

Expanded carrier screening for recessive genetic disorders: a review

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The American College of Obstetricians and Gynecologists recommends carrier screening for couples planning for pregnancy or in early pregnancy. Expanded carrier screening is cost-effective to identify the carrier status of multiple debilitating recessive disorders. Knowledge of the reproductive risk enables carrier couples to decide the best reproductive options for their family. Nonetheless, proper pre-test and post-test genetic counselling is necessary to explain the limitation of testing methodologies and potential phenotypic variabilities.

Keywords: Genetic carrier screening; Genetic counseling; Genetic diseases, X-linked

Introduction

Recessive genetic disorders include autosomal and X-linked recessive disorders. If a couple are both carriers of pathogenic variants in the same gene responsible for an autosomal recessive disorder, their offspring has 25% risk of inheriting both defective gene copies and becomes affected by the disorder. The risk is independent of the fetal sex. If a woman is a carrier of an X-linked recessive disorder, her male offspring has 50% risk of inheriting the defective chromosome and becomes affected by the disorder, and her female offspring has 50% risk of being a carrier of the disorder.

Carriers of autosomal recessive disorders are usually asymptomatic and do not have family history of an affected individual. Without prior genetic screening, couples are found to be carriers only after an affected child is born and diagnosed with a severe autosomal recessive disorder. The risk of inheritance depends on the probability of a couple having the same defective gene. Those with autosomal recessive disorder are commonly identified as the first affected person in the family. Family history is less informative owing to the decreasing family size; a negative family history is not reassuring for not being a carrier of recessive disorders.

To identify couples at risk of having children with severe recessive disorders, carrier screening should be offered before pregnancy or at early stage of pregnancy. Couples who are both carriers of autosomal recessive disorders or women who are carriers of X-linked recessive disorders should receive genetic counselling for their reproductive options. Pre-pregnant couples at risk of having children

with severe recessive disorders can be offered in-vitro fertilisation and pre-implantation genetic diagnosis. Pregnant women can be offered prenatal diagnostic testing using chorionic villi sample or amniotic fluid sample to guide pregnancy management and improve early neonatal care.

Recommendations by professional bodies

American College of Obstetricians and Gynecologists (ACOG) recommends carrier screening for women considering pregnancy or already pregnant regardless of screening strategy or ethnicity¹. ACOG and the American College of Medical Genetics and Genomics (ACMG) used to recommend carrier screening based on racial or ethnic background for a limited number of diseases such as cystic fibrosis and haemoglobinopathies for Asian^{2,3}. Since 2008, ACMG has recommended carrier screening for spinal muscular atrophy for all ethnic groups as the disease is present in all populations⁴. Since 2017, ACOG has recommended carrier screening for spinal muscular atrophy for all couples⁵. However, ethnicity-based screening is limited by the difficulty in assigning ethnic groups, changes in social structures, inter-ethnic marriage, and unknown ancestry. Individual genetic disorders are rare and thus ethnicity-based screening is not cost-effective, as only a small number of genetic disorders are screened for different ethnic groups.

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Instead of single gene testing for individual genetic disorders, next generation sequencing enables expanded carrier screening for hundreds of genetic disorders using a single sample and results in a quick turnaround time and markedly reduction in cost. In a retrospective review of expanded carrier screening for 108 disorders in a multiethnic population, at least one mutation was found in 24% of subjects, and 127 couples were identified to be carrier couples⁶. Expanded carrier screening identified 77% and 66% of carriers who would have been missed based on the ethnic-based approach by the ACOG guidelines and the ACMG recommendations, respectively.⁶ Since 2017, ACOG has recommended expanded carrier screening for pre-pregnancy and prenatal carrier screening¹.

ACOG recommends genetic counselling for consanguineous couples on the increased risk of recessive disorders being expressed in their offspring and the limitations and benefits of ethnicity-based screening¹. In Hong Kong, the overall prevalence of parental consanguinity was 0.6%, of which most were ethnic Pakistani⁷. Offspring of consanguineous parents has significantly higher risk of recessive disorders (odds ratio [OR]=8.7), structural abnormalities (OR=4.55), and developmental delay (OR=6.72)⁷. It is important to identify consanguineous couples for preconception or prenatal genetic counselling on the increased risk of recessive disorders. Thorough review of family history of consanguineous couples is required to identify any suspicious recessive disorder for specific diagnosis and carrier screening. Expanded carrier screening should be offered to consanguineous couples who are considering pregnancy even without a positive family history. However, expanded carrier screening cannot include all recessive disorders and is not 100% sensitive. Detailed pre-test and post-test counselling for the limitation of expanded carrier screening is necessary.

When should expanded carrier screening be offered?

ACOG recommends carrier screening before pregnancy to allow adequate time for detailed counselling for reproductive options such as preimplantation genetic testing or prenatal diagnostic testing⁵. One option is to screen women first followed by men if women are found to be a carrier. This sequential testing minimises the test cost. In addition, ACOG recommends provision of information about carrier screening to every pregnant woman⁵. If the couple are both carriers of a severe autosomal recessive disorders, prenatal diagnostic testing should be arranged

if time allowed. Owing to the time constraint, concurrent carrier screening of the couple can shorten the turnaround time despite an increased test cost. The limited time for prenatal diagnostic testing and decision making may increase the anxiety of the couple and the risk of termination of pregnancy in second trimester.

The acceptance of carrier screening is higher for couple who received genetic counselling before pregnancy. The uptake of carrier screening was 68.7% and 35.1% for couple who were counselled preconceptionally and during pregnancy, respectively⁸. Factors such as indication for genetic counselling, maternal and paternal family history of genetic diseases, maternal and paternal age, ethnicity, multigestational pregnancies, and previous miscarriages were not significantly associated with the acceptance rate of expanded carrier screening⁸. Although the underlying cause of the difference in uptake was not identified, it was postulated that limited pregnancy options after prenatal diagnostic testing affected the willingness of couple to undergo expanded carrier screening⁸.

Expanded carrier screening

ACOG recommends screening for disorders having a carrier frequency of 1 in ≥ 100 , a well-defined phenotype, and a detrimental effect on quality of life; requiring surgical or medical intervention; or having an early onset in life⁵. ACOG does not recommend screening of disorders with an adult onset⁵. ACMG recommends screening for disorders that most at-risk couples would consider having a prenatal diagnosis to facilitate decision-making⁹. ACMG recommends clinicians to provide options to patients to include disorders with mild phenotype, variable expressivity, or incomplete penetrance. ACMG recommends provision of consent for screening for adult-onset disorders.

Commercial carrier screening panels include a variety of disorders. Some panels only include disorders that are recommended by the ACOG and ACMG with elevated carrier frequency across ethnicities and well-defined severe phenotypes that impact quality of life. Other panels include expanded number of disorders that may not fulfill the ACOG and ACMG recommendations and have variable phenotype, reduced penetrance, or adult onset. Pre-test and post-test counselling for disorders with variable phenotype, reduced penetrance, or adult onset is complicated and time consuming. Clinician may review the disorder lists by different providers and decide the most appropriate panel for their patients.

Pre-test counselling

Disease panel

According to the joint statement by ACMG, ACOG, National Society of Genetic Counselors, Perinatal Quality Foundation, and the Society of Maternal Fetal Medicine, it is not practical or necessary to fully explain the clinical and test characteristics of all disorders in the panel individually³. The committee recommends clinicians to broadly describe the types of disorders being screened for, the common features, and the limitation of the screening in the pretest education and consenting³. For example, couple should be simply advised that the panel includes screening for disorders with shortened life expectancy such as spinal muscular atrophy, cystic fibrosis, Krabbe disease; disorders that carry risk for intellectual disability such as Fragile X syndrome, Smith-Lemli-Opiz syndrome; disorders that carry risk for significant morbidity (blindness or deafness) such as Bardet-Biedl syndrome, Pendred syndrome; and disorders that may improve with early intervention of the fetus or infant such as congenital adrenal hyperplasia and galactosemia.

Benefits of testing

Expanded carrier screening enables identification of the carrier status and understanding of the risk of inheriting recessive disorder to the offspring so as to provide pregnancy options including pre-implantation genetic testing or prenatal diagnostic testing for carrier couples. As effective treatment is not available in many of disorders, knowing the reproductive risks enables couple to make decision.

In Hong Kong, universal antenatal screening for thalassaemia carrier relies on the detection of low mean corpuscular volume, which is included in the routine antenatal blood testing¹⁰. For women with low mean corpuscular volume, haemoglobin pattern is investigated for beta thalassaemia (increased in A2 level) or alpha thalassaemia carriers (presence of H inclusion bodies). Further genotyping is required if prenatal diagnostic testing is needed or for cases with uncertain results. In expanded carrier screening, sequencing is performed for *HBB* gene and *HBA* gene responsible for beta thalassaemia and alpha thalassaemia, respectively. Expanded carrier screening enables direct genotyping of thalassaemia carriers to shorten the time and minimise resources required for the diagnosis.

For some genetic disorders, knowledge of at-risk couple enables earlier diagnosis and intervention

for the affected child and might improve outcome. For example, prenatal treatment with dexamethasone for fetus of congenital adrenal hyperplasia carrier couple can be provided to reduce virilisation of female fetus in utero owing to the increased exposure to androgens. Early dexamethasone initiation before 7-week gestation with maintenance dose during the whole gestation resulted in normal feminine genitalia in 80% to 85% of girls with congenital adrenal hyperplasia¹¹. Non-invasive prenatal testing for fetal sex enables early fetal sex determination to guide cessation of dexamethasone treatment for male fetus. In addition, affected infants can benefit from early initiation of glucocorticoid and mineralocorticoid treatment before a potentially life-threatening salt-wasting crisis.

Identification of carrier status in one family member may trigger carrier screening of other members planning for pregnancy. This improves understanding of reproductive risks in the family and promotes autonomy in reproductive choices.

Limitation of testing

To avoid difficult interpretation and counselling of uncertain results, most laboratories only report well-established pathogenic variants. Although this approach is well accepted by clinicians, it may miss potentially clinically significant variants that is unknown to be pathogenic at present owing to limited genetic knowledge¹². A negative screening report is issued for individuals with variants that may be reclassified as pathogenic in future. Thus, clinician must explain to patients in details that expanded carrier screening only reports well-established variants and that interpretation of pathogenicity of the variants is based on the best available evidence at the time of testing. A negative screening report could not totally exclude their carrier status. There is still residual risk of their offspring being affected with disorders included in the panel because the couple may be carriers of a pathogenic variant that is classified as of uncertain clinical significance at the time of testing, or because of new mutation.

Spinal muscular atrophy is a common genetic disease across all ethnic groups; detection of carriers relies on targeted copy number analysis to determine the copy number of exon 7 of the *SMN1* gene. Individuals are classified as carrier if only one copy of *SMN1* is detected. However, about 4% of carriers lack *SMN1* in one of the chromosomes but have two gene copies in the other¹³. These '2/0 carriers' cannot be detected by the copy number analysis¹⁴. In addition, copy number analysis cannot

exclude carriers secondary to single point mutation in the *SMN1* genes. Thus, the detection rate of carriers for spinal muscular atrophy is 93% only. Clinicians should counsel the couple about the chance of residual risk of being a carrier owing to the limitation of the methodology. For couple with a family history of spinal muscular atrophy, genotyping of the proband is important to guide familial carrier screening. If the proband is found to have mutation in the *SMN1* gene instead of deletion, targeted mutation testing should be arranged for the family members instead of the expanded carrier screening panel.

The phenotype of some genetic disorders varies depending on the genotype. Some disorders are associated with incomplete penetrance and intra-familial variability so that not all individuals with the same variant of the gene manifest, and for those who manifest may have various severity of symptoms. Thus, clinicians should explain that a positive screening result may not precisely predict the phenotype of an affected individuals.

Post-test counselling

Negative result

Couple should be counselled about the possibility of residual risk of being carrier of the disorders screened. Also, the screening can only lower the risk of the couple being a carrier of the disorders included in the panel. Owing to the limitation of testing, newborn screening for inborn error of metabolism is still recommended after a negative carrier screening.

Positive result (carrier)

Genetic counselling should be offered to carriers of recessive disorders. Depending on the manifestation, partner testing may be offered for autosomal recessive disorders to screen for partner carrier status.

GJB2-related non-syndromic hearing loss has

variable phenotypes and poses challenges in counselling regarding prognosis and pregnancy options. Variants in *GJB2* gene is a common cause of hereditary non-syndromic hearing loss. However, the phenotype of variants in the *GJB2* gene is highly variable. For example, *GJB2* c.109G>A is a common variant for the Chinese population. The total heterozygous and homozygous carrier frequencies of *GJB2* c.109G>A were 10.29% and 0.22%, respectively¹⁵. Therefore, this variant is commonly identified in expanded carrier screening. However, c.109G>A variant is associated with milder degree of hearing loss compared with c.35delG and c.235delC variants¹⁶⁻²¹. Thus, for carrier couple of variants in *GJB2* gene, genetic counselling about the possible phenotype should be provided before consideration of pregnancy options such as prenatal diagnostic testing or preimplantation genetic diagnosis.

Female carriers of X-linked recessive disorders or couple carriers of the same gene should be counselled about the inheritance risk and the option of prenatal diagnosis or preimplantation genetic testing.

Positive result (adult-onset disorders or disorders with variable phenotype)

Those found to be affected with adult-onset disorders or disorders with variable phenotype should be referred to clinical geneticists and physicians for thorough assessment and counselling.

Conclusion

Expanded carrier screening is cost-effective to identify carriers of severe debilitating recessive disorders. Clinicians should provide detailed pre-test and post-test counselling regarding the limitation of testing methodology, the possibility of residual reproductive risk, and the phenotypic variability.

Declaration

The authors have no conflicts of interest to disclose.

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