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
Shimizu W	Clinical impact of genetic studies in lethal inherited cardiac arrhythmias.	Circ J	72	1926-1936	2008
Shimizu W	Genetics of congenital long QT syndrome and Brugada syndrome.	Future Cardiology	4	379-389	2008
Nagaoka I, Shimizu W, Itoh H,Yamamoto S, Sakaguchi T, Oka Y, Tsuji K, Ashihara T, Ito M, Yoshida H, Ohno S, Makiyama T, Miyamoto Y, Kamakura S, Akao M, Horie M	Mutation site dependent variability of cardiac events in Japanese LQT2 form of congenital long-QT syndrome.	Circ J	72	694-699	2008
Makita N, Behr E, Shimizu W, Horie M, Sunami A, Crotti L, Schulze-Bahr E, Fukuhara S, Mochizuki N, Makiyama T, Itoh H, Christiansen M, McKeown P, Miyamoto K, Kamakura S, Tsutsui H, Schwartz PJ, George AL, Roden DM	The E1784K mutation in SCN5A is associated with mixed clinical phenotype of type 3 long QT syndrome.	J Clin Invest	118	2219-2229	2008
Aiba T, Yamagata K, Shimizu W, Taguchi A, Satomi K, Noda T, Okamura H, Suyama K, Aihara N, Kamakura S, Kurita T	Electrophysiologic study-guided amiodarone for sustained ventricular tachyarrhythmias associated with structural heart diseases.	Circ J	72	88-93	2008
Horigome H, Iwashita H, Yoshinaga M, Shimizu W	Magnetocardiographic demonstration of torsade de pointes in a fetus with congenital long QT syndrome.	J Cardiovasc Electrophysiol	19	334-335	2008
Sumitomo N, Shimizu W, Taniguchi K, Hiraoka M	Ca^{2+} channel blocker and adenosine triphosphate terminate bidirectional ventricular tachycardia in a patient with Andersen-Tawil syndrome.	Heart Rhythm	5	498-499	2008
Sakaguchi T, Shimizu W, Itoh H, Noda T, Miyamoto Y, Nagaoka I, Oka Y, Ashihara T, Ito M, Tsuji K, Ohno S, Makiyama T, Kamakura S, Horie M	Age-related triggers for life-threatening arrhythmia in the genotyped long-QT syndrom.	J Cardiovasc Electrophysiol	19	794-799	2008
Nagai T, Shimizu W, Ogimoto A, Higaki J, Okayama H	Ventricular fibrillation induced by a narrow QRS complex tachycardia in a patient with Brugada syndrome.	J Cardiovasc Electrophysiol	20	106-107	2008
Wu G, Ai T, Kim JJ, Mohapatra B, Xi Y, Li Z, Abbasi S, Purevjav E, Samani K, Ackerman MJ, Qi M, Moss AJ, Shimizu W, Towbin JA, Cheng J, Vatta M	Alpha-1-Syntrophin mutation and the long QT syndrome: a disease of sodium channel disruption.	Circ Arrhythmia and Electrophysiol	1	193-201	2008

Burashnikov A, Shimizu W, Antzelevitch C	Fever accentuates transmural dispersion of repolarization and facilitates the development of early afterdepolarizations and torsade de pointes under long QT conditions.	Circ Arrhythmia and Electrophysiol	1	202-208	2008
Wang D, Crotti L, Shimizu W, Pedrazzini M, Cantu F, De Filippo P, Kishiki K, Miyazaki A, Ikeda T, Schwartz PJ, George AL	Malignant perinatal variant of long-QT syndrome caused by a profoundly dysfunctional cardiac sodium channel mutation.	Circ Arrhythmia and Electrophysiol	1	370-378	2008
Liu JF, Goldenberg I, Moss AJ, Shimizu W, Wilde AA, Hofman N, McNitt S, Zareba W, Miyamato Y, Robinson JL, Andrews ML	Phenotypic variability in Caucasian and Japanese patients with matched LQT1 mutations.	Ann Noninvasive Electrocardiol	13	234-241	2008
Kandori A, Ogata K, Miyashita T, Watanabe Y, Tanaka K, Murakami M, Oka Y, Takaki H, Hashimoto S, Yamada Y, Komamura K, Shimizu W, Kamakura S, Watanabe S, Yamaguchi I	Standard template of adult Magnetocardiogram.	Ann Noninvasive Electrocardiol	13	391-400	2008
Takigawa M, Noda T, Shimizu W, Miyamoto K, Okamura H, Satomi K, Suyama K, Aihara N, Kamakura S, Kurita T	Seasonal and circadian distributions of ventricular fibrillation in patients with Brugada syndrome.	Heart Rhythm	5	1523-1527	2008
Yokokawa M, Ohnishi S, Ishibashi-Ueda H, Obata H, Otani K, Miyahara Y, Tanaka K, Shimizu W, Nakazawa K, Kangawa K, Kamakura S, Kitamura S, Nagaya N	Transplantation of mesenchymal stem cells improves atrioventricular conduction in a rat model of complete atrioventricular block.	Cell Transplant	17	1145-1155	2008
Viskin S, Wilde AAM, Tan HL, Antzelevitch C, Shimizu W, Belhassen B	Empiric quinidine therapy for asymptomatic Brugada syndrome. Time for a Prospective registry.	Heart Rhythm	6	401-404	2009
Aiba T, Shimizu W, Noda T, Okamura H, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S	Noninvasive characterization of intra-atrial re-entrant tachyarrhythmias after surgical repair of congenital Heart Diseases.	Circ J	73	451-460	2009
Ohno S, Toyoda F, Zankov D, Yoshida H, Makiyama T, Tsuji K, Honda T, Obayashi K, Ueyama H, Shimizu W, Miyamoto Y, Kamakura S, Matsuura H, Kita T, Horie M	Novel KCNE3 mutation reduces repolarizing potassium current and causes long QT syndrome.	Hum Mutat	30	557-563	2009
Jons C, Moss AJ, Lopes CM, McNitt S, Zareba W, Goldenberg I, Qi M, Wilde AAM, Shimizu W, Kanters JK, Towbin J, Ackerman MJ, Robinson J	Mutations in conserved amino acids in the KCNQ1 channel and risk of cardiac events in type-1 long QT syndrome.	J Cardiovasc Electrophysiol		in press	2009
清水　渉	遺伝情報に基づいた先天性QT延長症候群の管理と治療	日本小児循環器学会雑誌	24	27-33	2008
清水　渉, 相庭武司, 栗田隆志, 里見和浩, 横川美樹, 岡村英夫, 野田　崇, 須山和弘, 相原直彦, 鎌倉史郎	Brugada症候群における性差と加齢.	心電図	28	147-157	2008
清水　渉	遺伝子異常による心室頻拍/心室細動.	臨床と研究	85	95-99	2008

清水　渉	Brugada症候群における遺伝子診断. 5.不整脈と関連遺伝子.「循環器病の発症・増悪関連遺伝子 –最近の話題-」	循環器科	63	568-574	2008
清水　渉	9. Brugada症候群の心電図学的診断 -特徴的な波形の成立機序-. 特集「致死性不整脈をきたす疾患 –診断と治療-」	Heart View	12	66-71	2008
清水　渉	致死性不整脈の遺伝情報に基づいた治療	臨床薬理の進歩	29	133-142	2008
清水　渉	Brugada症候群. 特集「不整脈治療最前線」.	クリニシアン	573	90-97	2008
清水　渉	はじめに. Brugada症候群 - 臨床と研究の最近動向.	医学のあゆみ	227	1021	2008
清水　渉	イントロダクション. 不整脈の遺伝子診断. HEART's　Selection.	心臓	40	1053-1054	2008
山形研一郎, 清水　渉, 河田　宏, 岡村英夫, 野田　崇, 里見和浩, 須山和弘, 栗田隆志, 相原直彦, 鎌倉史郎	Brugada症候群症例の予後調査.	心電図	28	(Suppl 4) 2-5	2008
野田　崇, 清水　渉	後天性(二次性)Brugada症候群の機序と成因. Brugada症候群 - 臨床と研究の最近動向.	医学のあゆみ	227	1035-1040	2008
清水　渉	9. 2相リエントリー 特集「電気生理検査をどう活かすか」	Heart View	13	63-70	2009
清水　渉	87. 先天性QT延長症候群の診断における運動負荷試験の限界とカテコラミン負荷試験の有用性.	循環器検査のグノーティ・セアウトン		印刷中	2009
清水　渉	Brugada症候群の基礎から最新の治療まで.	Therapeutic Research 30		印刷中	2009
Ohno S, Kubota T, Yoshida H, Tsuji K, Makiyama T, Yamada S, Kuga K, Yamaguchi I, Kita T, Horie M	A novel mutation associated with Jervell and Lange-Nielsen syndrome　in a Japanese family.	Circ J	72	687-693	2008
Sakaguchi T, Itoh H, Ding WG, Tsuji K, Nagaoka I, Oka Y, Ashihara T, Ito M, Yumoto Y, Zenda N, Higashi Y, Takeyama Y, Matsuura H, Horie M	Hydroxyzine, a First Generation H1-Receptor Antagonist, Inhibits Human Ether-a-go-go-Related Gene (HERG) Current and Causes Syncope in a Patient With the HERG Mutation	J Pharmacol Sci	108	462-471	2008
Wu J, Ding WG, Matsuura H, Tsuji K, Zang WJ, Horie M	Inhibitory actions of LY294002, a phosphatidylinositol 3-kinase inhibitor,on the human Kv1. 5 channel.	Br J Pharmacol		in press	2009
Samani K, Ai T, Makiyama T, Wu G, Vatta M, Sohma Y, Xi Y, Itoh I, Ueyama T, Shimizu A, Horie M, Cheng J	A subclinical SCN5A mutation associated with drug-induced Brugada type ECG	J Cardiovasc Electrophysiol		in press	2009

Tamaki S, Nakamura Y, Tabara Y, Okamura T, Kanda H, Kita Y, Kadowaki T, Tsujita Y, Turin T C, Horie M, Miki T, Ueshima H.	Association between polymorphism of the AGTR1 and cardiovascular events in a Japanese general sample (The Shigaraki Study) .	Int J Cardiol		in press	2009
Itoh H, Sakaguchi T, Ashihara T, Ding G W, Nagaoka I, Oka Y, Nakazawa Y, Yao T, Jo H, Ito M, Matsuura H, Horie M	A Novel KCNH2 Mutation as a Modifier for Short QT Interval.	Int J Cardiol		in press	2009
Ohashi N, Mitamura H, Ogawa S.	Development of newer calcium channel antagonists: Therapeutic potential of efonidipine in preventing electrical remodelling during atrial fibrillation.	Drugs	69	21-30	2009
Ogawa S, Yamashita T, Yamazaki T, Aizawa Y, Atarashi H, Inoue H, Ohe T, Ohtsu H, Okumura K, Katoh T, Kamakura S, Kumagai K, Kurachi Y, Kodama I, Koretsune Y, Saikawa T, Sakurai M, Sugi K, Tabuchi T, Nakaya H, Nakayama T, Hirai M, Fukatani M, Mitamura H; for the J-RHYTHM Investigators.	Optimal treatment strategy for patients with paroxysmal atrial fibrillation.	Circ J	73	242-248	2009
Shiroshita-Takeshita A, Mitamura H, Ogawa S, Nattel S.	Rate-dependence of atrial tachycardia effects on atrial refractoriness and atrial fibrillation maintenance.	Cardiovasc Res	81	90-97	2009
Inoue H, Fujiki A, Origasa H, Ogawa S, Okumura K, Kubota I, Aizawa Y, Yamashita T, Atarashi H, Horie M, Ohe T, Doi Y, Shimizu A, Chishaki A, Saikawa T, Yano K, Kitabatake A, Mitamura H, Kodama I, Kamakura S.	Prevalence of atrial fibrillation in the general population of Japan: An analys is based on periodic health examination.	Int J Cardiol		In press	2009
相澤義泰	不整脈と遺伝子診断	心臓	40	1074-1080	2008
三好俊一郎	不整脈と遺伝子	最新医学	63	1916-1923	2008
Ikrar T, Hanawa H, Watanabe H, Okada S, Aizawa Y, Ramadan MM, Komura S, Yamashita F, Chinushi M, Aizawa Y.	A double-point mutation in the selectivity filter site of the KCNQ1 potassium channel results in a severe p henotype, LQT1, of long QT syndrome.	J Cardiovasc Electrophysiol	19	541-549	2008
Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, Demolombe S, Probst V, Anselme F, Escande D, Wiesfeld AC, Pfeufer A, Kääb S, Wichmann HE,	Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans.	J Clin Invest	118	2260-2268	2008

Hasdemir C, Aizawa Y, Wilde AA, Roden DM, Bezzina CR.					
Chinushi M, Izumi D, Iijima K, Ahara S, Komura S, Furushima H, Hosaka Y, Aizawa Y.	Antiarrhythmic vs. pro-arrhythmic effects depending on the intensity of adrenergic stimulation in a canine anthopleurin-A model of type-3 long QT syndrome.	Europace	10	249-255	2008
Ikrar T, Hanawa H, Watanabe H, Aizawa Y, Ramadan MM, Chinushi M, Horie M, Aizawa Y.	Evaluation of channel function after alteration of amino acid residues at the pore center of KCNQ1 channel.	Biochem Biophys Res Commun	378	589-594	2009
Kusano KF	Brugada phenotype and prostate cancer	Circ J	73	35-36	2009
Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, Morita H, Nishii N, Watanabe A, Tada T, Murakami M, Miyaji K, Hiramatsu S, Nakagawa K, Tanaka M, Miura A, Kimura H, Fuke S, Sumita W, Sakuragi S, Urakawa S, Iwasaki J, Ohe T	Atrial fibrillation in patients with Brugada syndrome: Relationship of gene mutation, electrophysiology and clinical backgrounds	J Am Coll Cardiol	51	1169-1175	2008
Nagase S, Kusano KF, Morita H, Nishii N, Banba K, Watanabe A, Hiramatsu S, Nakamura K, Sakuragi S, Ohe T	Longer repolarization in the epicardium at the right ventricular outflow tract causes type 1 electrocardiogram in patients with Brugada syndrome.	J Am Coll Cardiol	51	1154-1161	2008
Tada T, Kusano KF, Nagase S, Banba K, Miura D, Nishii N, Watanabe A, Nakamura K, Morita H, Ohe T	Clinical significance of macroscopic T wave alternans after sodium channel blocker administration in patients with Brugada syndrome	J Cardiovasc Electrophysiol	19	56-61	2008
Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J	Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome	Circulation	118	1697-1704	2008
草野研吾	Brugada症候群に対する薬物治療－内服治療や心室細動storm時の対応	医学のあゆみ	227	1059-1062	2008
Uchiyama K, Hayashi K, Fujino N, Konno T, Sakamoto Y, Sakata K, Kawashiri MA, Ino H, Yamagishi M.	Impact of QT variables on clinical outcome of genotyped hypertrophic cardiomyopathy.	Ann Noninvasive Electrocardiol	14	65-71	2009
Funada A, Hayashi K, Ino H, Fujino N, Uchiyama K, Sakata K, Masuta E, Sakamoto Y, Tsubokawa T, Yamagishi M.	Assessment of QT intervals and prevalence of short QT syndrome in Japan.	Clin Cardiol	31	270-274	2008
Kaneda T, Naruse C, Kawashima A, Fujino N, Oshima T, Namura M, Nunoda S, Mori S, Konno T, Ino H, Yamagishi M, Asano M.	A novel beta-myosin heavy chain gene mutation, p.Met531Arg, identified in isolated left ventricular non-compaction in humans, results in left ventricular hypertrophy that progresses to dilation in a mouse model.	Clin Sci (Lond)	114	431-440	2008
Sakata K, Ino H, Fujino N, Nagata M, Uchiyama K, Hayashi K, Konno T, Inoue M,	Exercise-induced systolic dysfunction in patients with non-obstructive hypertrophic cardiomyopathy and	Heart	94	1282-1287	2008

Kato H, Sakamoto Y, Tsubokawa T, Yamagishi M.	mutations in the cardiac troponin genes.				
林研至、坂元裕一郎、藤野陽、井野秀一、山岸正和	QT延長症候群における遺伝子診断	循環器科	63	561-567	2008
林　研至　坂元裕一郎 井野秀一　山岸正和	遺伝子診断を踏まえたQT延長・Brugada症候群の治療	Heart View	12	117-123	2008
Shan L, Makita N, Xing Y, Watanabe S, Futatani T, Ye F, Saito K, Ibuki K, Watanabe K, Hirono K, Uese K, Ichida F, Miyawaki T, Origasa H, Bowles NE, Towbin JA	SCN5A variants in Japanese patients with left ventricular noncompaction and arrhythmia.	Mol Genet Metab	93	468-474	2008
Makita N, Mochizuki N, Tsutsui H	Absence of a trafficking defect in R1232W/T1620M, a double SCN5A mutant responsible for Brugada syndrome.	Circ J	72	1018-1019	2008
Otagiri T, Kijima K, Osawa M, Ishii K, Makita N, Matoba R, Hayasaka K	Cardiac ionc channel gene mutations in sudden infant death syndrome.	Pediatreic Res	64	482-487	2008
Tsurugi T, Nagatomo T, Abe H, Oginosawa Y, Takemasa H, Kohno R, Makita N, Makielski JC, Ttsuji Y	Differential modulation of late sodium current by protein kinase A in R1623Q mutant of LQT3.	Life Sci	In press		
蒔田直昌	心房細動と遺伝子異常	循環器科	63	221-227	2008
蒔田直昌	心筋イオンチャネル病	Medical Practice	25	1021-1022	2008
蒔田直昌	Brugada症候群の遺伝子変異	Heart View	12	1098-1105	2008
蒔田直昌	QT延長症候群と遺伝子異常と臨床	心臓	40	1060-1065	2008
蒔田直昌	Brugada症候群の分子生物学的。薬理学的機序と遺伝子診断	医学のあゆみ	227	1023-1028	2009
Miyamoto Y, Shi D, Nakajima M, Ozaki K, Sudo A, Kotani A, Uchida A, Tanaka T, Fukui N, Tsunoda T, Takahashi A, Nakamura Y, Jiang Q, Ikegawa S	Common variants in DVWA on chromosome 3p24.3 are associated with susceptibility to knee osteoarthritis	Nature Genetics	40	994-998	2008
Hirose Y, Chiba K, Karasugi T, Nakajima M, Kawaguchi Y, Mikami Y, Furuichi T, Mio F, Miyake A, Miyamoto T, Ozaki K, Takahashi A, Mizuta H, Kubo T, Kimura T, Tanaka T, Toyama Y, Ikegawa S	A functional polymorphism in THBS2 that affects alternative splicing and MMP binding is associated with lumbar-disc herniation	American Journal of Human Genetics	82	1122-1129	2008
Mototani H, Iida A, Nakajima M, Furuichi T, Miyamoto Y, Tsunoda T, Sudo A, Kotani A, Uchida A,	A functional SNP in EDG2 increases susceptibility to knee osteoarthritis in Japanese	Human Molecular Genetics	17	1790-1797	2008

Ozaki K, Tanaka Y, Nakamura Y, Tanaka T, Notoya K, Ikegawa S					
Suna S, Sakata Y, Shimizu M, Nakatani D, Usami M, Matsumoto S, Mizuno H, Ozaki K, Takashima S, Takeda H, Tanaka T, Hori M, Sato H	Lymphotoxin-α3 mediates monocyte-endothelial interaction by TNFR I/NF-κB signaling	Biochemical and Biophysical Research Communications	379	374-378	2009
Ozaki K, Sato H, Inoue K, Tsunoda T, Sakata Y, Mizuno H, Lin T-H, Miyamoto Y, Aoki A, Onouchi Y, Sheu S-H, Ikegawa S, Odashiro K, Nobuyoshi M, Juo S-H H, Hori M, Nakamura Y, Tanaka T	SNPs in BRAP associated with risk of myocardial infarction in Asian populations	Nature Genetics	in press		2009
田中敏博	SNPとハプロタイプ地図	成人病と生活習慣病	38	1123-1126	2008
尾崎浩一、田中敏博	虚血性心疾患と関連遺伝子	循環器科	63	517-522	2008
尾崎浩一、田中敏博	心筋梗塞のゲノムワイド関連解析	医学のあゆみ	225	781-786	2008
角田達彦、田中敏博, 中村祐輔	国際HapMapプロジェクト	実験医学増刊号	26	998-1002	2008
Makiyama T, Akao M, Shizuta S, Doi T, Nishiyama K, Oka Y, Ohno S, Nishio Y, Tsuji K, Itoh H, Kimura T, Kita T, Horie M.	A novel SCN5A gain-of-function mutation M1875T associated with familial atrial fibrillation.	J Am Coll Cardiol.	52	1327-34	2008
Makiyama T, Akao M, Haruna Y, Tsuji K, Doi T, Ohno S, Nishio Y, Kita T, Horie M.	Mutation analysis of the glycerol-3 phosphate dehydrogenase-1 like (GPD1L) gene in Japanese patients with Brugada syndrome.	Circ J.	72	1705-06	2008
牧山武、赤尾昌治	Brugada症候群とその類縁疾患（進行性伝導欠損（PCCD）、家族性洞不全症候群、など）の基礎、診断、治療	心臓	40	1066-1073	2008

Ⅳ．研究成果の刊行物・別刷り

Circ J 2008; **72:** 1926–1936

Clinical Impact of Genetic Studies in Lethal Inherited Cardiac Arrhythmias

Wataru Shimizu, MD

Over the past decade, molecular genetic studies have established a link between a number of inherited cardiac arrhythmias, including congenital long QT syndrome (LQTS) and Brugada syndrome (BrS), and mutations in genes encoding for ion channels or other membrane components. Twelve forms of LQTS have been identified in 50–70% of clinically affected patients. Genotype–phenotype correlations have been rigorously investigated in LQT1, LQT2 and LQT3 syndromes, which constitute more than 90% of genotyped LQTS patients, enabling stratification of risk and effective treatment of genotyped patients. Genotype-specific triggers for both the cardiac events and the clinical course have been reported, and genotype-specific therapy has been already introduced. More recently, mutation site-specific differences in the clinical phenotype have been reported in LQT1 and LQT2 patients, indicating the possibility of mutation site-specific management or treatment. In contrast, only one-third of BrS patients can be genotyped, and data on genotype–phenotype relationships in clinical studies are limited. A Haplotype B consisting of 6 individual DNA polymorphisms within the proximal promoter region of the *SCN5A* gene was recently identified only in Asians (frequency 22%). Individuals with Haplotype B show significantly longer duration of both PQ and QRS than those without Haplotype B, indicating that Haplotype B likely contributes to the higher incidence of BrS in Asian populations. (*Circ J* 2008; **72:** 1926–1936)

Key Words: Brugada syndrome; Genotype; Ion channel; Long QT syndrome; Sudden death

Advances in molecular genetic studies since the late 1990s have established a link between a number of lethal inherited cardiac arrhythmias and mutations in genes encoding for ion channels or other membrane components.[1–11] Most inherited cardiac arrhythmias have been linked to ion channelopathies giving rise to primary electrical diseases, including congenital and acquired long QT syndrome (LQTS),[1,2] Brugada syndrome (BrS),[3] progressive cardiac conduction defect (Lenegre disease),[4] catecholaminergic polymorphic ventricular tachycardia (CPVT),[5,6] arrhythmogenic right ventricular cardiomyopathy,[7] familial atrial fibrillation,[8] familial sick sinus syndrome,[9,10] and short QT syndrome[11] (Table1). Among these primary electrical diseases, congenital LQTS is the Rosetta stone for understanding the genetic basis of inherited cardiac arrhythmias,[12] because the responsible mutations can be identified in multiple genes encoding different ion channels or membrane adaptor in approximately 50–70% of clinically affected patients. Similarly, causative mutations can be detected in the ryanodine receptor (*RyR2*) gene or calsequestrine gene in more than 60% of clinically diagnosed CPVT patients.[13] BrS is another common inherited cardiac arrhythmia syndrome, and responsible mutations have been identified in 6 genes; however, only one-third of patients with BrS can be genotyped. Responsible mutations have been identified much less in other inherited cardiac arrhythmias, so genetic screening is much more challenging. This review focuses on the recent progress in molecular genetic studies and their clinical impact on the inherited cardiac arrhythmias, congenital LQTS and BrS.

(Received October 6, 2008; accepted October 9, 2008; released online November 4, 2008)

Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan
Mailing address: Wataru Shimizu, MD, Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: wshimizu@hsp.ncvc.go.jp

Congenital LQTS

Prolonged QT interval and polymorphic ventricular tachycardia, known as torsades de pointes (TdP), recorded on an electrocardiogram (ECG) are trademarks of congenital LQTS (Fig 1).[12,14] The clinical diagnosis of congenital LQTS is mainly based on the corrected (QTc) interval at rest, and cardiac events such as syncope, aborted cardiac arrest and sudden cardiac death because of TdP.[14] However, the ECG diagnosis at rest has long been reported to miss some patients affected by congenital LQTS, as evidenced

Table 1 Genotype of Inherited Cardiac Arrhythmias

Congenital LQTS	*Romano-Ward*	*(1995-) CLQT 1-12*
	JLN	*(1997-) JLN 1, 2*
Acquired LQTS		*(1997-) ALQTS 1-2*
BrS		*(1998-) BrS 1-2*
PCCD		*(1999-) PCCD 1*
CPVT		*(2001-) CPVT 1, 2*
Familial SSS		*(2003-) SSS 1, 2*
Familial AF		*(2003-) AF 1-5*
ARVC		*(2004-) ARVC 1-5*
SQTS		*(2004-) SQTS 1-5*

LQTS, long QT syndrome; JLN, Jervell & Lange-Nielsen; BrS, Brugada syndrome; PCCD, progressive cardiac conduction defect; CPVT, catecholaminergic polymorphic ventricular tachycardia; SSS, sick sinus syndrome; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; SQTS, short QT syndrome.

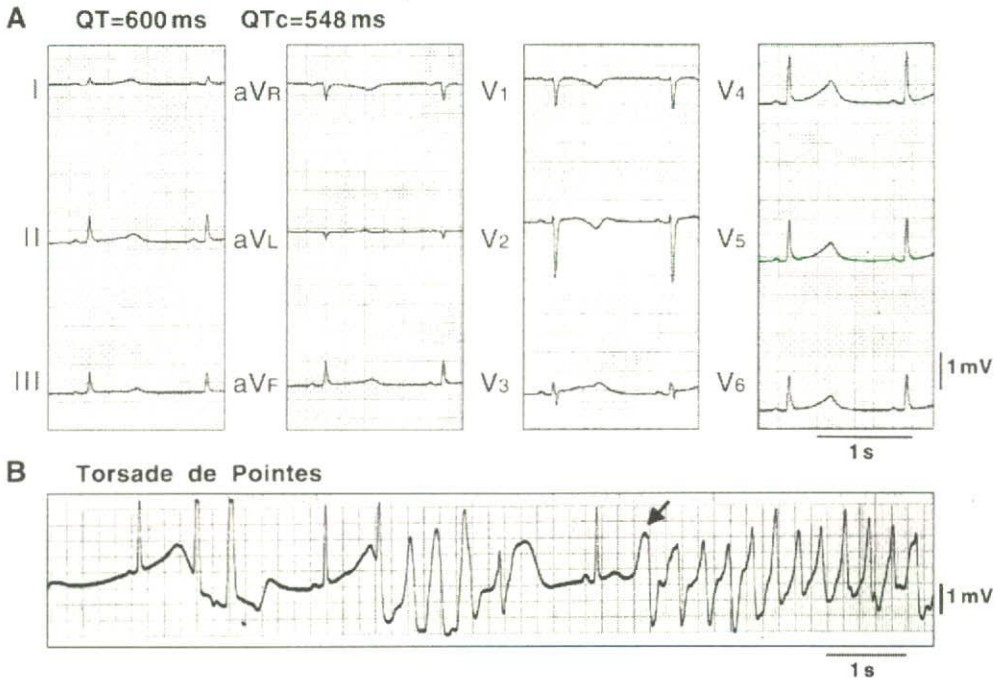

Fig 1. Twelve-lead electrocardiogram and torsades de pointes (TdP) in a patient with LQT2 syndrome. (A) Remarkable QT prolongation (corrected QT (QTc) interval=548 ms) and a low amplitude T wave with a notched configuration are seen. (B) TdP was induced following the typical short–long–short initiating sequence.

Table 2 Defect of Ion Channel or Membrane Adaptor Responsible for Congenital LQTS

Loci	*Chromosome*	*Gene*	*Ion channel*
Romano-Ward syndrome			
LQT1	*11 (11p15.5)*	*KCNQ1*	I_{Ks}
LQT2	*7 (7q35-36)*	*KCNH2*	I_{Kr}
LQT3	*3 (3p21-23)*	*SCN5A*	I_{Na}
LQT4	*4 (4q25-27)*	*Ankyrin-B*	*Na-K ATPase*, $I_{Na\ Ca}$
LQT5	*21 (21q22.1-q22.2)*	*KCNE1*	I_{Ks}
LQT6	*21 (21q22.1-q22.2)*	*KCNE2*	I_{Kr}
LQT7	*17 (17q23.1-24.2)*	*KCNJ2*	I_{K1}
LQT8	*12 (12p13.3)*	*CACNA1C*	$I_{Ca\text{-}L}$
LQT9	*3 (3p25)*	*CAV3*	I_{Na}
LQT10	*11 (11q23.3)*	*SCN4B*	I_{Na}
LQT11	*7 (7q21-q22)*	*AKAP-9*	I_{Ks}
LQT12	*20 (20q11.2)*	*SNTA1*	I_{Na}
JLN syndrome			
JLN1	*11 (11p15.5)*	*KCNQ1 (homozygous)*	I_{Ks}
JLN2	*21 (21q22.1-q22.2)*	*KCNE1 (homozygous)*	I_{Ks}

Abbreviations see in Table 1.

by syncopal events occurring among family members with a "normal" QT interval;[15] therefore, provocative testing using catecholamine infusion or exercise was developed to unmask concealed forms of congenital LQTS, before genetic screening became available![16–20]

Genotype in Congenital LQTS

Because familial forms of congenital LQTS have long been recognized, a genetic background (inheritance) has long been expected. Since the first 2 genes responsible for LQTS were identified in 1995,[21,22] molecular genetic studies have revealed 12 forms of Romano-Ward-type congenital LQTS caused by mutations in the genes of the potassium, sodium and calcium channels or the membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17, 20 and 21 (Table2).[23–31] Mutations in *KCNQ1* and *KCNE1*, the α and β subunits of the potassium channel gene, are responsible for defects (loss of function) in the slowly activating component of the delayed rectifier potassium current (I_{Ks}) underlying the LQT1 and LQT5 forms of LQTS.[32,33] Mutations in *KCNH2* and *KCNE2* cause defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}), which is responsible for the LQT2 and LQT6 forms.[21,34] Mutations in *SCN5A*, the gene that encodes the α subunit of the sodium channel, result in an increase (gain of function) in the late sodium current (I_{Na}), which is responsible for LQT3.[22] Mutations in *KCNJ2* encoding the inward rectifier potassium current (I_{K1}) underlie Andersen's

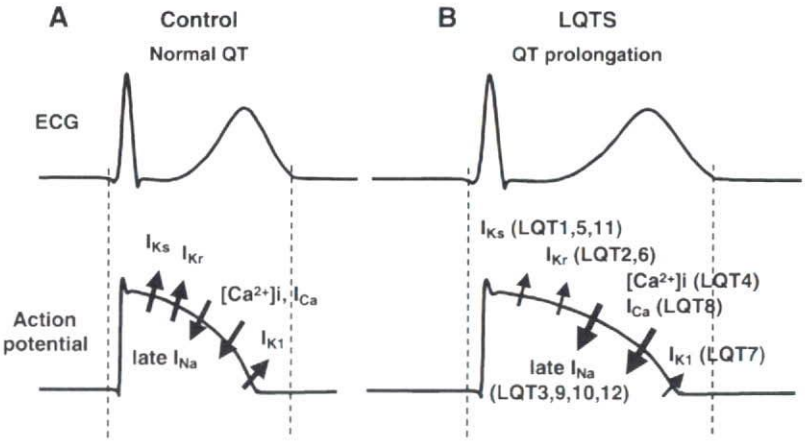

Fig 2. Ionic mechanism of QT prolongation in the LQT1 to LQT12 forms. Decreases in the outward potassium currents (I_{Ks}, I_{Kr}, I_{K1}) or increases in the inward sodium or calcium current (late I_{Na}, $I_{Ca\text{-}L}$) prolong the action potential duration, resulting in prolongation of the QT interval in all 12 genetic forms. ECG, electrocardiogram.

syndrome (LQT7), in which QT prolongation and ventricular arrhythmias are accompanied by periodic paralysis and dysmorphic features.[24] A mutation in *Ankyrin-B*, a member of a family of versatile membrane adapters, produces intracellular calcium overload, which underlies LQT4 syndrome and is associated with sinus bradycardia and paroxysmal atrial fibrillation, in addition to QT prolongation.[25] A mutation in *CACNA1C* is reported to be responsible for the defect in the L-type calcium current ($I_{Ca\text{-}L}$) underlying the LQT8 form, an arrhythmia disorder associated with dysfunction in multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism.[26] *CAV3* encoding caveolin-3 and *SCN4B* encoding *NavB4*, an auxiliary subunit of the cardiac sodium channel, are also reported to be associated with the LQT9 and LQT10 forms, respectively. Mutations in both genes result in a gain of function of late I_{Na}, thus causing an LQT3-like phenotype.[27,28] *AKAP-9* encoding Yotiao, which assembles *KCNQ1*, is reported to be linked to the LQT11 form.[29] Most recently, we and others reported mutations in a cytoskeletal protein syntrophin-α1 (*SNTA1*), which interacts with the cardiac sodium channel, thus resulting in an LQT3-like phenotype (LQT12).[30,31] At least some cases of sudden infant death syndrome (SIDS) are attributable to congenital LQTS.[35] Mutations in *SCN5A*,[35,36] *CAV3*,[37] *KCNQ1*[38] and *KCNH2*[38] are reported to be associated with SIDS. As a common mechanism, decreases in the outward potassium currents (I_{Ks}, I_{Kr}, I_{K1}) or increases in the inward sodium or calcium current (late I_{Na}, $I_{Ca\text{-}L}$) prolong the action potential duration (APD), resulting in prolongation of the QT interval, a common phenotype in LQTS in all 12 genetic forms (Fig 2). Among the 12 forms, the LQT1 and LQT2 syndromes are the most common genetic variants, and each accounts for approximately 40% of genotyped patients; LQT3 syndrome accounts for approximately 10% of genotyped patients.[23] Because the LQT1, LQT2 and LQT3 syndromes constitute more than 90% of genotyped patients with LQTS, the genotype–phenotype correlation has been rigorously investigated, and enables stratification of risk and effective treatment of genotyped patients with these 3 major forms.[23]

Autosomal recessive forms (JLN1 and JLN2) of the Jervell & Lange-Nielsen syndrome are associated with neurosensory deafness and generally more prominent QT prolongation and more severe ventricular arrhythmias compared with the autosomal dominant forms of the Romano-Ward syndrome.[39] JLN1 and JLN2 are reported to be responsible for homozygous or compound heterozygous mutations in the *KCNQ1* and/or *KCNE1* genes. Approximately 8% of LQTS patients carries homozygous or compound heterozygous mutations in 2 LQTS-causing genes, and are reported to have longer QTc and 3.5-fold more risk of cardiac arrest.[40] On the other hand, an autosomal recessive form of LQT1 syndrome without neurosensory deafness was reported by Priori et al.[41] Some single mutations in the *SCN5A* gene are reported to cause multiple phenotypes, such as BrS, sick sinus syndrome, and conduction disease, in addition to the LQT3 phenotype.[42,43]

Genotype–Phenotype Relationships in Congenital LQTS

T-Wave Morphology on the ECG A series of experimental studies using arterially-perfused canine wedge preparations have revealed that intrinsic transmural electrical heterogeneity of ventricular repolarization from the epicardial, mid-myocardial to the endocardial cells contributes to ST-T morphology and the QT interval on ECG, especially in the left precordial (V_{4-6}) leads, which are thought to reflect the potentials of the left ventricular anterolateral wall.[44–46] Under normal conditions, repolarization of the epicardial action potential occurs first, coinciding with the peak of the normal T wave, whereas repolarization of the longest action potential in the mid-myocardial layer coincides with the end of the T wave.[44] Repolarization of endocardial cells usually occurs between repolarization of the epicardial and mid-myocardial cells.[44] The amplified transmural electrical heterogeneity of ventricular repolarization associated with differential modification of ionic currents in each cell type, which is caused by mutations in each LQTS gene, results in genotype-specific T-wave morphology on the ECG.[44,45] Moss et al first proposed genotype-specific T-wave morphology in genotyped patients with the LQT1, LQT2 and LQT3 forms in 1995.[47] Broad-based, prolonged T waves are more commonly observed in LQT1 syndrome; low-amplitude T waves with a notched or bifurcated configuration are more frequently observed in LQT2; and late-appearing T waves with a prolonged isoelectric ST-segment are more specific in LQT3 syndrome. The genotype-specific T-wave pattern was further evaluated by Zhang et al in 2000, and numerous exceptions are reported for all 3 genotypes.[48]

Natural History Zareba et al suggested a higher cumulative probability of cardiac events in LQT1 and LQT2 patients than in LQT3 patients.[49] More than 50% of patients

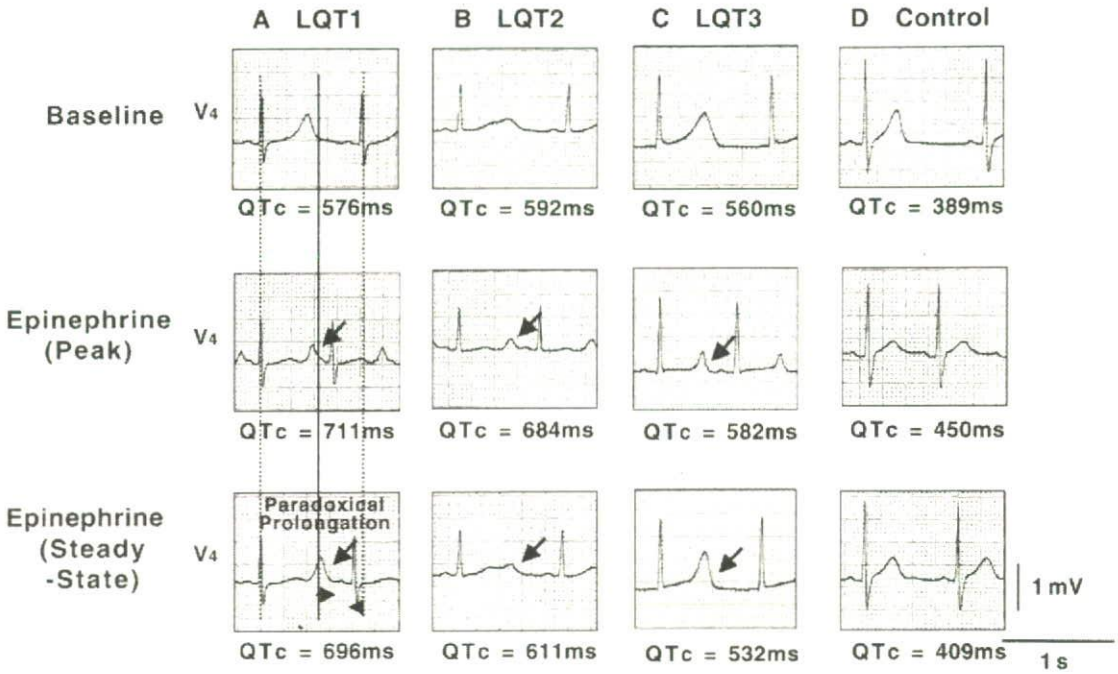

Fig 3. Genotype-specific responses of the corrected QT (QTc) interval to epinephrine provocative testing in patients with LQT1, LQT2 and LQT3 syndromes. Shown are V_4 lead electrocardiogram recordings under baseline conditions, at peak and steady-state epinephrine effects in LQT1 (A), LQT2 (B), LQT3 (C) and Control (D) patients. The QTc was prominently prolonged from 576 to 711 ms at peak epinephrine effect, and remained prolonged at the steady-state (696 ms) in the LQT1 patient. In the LQT2 patient, the QTc was also markedly prolonged from 592 to 684 ms at peak, but returned to the baseline level at the steady-state (611 ms). It was much less prolonged (LQT3: 560 to 582 ms, Control: 389 to 450 ms) at the peak in LQT3 and Control patients than in either the LQT1 or LQT2 patients, and was shortened to the baseline level at the steady-state (532, 409 ms). Modified from Shimizu et al. *Heart Rhythm* 2004; **1**: 276–283[17] with permission.

experience cardiac events before age 40 years in the LQT1 and LQT2 syndromes, whereas less than 30% of patients do so in LQT3 syndrome; however, the lethality of the cardiac events is significantly higher in LQT3 patients than in LQT1 or LQT2 patients. Generally, male patients experience their first cardiac events at a younger age than female patients.[50] Approximately 90% of first cardiac events occur before the age of 15 years in male patients, particularly in LQT1 males, whereas female patients do not rarely experience their first cardiac events after the age of 20.[50] These tendencies were recently confirmed using the largest cohort of LQT1 syndrome patients.[51] The data suggested that LQT1 males before age 13 years and LQT1 females after age 13 years had a significant and independent clinical risk associated with first cardiac events.[51]

Triggers for Cardiac Events Genotype-specific triggers for cardiac events have been reported in patients with LQT1, LQT2 and LQT3 syndromes.[12,52,53] Cardiac events occur most frequently during exercise (62%), and swimming is a common trigger in LQT1 syndrome.[52] LQT2 and LQT3 patients are less likely to have cardiac events during exercise (13% and 13%, respectively) and more likely to have cardiac events during rest/sleep (29% and 39%, respectively).[52] In LQT2 syndrome, being startled by an auditory stimulus (telephone, alarm clock, ambulance siren etc) is a specific trigger.[52,53] LQT2 women are reported to be most susceptible to cardiac events in the postpartum period.[54] The differential sensitivity in cardiac events to sympathetic (β-adrenergic) stimulation has been suggested to be caused by the differential response of ventricular repolarization to sympathetic stimulation in both experimental studies employing arterially perfused wedge preparations[45,46] and in clinical studies using catecholamine provocative testing or exercise testing.[16–20]

Catecholamine Provocative Testing

Infusion of isoproterenol, a β-adrenergic agonist, or epinephrine, an α- + β-adrenergic agonist, has been used as a provocative test in patients with LQTS since the 1980s.[55] Before the discovery of distinct genetic subtypes of congenital LQTS, the responses to either epinephrine or isoproterenol were extremely heterogeneous, and deemed impossible to interpret. Now, however, the heterogeneous response is understood to stem from underlying genetic heterogeneity, and genotype-specific responses to epinephrine can be exploited to expose different genotypes of LQTS in its otherwise concealed state, particularly LQT1 syndrome. Although isoproterenol is still used occasionally, recent major insights have been gleaned from using epinephrine. The 2 major protocols developed for epinephrine provocative testing include the escalating-dose protocol by Ackerman's group (Mayo protocol),[18,19] and bolus injection followed by brief continuous infusion by my group (Shimizu protocol).[16,17,19]

The bolus (Shimizu) protocol was developed on the basis of a differential response of the APD and QT interval to sympathetic stimulation with isoproterenol between experimental models of LQT1, LQT2 and LQT3 using arterially-perfused canine left ventricular wedge preparations.[46] Clinical data from the use of the bolus protocol suggested that sympathetic stimulation produces genotype-specific

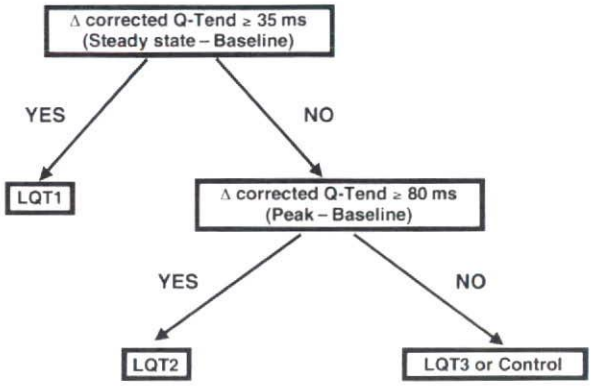

Fig 4. Genotype prediction by epinephrine provocative testing in patients with LQT1, LQT2 and LQT3 syndromes. Flow chart predicting genotype with epinephrine provocative testing. Modified from Shimizu et al. *Heart Rhythm* 2004; **1**: 276–283[17] with permission.

responses of the QTc interval in patients with LQT1, LQT2 and LQT3 syndromes (Fig 3)[16,17,19] Epinephrine remarkably prolongs the QTc interval at peak effect when the heart rate is maximally increased (1–2 min after the bolus injection), and the QTc remains prolonged during the steady-state epinephrine effect (3–5 min) in patients with LQT1[16,17,19] In LQT1 patients, a paradoxical QT prolongation, defined as an absolute increase in the QT (not QTc) interval, despite a shortening of the RR interval, is often observed during epinephrine infusion. Ackerman et al reported that the paradoxical QT prolongation had a sensitivity of 92.5%, specificity of 86%, positive predictive value of 76%, and negative predictive value of 96% for LQT1 patients vs non-LQT1 patients[18] In the bolus protocol, QTc is also prolonged at peak epinephrine effect (during bolus) in patients with LQT2, but returns to close to the baseline level at steady-state epinephrine effect[17,19] In contrast, the QTc is less prolonged at peak epinephrine effect in LQT3 patients than in LQT1 or LQT2 patients, and is abbreviated below the baseline level at steady-state epinephrine effect[17,19] Using the steady-state epinephrine effect, an improvement of clinical ECG diagnosis (sensitivity) from 68% to 87% in 31 patients with LQT1 syndrome and from 83% to 91% in 23 patients with LQT2 syndrome, but not in 6 patients with LQT3 syndrome (from 83% to 83%), was reported[17] The bolus protocol of epinephrine effectively predicts the underlying genotype of LQT1, LQT2 and LQT3 (Fig 4)[17,19] The prolongation of QTc ≥35ms at steady-state epinephrine effect can differentiate LQT1 from LQT2, LQT3 or control patients with a predictive accuracy ≥90%. The prolongation of QTc ≥80 ms at peak epinephrine effect can differentiate LQT2 from LQT3 or control patients with predictive accuracy of 100%. Although induction of TdP or ventricular fibrillation (VF) is extremely uncommon, intravenous β-blockers and a cardioverter defibrillator need to be available during testing.

Because molecular diagnosis is still unavailable in many institutes and is time-consuming, a clinical diagnosis of patients with concealed LQTS by epinephrine provocative testing can direct appropriate counseling and facilitate the initiation of preventive measures such as avoidance of QT-prolonging drugs. Moreover, a presumptive, pre-genetic diagnosis of either LQT1, LQT2, or LQT3 based on the response to epinephrine can guide genotype-specific treatment strategies.

Table 3 Genotype-Specific Therapy Based on Clinical and Experimental Data in LQTS

	LQT1	*LQT2*	*LQT3*
Prevalence	*40%*	*30–40%*	*10%*
Exercise restriction	+++++	+++	–
β-blockers	+++++	+++	–
Potassium supply	++?	++++	++?
Class IB sodium channel blockers	+++	+++	+++++
Calcium channel blockers	+++	+++	++?
Potassium channel openers	++	++	–
Pacemaker	++	++++	+++++
ICD	++++	++++	+++++

ICD, implantable cardioverter-defibrillator; +++++, most effective. Other abbreviation see in Table 1.

Genotype-Specific Therapy

Based on the natural history and specific sensitivity to sympathetic stimulation or catecholamine in the LQT1 syndrome, stricter exercise restriction, in particular swimming or diving, is required, especially for LQT1 males[12] Exercise restriction is also required in LQT2 syndrome[12]

Although β-blockers are empirically believed to be the most effective therapy for patients with congenital LQTS, they are not protective in all LQTS patients. Since molecular genetic studies have become available, genotype-specific pharmacological and non-pharmacological therapies have been introduced clinically, based on data derived from both clinical and experimental studies (Table 3).

In LQT1 patients, β-blockers frequently suppress episodes of syncope and sudden cardiac death[52] Data from a recent international cohort of 600 LQT1 patients has suggested that time-dependent β-blocker use is associated with a significant 74% reduction in the risk of first cardiac events[51] Mexiletine, a class IB sodium channel blocker, which blocks late I_{Na}, or verapamil, an $I_{Ca\text{-}L}$ blocker, may warrant consideration as adjunctive therapy to β-blockers in LQT1 patients, based on ECG changes with these agents or experimental data[44,45] An implantable cardioverter-defibrillator (ICD) is indicated for LQTS patients who have suffered an aborted cardiac arrest and/or who have repetitive episodes of syncope in the presence of β-blockers.

Beta-blockers are also the first choice as pharmacological therapy in LQT2 patients, but the recurrence rate is higher than in LQT1 patients[52] Increase in the extracellular potassium concentration by exogenously administered potassium or long-term oral potassium administration has been reported to shorten the QT interval in LQT2 patients[56] The indication for an ICD is similar to that in LQT1 syndrome. My group recently reported that patients with LQT2 syndrome show a specific short–long–short initiating pattern of TdP more frequently than those with LQT1 syndrome[57] so pacemaker therapy is expected to be more effective in LQT2 than in LQT1 patients by suppressing that specific pattern[57]

In LQT3 patients, β-blockers are less effective than in LQT1 or LQT2 patients[52] Mexiletine is more effective for abbreviating the QT interval in LQT3 than in LQT1 or LQT2 syndrome, and is therefore a promising therapeutic choice in LQT3 syndrome. Pacemaker therapy may be most beneficial in LQT3 patients with bradycardia, based on the experimental data.

Genotype-specific therapy is unknown for the other forms: LQT4, LQT5, LQT6, LQT7, LQT8, LQT9, LQT10, LQT11, and LQT12. Beta-blockade is the first-line therapy in patients with LQT4, LQT5, LQT6, LQT7, LQT8 and

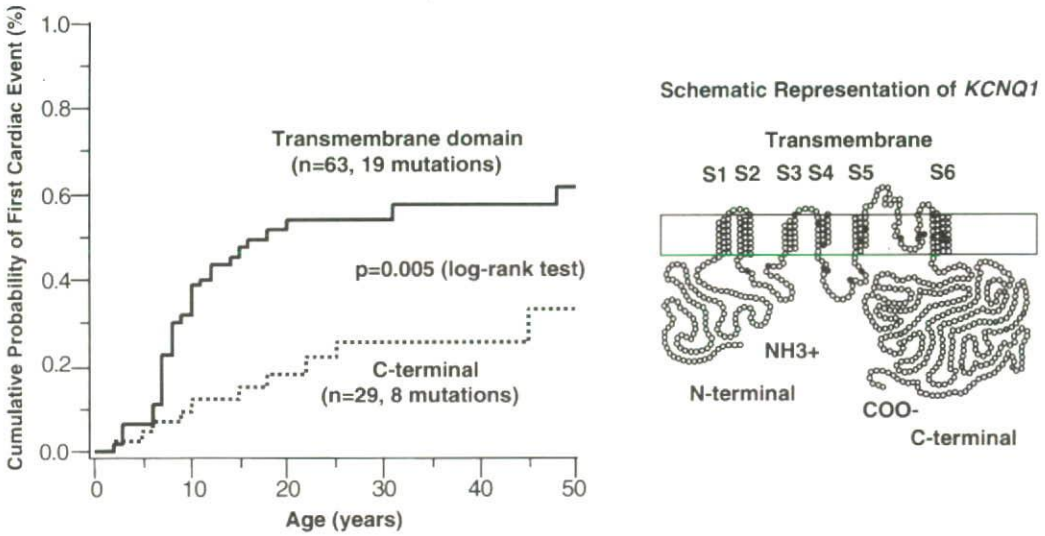

Fig 5. Kaplan-Meier cumulative cardiac event curves from birth to age 50 for patients with *KCNQ1* mutations located in transmembrane regions (n=66, 19 mutations; closed circles) and the C-terminal regions (n=29, 8 mutations; gray circles) in LQT1 syndrome. The difference in the clinical course by mutation location was significant (log-rank, p=0.005), with a greater risk of first cardiac events in patients with transmembrane mutations than in those with C-terminal mutations. Modified from Shimizu et al. *J Am Coll Cardiol* 2004; **44:** 117–125[59] with permission.

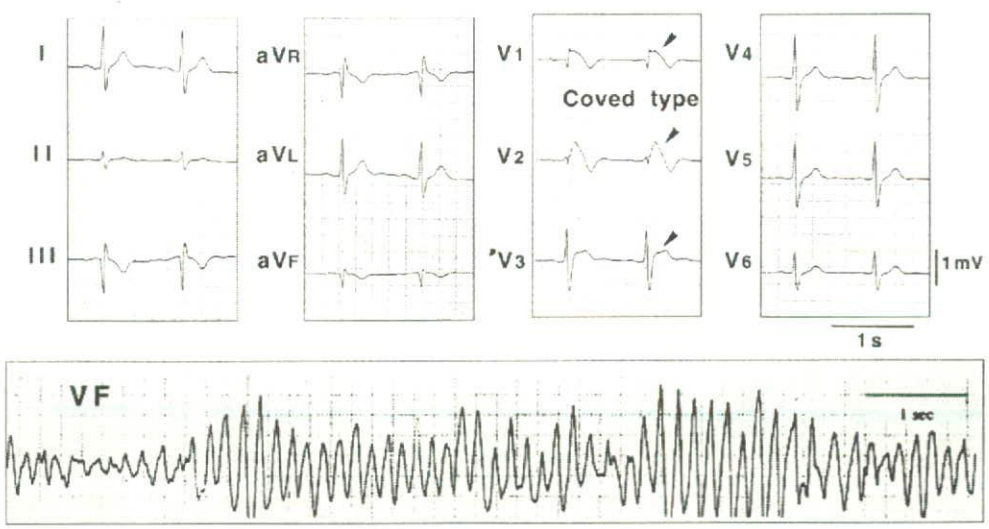

Fig 6. Twelve-lead electrocardiogram and ventricular fibrillation (VF) in a patient with Brugada syndrome. Spontaneous type 1 coved-type ST-segment elevation is recorded in leads V_1 and V_2 (arrows).

LQT12, and unknown LQTS genotypes. The class IB sodium channel blocker, mexiletine, may be theoretically effective in LQT9, LQT10, and LQT12 patients.

Possibility of Mutation Site-Specific Therapy

The structure of each cardiac ion channel, or correspondence between the mutation site and channel function, has been increasingly elucidated, suggesting mutation site-specific differences in the severity of the clinical phenotype or responses to therapy in each genotype. From data in the International LQTS Registry, Moss et al suggested that LQT2 patients with mutations in the pore region of *KCNH2* had a greater risk of arrhythmia-related cardiac events than patients with non-pore mutations;[58] thus indicating the possibility of mutation site-specific management or treatment of LQT2 syndrome. With regard to LQT1 syndrome, in 2004 the arrhythmic risk and sensitivity to sympathetic stimulation with treadmill exercise testing was compared between Japanese LQT1 patients with transmembrane mutations and those with C-terminal mutations in *KCNQ1*, and the LQT1 patients with transmembrane mutations showed a longer QTc interval and more frequent LQTS-related cardiac events than those with C-terminal mutations (Fig 5).[59] Moreover, the QTc interval was more prominently increased with exercise in patients with transmembrane mutations.[59] The international cohort of 600 LQT1 patients recently confirmed the Japanese data,[51] suggesting that transmembrane mutations and mutations with dominant-negative functional effect adversely influence the outcome of LQT1 patients, independent of traditional clinical risk factors and β-blocker

Table 4 Defect of Ion Channel or Membrane Adaptor Responsible for BrS

Loci	*Chromosome*	*Gene*	*Ion channel*
BrS1	*3 (3p21-24)*	*SCN5A*	I_{Na}
BrS2	*12 (12p13.3)*	*CACNA1C*	$I_{Ca\text{-}L}$
BrS3	*10 (10p12.33)*	*CACNB2*	$I_{Ca\text{-}L}$
BrS4	*3 (3p21)*	*GPD1-L*	I_{Na}
BrS5	*19 (19q13.1)*	*SCN1B*	I_{Na}
BrS6	*11 (11q13-q14)*	*KCNE3*	I_{to}

Abbreviation see in Table 1.

therapy.

Brugada Syndrome

In 1992, Brugada and Brugada first reported 8 patients with a history of aborted sudden cardiac death caused by VF and a characteristic ECG pattern, consisting of right bundle branch block (RBBB) and ST-segment elevation in the right precordial ECG leads (V_{1-3}) as a distinct clinical entity.[60–65] The Brugada Consensus Report in 2002 suggested 3 patterns of ST-segment elevation:[63] the type 1 ST-segment elevation is characterized by a coved-type ST-segment elevation displaying J-wave amplitude or ST-segment elevation ≥0.2 mV with or without a terminal negative T wave (Fig 6); type 2 and type 3 ST-segment elevations show a saddleback configuration, which has a high take-off ST-segment elevation (≥0.2 mV), followed by a gradually descending ST-segment elevation (type 2 ≥0.1 mV, type 3 <0.1 mV above the baseline) and a positive or biphasic T wave. ST-segment elevation is often accentuated and the coved type ST-segment elevation is more frequently recognized just before and after episodes of VF.[66,67] The second Consensus Report published in 2005 emphasized that type 1 ST-segment elevation is required to diagnose BrS,[64] because the type 1 ECG is reported to relate to a higher incidence of VF and sudden cardiac death. Type 1 ST-segment elevation recorded only in the higher (3rd and 2nd intercostal spaces) V_{1-2} leads is reported to show a similar prognostic value for subsequent cardiac events as that recorded in the standard V_{1-2} leads.[64,68–70] The prevalence of BrS is estimated to be up to 5 per 10,000 inhabitants, and is an important cause of sudden cardiac death of middle-aged males, particularly in Asian countries.[64,65] BrS usually manifests during adulthood,[64] and more than 80–90% of patients clinically affected are men.

Genotype in BrS (Table 4)

In 1998, Chen et al identified the first mutation linked to BrS in *SCN5A*, the I_{Na} gene that is responsible for the LQT3 form of congenital LQTS.[3] *SCN5A* mutations are reported to account for 18–30% of clinically diagnosed BrS patients at present.[64] Functional analysis using expression systems has shown that all *SCN5A* mutations so far identified result in decreased (loss of function) I_{Na} by several mechanisms,[65] including (1) lack of expression of the sodium channel; (2) a shift in the voltage dependence and time dependence of I_{Na} activation, inactivation or reactivation; (3) entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly; (4) accelerated inactivation of the sodium channel; or (5) a trafficking defect. The 2nd and 3rd mutations linked to BrS were reported by Antzelevitch et al in 2007, when they identified mutations in *CACNA1C* or *CACNB2*, the gene encoding the $\alpha 1$ or $\beta 2b$ subunit of the L-type calcium channel, in 3 probands with Brugada-like ST-segment elevation associated with a short QT interval.[71] Heterologous expression studies for the mutations revealed loss of function of $I_{Ca\text{-}L}$. Thereafter, London et al identified a mutation in a conserved amino acid of the glycerol-3-phosphate dehydrogenase 1-like (*GPD1-L*) gene in affected individuals of a large Brugada family.[72] The *GPD1-L* mutation decreases *SCN5A* surface membrane expression and reduces I_{Na}, thus causing BrS.[72] Watanabe et al recently identified a nonsense mutation (W179X) in *SCN1B*, which encodes the function-modifying sodium channel $\beta 1$ subunit, in a family with BrS associated with cardiac conduction disease.[73] They reported that the I_{Na} current was decreased when α subunit ($Na_V1.5$) of the sodium channel was coexpressed with the mutant $\beta 1$ subunit compared with when it was coexpressed with the wild-type $\beta 1$ subunit. More recently, Delpon, Antzelevitch et al reported a missense mutation (R99H) in *KCNE3*, which encodes the potassium channel β subunit and interacts with Kv4.3 (transient outward current: I_{to}) channel, in a proband with BrS.[74] Coexpression of the mutant *KCNE3* with *KCND3*, which encodes Kv4.3, increases the I_{to} intensity (gain of function) compared with that by the coexpression of wild-type *KCNE3* with *KCND3*.[74] Thus, decreases in the inward sodium or calcium current (late I_{Na}, $I_{Ca\text{-}L}$) or increases in the outward potassium currents (I_{to}) produce a Brugada phenotype in all 6 genotypes, as indicated by previous experimental studies; however, approximately two-thirds of Brugada patients have not yet been genotyped, suggesting the presence of genetic heterogeneity.[65]

Genotype–Phenotype Correlations in BrS

The genotype–phenotype correlation in BrS has been less investigated than that in congenital LQTS, because more than two-thirds of patients clinically affected with BrS are not genotyped. Mild conduction abnormalities, such as widening of the P wave, prolongation of the QRS duration, PQ interval, and HV interval, and a higher incidence of RBBB have been described in patients with BrS, especially those with the *SCN5A* mutation.[64] Significantly longer PQ and HV intervals at baseline and a larger increase in the PQ and QRS intervals after sodium channel blockers have been reported by Smits et al in Brugada patients with *SCN5A* mutations than in those without *SCN5A* mutations.[75] Several ECG parameters were measured during long-term follow up and prospectively compared between Brugada patients with and without the *SCN5A* mutation by Yokokawa and co-workers, with the results suggesting that P wave, QRS, S wave durations, and PQ intervals were all significantly longer, and the S wave amplitude was significantly deeper in the *SCN5A*-positive group than in the *SCN5A*-negative group (Figs 7,8).[76] In addition, the PQ interval and QRS duration in lead V_2 were prolonged more markedly with aging in the

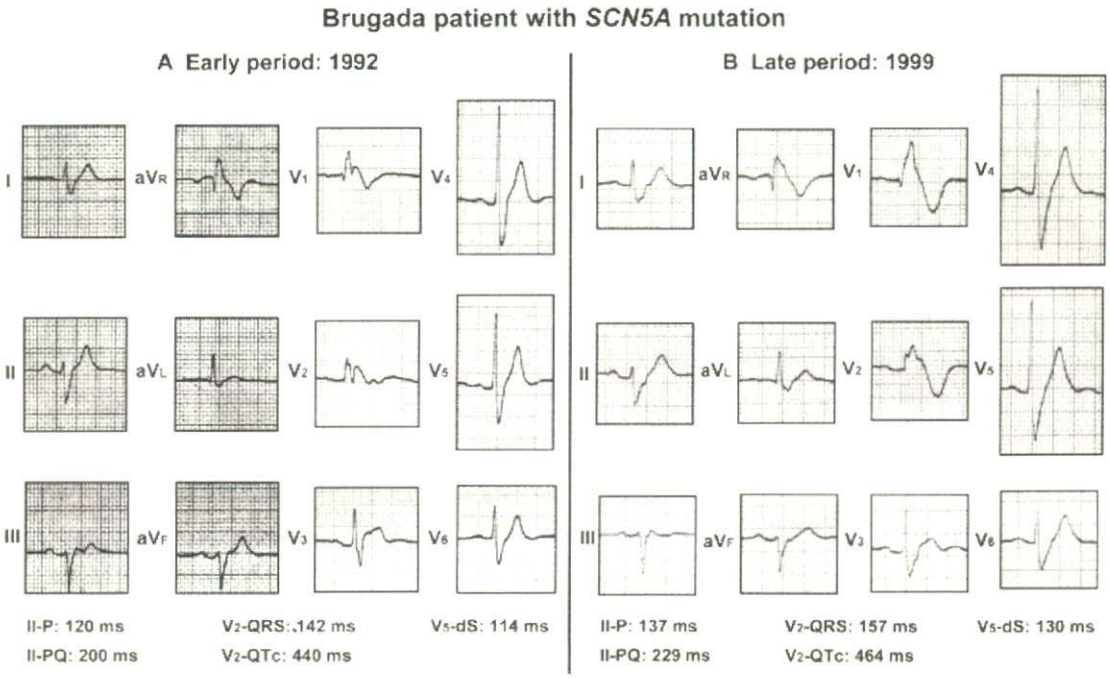

Fig 7. Twelve-lead electrocardiogram in the early and late periods during follow-up (7 years) in a Brugada patient with the *SCN5A* mutation. The P wave (lead II), QRS (lead V_2), and S wave (lead V_5) durations and PQ interval (lead II) are prolonged, even in the early period (47 years old) (A). The S wave amplitude (lead V_5) is also deep, and the QRS axis is deviated to the left. The corrected QT (QTc) interval (lead V_2) is borderline prolonged. In the late period (B), all these parameters are further increased. Modified from Yokokawa et al. *Am J Cardiol* 2007; **100:** 649–655[70] with permission.

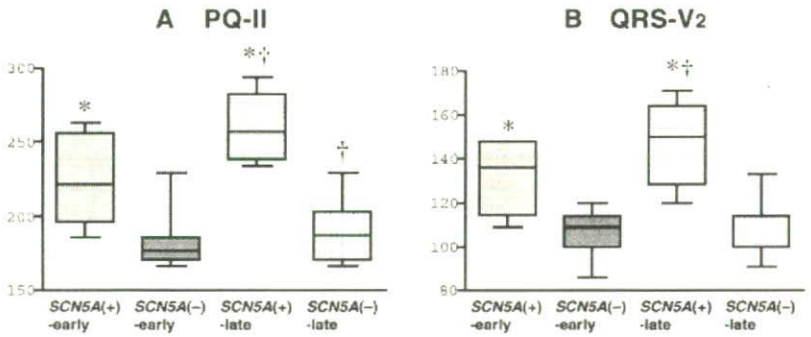

Fig 8. Electrocardiographic parameters during long-term follow-up in 8 Brugada patients with the *SCN5A* mutation and in 36 Brugada patients without the mutation. Both the PQ interval in lead II (A) and the QRS duration in lead V_2 (B) are significantly longer in the *SCN5A*-positive (+) group than in the *SCN5A*-negative (−) group in both the early and late periods. Both the PQ interval and QRS duration increased with aging during follow-up in both groups, but more prominently in the *SCN5A*(+) group than in the *SCN5A*(−) group. *$p<0.05$ vs *SCN5A*(−), †$p<0.05$ vs early.

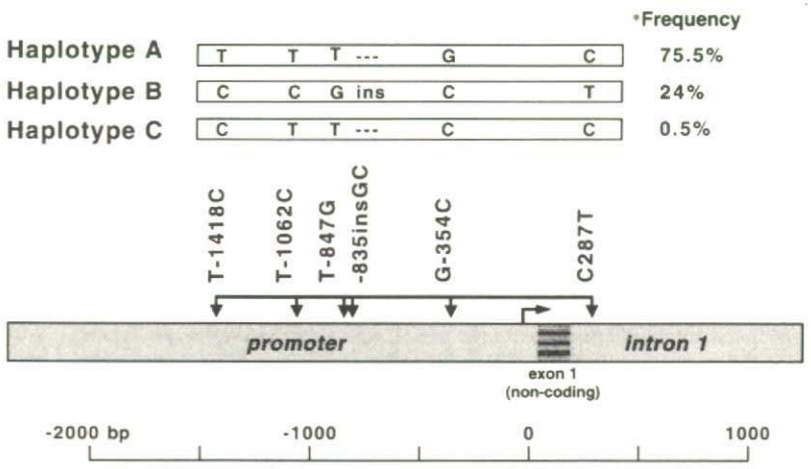

Fig 9. Haplotypes identified within the proximal promoter region of the *SCN5A*, a cardiac sodium channel gene. The 6 polymorphisms are in near-complete linkage disequilibrium. Haplotype A is designated as containing all common alleles, and Haplotype B as containing all minor alleles. The discordant haplotype is designated Haplotype C. *Frequency in the Japanese (control) population. Modified from Bezzina et al. *Circulation* 2006; **113:** 338–344[79] with permission.

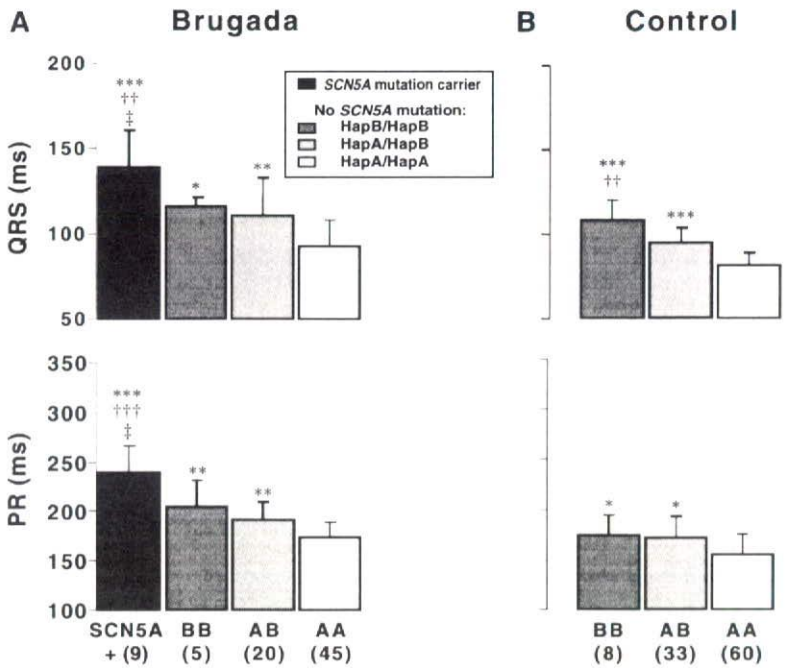

Fig 10. *SCN5A* promoter haplotype (Hap) pair effects on QRS duration in lead V6 and PR duration in lead II in patients with Brugada syndrome and control subjects. In Brugada patients without the *SCN5A* mutation and in control subjects, both QRS and PR durations show a gene-dose effect, being longest in HapB homozygotes (BB), intermediate in HapA/HapB heterozygotes (AB) and shortest in HapA homozygotes (AA). Brugada patients with the *SCN5A* mutation show longer QRS and PR durations than those without the *SCN5A* mutations. Patient numbers are indicated in parentheses. Data are mean±SD. Modified from Bezzina et al. *Circulation* 2006; **113:** 338–344[79] with permission. *p<0.05; **p<0.001; ***p<0.0001 vs HapA/HapA. †p<0.05; ††p<0.001; †††p<0.0001 vs HapA/HapB. ‡p<0.05 vs HapB/HapB.

SCN5A-positive group than in the *SCN5A*-negative group during the follow-up period (Figs 7,8).[76] Frustaci et al reported significant myocyte apoptosis in both the right and left ventricular myocardium in a histological study in Brugada patients with *SCN5A* mutations, and suggested that abnormal function of the sodium channels may lead to a masked degree of cellular damage, contributing to arrhythmic events.[77] These electrocardiographic and histologic data indicate that progressive depolarization abnormalities (conduction slowing) with aging may contribute to the pathogenesis of BrS.

SCN5A Promoter Polymorphism

The incidence of BrS is significantly higher in Asian countries, including Japan, than in the USA and European countries.[64] It has been reported that common polymorphisms may modulate the activity of the primary disease-causing mutation in inherited cardiac arrhythmias, and/or influence the susceptibility to arrhythmia even in the general population.[78] The common polymorphisms are expected to relate to ethnic differences in the clinical phenotype in inherited cardiac arrhythmias, including BrS, because some common polymorphisms are ethnically dependent. A Haplotype B consisting of 6 individual DNA polymorphisms in near-complete linkage disequilibrium within the proximal promoter region of the *SCN5A* gene has been identified in only Asians (allele frequency of 22%), but not in Caucasians or African–Americans (Fig 9).[79] Luciferase reporter activity of the Haplotype B is reduced by 62% in cardiomyocytes compared with the wild type, Haplotype A.[79] The relationship between the *SCN5A* promoter haplotype and indices of conduction velocity, PR and QRS durations was further analyzed in a cohort of 71 Japanese BrS subjects without the *SCN5A* mutation and in 102 Japanese controls to examine the role of Haplotype B in cardiac conduction. PR and QRS durations were significantly longer in the Haplotype B individuals, with a gene-dose effect in both groups (Fig 10).[79] Moreover, the increases in both the PR and the QRS duration with sodium channel blockers were genotype-dependent and a gene-dose effect was also observed.[79] These data demonstrate that Haplotype B within the *SCN5A* promoter region alone does not give rise to BrS; however, it is possible that the *SCN5A* promoter Haplotype B contributes to the higher incidence of BrS in Asian populations, in combination with other as-yet-unknown factors.

Conclusions

Genetic studies and the genotype–phenotype correlation in lethal inherited cardiac arrhythmias have encouraged cardiologists to perform genotype-specific, so-called tailor-made, management and therapy, and possibly mutation site-specific therapy in patients with genotyped congenital LQTS. Genetic studies are now an important diagnostic tool for stratifying risk and effectively managing and treating genotyped patients. Reflecting the clinical impact of genetic studies in the real world of management and therapy for patients with congenital LQTS, genetic studies to screen for the LQTS gene have been reimbursed by National Insurance in Japan since April 1, 2008. On the other hand, genetic studies of other inherited arrhythmias, including BrS, are still experimental, and further investigations of the genotype–phenotype correlations are required.

Acknowledgments

Dr W Shimizu was supported by the Uehara Memorial Foundation, and health sciences research grants (H18-Research on Human Genome-002) from the Ministry of Health, Labour and Welfare, Japan.

References

1. Keating M, Atkinson D, Dunn C, Timothy K, Vincent GM, Leppert M. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene. *Science* 1991; **252:** 704–706.
2. Donger CD, Denjoy I, Berthet M, Neyroud N, Cruaud C, Bennaceur M, et al. KVLQT1 C-terminal missense mutation causes a forme fruste long-QT syndrome. *Circulation* 1997; **96:** 2778–2781.
3. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et

al. Genetic basis and molecular mechanisms for idiopathic ventricular fibrillation. *Nature* 1998; **392:** 293–296.
4. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, et al. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet* 1999; **23:** 20–21.
5. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001; **103:** 196–200.
6. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation* 2001; **103:** 485–490.
7. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. *Nat Genet* 2004; **36:** 1162–1164.
8. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003; **299:** 251–254.
9. Veldkamp MW, Wilders R, Baartscheer A, Zegers JG, Bezzina CR, Wilde AA. Contribution of sodium channel mutations to bradycardia and sinus node dysfunction in LQT3 families. *Circ Res* 2003; **92:** 976–983.
10. Schulze-Bahr E, Neu A, Friederich P, Kaupp UB, Breithardt G, Pongs O, et al. Pacemaker channel dysfunction in a patient with sinus node disease. *J Clin Invest* 2003; **111:** 1537–1545.
11. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 2004; **109:** 30–35.
12. Shimizu W. The long QT syndrome: Therapeutic implications of a genetic diagnosis. *Cardiovasc Res* 2005; **67:** 347–356.
13. Liu N, Ruan Y, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. *Prog Cardiovasc Dis* 2008; **51:** 23–30.
14. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: An update. *Circulation* 1993; **88:** 782–784.
15. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: A prospective international study. *Circulation* 1985; **71:** 17–21.
16. Shimizu W, Noda T, Takaki H, Kurita T, Nagaya N, Satomi K, et al. Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long QT syndrome. *J Am Coll Cardiol* 2003; **41:** 633–642.
17. Shimizu W, Noda T, Takaki H, Nagaya N, Satomi K, Kurita T, et al. Diagnostic value of epinephrine test for genotyping LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Heart Rhythm* 2004; **1:** 276–283.
18. Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: Diagnostic accuracy of the paradoxical QT response. *Circulation* 2006; **113:** 1385–1392.
19. Shimizu W, Ackerman MJ. Provocative testing in inherited arrhythmias. *In*: Gussak I, Antzelevitch C, Wilde A, Friedman P, Ackerman MJ, Shen WK, editors. Electrical diseases of the heart: Genetics, mechanisms, treatment, prevention. Springer, UK; 2007; 424–433.
20. Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long QT syndrome. *Circulation* 2003; **107:** 838–844.
21. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I_{Kr} potassium channel. *Cell* 1995; **81:** 299–307.
22. Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995; **80:** 805–811.
23. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, et al. Spectrum of mutations in long-QT syndrome genes: KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation* 2000; **102:** 1178–1185.
24. Plaster NM, Tawil R, Tristani-Firouzi M, Canún S, Bendahhou S, Tsunoda A, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* 2001; **105:** 511–519.
25. Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, duBell WH, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* 2003; **421:** 634–639.
26. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 2004; **119:** 19–31.
27. Vatta M, Ackerman MJ, Ye B, Makielski JC, Ughanze EE, Taylor EW, et al. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. *Circulation* 2006; **114:** 2104–2112.
28. Medeiros-Domingo A, Kaku T, Tester DJ, Iturralde-Torres P, Itty A, Ye B, et al. SCN4B-encoded sodium channel beta4 subunit in congenital long-QT syndrome. *Circulation* 2007; **116:** 134–142.
29. Chen L, Marquardt ML, Tester DJ, Sampson KJ, Ackerman MJ, Kass RS. Mutation of an A-kinase-anchoring protein causes long-QT syndrome. *Proc Natl Acad Sci USA* 2007; **104:** 20990–20995.
30. Ueda K, Valdivia C, Medeiros-Domingo A, Tester DJ, Vatta M, Farrugia G, et al. Syntrophin mutation associated with long QT syndrome through activation of the nNOS-SCN5A macromolecular complex. *Proc Natl Acad Sci USA* 2008; **105:** 9355–9360.
31. Wu G, Ai T, Kim JJ, Mohapatra B, Xi Y, Li Z, et al. Alpha-1-syntrophin mutation and the long QT syndrome: A disease of sodium channel disruption. *Circ Arrhythmia Electrophysiol* 2008; **1:** 193–201.
32. Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL, et al. Coassembly of KvLQT1 and minK (IsK) proteins to form cardiac I_{Ks} potassium channel. *Nature* 1996; **384:** 80–83.
33. Barhanin J, Lesage F, Guillemare E, Fink M, Lazdunski M, Romey G. KvLQT1 and IsK (minK) proteins associate to form the I_{Ks} cardiac potassium current. *Nature* 1996; **384:** 78–80.
34. Abbott G W, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, et al. MiRP1 forms I_{Kr} potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999; **97:** 175–187.
35. Schwartz PJ, Crotti L. Can a message from the dead save lives? *J Am Coll Cardiol* 2007; **49:** 247–249.
36. Wedekind H, Smits JP, Schulze-Bahr E, Arnold R, Veldkamp MW, Bajanowski T, et al. De novo mutation in the SCN5A gene associated with early onset of sudden infant death. *Circulation* 2001; **104:** 1158–1164.
37. Cronk LB, Ye B, Kaku T, Tester DJ, Vatta M, Makielski JC, et al. Novel mechanism for sudden infant death syndrome: Persistent late sodium current secondary to mutations in caveolin-3. *Heart Rhythm* 2007; **4:** 161–166.
38. Rhodes TE, Abraham RL, Welch RC, Vanoye CG, Crotti L, Arnestad M, et al. Cardiac potassium channel dysfunction in sudden infant death syndrome. *J Mol Cell Cardiol* 2008; **44:** 571–581.
39. Splawski I, Timothy KW, Vincent GM, Atkonson DL, Keating MT. Molecular basis of the long-QT syndrome associated with deafness. *N Engl J Med* 1997; **336:** 1562–1567.
40. Westenskow P, Splawski I, Timothy KW, Keating MT, Sanguinetti MC. Compound mutations: A common cause of severe long-QT syndrome. *Circulation* 2004; **109:** 1834–1841.
41. Priori SG, Schwartz PJ, Napolitano C, Bianchi L, Dennis A, De Fusco M, et al. A recessive variant of the Romano-Ward long-QT syndrome? *Circulation* 1998; **97:** 2420–2425.
42. Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. *Circ Res* 1999; **85:** 1206–1213.
43. Makita N, Behr E, Shimizu W, Horie M, Sunami A, Crotti L, et al. The E1784K mutation in SCN5A is associated with mixed clinical phenotype of type 3 long QT syndrome. *J Clin Invest* 2008; **118:** 2219–2229.
44. Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation* 1997; **96:** 2038–2047.
45. Shimizu W, Antzelevitch C. Cellular basis for the electrocardiographic features of the LQT1 form of the long QT syndrome: Effects of β-adrenergic agonists, antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 1998; **98:** 2314–2322.
46. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol* 2000; **35:** 778–786.
47. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* 1995; **92:** 2929–2934.
48. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation* 2000; **102:** 2849–2855.
49. Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, et al. Influence of the genotype on the clinical course of the long-QT syndrome. *N Engl J Med* 1998; **339:** 960–965.
50. Locati EH, Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Lehmann MH, et al. Age- and sex-related differences in clinical manifestations

in patients with congenital long-QT syndrome: Findings from the international LQTS registry. *Circulation* 1998; **97:** 2237–2244.
51. Moss AJ, Shimizu W, Wilde AAM, Towbin JA, Zareba Z, Robinson JL, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 2007; **115:** 2481–2489.
52. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: Gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; **103:** 89–95.
53. Wilde AAM, Jongbloed RJE, Doevendans PA, Duren DR, Hauer RNW, van Langen IM, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQT2) patients from KVLQT1-related patients (LQT1). *J Am Coll Cardiol* 1999; **33:** 327–332.
54. Khositseth A, Tester DJ, Will ML, Bell CM, Ackerman MJ. Identification of a common genetic substrate underlying postpartum cardiac events in congenital long QT syndrome. *Heart Rhythm* 2004; **1:** 60–64.
55. Schechter E, Freeman CC, Lazzara R. Afterdepolarizations as a mechanism for the long QT syndrome: Electrophysiologic studies of a case. *J Am Coll Cardiol* 1984; **3:** 1556–1561.
56. Compton SJ, Lux RL, Ramsey MR, Strelich KR, Sanguinetti MC, Green LS, et al. Genetically defined therapy of inherited long-QT syndrome: Correction of abnormal repolarization by potassium. *Circulation* 1996; **94:** 1018–1022.
57. Tan HL, Bardia A, Shimizu W, Moss AJ, Schulze-Bahr E, Noda T, et al. Genotype-specific onset of arrhythmias in congenital long QT syndrome: Possible therapy implications. *Circulation* 2006; **114:** 2096–2103.
58. Moss AJ, Zareba W, Kaufman ES, Gartman E, Peterson DR, Benhorin J, et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. *Circulation* 2002; **105:** 794–799.
59. Shimizu W, Horie M, Ohno S, Takenaka K, Yamaguchi M, Shimizu M, et al. Mutation site-specific differences in arrhythmic risk and sensitivity to sympathetic stimulation in LQT1 form of congenital long QT syndrome: Multi-center study in Japan. *J Am Coll Cardiol* 2004; **44:** 117–125.
60. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome: A multicenter report. *J Am Coll Cardiol* 1992; **20:** 1391–1396.
61. Antzelevitch C, Brugada P, Brugada J, Brugada R, Shimizu W, Gussak I, et al. Brugada syndrome: A decade of progress. *Circ Res* 2002; **91:** 1114–1118.
62. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, et al. Natural history of Brugada syndrome: Insights for risk stratification and management. *Circulation* 2002; **105:** 1342–1347.
63. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Proposed diagnostic criteria for the Brugada syndrome: Consensus report. *Circulation* 2002; **106:** 2514–2519.
64. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: Report of the Second Consensus Conference: Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005; **111:** 659–670.
65. Shimizu W, Aiba T, Kamakura S. Mechanisms of disease: Current understanding and future challenges in Brugada syndrome. *Nat Clin Pract Cardiovasc Med* 2005; **2:** 408–414.
66. Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* 1997; **95:** 2277–2285.
67. Matsuo K, Shimizu W, Kurita T, Inagaki M, Aihara N, Kamakura S. Dynamic changes of 12-lead electrocardiograms in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 1998; **9:** 508–512.
68. Shimizu W, Matsuo K, Takagi M, Tanabe Y, Aiba T, Taguchi A, et al. Body surface distribution and response to drugs of ST segment elevation in the Brugada syndrome: Clinical implication of 87-leads body surface potential mapping and its application to 12-leads electrocardiograms. *J Cardiovasc Electrophysiol* 2000; **11:** 396–404.
69. Shimizu W, Aiba T, Kamakura S. Mechanism and new findings in the Brugada syndrome. *Circ J* 2007; **71**(Suppl A): A-32–A-39.
70. Miyamoto K, Yokokawa M, Tanaka K, Nagai T, Okamura H, Noda T, et al. Diagnostic and prognostic value of type 1 Brugada electrocardiogram at higher (third or second) V1 to V2 recording in men with Brugada syndrome. *Am J Cardiol* 2007; **99:** 53–57.
71. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, et al. Loss of function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST segment elevation, short QT intervals and sudden cardiac death. *Circulation* 2007; **115:** 442–449.
72. London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. *Circulation* 2007; **116:** 2260–2268.
73. Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, et al. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 2008; **118:** 2260–2268.
74. Delpón E, Cordeiro JM, Núñez L, Thomsen PEB, Guerchicoff A, Pollevick GD, et al. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ Arrhythmia Electrophysiol* 2008; **1:** 209–218.
75. Smits JP, Eckardt L, Probst V, Bezzina CR, Schott JJ, Remme CA, et al. Genotype-phenotype relationship in Brugada syndrome: Electrocardiographic features differentiate *SCN5A*-related patients from non-*SCN5A*-related patients. *J Am Coll Cardiol* 2002; **40:** 350–356.
76. Yokokawa M, Noda T, Okamura H, Satomi K, Suyama K, Kurita T, et al. Comparison of long-term follow-up of electrocardiographic features in Brugada syndrome between the SCN5A-positive probands and the SCN5A-negative probands. *Am J Cardiol* 2007; **100:** 649–655.
77. Frustaci A, Priori SG, Pieroni M, Chimenti C, Napolitano C, Rivolta I, et al. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. *Circulation* 2005; **112:** 3680–3687.
78. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002; **297:** 1333–1336.
79. Bezzina CR, Shimizu W, Yang P, Koopmann TT, Tanck MWT, Miyamoto Y, et al. A common sodium channel promoter haplotype in Asian subjects underlies variability in cardiac conduction. *Circulation* 2006; **113:** 338–344.

Genetics of congenital long QT syndrome and Brugada syndrome

Wataru Shimizu
National Cardiovascular Center, Division of Cardiology, Department of Internal Medicine, 5-7-1 Fujishiro-dai, Suita, Osaka, 565-8565 Japan
Tel.: +81 6 6833 5012; Fax: +81 6 6872 7486; wshimizu@hsp.ncvc.go.jp

The inherited cardiac arrhythmias including the congenital and acquired long QT syndrome (LQTS), Brugada syndrome, progressive cardiac conduction defect, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular cardiomyopathy, familial atrial fibrillation, familial sick sinus syndrome and short QT syndrome, are linked to mutations in genes encoding for ion channels or other membrane components. Eleven forms of congenital LQTS have been identified and these are caused by mutations in genes of the potassium, sodium and calcium channels or membrane adapter. Genotype–phenotype correlations have been rigorously investigated, especially in the LQT1, LQT2 and LQT3 forms, which constitute more than 90% of genotyped patients. On the other hand, causative mutations were identified much less in patients with Brugada syndrome, therefore data on genotype–phenotype relationships are limited.

Recent advances in molecular genetics research has established a link between a number of lethal inherited cardiac arrhythmias and mutations in genes encoding for ion channels or other membrane components. These inherited cardiac arrhythmias include the congenital and acquired long QT syndrome (LQTS) [1,2], Brugada syndrome [3], progressive cardiac conduction defect (Lenegre disease) [4], catecholaminergic polymorphic ventricular tachycardia (CPVT) [5,6], arrhythmogenic right ventricular cardiomyopathy [7], familial atrial fibrillation [8], familial sick sinus syndrome [9,10] and short QT syndrome [11]. The congenital LQTS is a Rosetta stone for studying the genetic basis of inherited cardiac arrhythmias, since 50–70% of clinically affected patients with congenital LQTS are now genotyped, and multiple genes encoding the different ion channels or membrane adaptor have been identified. Therefore, the genotype–phenotype correlation has been rigorously investigated in genotyped patients with congenital LQTS, and enabled us to stratify risk and to effectively treat the genotyped patients. By contrast, responsible mutations have been identified much less in other inherited cardiac arrhythmias except for CPVT. Responsible mutations can be identified in more than 60% of clinically diagnosed CPVT patients [12]. Approximately 20–40% of patients with Brugada syndrome can be genotyped, therefore the genetic screening is much more challenging.

Keywords: action potential, Brugada syndrome, genes, genotype, phenotype, QT interval, ST segment, sudden death, Torsade de Pointes, ventricular fibrillation

future medicine fsg

Genetics of congenital LQTS

Congenital LQTS is characterized by QT prolongation in the electrocardiogram (ECG) and its trademark dysrhythmia of polymorphic ventricular tachycardia known as Torsade de Pointes (TdP) [13]. The clinical diagnosis of LQTS is mainly based on the resting corrected (QTc) interval, cardiac events such as syncope, aborted cardiac arrest and sudden cardiac death, and a family history of apparent LQTS [14]. However, the electrocardiographic diagnosis at rest has long been expected to miss some patients affected by congenital LQTS, as evidenced by syncopal events occurring among family members with a 'normal' QT interval [15]. Diagnosis sometimes relies on the ECG during exercise in addition to the resting ECG, especially in LQT1 [16]. The first two genes responsible for LQTS were identified in 1995 [17,18], thereafter, molecular genetic studies have revealed a total of eleven forms of Romano–Ward type congenital LQTS caused by mutations in genes of the potassium, sodium and calcium channels or membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17 and 21 (**Table 1**) [19–25]. Mutations in *KCNQ1* and *KCNE1*, the α and β subunits of the potassium channel gene, are responsible for loss of function defects in the slowly activating component of the delayed rectifier potassium current (I_{Ks}), which underlies the LQT1 and LQT5 forms of LQTS [26,27]. Mutations in *KCNH2* and *KCNE2* cause defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}), which is responsible for the LQT2 and LQT6 forms [17,28]. Mutations in *SCN5A*, the gene that encodes the α subunit of the sodium channel, result in an increase (gain of function) in the late sodium current (I_{Na}) responsible for LQT3 [18].

10.2217/14796678.4.4.xxx ISSN 1479-6678