor gene mutations in Japanese population.	Atherosclerosis.	165(2)	335-342	2002
Huang Z, Inazu A, Nohara A, Higashikata T, Mabuchi H.	Cholesteryl ester transfer protein inhibitor (JTT-705) and the development of atherosclerosis in rabbits with severe hypercholesterolaemia.	Clin Sci (Lond)	103(6)	587-594	2002
Huang Z, Inazu A, Kawashiri MA, Nohara A, Higashikata T, Mabuchi H.	Dual Effects on HDL Metabolism by Cholesteryl Ester Transfer Protein Inhibition in HepG2 Cells.	Am J Physiol Endocrinol Metab.	284(6)	E1210-9	2003
Higashikata T, Mabuchi H.	Long-term effect of low-density lipoprotein apheresis in patients with heterozygous familial hypercholesterolemia.	Therap Apher Dial.	7(4)	402-7	2003
Lu H, Inazu A, Moriyama Y, Higashikata T, Kawashiri MA, Yu W, Huang Z, Okamura T, Mabuchi H.	Haplotype analyses of cholesteryl ester transfer protein gene promoter: a clue to an unsolved mystery of TaqIB polymorphism.	J Mol Med.	81(4)	246-55	2003

Ohta T, Takata K. Katsuren K, Fukuyama S	The Influence of the Acyl-CoA:Cholesterol Acyltransferase-1 Gene (-77G/A) Polymorphisms on Plasma Lipid and Apolipoprotein Levels in Normolipidemic and Hyperlipidemic Subjects. Biochim Biophys Acta	Biochim Biophys Acta	1682	56-62	2004
Simabukuro T, Sunagawa M, Ohta T	Low-Density Lipoprotein Particle Size and Its Regulatory Factors in School Children	J Clin Endocrinol Metab	89	2923-2927	2004
Fukuyama S, Hiramatsu M, Akagi M, Higa M, Ohta T	Novel Mutations of the Chloride Channel Kb (ClC-Kb) Gene in Two Japanese Patients Clinically diagnosed as Bartter Syndrome with Hypocalciuria	J Clin Endocrinol Metab	89	5847-5850	2004
Yamamoto T, Shimano H, Nakagawa Y, Ide T, Yahagi N, Matsuzaka T, Nakakuki M, Takahashi A, Suzuki H, Sone H, Toyoshima H, Sato R, Yamada N	SREBP-1 interacts with HNF-4alpha and interferes with PGC-1 recruitment to suppress hepatic gluconeogenic genes	J Biol Chem	279	12027-35	2004
Ide T, Shimano H, Yahagi N, Matsuzaka T, Nakakuki M, Yamamoto T, Nakagawa Y, Takahashi A, Suzuki H, Sone H, Toyoshima H, Fukamizu A, Yamada N	SREBPs suppress IRS-2-mediated insulin signalling in the liver	Nat Cell Biol	6	351-7	2004
Ohashi K, Osuga J, Tozawa R, Kitamine T, Yagyu H, Sekiya M, Tomita S, Okazaki H, Tamura Y, Yahagi N, Iizuka Y, Harada K, Gotoda T, Shimano H, Yamada N, Ishibashi S.	Early embryonic lethality caused by targeted disruption of the 3-hydroxy-3-methylglutaryl-CoA reductase gene.	J Biol Chem.	278	42936-41	2003
Iida KT, Kawakami Y, Suzuki M, Shimano H, Toyoshima H, Sone H, Shimada K, Iwama Y, Watanabe Y, Mokuno H, Kamata K, Yamada N.	Effect of thiazolidinediones and metformin on LDL oxidation and aortic endothelium relaxation in diabetic GK rats.	Am J Physiol Endocrinol Metab.	284(6)	E1125-30	2003
Yahagi N, Shimano H, Matsuzaka T, Najima Y, Sekiya M, Nakagawa Y, Ide T, Tomita S, Okazaki H, Tamura Y, Iizuka Y, Ohashi K, Gotoda T, Nagai R, Kimura S, Ishibashi S, Osuga J, Yamada N.	p53 Activation in adipocytes of obese mice.	J Biol Chem.	278	25395-400	2003
Sone H, Shimano H, Ebinuma H, Takahashi A, Yano Y, Iida KT, Suzuki H, Toyoshima H, Kawakami Y, Okuda Y, Noguchi Y, Ushizawa K, Saito K, Yamada N.	Physiological changes in circulating mannose levels in normal, glucose-intolerant, and diabetic subjects.	Metabolism.	52(8)	1019-27	2003
Yokoo T, Toyoshima H, Miura M, Wang Y, Tada Iida K, Suzuki H, Sone H, Shimano H, Gotoda T, Nishimori S, Tanaka K, Yamada N.	p57Kip2 regulates actin dynamics by binding and translocating LIM-kinase 1 to the nucleus.	J Biol Chem.	278 (52)	52919-52923	2003

Sone H, Shimano H, Sakakura Y, Inoue N, Amemiya-Kudo M, Yahagi N, Osawa M, Suzuki H, Yokoo T, Takahashi A, Iida K, Toyoshima H, Iwama A, Yamada N:	Acetyl-coenzyme A synthetase is a lipogenic enzyme controlled by SREBP-1 and energy status.	Am J Physiol Endocrinol Metab	282	E222-E230	2002
Yoshikawa T, Shimano H, Yamada N, et al.	Polyunsaturated fatty acids suppress sterol regulatory element-binding protein-1c promoter activity by inhibition of liver X receptor (LXR) binding to LXR response elements.	J.Biol.Chem	277(3)	1705-1711	2002
Matsuzaka T, Shimano H, Yahagi N, Amemiya-Kudo M, Okazaki H, Tamura Y, Iizuka Y, Ohashi K, Tomita S, Sekiya M, Hasty A, Nakagawa Y, Sone H, Toyoshima H, Ishibashi S, Osuga J, Yamada N.	Insulin-independent induction of sterol regulatory element-binding protein-1c expression in the livers of streptozotocin-treated mice	Diabetes	53	560-9	2004
Iida KT, Suzuki H, Sone H, Shimano H, Toyoshima H, Yatoh S, Asano T, Okuda Y, Yamada N:	Insulin inhibits apoptosis of macrophage cell line, THP-1 cells, via phosphatidylinositol-3-kinase-dependent pathway.	Arterioscler Thromb Vasc Biol	22	380-386	2002
Yahagi N, Shimano H, Yamada N, et al.	Absence of sterol regulatory element-binding protein-1 (SREBP-1) ameliorates fatty livers, but not obesity or insulin resistance in Lepob/Lepob mice.	J Biol Chem.	277	19353-7	2002
Iida KT, Kawakami Y, Suzuki H, Sone H, Shimano H, Toyoshima H, Okuda Y, Yamada N	PPARgamma ligands, troglitazone and pioglitazone, up-regulate expression of HMG-CoA synthase and HMG-CoA reductase gene in THP-1 macrophages.	FEBS Lett	520	177-181	2002
Okazaki H, Osuga JI, Tsukamoto K, Isoo N, Kitamine T, Tamura Y, Tomita S, Sekiya M, Yahagi N, Iizuka Y, Ohashi K, Harada K, Gotoda T, Shimano H, Kimura S, Nagai R, Yamada N, Ishibashi S:	Elimination of cholesterol ester from macrophage foam cells by adenovirus-mediated gene transfer of hormone-sensitive lipase.	J Biol Chem	277	31893-31899	2002
Matsuzaka T, Shimano H, Yahagi N, Yoshikawa T, Amemiya-Kudo M, Hasty AH, Okazaki H, TamuraY, Iizuka Y, Ohashi K, Osuga J, Takahashi A, Yato S, Sone H, Ishibashi S, Yamada N:	Cloning and characterization of a mammalian fatty acyl-CoA elongase as a lipogenic enzyme regulated by SREBPs.	J Lipid Res.	43(6)	911-920	2002
Amemiya-Kudo M, Shimano H, Hasty AH, Yahagi N, Yoshikawa T, Matsuzaka T, Okazaki H, Tamura Y, Iizuka Y, Ohashi K, Osuga JI, Harada K, Gotoda T, Sato R, Kimura S, Ishibashi S, Yamada N:	Transcriptional activities of nuclear SREBP-1a, -1c, and -2 to different target promoters of lipogenic and cholesterogenic genes.	J Lipid Res	43	1220-1235	2002

Okazaki H, Osuga JI, Tamura Y, Yahagi N, Tomita S, Shionoiri F, Iizuka Y, Ohashi K, Harada K, Kimura S, Gotoda T, Shimano H, Yamada N, Ishibashi S:	Lipolysis in the Absence of Hormone-Sensitive Lipase: Evidence for a Common Mechanism Regulating Distinct Lipases.	Diabetes	51	3368-3375	2002
Sone H, Takahashi A, Shimano H, Ishibashi S, Yoshino G, Morisaki N, Saito Y, Kawazu S, Teramoto T, Fujita T, Shiba T, Iwamoto Y, Kuzuya N, Akanuma Y, Yamada N:	HMG-CoA reductase inhibitor decreases small dense low-density lipoprotein and remnant-like particle cholesterol in patients with type-2 diabetes.	Life Sci	71	2403-2412	2002
Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N	Energy intake and obesity in Japanese patients with type 2 diabetes	Lancet	363	248-249	2004
Sone H, Mizuno S, Ohashi Y, Yamada N	Type 2 diabetes prevalence in Asian subjects	Diabetes Care	27	1251-1252	2004
Sone H, Mizuno S, Aida R, Ohashi Y, Yamada N.	Alcohol Use and Diabetes Mellitus	Ann Intern Med	141	408-9	2004
Sone H, Yamada N, Mizuno S, Ohashi Y, Ishibashi S, Yamazaki Y.	Requirement for hypertension and hyperlipidemia medication in U.S. and Japanese patients with diabetes	Am J Med	117	711-2	2004
Kon Koh K, Yeal Ahn J, Hwan Han S, Kyu Jin D, Sik Kim H, Cheon Lee K, Kyun Shin E, Sakuma I	Effects of fenofibrate on lipoproteins, vasomotor function, and serological markers of inflammation, plaque stabilization, and hemostasis	Atherosclerosis	174(2)	379-383	2004
Sugawara T, Fujii S, Zaman A K, Goto D, Furumoto T, Imagawa S, Dong J, Sakuma I, Jesmin S, Togashi H, Yoshioka M, Koyama T, Kitabatake A:	Coronary capillary network remodeling and hypofibrinolysis in aged obese diabetic rats: implications for increased myocardial vulnerability to ischemia.	Mol Cell Biochem	248(1-2)	165-170	2003
Jesmin S, Sakuma I, Hattori Y, Kitabatake A:	Role of Angiotensin II in Altered Expression of Molecules Responsible for Coronary Matrix Remodeling in Insulin-Resistant Diabetic Rats.	Arterioscler Thromb Vasc Biol	23(11)	2021-2026	2003
I Sakuma, M Liu, A Sato, T Hayashi, A Iguchi, A Kitabatake, Yi Hattori.	Endothelium-dependent hyper- polarization and relaxation in mesenteric arteries of middle-aged rats: influence of oestrogen.	Br J Phramacol	135(1)	48-54	2002
I Sakuma, Y Akaishi, H Tomioka, A Sato, A Kitabatake, Y Hattori:	Interactions of sildenafil with various coronary vasodilators in isolated porcine coronary artery.	Eur J Pharmacol	437	155-163	2002
Matsuzaki M, Hiramori K, Imaizumi T, Kitabatake A, Hishida H, Nomura M, Fujii T, Sakuma I, Fukami K, Honda T, Ogawa H, Yamagishi M:	Intravascular ultrasound evaluation of coronary plaque regression by low density lipoprotein-apheresis in familial hypercholesterolemia. The Low Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial (LACMART).	J Am Coll Cardiol	40(2)	220-227	2002