

Viewpoint

Standing on the Shoulders of Giants: J.A.P. Paré and the Birth of Cardiovascular Genetics

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ABSTRACT

Sudden death and stroke afflicted a family from rural Quebec with such frequency as to be called the Coaticook curse by the local community. In Montreal in the late 1950s, a team of physicians led by J.A.P. Paré investigated this family for inherited cardiovascular disease. Their efforts resulted in an extensive and now classic description of familial hypertrophic cardiomyopathy. A quarter of a century later, the same family was the subject of linkage analysis and direct sequencing, culminating in the isolation of a mutation in the gene encoding the β myosin heavy chain. *MYH7* was the first gene implicated in a cardiovascular disease, which paved the way for identification of mutations in other heritable disorders, mechanistic studies, and clinical applications, such as predictive testing. The present era of cardiovascular genomics arguably had its inception in the clinical observations of Dr Paré and his colleagues more than 50 years ago.

RÉSUMÉ

Dans une petite communauté rurale du Québec, une famille avait été tellement éprouvée par les morts subites et les AVC que ses concitoyens avaient surnommé ce phénomène la malédiction de Coaticook. À Montréal, à la fin des années 1950, une équipe de médecins menée par le D^r J.A.P. Paré a étudié cette famille qui semblait atteinte d'une maladie cardiovasculaire héréditaire. Ces travaux ont donné lieu à une description détaillée et désormais classique de la cardiomyopathie hypertrophique familiale. Un quart de siècle plus tard, cette même famille a fait l'objet d'une analyse par liaison génétique et de séquençage direct qui s'est soldée par la découverte d'une mutation du gène codant pour la chaîne lourde de la bêta-myosine. Le gène *MYH7* a été le premier gène associé à la maladie cardiovasculaire. Sa découverte a ouvert la voie à l'identification de mutations liée à d'autres affections héréditaires, à des études mécanistiques et à des applications cliniques comme les tests de dépistage génétique. On peut donc affirmer que les travaux effectués par le D^r Paré et ses collègues, il y a de cela plus de 50 ans, ont constitué le premier jalon de la génomique cardiovasculaire telle que nous la connaissons aujourd'hui.

In the past we spoke of genetics; the term now in vogue is genomics. Renaming of the field reflects the gradual shift in focus from single-gene quests to investigation of the whole genome, but is only the tip of the iceberg.¹ The growing interest in gene-gene interactions has rendered the conventional vocabulary of disease-causing mutations and “benign” polymorphisms anachronistic. Replacing it is the more generic terminology of effect sizes and sequence variants, customarily subdivided into rare and common according to mean allele frequency. The study of genetic variation as such necessitates evaluation of not only families but also vast

cohorts. Even the long-accepted dichotomy between simple Mendelian and complex traits has been supplanted by a continuum. At one end is an identifiable primary (causal) gene that interacts with modifiers; the sharing of influence between multiple genes then becomes progressively more important, until the primacy of any individual gene is no longer discernible.²

If turf boundaries seem increasingly blurred, it is because the evolving field calls for a cross-disciplinary approach. The ability to perform statistical analysis of large quantities of data, at one time the province of population geneticists, is now also required of molecular geneticists.¹ Interpretation of the data generated entails bioinformatics, which attracts physical and life scientists. The advances in technology that have spurred these developments have also facilitated commercialization of genetic testing, bringing genomics out of the academic laboratory and into the public eye.^{1,3}

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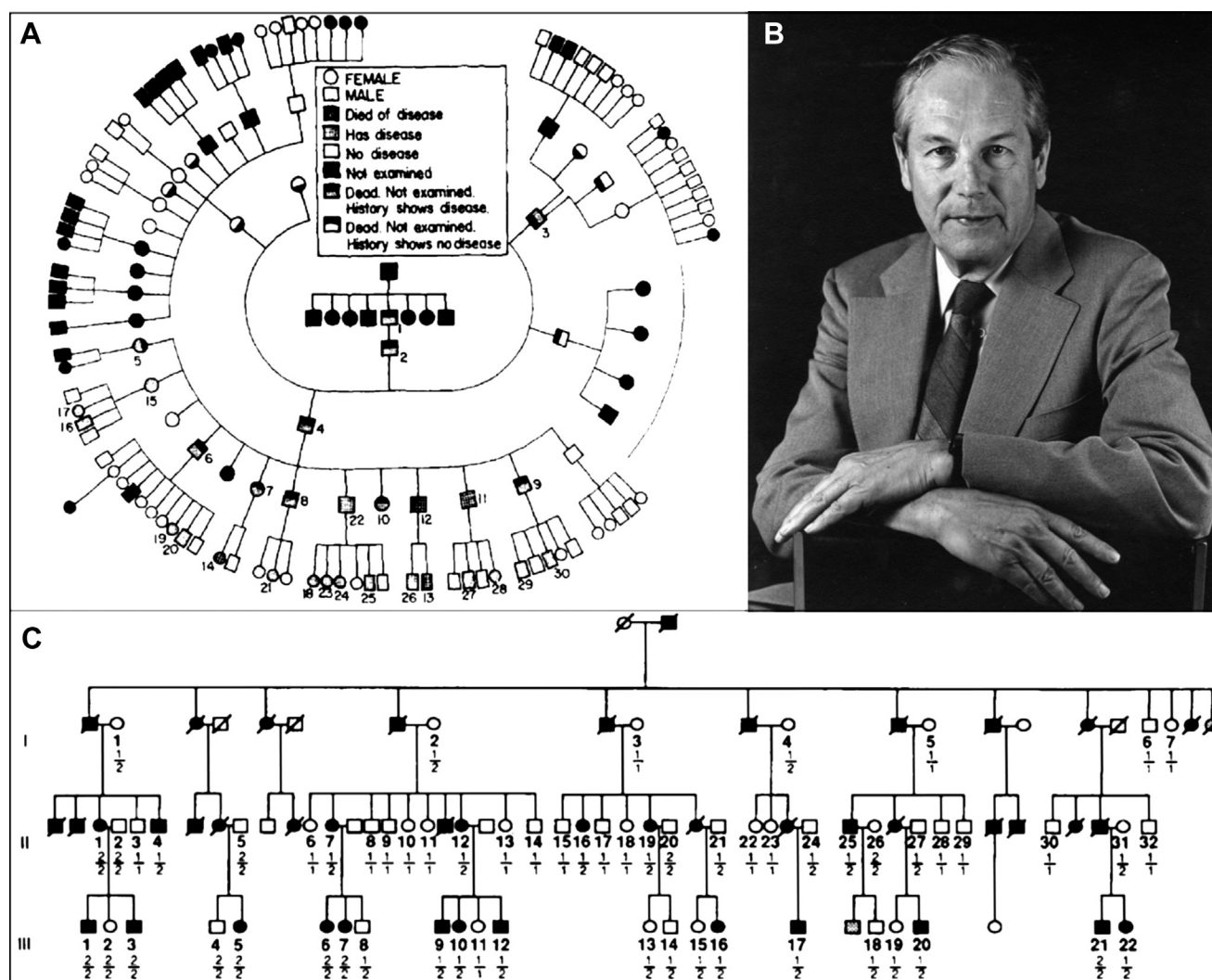


Figure 1. (A) Shows the original genealogical chart compiled by Dr Paré and colleagues and published in 1961.⁵ (B) A photograph of Dr Paré. (C) The revised pedigree constructed for the linkage study in the late 1980s.⁶ Squares denote men and circles women. The symbols are shaded for those affected, clear for those unaffected, and hatched for those not examined. Slashes indicate deceased family members. (A) Reproduced from Paré et al.⁵ with permission from Elsevier. (B) Reproduced from Paré⁷ with permission from Peter Paré. (C) Reproduced from Jarcho et al.⁶ with permission from the Massachusetts Medical Society.

Nevertheless, as Allan C. Spradling pointed out, the advent of genomics is not a unique watershed in genetic history. Recognizable in retrospect are 4 successive “revolutionary” eras: classical genetics, molecular genetics, molecular cloning and, most recently, genomics.⁴ Galvanized by technological advances, each of these eras provided fresh insights into genomes, demanded expansion of the skill set of those working in the field, and enhanced clinical relevance and public interest in their work. Despite the justifiable enthusiasm that hailed each era, however, none proved to be a magic bullet, and each owed much to its predecessors.⁴ Herein we revisit the roots of cardiovascular genetics, which arguably began with the description of hereditary cardiovascular dysplasia—now known as hypertrophic cardiomyopathy—in a large Canadian family.⁵

In the fall of 1957, 2 brothers aged 39 and 41 years were coincidentally admitted to the Royal Victoria Hospital in Montreal with unexplained cardiomegaly and a history of cerebrovascular accidents. The family history included a

conspicuously high incidence of strokes and premature sudden deaths (at ages younger than 45 years), to which the local community referred as the Coaticook curse, after the small town in rural Quebec where the family resided. Suspecting an inherited condition, the team of physicians—led by a chest physician, Dr J.A.P. (Peter) Paré—undertook an extensive family study (Fig. 1). Over the following 2 years, they obtained relevant available details on the deceased and evaluated surviving relatives. Initial screening included clinical history, physical examination, electrocardiography, and chest radiography; most of those with abnormalities returned for reassessment 1 year later.⁵

Because no postmortem examinations had been conducted, relatives served as the primary source of information on the deceased individuals. Presumptive retrospective diagnoses were made if family members recalled symptoms of cardiac disease and/or premature sudden death in the deceased, and corroborated in 2 cases based on archived electrocardiograms.

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