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Targeted carrier screening for four recessive disorders: High detection rate within a founder population

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ABSTRACT

In a genetically isolated community in the Netherlands four severe recessive genetic disorders occur at relatively high frequency (pontocerebellar hypoplasia type 2 (PCH2), fetal akinesia deformation sequence (FADS), rhizomelic chondrodysplasia punctata type 1 (RCDP1), and osteogenesis imperfecta (OI) type IIB/III. Over the past decades multiple patients with these disorders have been identified. This warranted the start of a preconception outpatient clinic, in 2012, aimed at couples planning a pregnancy.

The aim of our study was to evaluate the offer of targeted genetic carrier screening as a method to identify high-risk couples for having affected offspring in this high-risk subpopulation.

In one year, 203 individuals (92 couples and 19 individuals) were counseled. In total, 65 of 196 (33.2%) tested individuals were carriers of at least one disease, five (7.7%) of them being carriers of two diseases. Carrier frequencies of PCH2, FADS, RCDP1, and OI were 14.3%, 11.2%, 6.1%, and 4.1% respectively. In individuals with a positive family history for one of the diseases, the carrier frequency was 57.8%; for those with a negative family history this was 25.8%. Four PCH2 carrier-couples were identified.

Thus, targeted (preconception) carrier screening in this genetically isolated population in which a high prevalence of specific disorders occurs detects a high number of carriers, and is likely to be more effective compared to cascade genetic testing. Our findings and set-up can be seen as a model for carrier screening in other high-risk subpopulations and contributes to the discussion about the way carrier screening can be offered and organized in the general population.

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1. Introduction

Autosomal recessive childhood diseases cause serious morbidity and/or mortality in at least 25 of 10 000 children [Sankaranarayanan, 1998; United Nations, 2001]. Genetic counseling and carrier testing aims to identify carrier couples with a 1-in-4 (25%) risk of affected offspring, enabling autonomous reproductive decisions, which consequently might reduce perinatal morbidity and mortality. If carrier testing is performed before pregnancy (preconception), couples are able to make the most informed reproductive choices at least time constraints, and this is therefore generally considered as the ideal timing. These reproductive options include refraining from having children, preimplantation genetic diagnosis (PGD), prenatal diagnosis (chorionic villus sampling or amniocentesis), sperm/egg donation, adoption or accepting the genetic risk. When carrier couples are identified during pregnancy, accepting the risk of having an affected child or prenatal diagnosis are the only options. In the Netherlands, termination of pregnancy is allowed up to 24 weeks. Termination for severe fetal disorders after 24 weeks of gestation may be excepted from legal prosecution provided adherence to stringent criteria and assessment of the case by an expert committee appointed by the ministries of Health and Justice [van Eerden et al., 2014].

Different strategies can be used for genetic carrier testing for autosomal recessive disorders. At this moment, standard clinical care in the Netherlands, as in many European countries, is cascade

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genetic carrier testing. This means that testing is targeted at close relatives and partners of previously identified patients and carriers. In contrast, population *carrier screening* is defined as the detection of carrier status in persons who do not have an a-priori increased risk for having a child with a certain disease based on their family history [Castellani et al., 2010]. For example in the US, preconception and prenatal population-based carrier screening for cystic fibrosis (CF) is recommended for couples with no family history of CF since 2001 [Grody et al., 2001]. In some well-defined ethnic groups, the prevalence of specific genetic disorders is relatively high and the mutations in a given gene are often limited to one or a few specific, so-called founder mutations. In these subpopulations, ethnicity-(or ancestry-) based targeted carrier screening for population-specific mutations is considered an effective way to inform and identify carrier couples for disorders that are generally (very) rare. Examples are carrier screening in individuals of Eastern European Jewish (Ashkenazi) descent [ACOG Committee Opinion, 2009; Monaghan et al., 2008] and carrier screening for hemoglobinopathies in ethnic populations from Africa, the Mediterranean and Southeast Asia [ACOG, 2001; Cousens et al., 2010].

Also in genetically isolated populations, rare genetic disorders can be relatively prevalent. In these genetic isolates, the vast majority of the couples are both members of the same population. As a result of the common ancestral origin and genetic bottleneck effect, many disease-causing founder mutations can occur at relatively high frequencies.

In a small community in the Netherlands, with common ancestral origin, several genetic disorders are more frequent than in other parts of the Netherlands. In the past decades, multiple patients with four rare severe disorders have been identified in this village: pontocerebellar hypoplasia type 2 (PCH2) (MIM 277470), fetal akinesia deformation sequence (FADS) (MIM 208150), rhizomelic chondrodysplasia punctata type 1 (RCDP1) (MIM 215100), and osteogenesis imperfecta (OI) type IIB/III (MIM 610682). Children with these disorders suffer significant morbidity and have a severely reduced lifespan. In this community, prospective parents are at relatively high risk of having a child with one of these four severe disorders. In 2012, this warranted the start of a preconception outpatient clinic in collaboration with the local midwifery practice, aimed at couples planning a pregnancy.

In this article the results of the first year of the outpatient clinic are presented. It is shown that targeted (preconception) carrier screening of high frequent genetic disorders can be a well-suited way of carrier testing in genetically isolated populations.

2. Patients and methods

2.1. Setting

Targeted carrier screening was offered in a fishing village along the former Zuiderzee in the Netherlands, which was founded in the 14th century by seven to 20 families. It is a typical Roman Catholic village, in great contrast to its Protestant environment. Due to religious and social factors, it is still a close-knit village. The village has about 21 500 inhabitants, about 7100 persons of reproductive age (20–45 years), and a birth rate of about 250 births/year.

2.2. Genetic disorders

In the past two decades, founder mutations have been identified for PCH2, FADS, RCDP1, and OI IIB/III. An estimated 2–4 of the 250 children born in the genetically isolated village are annually affected with one of these four severe autosomal recessive diseases. The clinical characteristics of the four diseases, the genes, and mutations are described in Box 1.

In the community described, also other (non-lethal) disorders are highly frequent. Founder mutations have been found for phenylketonuria (PKU) (MIM 261600), [Oorthuys et al., 1985] primary ciliary dyskinesia (PCD) (MIM 615067), [Onoufriadis et al., 2013] retinitis pigmentosa (RP) (MIM 268000), [den Hollander et al., 1999; van Soest et al., 1994] and pseudoxanthoma elasticum (PXE) (MIM 264800) [Bergen et al., 2000; van Soest et al., 1997].

2.3. Outpatient clinic

In collaboration with the local midwifery practice, we started an outpatient clinic in September 2012 providing a preconception care consultation and offering genetic screening for the four founder

Box 1
The four severe autosomal recessive disorders occurring in high frequency in the genetically isolated community in the Netherlands.

- PCH2 is a progressive neurodegenerative disorder characterized by hypoplasia/atrophy of the cerebellum and pons, progressive microcephaly, extrapiramidal dyskinesias, dystonia, seizures, and severe cognitive and motor handicaps. Most infants die during infancy or childhood. [Barth et al., 1990] In 2008 the *TSEN54*-gene was identified in patients with PCH2 from the genetic isolate [Budde et al., 2008]. All affected individuals from the above-mentioned genetic isolate carry the homozygous c.919G > T (p.Ala307Ser)-mutation in the *TSEN54*-gene.
- FADS generally refers to a heterogeneous group of disorders characterized by decreased or absent fetal movements, multiple joint contractures, pulmonary hypoplasia, poor muscle bulk, and craniofacial anomalies (ocular hypertelorism, low-set ears, retromicrognathia). [Hall, 2009] The pregnancy is usually complicated by intrauterine growth retardation, polyhydramnios, and premature birth. Most infants die within two hours of birth due to severe pulmonary hypoplasia. The specific founder mutation of FADS was recently identified in the genetic isolate through homozygosity mapping of two FADS patients. All patients in the village are homozygous for the c.1724T > C (p.Ile575Thr)-mutation in the *MUSK*-gene [Tan-Sindhunata et al., 2014].
- RCDP1 is a peroxisomal disorder characterized by rhizomelia, widespread epiphyseal calcifications, profound growth retardation, severe intellectual disability, cataracts, and ichthyosis. The majority of patients do not survive the first decade of life and some die in the neonatal period. Individuals with RCDP1 from the genetic isolate carry the homozygous c.875T > A (p.Leu292X)-mutation in the *PEX7*-gene [Braverman et al., 1997; Braverman et al., 2000].
- OI is a congenital bone disorder characterized by susceptibility to bone fractures, severe bone deformities, and short stature. It can be subdivided into several types with a wide range of severity. Patients from the genetic isolate have OI type IIB (perinatally lethal OI) or OI type III (progressively deforming OI). Most cases of OI type IIB die within the first year of life due to respiratory failure. OI type III-patients already have multiple fractures, starting intrauterine or in the newborn period with progressive deformities, resulting in short stature and severe ambulatory restriction. The genetic cause of both types of OI in the genetic isolate is the c.21_22dupGG (p.Ala8fs)-mutation in the *CRTAP*-gene [van Dijk et al., 2009].

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