Genetically isolated populations

Implications for genetic care

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Chapter 8

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.
INTRODUCTION

The general Dutch population is relatively outbred. 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 to the nation-wide 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 1-in-4 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), targeted carrier screening for severe and frequent disorders in different isolated (mainly Arab and Druze) communities in Israel, screening for four recessive diseases in the Saguenay-Lac-Saint-Jean region of Quebec, Canada, and screening for four severe autosomal recessive disorders in a Dutch genetically isolated community.

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. An increasing number of mainly commercial laboratories offer these screening panels.

However, the carrier frequencies of several autosomal recessive disorders in genetically isolated populations can be very skewed from nation-wide or world-wide 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.
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 semi-systematically by using the key words ‘genetically isolated population’, ‘founder’, ‘mutation’, ‘gene’ and ‘Dutch’ or ‘Netherlands’. Also, eleven 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. 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

### 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.
of the Netherlands (GoNL) project (http://www.nlgenome.nl, accessed February 24, 2017).

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 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.
Table 1. Founder mutations in different Dutch genetically isolated communities and the coverage of these mutations in expanded carrier screening tests.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OMIM</th>
<th>Disease severity</th>
<th>Gene</th>
<th>Mutation</th>
<th>Population</th>
<th>Carrier frequency genetic isolate</th>
<th>Carrier frequency Dutch general population</th>
<th>Counsyl</th>
<th>GenPath Diagnostics</th>
<th>Mount Sinai</th>
<th>Pathway Genomics</th>
<th>Recombine</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Aklnasia Deformation Sequence (FADS)</td>
<td>208150</td>
<td>4</td>
<td>MUSK</td>
<td>c.1724T&gt;C p.(ile575Thr)</td>
<td>1</td>
<td>8.1-11.2%</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.20</td>
<td></td>
</tr>
<tr>
<td>Osteogenesis Imperfecta Type III (OI)</td>
<td>610682</td>
<td>3</td>
<td>CRTAP</td>
<td>c.21_22dupGG p.(Ala8fs)</td>
<td>1</td>
<td>4.1%</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.21</td>
<td></td>
</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>261600</td>
<td>3</td>
<td>PAH</td>
<td>c.1315+1G&gt;A</td>
<td>1</td>
<td>9.2%</td>
<td>&lt;0.2%</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Pontocerebellar hypoplasia type 2 (PCH2)</td>
<td>277470</td>
<td>4</td>
<td>TSEN54</td>
<td>c.919G&gt;T p.(Ala307Ser)</td>
<td>1</td>
<td>15.14.3%</td>
<td>0.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>7.23,24</td>
<td></td>
</tr>
<tr>
<td>Primary Ciliary Dyskinesia (PCD)</td>
<td>615067</td>
<td>2</td>
<td>CCDC114</td>
<td>c.742G&gt;A p.(Gly248Trp)</td>
<td>1</td>
<td>10%</td>
<td>0.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Pseudoxanthoma Elasticum (PXE)</td>
<td>264800</td>
<td>3</td>
<td>ABCC6</td>
<td>c.775delT p.(Trp259Glyfs)</td>
<td>1</td>
<td>15 cases described (~21,500)</td>
<td>0.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>26,27</td>
<td></td>
</tr>
<tr>
<td>Retinitis Pigmentosa type 12 (RP12)</td>
<td>600105</td>
<td>2</td>
<td>CRB1</td>
<td>c.3122T&gt;C p.(Met1041Thr)</td>
<td>1</td>
<td>4.1%</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>28,29</td>
<td></td>
</tr>
<tr>
<td>Rhizomelic Chondrodysplasia Punctata Type 1 (RCDP1)</td>
<td>215100</td>
<td>4</td>
<td>PEX7</td>
<td>c.875T&gt;A p.(Leu292X)</td>
<td>1</td>
<td>6.1%</td>
<td>&lt;0.2%</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Van Buchem Disease (VBCH)</td>
<td>239100</td>
<td>3</td>
<td>SOST</td>
<td>52 kb deletion approximately 35 kb downstream of gene</td>
<td>2</td>
<td>≥13 cases described (~20,000)</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30,31</td>
<td></td>
</tr>
<tr>
<td>Congenital retinal dysrophy</td>
<td>204100</td>
<td>2</td>
<td>RPE65</td>
<td>c.1102G&gt;T p.(Ty368His)</td>
<td>2</td>
<td>3.1-7.7%</td>
<td>0.4%</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>32,33</td>
<td></td>
</tr>
<tr>
<td>Retinitis Punctata Albinvosa (RPA)</td>
<td>130880</td>
<td>2</td>
<td>LRAT</td>
<td>c.12delC p.(Met50CysX33)</td>
<td>2</td>
<td>4 cases described (~20,000)</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>VUli syndrome (variant form)</td>
<td>242840</td>
<td>4</td>
<td>EPG5</td>
<td>c.4692G&gt;A p.(Arg1621Gln)</td>
<td>2</td>
<td>±10% (pc)</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Bcnific Rcenr Intrahaepatic Cholestasis (BRIC)</td>
<td>243000</td>
<td>2</td>
<td>ATP8B1</td>
<td>c.2032-3C&gt;A, skipping of exon 24</td>
<td>3</td>
<td>≥7 cases described (~20,000)</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>35-37</td>
<td></td>
</tr>
<tr>
<td>Chudley-McCullough syndrome (CMCS)</td>
<td>604213</td>
<td>2</td>
<td>GPM2</td>
<td>c.1473delG p.(Phe492SerfsX5)</td>
<td>4</td>
<td>3 cases described (~15,000)</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>38,39</td>
<td></td>
</tr>
<tr>
<td>Juvenile neuronal ceroid lipofuscinosis (CLN3)</td>
<td>204260</td>
<td>4</td>
<td>CLN3</td>
<td>1.02 kb deletion</td>
<td>5</td>
<td>17 cases described</td>
<td>0.6%</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Parkinson disease type 7 (PARK7)</td>
<td>606324</td>
<td>3</td>
<td>DJ-1</td>
<td>14 kb deletion</td>
<td>6</td>
<td>0.9%</td>
<td>&lt;0.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>
Founder populations run a risk of being overlooked.  

**Abbreviations:** +, presence of the mutation in panel; −, absence of the mutation in panel; pc personal communications; *, a selection of mutations is included in the carrier screening, but the founder mutation is not.

- **Disease severity:** 1 = mild, 2 = moderate, 3 = severe, 4 = profound.  
  - Scoring independently by IM and IK. Discrepancies were discussed until consensus was reached.

- **Six different Dutch founder populations (coded from 1 to 6).**  
  - 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.

- **Derived from Genome of the Netherlands (GoNL) project:** http://www.ngenome.nl; accessed 23 February 2017.


Examples are the Amish, Mennonite, and Hutterite Genetic Disorder Database (www.biochemgenetics.ca/plainpeople), and the Israeli National Genetic Database (www.goldenhelix.org/israeli). 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 and carrier screening for nine disorders in individuals of Ashkenazi Jewish descent. 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 unlikely to alter reproductive plans is an important point to take into consideration.

In the meantime, descendants from genetically isolated populations should be made aware that a (commercial) routine ECS panel may not be appropriate and can give false reassurance because the population-specific genes and/or mutations are not covered. Currently, this information is not mentioned by expanded carrier test providers.

Not only genetically isolated populations, but also consanguineous couples and populations with a high rate of consanguineous unions have an increased risk of having a child with an autosomal recessive disorder. Many of these disorders are rare disorders which are also not covered in the (commercial) routine ECS panels. These panels may therefore also not be appropriate for use in consanguineous couples and in countries/populations with a high rate of consanguineous unions.
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.

CONFLICT OF INTEREST

All authors are affiliated to a hospital that offers expanded carrier screening in a non-commercial setting.
LH supervises research evaluating carrier screening, financially supported by the Netherlands Organization for Health Research and Development (ZonMw grant no. 209040001).
REFERENCES


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