EDITORIAL

Twenty-First Century Diseases: Commonly Rare and Rarely Common?

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Abstract

Alzheimer's drugs are failing at a rate of 99.6%, and success rate for drugs designed to help patients with this form of dementia is 47 times less than for drugs designed to help patients with cancers (www.scientificamerican.com/article/why-alzheimer-s-drugs-keep-failing/2014). How can it be so difficult to produce a valuable drug for Alzheimer's disease? Each human has a unique genetic and epigenetic makeup, thus endowing individuals with a highly unique complement of genes, polymorphisms, mutations, RNAs, proteins, lipids, and complex sugars, resulting in distinct genome, proteome, metabolome, and also microbiome identity. This *editorial* is taking into account the uniqueness of each individual and surrounding environment, and stresses the point that a more accurate definition of a "common" disorder could be simply the amalgamation of a myriad of "rare" diseases. These rare diseases are being grouped together because they share a rather constant complement of common features and, indeed, generally respond to empirically developed treatments, leading to a positive outcome consistently. We make the case that it is highly unlikely that such treatments, despite their statistical success measured with large cohorts using standardized clinical research, will be effective *on all patients* until we increase the depth and fidelity of our understanding of the individual "rare" diseases that are grouped together in the "buckets" of common illnesses. *Antioxid. Redox Signal.* 27, 511–516.

Keywords: rare diseases, sudden cardiac death, Kaposi's sarcoma, virus cooperation, 21st century medicine, common illnesses

Success of Western Medicine and Pattern Recognition

AS WE ENGAGE in a deep dive into human illnesses for the "precision medicine" initiative, it is important to realize that most human conditions are traditionally organized and classified according to the interpretation of individuals who, in good faith, have used pattern recognition to connect various signs and symptoms, radiology, laboratory, and other pathology data to establish particular diseases or disease states.

Over time, powered by the accelerated progress of medical sciences, a better definition for each disorder evolved with the addition of newly discovered signs and symptoms, modern diagnostic tools and criteria generated by imaging techniques (radiology testing, magnetic resonance, positron emission tomography scan, *etc.*), the study of clinical laboratory markers, pathophysiology testing, microbiological analysis of body fluids and tissues, and the refinement of

molecular tissue imaging (chromosomes, DNA, RNA, metabolites, and other antigens) (The Flexner Era) (10, 13).

It is notable that although reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been shown to have an essential role in signaling or other critical cellular decisions (5, 19, 38), and in practically all disease processes, from cardiovascular diseases to cancers as examples (15, 36), little, if any, of the substantial body of knowledge concerning these moieties has contributed to clinical advances (20).

The Biased Concept of Rare and Common Disease: Moving to 21st Century Medicine

A "rare" or "orphan" disease by definition is a disease that is infrequent as only a small number of individuals are affected with it (33, 34). Usually, these illnesses are associated with genetic mutations and susceptibility and are endemic to

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certain ethnic groups or geographically defined populations. In some instances, these “rare” diseases may have been promoted by viral, bacterial, fungal or parasitic infections, allergies, environmental contaminants, or may be because of metabolic, degenerative, inflammatory, or proliferative processes. The symptoms may not be evident throughout the entire life of the affected individual, and when displayed, they may not necessarily be that unusual, specific, or “rare.” There are upward of an estimated 6500 diseases currently classified as rare, affecting 200,000 individuals or less; however, both these numbers keep on increasing as our ability to diagnose genetic and molecular deficiencies improves (33, 34). On the contrary, “common” illnesses are those that affect a large number of individuals and are, therefore, diagnosed in higher numbers and often have a global distribution. “Common” diseases may cause a few or many symptoms that can be similar or even identical to those found in “rare” diseases. Individuals with so-called common diseases may have a number of symptoms that are shared by all affected, but also other distinct and more specific symptoms that result in the reclassification of the “common” disease in the bin of “not as common” or even “rare” illnesses (Fig. 1). Not only shall we need to increase the depth of our knowledge and understanding of human illnesses but also need to adopt, as a profession of healthcare providers, changing concepts, and, at times, even some aspects of our medical tradition.

Sudden Cardiac Death: Common Endpoint That Results from Many “Rare” Conditions

Sudden cardiac death (SCD) is a complex and deadly condition wherein the heart suddenly arrests (cardiac arrest, by definition, within 60 min of the onset of any symptoms), and as a consequence the victim loses consciousness and then,

FIG. 1. Illnesses: commonly rare, rarely common. The figure illustrates the fact that a particular common illness may in fact represent the amalgamation of a myriad of rare diseases (RD1, RD2, RDn...) that share a common bin of signs, symptoms, and other imaging and laboratory characteristics. Effective treatment of *all* of these patients within the common bin may require more extensive molecular characterization of the individual RD components.

in most cases, dies a few minutes later (29, 30, 37). SCD is responsible for >50% of cardiac deaths, and ~300,000 deaths per year in the United States (29, 30). It is striking that often SCD is the first manifestation of a cardiac condition for an individual patient, no matter the age (4, 29, 30, 37). In other words, the individual may live a life of 10, 20, 40, 80 years or more without any symptoms of cardiovascular disease, at least no perceived symptoms of cardiovascular disease, until the onset of SCD. It is known that >80% of patients with SCD do have substantial coronary artery disease, which is the most common underlying cause of the subsequent cardiac arrest (4, 18, 29, 30, 37). Coronary artery disease, or the accumulation of atheroma within coronary vessels, as a result of several identified risk factors, including age, inflammation, smoking, low-density lipoprotein cholesterol, hypertension, diabetes, *etc.* (12), creating stenosis of the artery and diminution in blood flow, is the primary cause of myocardial infarction (MI). MI corresponds to a sudden ischemic event of the heart that is caused by a substantial reduction in blood flow to a section of the heart tissue, often as the result of rupture, or erosion, of an atheroma plaque in the culprit coronary artery, which, in turn, triggers the formation of an occlusive thrombus, ischemia-induced arrhythmia, and the SCD event (15, 16, 18). Many of these events have been shown to require the participation of ROS (5) and at multiple levels of the molecular pathway leading to SCD; however, antioxidant therapy as currently conceived and applied has failed to improve the outcome of patients (11, 32). It is the detailed understanding of the many molecular reactions taking place in the arterial wall and the blood during these events, including the expansion of atherosclerosis inflammation that causes them, which will allow for effective therapeutic interventions that target the participation of ROS, and possibly RNS, to the relevant pathological processes (5, 21).

Although susceptibility for arrhythmia may augment the risk of SCD in a particular SCD individual, it is the micro-environment of ischemic myocardium that is the determinant for the SCD arrhythmic event, with or without scar tissue (4, 18, 29, 30, 37). It has also been shown that most individuals who develop SCD have remarkably accelerated atherosclerosis (the formation of the coronary atheroma) (18). The consequence is that by age 40–50 years, victims will present with a complement of atheroma lesions in their coronary tree that is worse than what would be expected in someone 80 or 90 years old with a more standard form of atherosclerosis (4, 18, 29, 30, 37). Even for younger individuals with SCD (30–35 years), coronary artery disease seems to be the primary etiology of SCD (4). The mechanism responsible for this accelerated formation of atheroma remains unknown. It is instructive to note that, thus far, large scale and nonbiased studies of the human genome have indicated that most genes that increase susceptibility for coronary artery disease and MI are linked to inflammation, immunity, endothelial and smooth muscle cell growth, cell–cell contact, immune cells, stem cells, cell motility, and other cellular and molecular moieties (3, 27). Many of these processes have been shown to involve ROS and RSN (5, 15). Hence, it is tempting to speculate that these individuals with early onset and rapidly evolving atherosclerosis have a susceptibility related to excessive arterial inflammation (as a result of circulating lipids or other noxious stimuli), and also, lack of effective artery repair, which is required to maintain arterial homeostasis

over a lifetime (16) (Fig. 2). The silver lining of recent discoveries in this field is that, although genetic susceptibility seems to affect especially younger individuals, as elegantly demonstrated by the Swedish Twin Registry (25), response to the pharmaceutical workhorse of primary and secondary prevention of coronary artery disease and consequent thromboembolic events, the statins, are especially beneficial for individuals with a high genetic risk, no matter what change in cholesterol level might result from treatment (28). Even if, for individuals with the greatest burden of coronary plaques because of genetic susceptibility, the traditional risk factors for atherosclerosis are not particularly increased, homeostasis of the arterial tissue in their cardiac vessels may be reached through the use of statins (28), and possibly novel cellular treatments (17).

Other causes of SCD are not related to atherosclerosis and its complications. In particular, victims of SCD can be very young, sometimes athletes, and develop SCD as a result of a “rare” condition of cardiac hypertrophy, the most common known cause of SCD in the very young (26). Cardiac hypertrophy can be triggered by genetic mutations that often lead to abnormal organization and/or functioning of the cytoskeleton inside cardiac cells (39).

An even smaller group of traits that are genetic in nature can lead to severe cardiac arrhythmia in the absence of athero-

sclerosis or hypertrophy. Instead, these patients seem to be victims of a mutation that increases substantially their susceptibility for a severely abnormal cardiac rhythm, and, therefore, triggers SCD (24). A relatively well-defined group of mutations is responsible for what is called a long QT syndrome (24), and a common framework for such events of SCD in these patients appears to be a dysfunctional ion channel or channelopathy (24, 35). Some arrhythmias that can lead to SCD may involve ROS and result from inherited disorders such as in Kearns–Sayre syndrome, a rare disease, and in this case, the diseased mitochondria seems to be the source for ROS, and yet no specific therapies have been developed that target ROS in the pathophysiology of such disorders (31).

Other “rare” mechanisms that are not because of atherosclerotic coronary artery disease, cardiac hypertrophy, or channelopathies include rare conditions such as valve disorders, arrhythmogenic right ventricular dysplasia, hemochromatosis, coronary anomaly, or sarcoidosis as examples of “rare” diseases that can cause common SCD (40). Consequently, it is clear that many “rare” categorized conditions can result in common SCD, and the SCD case is an example of an endpoint to a disease that is the result of a compendium of factors, including common and rare contributing factors, thus validating our belief that a common disease process is a compendium of rare diseases.

FIG. 2. Arterial homeostasis, balance between injury and repair. Two-by-two table that illustrates how atherosclerosis, the underpinning condition for the majority of sudden cardiac death cases, results from imbalance between risk factors (smoking, cholesterol, *etc.*) and ability for arteries to self-repair. Instructively, individuals with nearly zero risk factors may develop dangerous lesions in their coronaries (because of lack of efficient arterial repair), whereas individuals with severe risks may have clean arteries (as a result of highly efficient repair), thus illustrating the complexity of processes underlying common illnesses, and thus it is tempting to speculate that common illnesses represent the amalgamation of rare conditions.

When a Rare Disease Gets a Ticket to Ride as a Common Illness: ROS and Virus Cooperation

Kaposi’s sarcoma (KS) is diagnosed on the base of one or multiple discolored (purplish) lesions of the skin or mucosa. The virus that causes Kaposi’s lesions is Human Herpes Virus 8, better known today as KS-associated Herpes Virus (KSHV) (8). Before the AIDS pandemic, KS was a rare disease, found only on the skin/mucosa of elderly men of countries surrounding the Mediterranean Sea and in Africa (6, 14). Upon creating a transgenic model in mice based on expression of a constitutively active mutant of human Rac1 (RacCA), driven by the alpha-smooth muscle actin promoter, we were able to reconstitute, serendipitously, but faithfully, KS-like tumors (23). This KS model, obtained in complete absence of KSHV, is unsurpassed at the tissue level (appearance of the skin lesions, strong angiogenesis surrounding tumors, affecting bare skin—tail mainly—and mucosa of the mouse in the absence of induced immune deficiency) (Fig. 3), cellular (typical spindle cells), molecular and genetic (transcriptome), and even clinical characteristics (older animals, male to female ratio of >10/1) typical of pre-HIV KS disease (22, 23). This model is a paradigm for tumors that are fermented through mechanisms involving superoxide and ROS-driven cell proliferation (as reported for the first time by our team, 4). Rac1 is robustly expressed in human KS lesions and other mouse models of KS (7, 22), and evidence that ROS are essential for tumor formation and proliferation is provided by the ability of ROS scavengers to prevent entirely tumor formation and growth (7, 22, 23). Hence, the prevention and treatment of KS could be enhanced markedly by the use of Rac1 and NADPH oxidase-specific inhibitors or ROS scavengers.

Since the beginning of the AIDS pandemic, millions of patients have suffered from KS, and KS is still the most frequent cancer lesion found in Sub-Saharan Africa, although it has become rare again in countries where AIDS treatment

FIG. 3. Virus cooperation. KS is caused by KSHV. KS activates Rac1 that, in turn, induces the production of ROS by NADPH oxidase, which is necessary for the genesis of KS tumors. KS has expanded from a rare disease for elderly men in the Mediterranean Basin and Africa to a ubiquitous cancer, as a consequence of the HIV pandemic, and still is the leading cancer in Sub-Saharan Africa. This example demonstrates that, as a result of “virus cooperation,” a rare disease like KS can become a highly frequent illness for humans around the world, in <10 years. *Top inset:* Typical KS lesions in human skin caused by KSHV. *Bottom inset:* KS-like lesions in mouse skin, caused by a constitutively activated mutant of Rac1 (V12), in the absence of KSHV (23). KS, Kaposi’s sarcoma; KSHV, KS-associated Herpes Virus; ROS, reactive oxygen species.

leading to recovery of CD4-T cells is readily available and applied effectively (6, 8, 14). Hence, Kaposi’s sarcoma is an example of a rare disease for which the permissive environment created by HIV infection allowed KS to penetrate the human population in just a few years, thus becoming a common illness. It is instructive that KSHV activation of Rac1, and consequent production of ROS by NADPH oxidase, are instrumental to the ability of KSHV to trigger the genesis of sarcoma cells (Fig. 3). In experimental models, it appears that replication of one virus (HIV) may enhance the replication of the other (KSHV). Indeed, the loss of T cell proliferative response to KSHV in HIV-infected men prevents the immune system of KSHV-infected individuals to mount the protective response required to prevent KS development (2). Thus, this example, based on virus cooperation, exemplifies the rapid expansion of a rare disease into a common disease and illustrates how “environmental factors” (like the proliferation and transmission of the AIDS virus) are able to blur the distinction between common and rare illnesses. This example also indicates that a particular disorder can be triggered by factors as different as a virus (KS), and the mutation of a proto-oncogene leading to the regulated production of superoxide and other ROS.

Conclusions

We have reviewed conditions like SCD that encompass a myriad of common and rare diseases. We also reviewed rare diseases like KS that, all the sudden, and as a consequence of virus cooperation, become common diseases. In both instances, it appears that ROS and RNS are ubiquitously involved and participate to a myriad of critical molecular

reactions, and in one instance, the accurate (toward molecular targets like Rac1) and precise (timely and effective concentration of ROS scavenger) use of antioxidants was able to prevent lesion formation. It is likely that the analysis of increasingly large databases obtained from diverse human populations will result in the better characterization of the rare diseases that populate the bins of common illnesses. Such an unbiased approach is necessary to make progress with human conditions, like Alzheimer’s syndrome, that have been remarkably resistant to successful interventions. Alzheimer’s is a perfect example wherein manifestation of common symptoms of dementia and formation of brain plaques are categorized as one rather common disease. However, the reality is that we do not know enough about the etiology and molecular mechanism(s) of the disease process, and, thus, it is more than likely that Alzheimer’s is another case of a condition labeled as a common disease that is a compendium of rare diseases, and, therefore, the challenge in discovering effective drugs that work for everybody. Indeed, 40% of the U.S. population 85 years and above suffer from some degree of Alzheimer’s. It is the fine understanding of the rare diseases within their framework that could lead to new clues for therapeutic solutions. More than ever, such accomplishments will require team science, concerted efforts by teams of individuals highly diverse in their expertise, ideation process, and scientific backgrounds. Finding new cures for all “rare” diseases will be at the core of the new era of big data analysis, with *accuracy and precision* in both molecular and genetic diagnostics of deficiencies that lead to diseases, and individualized therapeutic interventions resulting from advances in biomedical technologies at the macro-, micro-, and nanoscale (1, 9). We believe that the understanding of the concept of “rare-to-common” diseases is an important step in executing the *Precision Medicine Initiative* currently being pursued to tailor therapies and interventions through cutting edge biomedical discoveries (1, 9).

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References

1. Antman EM and Loscalzo J. Precision medicine in cardiology. Review. *Nat Rev Cardiol* 13: 591–602, 2016.
2. Aoki Y and Tosato G. HIV-1 Tat enhances Kaposi sarcoma-associated herpesvirus (KSHV) infectivity. *Blood* 104: 810–814, 2004.
3. Arnar DO, Andersen K, and Thorgeirsson G. Genetics of cardiovascular diseases: lessons learned from a decade of genomics research in Iceland. *Scand Cardiovasc J* 50: 260–265, 2016.
4. Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, Davis AM, Thompson T, Connell V, Wallace J, Naylor C, Crawford J, Love DR, Hallam L, White J, Lawrence C, Lynch M, Morgan N, James P, du Sart D, Puranik R, Langlois N, Vohra J, Winship I, Atherton J, McGaughan J, Skinner JR, and Semsarian C. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med* 374: 2441–2452, 2016.
5. Brown DI and Griendling KK. Regulation of signal transduction by reactive oxygen species in the cardiovascular system. *Circ Res* 116: 531–549, 2015.

6. Cavallin LE, Goldschmidt-Clermont PJ, and Mesri EA. Molecular and cellular mechanisms of KSHV oncogenesis of Kaposi's sarcoma associated with HIV/AIDS. *PLoS Pathog* 10: e1004154, 2014.
7. Cavallin LE, Ma Q, Goldschmidt-Clermont P, and Mesri EA. KSHV-mediated ROS induction defines novel therapeutic targets in Kaposi's sarcoma. *Infect Agent Cancer* 5(Suppl 1): A49, 2010.
8. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, and Moore PS. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 266: 1865–1869, 1994.
9. Collins FS and Varmus H. A new initiative on precision medicine. *N Engl J Med* 372: 793–795, 2015.
10. Cooke M, Irby DM, Sullivan W, and Ludmerer KM. American medical education 100 years after the Flexner report. *N Engl J Med* 355: 1339–1344, 2006.
11. Fortmann SP, Burda BU, Senger CA, Lin JS, and Whitlock EP. Vitamin and mineral supplements in primary prevention of cardiovascular disease and cancer: an updated systematic evidence review for the U.S. preventive services task force. *Ann Int Med* 159: 824–834, 2013.
12. Framingham Coronary Heart Disease Risk Score—MDCalc. The Framingham Coronary Heart Disease Risk Score estimates risk of heart attack in 10 years. Available at www.mdcalc.com/framingham-coronary-heart-disease-risk-score (accessed April 12, 2017).
13. Frenk J, Chen L, Bhutta ZA, Cohen J, Crisp N, Evans T, Fineberg H, Garcia P, Ke Y, Kelley P, Kistnasamy B, Afaf M, Naylor D, Pablos-Mendez A, Reddy S, Scrimshaw S, Sepulveda J, Serwadda D, and Zurayk H. Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. *Lancet* 376: 1923–1958, 2010.
14. Ganem D. KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. *J Clin Invest* 120: 939–949, 2010.
15. Glass CK and Witztum JL. Atherosclerosis: the road ahead. *Cell* 104: 503–516, 2001.
16. Goldschmidt-Clermont PJ, Dong C, Seo DM, and Velazquez OC. Atherosclerosis, inflammation, genetics, and stem cells: 2012 update. *Curr Atheroscler Rep* 14: 201–210, 2012.
17. Golpanian S, Difede D, Khan A, Schulman I, Landin AM, Tompkins BA, Heldman A, Miki R, Goldstein BJ, Mushtaq M, Levis S, Byrnes JJ, Lowery MH, Natsumeda M, Delgado C, Saltzman R, Vidrio C, Vidro M, Pujol MV, DaFonseca D, Green G, Oliva A, Premer CH, Medina A, Valasaki K, Florea V, Anderson E, Elkhazraty J, Mendizabal A, Goldschmidt-Clermont PJ, and Hare J. Allogeneic human mesenchymal stem cell infusions for aging frailty. *J Gerontol A Biol Sci Med Sci* 2017 [Epub ahead of print]; DOI: 10.1093/geronol/glx056.
18. Head T, Andreev V, Johnson N, Deo SK, Daunert S, and Goldschmidt-Clermont PJ. Discrete event simulation model of sudden cardiac death predicts high impact on preventive interventions. *Nat Sci Rep* 3: 1771, 2013.
19. Irani K, Xia Y, Zweier JL, Sollott SJ, Der CJ, Fearon ER, Sundaresan M, Finkel T, and Goldschmidt-Clermont PJ. Mitogenic signaling mediated by oxidants in Ras-transformed fibroblasts. *Science* 275: 1649–1652, 1997.
20. Kawagishi H and Finkel T. Unraveling the truth about antioxidants: ROS and disease: finding the right balance. *Nat Med* 20: 711–713, 2014.
21. Libby P, Bornfeldt KE, and Tall AR. Atherosclerosis: successes, surprises, and future. (Review and references therein). *Circ Res* 118: 531–534, 2016.
22. Marenberg ME, Risch N, Berkman LF, Floderus B, and de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. *N Engl J Med* 330: 1041–1046, 1994.
23. Ma Q, Cavallin LE, Leung HJ, Chiozzini C, Goldschmidt-Clermont PJ, and Mesri EA. A role for virally induced reactive oxygen species in Kaposi's sarcoma herpesvirus tumorigenesis. *Antioxid Redox Signal* 18: 80–90, 2013.
24. Ma Q, Cavallin LE, Yan B, Zhu S, Duran EM, Wang H, Hale LP, Dong C, Cesarman E, Mesri EA, and Goldschmidt-Clermont PJ. Antitumorigenesis of antioxidants in a transgenic Rac1 model of Kaposi's sarcoma. *Proc Natl Acad Sci U S A* 106: 8683–8688, 2009.
25. Marbán E. Cardiac channelopathies. *Nature* 415: 213–218, 2002.
26. Maron BJ, Doerer JJ, Haas TS, Tierney DM, and Mueller FO. Sudden death in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. *Circulation* 119: 1085–1092, 2009.
27. McPherson R and Tybjaerg-Hansen A. Genetics of coronary artery disease. *Circ Res* 118: 564–578, 2016.
28. Mega JL, Stitzel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, Nordio F, Hyde CL, Cannon CP, Sacks FM, Poulter NR, Sever PS, Ridker PM, Braunwald E, Melander O, Katheresan S, and Sabatine MS. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet* 385: 2264–2271, 2015.
29. Meyrburg RJ and Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation* 125: 1043–1052, 2012.
30. Mitrani RD and Myerburg RJ. Ten advances defining sudden cardiac death. *Trends Cardiovasc Med* 26: 23–33, 2016.
31. Montaigne D and Pentiah AD. Mitochondrial cardiomyopathy and related arrhythmias. *Card Electrophysiol Clin* 7: 293–301, 2015.
32. Myung S-K, Ju W, Cho B, Oh S-W, Park SM, Koo B-K, and Park B-J; Korean Meta-Analysis Study Group. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomized controlled trials. *BMJ* 346: f10, 2013.
33. National Center for Advancing Translational Sciences-Genetic and Rare Diseases Information Center or NCATS-GARD. 2017. Available at <https://rarediseases.info.nih.gov> (accessed March, 2017).
34. National Organization for Rare Disorders or NORD. 2017. Available at <https://rarediseases.org/for-patients-and-families/information-resources/rare-disease-information> (accessed March, 2017).
35. Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 358: 169–176, 2008.
36. Sabharwal SS and Schumacker PT. Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles'heel? *Nat Rev Cancer* 14: 709–721, 2014.
37. Sara JD, Eleid MF, Gulati R, and Holmes DR, Jr. Sudden cardiac death from the perspective of coronary artery disease. *Mayo Clin Proc* 89: 1685–1698, 2014.
38. Sundaresan M, Yu Z-X, Ferrans VJ, Irani K, and Finkel T. Requirement for generation of H₂O₂ for platelet-derived growth factor signaling transduction. *Science* 270: 296–299, 1995.
39. Wang L, Seidman JG, and Seidman CE. Narrative review: harnessing molecular genetics for the diagnosis and man-

- agement of hypertrophic cardiomyopathy. Review. *Ann Intern Med* 152: 513–520, 2010.
40. Zipes DP and Wellens HJJ. Sudden cardiac death. *Circulation* 98: 2334–2351, 1998.

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Abbreviations Used

KS = Kaposi's sarcoma
KSHV = KS-associated Herpes Virus
MI = myocardial infarction
RNS = reactive nitrogen species
ROS = reactive oxygen species
SCD = sudden cardiac death