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Expanded Carrier Screening Using Next-Generation Sequencing

As the number of known mutations associated with autosomal recessive genetic conditions rises, there is a greater need for expanded carrier screening.

Introduction

Taken as a group, inherited conditions account for ~20% of infant mortalities and ~18% of pediatric hospitalizations.[1] Inherited autosomal recessive conditions (Table 1), including cystic fibrosis (CF), sickle cell anemia, and Tay-Sachs disease, can be severe, or even life-threatening. In fact, a recent study of an ethnically diverse population screened 23,453 individuals for 108 inherited genetic conditions and found that ~24% of the individuals were carriers of at least 1 of the tested genetic conditions.[2] With current carrier screening focused on inherited conditions in specific ethnic groups, there is great potential to miss inherited genetic conditions in a more ethnically diverse population. Expanded carrier screening can help address this gap and provide an opportunity to identify more couples at risk for passing on an autosomal recessive condition. The question is how to perform expanded carrier screening in a timely, cost-efficient, accessible manner. Advances in next-generation sequencing (NGS), including push-button systems and ready-to-use kits, could make this technology an ideal platform for carrier screening.

Identify Individuals At Risk

Autosomal recessive conditions occur when an individual inherits 2 mutated alleles of the same gene, 1 from each parent. Individuals who have 1 copy of the recessive allele are known as carriers. Carriers themselves are typically asymptomatic and may not know that they carry the mutated gene, but can pass it to his or her children. If both individuals in a couple carry a mutation in the same gene, there is a 1 in 4 chance that their children will have the disorder (Figure 1).

Carrier screening can identify if a couple is at risk for passing a recessive genetic disorder to their children. Supported by genetic counseling, carrier screening programs have been successful in reducing the incidence of inherited diseases. The American College of Medical Genetics (ACMG) and American College of Obstetrics and Gynecology (ACOG) recommend that couples of reproductive age be offered carrier screening before conception.[3]

Knowing Enables Informed Decisions

Knowledge of carrier status allows at-risk couples to make informed reproductive choices. If both individuals test positive as carriers of the same recessive condition, they can review options such as *in vitro* fertilization (IVF) and preimplantation genetic diagnosis (PGD) to improve the chances of having an unaffected child. The couple can be prepared and obtain early intervention for children with certain disorders to improve outcomes. Individuals identified as carriers can also inform family members of their potential risk.

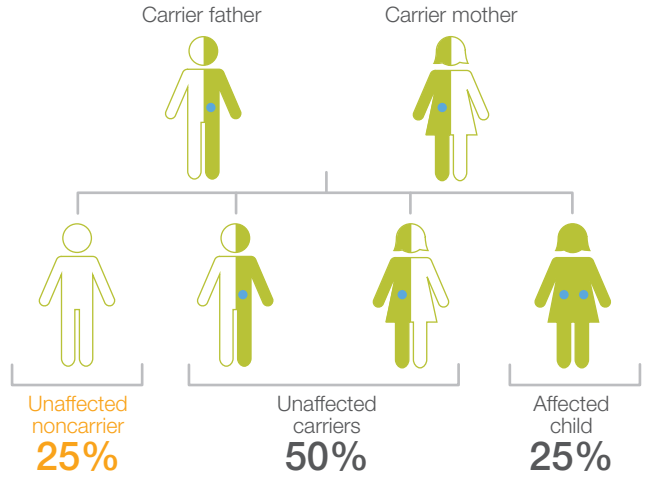

Figure 1: Inheritance Pattern of an Autosomal Recessive Condition— If 2 parents carry a mutation in the same gene, there is a 25% chance that the child will be affected, 50% chance that the child will be an unaffected carrier, and 25% chance that the child will not be affected or a carrier.

Table 1: Examples of Autosomal Recessive Genetic Disorders	
Cystic fibrosis	Spinal muscular atrophy
Tay-Sachs disease	Phenylketonuria (PKU)
Sickle cell anemia	Niemann-Pick disease
Beta thalassemia	Mucolipidosis IV
Hemoglobin C	Bloom syndrome
Canavan disease	Gaucher disease
Familial dysautonomia	Familial Mediterranean fever
Fanconi anemia (Type C)	Alpha thalassemia

NGS for Carrier Screening

For expanded carrier screening to be successful, it is necessary to evaluate multiple disease-associated genes across a substantial portion of the genome. Unlike traditional screening methods, NGS offers the depth and scalability to perform this intensive search in a timely, economical, and less labor-intensive manner.

Learn More

To learn more about expanded carrier screening using NGS, contact your local Illumina sales representative.

References

1. Kingsmore S. Comprehensive carrier screening and molecular diagnostic testing for recessive childhood diseases. *PLoS Currents*. 2012:e4f9877ab9878ffa9879.
2. Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med.* 2013; 15(3):178-86. doi: 10.1038/gim.2012.114.
3. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine—Points to consider. A joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol*. 2015; 125(3):653-662. doi: 10.1097/AOG.0000000000000666.

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