With expanded carrier screening, founder populations run the risk of being overlooked

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Abstract Genetically isolated populations exist worldwide. Specific genetic disorders, including rare autosomal recessive disorders may have high prevalences in these populations. We searched for Dutch genetically isolated populations and their autosomal recessive founder mutations. We investigated whether these founder mutations are covered in the (preconception) expanded carrier screening tests of five carrier screening providers. Our results show that the great majority of founder mutations are not covered in these screening panels, and these panels may thus not be appropriate for use in founder populations. It is therefore important to be aware of founder mutations in a population when offering carrier tests.

Keywords Founder population · Community · Carrier screening · Autosomal recessive · Netherlands

Introduction

The general Dutch population is relatively outbred (Ten Kate et al. 2014). However, several genetically isolated populations exist (for definitions of terms see Box 1). Also, in many other countries worldwide, genetically isolated populations are present. Often these populations are geographically, culturally, or for religious reasons isolated for centuries and as a consequence show less genetic variation. Because of the low genetic heterogeneity, these populations have proven to be very suitable for the identifications of genes involved both in Mendelian as well as in complex disorders. Bottleneck effects in the history of a population and/or founder effects may result in high prevalences of monogenic recessive disorders in these populations compared with the nationwide prevalences.

Because of high carrier frequencies in founder populations, carrier screening programs have been introduced in some of these populations. The aim of these programs is to identify carrier couples with a one-in-four risk of affected offspring, enabling autonomous reproductive decision making, which consequently might reduce perinatal morbidity and mortality. Examples are carrier screening programs for genetic disorders in people of Eastern European Jewish (Ashkenazi) descent (for example Tay-Sachs disease) (ACOG Committee on

Box 1 Definitions

Genetically isolated population or founder population: a population that is or was geographically, culturally, or for religious reasons isolated and as a consequence has restricted genetic variation.

Bottleneck effect: occurs when there is a sharp reduction in the size of a population due to a natural disaster or similar event with, as a consequence, reduction of the genetic variation in the population.

Founder effect: the reduction of genetic variation that occurs when a new population is founded by a small number of individuals (founders) from a larger population and this population remains isolated to other populations.

Founder mutation: a gene mutation on an identical haplotype background, observed with high frequency in a genetically isolated population in which one or more of the ancestors were carriers of the gene mutation.

Recurrent mutation: a gene mutation on more than one haplotype background, reoccurring multiple times in a population history.
targeted carrier screening for severe and frequent disorders in different isolated (mainly Arab and Druze) communities in Israel (Basel-Vanagaite et al. 2007; Falik-Zaccai et al. 2008; Zlotogora et al. 2009), screening for four recessive diseases in the Saguenay-Lac-Saint-Jean region of Quebec, Canada (Tardif et al. 2017), and screening for four severe autosomal recessive disorders in a Dutch genetically isolated community (Mathijssen et al. 2015).

Meanwhile, technological advances have enabled the development and offer of preconception expanded carrier screening (ECS) in which couples without an a priori increased risk of having a child with a genetic disorder can be screened for several (hundreds of) disorders simultaneously (Edwards et al. 2015; Henneman et al. 2016). An increasing number of mainly commercial laboratories offer these screening panels (Borry et al. 2011; Lazarin et al. 2013).

However, the carrier frequencies of several autosomal recessive disorders in genetically isolated populations can be very skewed from nationwide or worldwide carrier frequencies. In some genetically isolated populations, carrier frequencies of disorders which are rare or almost non-existent in the general population may be very high. In contrast, carrier frequencies of more frequent disorders in the general population may be very low in genetically isolated populations.

The aim of this study was to make an inventory of Dutch genetically isolated populations and their autosomal recessive founder mutations, and to investigate whether Dutch founder mutations are covered in the (preconception) expanded carrier screening tests of carrier screening providers.

Methods

We searched for genetically isolated populations in the Netherlands (total population 17 million people) and their founder mutations in the databases PubMed, On-line Mendelian Inheritance in Man (OMIM), and Google systematically by using the keywords “genetically isolated population,” “founder,” “mutation,” “gene,” and “Dutch” or “Netherlands.” Also, 11 Dutch clinical (molecular) geneticists were asked about their knowledge of genetically isolated populations and their specific founder mutations. Only autosomal recessive mutations were included. Recurrent mutations (Box 1) and Dutch founder mutations not related to a specific genetically isolated community were not included (Zeegers et al. 2004). To prevent possible stigmatization, the genetically isolated populations are numbered and the specific names of the villages are not mentioned.

Our purpose was not to be complete, but to illustrate the importance of being aware of founder populations and founder mutations. We therefore made a selection of founder mutations present in different genetically isolated populations for which the most information was available in the literature and from personal information.

Information about the carrier frequencies of founder mutations were derived from the scientific articles and personal communication with clinical (molecular) geneticists. Carrier frequencies in the Dutch general population were derived from The Genome of the Netherlands (GoNL) project (http://www.nlgenome.nl, accessed 24 February 2017) (The Genome of the Netherlands Consortium 2014).

We investigated whether the specific founder mutations were present or absent in the expanded carrier screening panels offered by five ECS providers.

Results

In Table 1, several founder mutations present in six different Dutch genetically isolated populations are shown, including the carrier frequencies of these disorders in the specific genetically isolated population and in the Dutch general population. As can be seen, the carrier frequencies of generally rare disorders are high in these genetically isolated populations.

For the five selected carrier screening providers, the coverage of 16 founder mutations in the carrier screening tests is shown. For each carrier screening provider, on average 2.8 (range 0–5) of the 16 founder mutations are covered in the test. Eleven (69%) of the founder mutations are covered in none of the five carrier screening tests. In the test of two providers, a selection of mutations in the specific gene of three disorders is included in the carrier screening test, but the founder mutation is not.

Discussion

In genetically isolated populations, carrier frequencies of genetic disorders can be very different from the carrier frequencies in the general population. The great majority of these founder mutations are not covered in the ECS panels of the five selected providers. This also applies to most of the founder mutations present in genetically isolated populations in other countries.

Offering a (commercial) routine ECS panel to inhabitants of these genetically isolated populations is not appropriate because it may give false reassurance to couples with an increased risk for founder mutations related disorders they are not being tested for.

For a reliable carrier test offer, it is therefore important to know the genetically isolated populations and their founder mutations in each country. Nationwide databases in which the genetically isolated populations, their relatively frequent genetic disorders, and the specific genes and mutations are listed, are a suitable solution. A database is not only very important.
| Disorder                              | OMIM  | Disease severity | Gene | Mutation                  | Population\(^b\) | Carrier frequency genetic isolate\(^c\) | Carrier frequency Dutch general population\(^d\) | Counsyl\(^f\) | GenPath Diagnostics\(^f\) | Mount Sinai\(^g\) | Pathway Genomics\(^h\) | Recombine\(^i\) | References                                      |
|--------------------------------------|-------|-----------------|------|---------------------------|------------------|-------------------------------------------|-----------------------------------------------|--------------|-----------------------------|------------------|---------------------------|----------------|----------------------------------|
| Fetal akinesia deformation sequence (FADS) | 208150| 4               | MUSK | c.1724T>C p.(Ile575Thr)   | 1                | 8.1–11.2%                                  | <0.2%                                        | –            | –                           | –                | –                         | –               | Mathijssen et al. (2015) and Tan-Sindhunata et al. (2015) |
| Osteogenesis imperfecta type IIIB/III (OI) | 610682| 3               | CRTAP | c.21_22dupGG p.(Ala88fs)  | 1                | 4.1%                                       | <0.2%                                        | –            | –                           | –                | –                         | –               | Mathijssen et al. (2015) and van Dijk et al. (2009) |
| Phenylketonuria (PKU)                | 261600| 3               | PAH  | c.1315+1G>A                | 1                | 9.2%                                       | <0.2%                                        | +            | +                           | +                | –                         | –               | Oorthuys et al. (1985) |
| Pontocerebellar hypoplasia type 2 (PCH2) | 277470| 4               | TSEN54 | c.919G>T p.(Ala307Ser)    | 1                | 1.5–14.3%                                  | 0.8%                                         | –            | –                           | –                | –                         | –               | Barth et al. (1990), Budde et al. (2008), and Mathijssen et al. (2015) |
| Primary ciliary dyskinesia (PCD)     | 615067| 2               | CCDC114 | c.742G>A p.(Gly248Thrfs)  | 1                | 10%                                        | 0.4%                                         | –            | –                           | –                | –                         | –               | Onoufriadis et al. (2013) |
| Pseudoxanthoma elasticum (PXE)       | 264800| 3               | ABCC6 | c.3775delT p.(Trp1259Glyfs)| 1                | 15 cases described (~21,500)               | 0.8%                                         | –            | –                           | –                | –                         | –               | Bergen et al. (2000) and Plomp et al. (2009) |
| Retinitis pigmentosa type 12 (RP12)  | 600105| 2               | CRB1  | c.1227T>C p.(Met404Thr)   | 1                | 4.1%                                       | <0.2%                                        | –            | –                           | –                | –                         | –               | Den Hollander et al. (1999) and Mathijssen et al. (2017) |
| Rhizomelic chondrodysplasia punctata type 1 (RCDP1) | 215100| 4               | PEX7  | c.875T>G p.(Leu292X)      | 1                | 6.1%                                       | <0.2%                                        | +            | +                           | +                | –                         | –               | Mathijssen et al. (2015) |
| Van Buchem disease (VBCH)            | 239100| 3               | SOST  | 52 kb deletion approximately 35 kb downstream of gene | 2                | ≥13 cases described (~20,000)               | <0.2%                                        | –            | –                           | –                | –                         | –               | Bakemans et al. (2002) and Van Buchem et al. (1995) |
| Congenital retinal dystrophy         | 204100| 2               | RPE65  | c.1102T>G p.(Tyr368His)   | 2                | 3.1–7.7%                                   | 0.4%                                         | –            | +                           | –                | –                         | –               | Schappert-Kimmigser et al. (1999) and Yzer et al. (2003) |
| Retinitis punctata albescens (RPA)   | 136880| 2               | LRAF  | c.12delC p.(Met6Cys6X53)  | 2                | 4 cases described (~20,000)                 | <0.2%                                        | –            | –                           | –                | –                         | –               | Litink et al. (2012) |
| Vici syndrome (variant form)         | 242840| 4               | EPG5  | c.4862G>A p.(Arg1621Gln)  | 2                | ≥10% (pc)                                   | <0.2%                                        | –            | –                           | –                | –                         | –               | De Koning et al. (1995), Houwen et al. (2006) |
| Benign recurrent intrahepatic         | 243300| 2               | ATP8B1 | c.2932-3C>A skipping of exon 24 | 3                | <0.2%                                      | –                                            | –            | –                           | –                | –                         | –               | De Koning et al. (1995), Houwen et al. (2006) |
Table 1 (continued)

| Disorder                        | OMIM     | Disease severity | Gene    | Mutation                          | Population<sup>b</sup> Carrier frequency genetic isolate<sup>c</sup> Dutch general population<sup>d</sup> | Carrier frequency Dutch general population<sup>d</sup> | GenPath Diagnostics<sup>e</sup> | Mount Sinai<sup>f</sup> | Pathway Genomics<sup>g</sup> | References                    |
|--------------------------------|----------|------------------|---------|-----------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------|-----------------------------|--------------------------|-----------------------------|---------------------------------|
| Cholestasis (BRIC)             | 604213   | 2                | GPSM2   | c.1473delG (p.(Phe492SerfsX5))    | ≥7 cases described (~20,000)                                                                  | <0.2%                                                    | −                          | −                         | −                          | Almomani et al. (2013) and Hendriks et al. (1999) |
| Chudley-McCullough syndrome (CMCS) | 204200   | 4                | CLN3    | 1.02 kb deletion                  | 17 cases described                                                                           | 0.5%                                                     | +                          | −                         | −                          | Taschner et al. (1995) |
| Parkinson disease type 7 (PARK7) | 606324   | 3                | DJ-1    | 14 kb deletion                    | 6 cases                                                                                       | 0.9%                                                     | <0.2%                      | −                         | −                          | Bonifati et al. (2003) |

<sup>a</sup> Disease severity: 1 = mild, 2 = moderate, 3 = severe, 4 = profound (Lazarin et al. 2014). Scored independently by IM and IK. Discrepancies were discussed until consensus was reached.

<sup>b</sup> Six different Dutch founder populations (coded from 1 to 6).

<sup>c</sup> If the carrier frequency in the genetically isolated community is not known, the number of cases described in the literature and the current population size of the genetically isolated community is noted.

<sup>d</sup> Derived from Genome of the Netherlands (GoNL) project, http://www.nlgenome.nl; accessed 23 February 2017.

<sup>e</sup> Family Prep Screen (113 disorders); https://www.counsyl.com/services/family-prep-screen; accessed 6 February 2017.

<sup>f</sup> InheriGen Plus (167 disorders); http://www.genpathdiagnostics.com/womens-health/inherigen; accessed 6 February 2017.

<sup>g</sup> NextStep Pan-Ethnic Carrier Screen (281 disorders); http://nextsteptest.com; accessed 6 February 2017.

<sup>h</sup> Carrier Status DNA Insight (72 disorders); https://www.pathway.com/carrier-status-dna-insight; accessed 6 February 2017.

<sup>i</sup> CarrierMap (315 disorders); http://www.recombine.com/carriermap; accessed 6 February 2017.

<sup>j</sup> A selection of mutations is included in the carrier screening, but the founder mutation is not included.

"+" presence of the mutation in panel. "−" absence of the mutation in panel, pc personal communications.
for carrier screening programs but also for making a rapid (differential) diagnosis by clinicians, genetic counseling, and research in these populations. For some genetically isolated populations such (online) databases are already available. Examples are the Amish, Mennonite, and Hutterite Genetic Disorder Database (www.biochemgenetics.ca/plainpeople) (Payne et al. 2011) and the Israeli National Genetic Database (www.goldenhelix.org/israeli) (Zlotogora 2010).

Ideally, a customized carrier test will be developed for each country/region in which both country/region-specific mutations as well as genetic isolate-specific founder mutations are present. This approach may also reduce potential stigmatization of genetic isolates, while specific mutations still are included.

In the Netherlands, carrier screening is only (partly) paid by health insurance companies in case of an increased risk of being a carrier; e.g. carrier screening for four autosomal recessive disorders in a genetically isolated community (Mathijsse et al. 2015) and carrier screening for nine disorders in individuals of Ashkenazi Jewish descent (Holtkamp et al. 2016). Recently, the Academic Medical Center in Amsterdam started a non-profit offer of carrier screening for 50 severe autosomal recessive disorders. Most of the severe disorders currently known in Dutch genetically isolated populations are included. Probably, in a non-commercial setting, it will be more likely to take into account the founder mutations present in founder populations than for commercial companies to include those mutations.

It is expected that in the near future, it will become possible to use whole-exome sequencing (WES) or whole-genome sequencing (WGS) for ECS, in which all known disease genes can be screened, including very rare disease genes prevalent in genetically isolated populations. However, correct interpretation of test-results (e.g. variants of unknown clinical significance) when using WES or WGS is complex. Also, the identification of carrier couples for mild disorders which are unclassified when using WES or WGS is complex. Also, the identification of test-results (e.g. variants of unknown clinical significance) when using WES or WGS is complex. Also, the identification of test-results (e.g. variants of unknown clinical significance) when using WES or WGS is complex. Also, the identification of test-results (e.g. variants of unknown clinical significance) when using WES or WGS is complex. Also, the identification of test-results (e.g. variants of unknown clinical significance) when using WES or WGS is complex. Also, the identification of test-results (e.g. variants of unknown clinical significance) when using WES or WGS is complex.

Conclusions

In genetically isolated populations, carrier frequencies of generally rare autosomal recessive founder mutations can be very high. The great majority of these founder mutations are not covered in most (commercial) routine ECS panels. It is important to be aware of founder populations and founder mutations when using these ECS panels and to check whether the mutations are covered. If these founder mutations are not covered, customized screening tests should be developed which include the founder mutations.

Compliance with ethical standards

Conflict of interest All authors are affiliated to a hospital that offers expanded carrier screening in a non-commercial setting.

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Consent This article does not contain any studies with human participants performed by any of the authors.

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