Recurrent and founder mutations in inherited cardiac diseases in the Netherlands

J.P. van Tintelen, A.A.M. Wilde, J.D.H. Jongbloed

Since the start of joint outpatient clinics with both cardiologists and clinical geneticists, in 1996, both the number of patients and the research activities in this field have tremendously grown. In 2001, around 600 patients were evaluated for a cardiological disorder in all Dutch departments of clinical genetics, being nearly 5% of all patients evaluated at a department of clinical genetics at that time. These figures rose to 2500 and 10%, respectively, in 2007. This growth can be attributed to several factors such as the expanding possibilities of DNA testing in potentially inherited cardiac disorders, highly motivated people working hard in the joint cardiogenetics outpatient clinics that are now available at all university medical centres and some secondary hospitals, and last but not least growing awareness of cardiologists that part of their daily clinical practice actually deals with families instead of individual patients.

These factors also attributed to growing cardiogenetic research in the Netherlands with some successful ongoing projects in close collaboration with the GENCOR registry on, for example, long-QT syndrome, hypertrophic cardiomyopathies (ESCAPE HCM), dilated cardiomyopathies due to mutations in the gene encoding lamin AC and arrhythmogenic right ventricular cardiomyopathy.[1]

To make readers of this journal more aware of some of the aspects of these disorders, an article series on recurrent or founder mutations underlying inherited cardiovascular diseases in the Netherlands will be launched. Recurrent mutations are identical mutations that arise independently of each other within a population, since the respective DNA nucleotide(s) are more vulnerable to damage-causing agents (i.e. ionising radiation, ultraviolet light, environmental chemicals) or mechanisms (i.e. mistakes in replication or recombination, depurination, deamination). Founder mutations are mutations that emerged in a population many generations ago and have subsequently spread among following generations. Founder mutations are characterised by the fact that their origin can be inferred by the unique chromosomal background on which the mutation occurred.

Until recently, the general idea was that mutations causing cardiovascular disorders were unique for the families in which they were identified and that founder mutations might occur, but at low frequency. This certainly accounts for diseases with a severe course, leading to death at a relatively young age (i.e. before the reproductive age). In this respect, first reports on inherited cardiovascular disorders focused on those cases. However, in recent years, growing numbers of families, including those with milder phenotypes, have visited our cardiogenetic outpatient clinics. In these families the disease generally manifests in the second or third decade of life and regularly even later. Therefore, most carriers of mutations causing such diseases reach the average reproductive age of 30 years, as calculated based on different observations by Zeegers et al.,[2] and will be able to transmit the respective mutation. This implies that founder mutations in patients with an inherited cardiovascular disease might be regularly expected. Indeed, quite a number of founder mutations have been identified in the Netherlands, such as in familial hypercholesterolaemia,[3] hypertrophic cardiomyopathy,[4] and arrhythmogenic right ventricular cardiomyopathy,[5] idiopathic ventricular fibrillation[6] and desmin-related cardiomyopathy.[7] In part, this can be explained by the availability of DNA diagnostics and clinical genetic care that enables recognition of these mutations.

Within the Netherlands, different classes of founder mutations can be recognised: mutations in genetic isolates, including large families, mutations not in isolates but with a regional distribution within the

J.P. van Tintelen
J.D.H. Jongbloed
Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
A.A.M. Wilde
Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Correspondence to: J.P. van Tintelen
Department of Genetics, University Medical Center Groningen, PO Box 30001, 9700 RB Groningen, the Netherlands
E-mail: j.p.van.tintelen@medgen.umcg.nl

Netherlands only, mutations that are shared with other Europeans, and/or mutations in descendents of Dutch emigrants. Several demographic aspects influenced the distribution of founder mutations in the Dutch population.[2] Firstly, before 1800 international immigration was an important demographic force that might explain the presence of founder mutations that are shared with other Europeans. After 1800 immigration declined, but started to be an important aspect again after the mid-20th century, although the latter will not have resulted in (novel) founder effects yet. Secondly, emigration affected the presence of Dutch founder mutations in other parts of the world. Dutch founder mutations can be identified in North America and South Africa in particular.[8,9] Thirdly, despite the relatively small size of the country, interesting differences within the Netherlands are recognised which originate mainly from geographic and religious isolation. Geographically, major rivers divided the North from the South, the Zuiderzee isolated people living on islands and peninsulas in the north-western parts of the Netherlands and the absence of developed transport systems resulted in endogamy of more isolated rural areas (i.e. Zeeland, Noord-Brabant). In addition, an overall effect of sharp religious cleavage and debate was the separation of the population of the Netherlands into three separate blocks leading to religious and social endogamy: Catholics, Protestants, and non-religious. Notably, a significant number of founder mutations have been identified in religious, linguistic or geographic isolates in the Netherlands.[2]

Acknowledging the existence of founder mutations and the related founder effects is important for both genetic research and patient care in inherited cardiovascular diseases. Patients carrying founder mutations also share neighbouring genetic regions. This observation can be exploited to identify the gene involved. The identification of founder mutations in the Netherlands and even in specific regions within the country enables dedicated molecular testing that will be cheaper and quicker. In addition, the significant number of patients carrying founder mutations enables studies focusing on relations between genotype and phenotype and the subsequent elucidation of factors underlying the clinical variability, including modifier genes.

In this issue of our journal, Postema et al.[10] give the first example of such a founder mutation in the *SCN5A* gene giving rise to a mixed phenotype of long QT syndrome, Brugada syndrome and progressive cardiac conduction defects and discuss the pending genotyping studies to identify genes modulating disease severity. In coming issues of this journal, the focus will be on some other of these founder or recurrent mutations underlying the spectrum of inherited cardiovascular diseases such as connective tissue disorders (Marfan syndrome) cardiomyopathies (DCM, HCM and ARVC), primary arrhythmia syndromes (long-QT syndrome, Brugada syndrome and idiopathic ventricular fibrillation) and disorders affecting haemostasis to make cardiologists more aware of the genetic background of these disorders. ■

References

1 Hermans JF, Christiaans I, van Tintelen JP, et al. GENCOR: a national registry for patients and families suffering from a familial heart disease in the Netherlands. Neth Heart J. 2006;14:272-6.
2 Zeegers MPA, van Poppel F, Vlietinck R, et al. Founder mutations among the Dutch. Eur J Hum Genet. 2004;12:591-600.
3 Fouchier SW, Kastelein JJ, Defesche JC. Update of the molecular basis of familial hypercholesterolemia in The Netherlands. Hum Mutat. 2005;26:550-6.
4 Alders M, Jongbloed R, Deelen W, et al. The 2373insG mutation in the MYBPC3 gene is a founder mutation, which accounts for nearly one-fourth of the HCM cases in the Netherlands. Eur Heart J. 2003;24:1848-53.
5 van Tintelen JP, Entius MM, Bhuiyan ZA, et al. Plakophilin-2 mutations are the major determinant of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation. 2006; 113:1650-8.
6 Alders M, Koopmann TT, Christiaans I, et al. Haplotype-sharing analysis implicates chromosome 7q36 harboring DPP6 in familial idiopathic ventricular fibrillation. Am J Hum Genet. 2009;84:468-76.
7 van Tintelen JP, van Gelder IC, Asimaki A, et al. Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. Heart Rhythm. In Press. DOI:10.1016/j.hrthm.2009.07.041
8 Defesche JC, Van Diermen DE, Hayden MR, et al. Origin and migration of an Afrikaner founder mutation FHAfrikaner-2 (V408M) causing familial hypercholesterolemia. Gene Geogr. 1996;10:1-10.
9 Crotti L, Spazzolini C, Schwartz PJ, et al. The common long-QT syndrome mutation KCNQ1/A341V causes unusually severe clinical manifestations in patients with different ethnic backgrounds: toward a mutation-specific risk stratification. Circulation. 2007;116:2366-75.
10 Postema PG, van den Berg MP, van Tintelen JP, et al. Founder mutations in the Netherlands - SCN5a 1795insD, the first described arrhythmia overlap syndrome and one of the largest and best characterised families worldwide. Neth Heart J. 2009;17:422-8.