Canadian Journal of Cardiology 31 (2015) 1094–1115

Review

The Genetics of Cardiovascular Disease in Canadian and International Aboriginal Populations

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ABSTRACT

For Aboriginal populations, as in all populations, understanding the genetic component of cardiovascular disease informs effective treatment and prevention strategies. The term, "genetics of cardiovascular disease," broadly includes the genetics of susceptibility for atherosclerosis, cardiomyopathy, arrhythmia, and congenital heart disease, collectively a major cause of mortality and morbidity throughout the life course. Aboriginal populations are often genetically and culturally distinct, and as would be expected with distinct ethnic differences, there are also differences in rates and types of heart disease, which supports the importance of understanding possible genetic factors that might alter susceptibility. In Canada, higher rates of congenital heart malformations have been identified in some Inuit and First Nations than in the non-Aboriginal population. Moreover, at least 3 different First Nations communities in Canada have been found to have disproportionately higher rates of congenital long QT syndrome, a genetic predisposition to arrhythmia and sudden cardiac death. Although rates of ischemic heart disease historically have been lower in

RÉSUMÉ

Dans les populations autochtones, comme dans l'ensemble des populations, la compréhension de la composante génétique de la maladie cardiovasculaire permet d'orienter la mise en place de stratégies de traitement et de prévention efficaces. Lorsqu'on parle de « la génétique de la maladie cardiovasculaire », il est globalement question de la prédisposition génétique à plusieurs affections, notamment l'athérosclérose, la cardiomyopathie, l'arythmie et la cardiopathie congénitale. Collectivement, ces affections sont une cause importante de mortalité et de morbidité tout au long de la vie. Les Autochtones forment souvent des peuples distincts tant culturellement que sur le plan génétique et, en général, les différences ethniques s'accompagnent aussi de différences quant à la prévalence et aux types de cardiopathies, d'où l'importance de bien comprendre les facteurs génétiques susceptibles d'influer sur les prédispositions. Au Canada, la fréquence des malformations cardiaques congénitales s'est révélée plus élevée au sein des populations inuites et de certaines Premières Nations que parmi la population non autochtone. De plus, au moins

The "genetics of cardiovascular disease (CVD)" broadly includes the genetics of susceptibility for atherosclerosis, cardiomyopathy, arrhythmia, and congenital heart disease.[1] A focus of study for more than 20 years,[2,3] genetic approaches have contributed significantly to the understanding of the underlying pathoetiology and risk susceptibility, and have also directed therapeutic strategies.[4,5] Although substantial progress has been made in understanding the numerous genetic factors involved in atherosclerosis, hypertension, and other risk factors for ischemic heart disease, few genetic markers have been integrated directly into medical practice although this could potentially increase. However, genomic technological advances integrated into health care have been partly responsible for the rapid progress made in the genetic understanding of inherited causes of sudden cardiac death in the young.[6,7] Genetic mutations responsible for cardiomyopathies and arrhythmias, often autosomal dominant with reduced penetrance, have been directly integrated into medical practice based on evidence that knowledge of the gene or mutation involved might direct treatment and reduce the risk of sudden death for affected individuals and family members.[8] Multidisciplinary cardiogenetics clinics have arisen worldwide in response to this quickly expanding field.[9-11]

Throughout the life course, heart disease has a significant effect on health and wellness. Furthermore, heart disease presentation is influenced by the interaction of genetics and the environment.[12] For example, the earliest presentation of

Received for publication May 13, 2015. Accepted July 9, 2015.

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See page 1110 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.07.005

Aboriginal populations, more recent evidence suggests equal or higher rates than in non-Aboriginal populations. Although relatively few Aboriginal communities in Canada have participated in research to explore the genetic component of cardiovascular disease, recent progress in research standards of practice that require collaborative approaches have opened the doors for more involvement. Herein we present what has been learned to date through research and the apparent gaps in the understanding of the genetics of heart disease in Canadian, American, Circumpolar, and other international Indigenous populations.

trois collectivités des Premières Nations canadiennes affichent des taux disproportionnellement élevés de syndrome du QT long congénital, une prédisposition génétique à l'arythmie et à la mort subite d'origine cardiaque. Bien que la fréquence de cardiopathie ischémique ait été dans le passé inférieure à la norme au sein des populations autochtones, de récentes données montrent qu'elle est maintenant égale ou supérieure à celle observée parmi les populations non autochtones. Relativement peu de groupes autochtones du Canada ont participé à des études visant à explorer la composante génétique de la maladie cardiovasculaire, mais des modifications récemment apportées aux normes de pratique en recherche, mettant de l'avant des approches de collaboration, ont ouvert la porte à une plus grande participation. Nous présentons ici un bilan des connaissances acquises jusqu'ici grâce à la recherche et décrivons les lacunes apparentes dans notre compréhension de la génétique de la cardiopathie propre aux peuples autochtones du Canada, de l'Amérique et de la région circumpolaire ainsi qu'aux populations indigènes d'autres pays.

heart disease, congenital heart malformations, affect nearly 1% of the general population.[13,14] Research into causes has identified a number of genes and chromosomal variants that contribute to syndromic and isolated congenital heart malformations,[15] but socioeconomic status and nutrition, are arguably as or even more important at the population level and might also influence variation in rates between populations,[16] supporting a role for genetic and nongenetic factors. First Nations people of Canada have higher rates of death from CVD than non-Aboriginal Canadians[17] in every income quintile and level of education, which suggests that underlying genetics along with social determinants need to be explored to fully understand the health care gaps. As in all populations, multifaceted Aboriginal health research that takes into consideration the interaction of environmental, social, and genetic factors has the potential to optimize the understanding of the underlying causes, and inform the development of effective treatments and prevention strategies.

Who Are the Aboriginal People of Canada?

'Aboriginal' is a term that describes the descendants of the 'original inhabitants' and in Canada includes 3 distinct populations, namely, First Nations, Inuit, and Métis, which combined comprise 4.3% of the Canadian population (1,400,685 people).[18] Currently, there are 618 different First Nations recognized[19]; they are considered to have entered the Americas at least 11,000 years ago.[20] The Métis arose after colonization with Europeans and developed as distinct communities with a culture that melded European and Native traditions.[21,22] The Inuit have historically lived in Arctic regions, likely having traversed the route of the Bering Strait approximately 4000 years ago.[23,24] There is great diversity within Aboriginal groups; for example, in British Columbia (BC) there are 198 First Nations, including 6 different language groups.[25] Life expectancy is more than 10 years less than in the non-Aboriginal population as a result of increased age-standardized mortality rates and high rates of infant mortality.[26,27] But there is also variability in health outcomes within and between Aboriginal populations and communities, which reflects genetic and socioeconomic realities. Although social determinants of health cannot be ignored as major determinants of health outcomes,[28] genetic background can interact with the environment, nutrition, and socioeconomic stressors[29,30] to exacerbate adverse outcomes or, in some cases, protect from them. But as important as genetic inquiry is to the understanding of pathogenesis, prevention, and therapeutics, some Aboriginal communities might be hesitant to participate in such studies.

Why Might There Be Aboriginal Community Concerns About Including Genetic Research in Health-Related Studies?

Historical reasons that might prevent Aboriginal people from participating in genetic research include: (1) secondary use of DNA and cell lines for research for which consent was not given[31] including research that traces ancestry[32]; (2) cultural beliefs that might be contradictory to potential research results[33,34]; (3) commercialization and patenting interests[35]; and (4) general concerns of vulnerability to exploitation of the Aboriginal communities for the benefit of mainstream science and economics. Recent increased involvement of Aboriginal scholars and community members has resulted in significant changes in research practice.[36,37] Participatory methods that are well established in social sciences and education disciplines have now been extended to health research that includes the use of biological samples[38,39] and are supported by the Canadian Institutes for Health Research[37] and endorsed within the revised Tri-Council Policy Statement Chapter 9.[40] Section 9.19 states, "As part of community engagement, researchers shall address and specify in the research agreement the rights and proprietary interests of individuals and communities, to the extent such exist, in human biological materials and associated data to be collected, stored and used in the course of the research."[40] Participatory methods[41] have now become the standard of practice for carrying out research with Aboriginal communities in Canada[42] and elsewhere[43] and model research in Quebec and Ontario for diabetes led the way.[44-46] Longstanding relationships between communities and researchers contributed significantly to the