WOMEN'S HEALTH

genpath

an OPKO Health Company

Increased Carrier Detection with Expanded Carrier Screening in Multiple Ancestries

Catherine Griswold, MGC[2]; Xinxin (Shirley) Yao, MS[2]*; Lisa Susswein, MS, MHA[1]; Adebanke F. Fagbemi, PhD[1]; Guido D. Pollevick, PhD[1]; Rachel T. Klein, MS[2]

[1] GENPATH/BIOREFERENCE LABORATORIES, INC., ELMWOOD PARK, NJ
[2] MYGENETEAM, MIAMI, FL

Introduction:

While the American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics and Genomics (ACMG) recommend general population reproductive carrier screening for cystic fibrosis (CF) and spinal muscular atrophy (SMA)[1,2], there are no guidelines to date routinely recommending expanded carrier screening for all reproductive patients. We sought to assess, by ancestry, the proportion of additional individuals who would be identified as a carrier via an expanded panel compared to CF and SMA screening alone.

Methods:

We queried a population of patients who had a 180 disorder expanded targeted carrier screening panel, which used next generation sequencing technology, at GenPath over a period of 18 months. Patient ethnicity was obtained from the test requisition. The five most commonly reported ethnicities were Hispanic, Caucasian, African American, Ashkenazi Jewish, and Asian. We excluded Ashkenazi Jewish patients from the analysis due to the known high carrier frequencies found in this population, reducing the dataset to four ethnicities. Cases were also excluded if ethnicity was not provided, reported to be only of non-Hispanic descent or if more than one ethnicity was reported.

To calculate expected carrier detection rates, we used an imputed detection rate for CF and SMA and then an actual rate of observation for other diseases. For CF and SMA, we deduced expected observation rates based on published literature on carrier frequency (Table 1) combined with our laboratory's detection rate for individuals of Hispanic, Caucasian, African American, and Asian descent. We then queried our laboratory's observed carrier frequencies in these four ethnicities for a 180 disorder expanded targeted carrier screen for diseases other than CF and SMA.

Table 1 Reported CF and SMA Carrier Frequencies

	Hispanic	Caucasian	African American	Asian
Reported CF Carrier Frequency	1/58	1/25	1/61	1/94
Reported SMA Carrier Frequency	1/117	1/35	1/66	1/53

Results:

Expanded carrier screening was performed on 2,468 self-reported Hispanic, 921 Caucasian, 339 African American, and 174 Asian individuals. The disorders with the highest observed carrier frequencies for each ethnicity are listed in Tables 2-5. The top three disorders among Hispanic individuals (excluding CF and SMA) were: beta hemoglobinopathies (1/36), deafness autosomal recessive 1A (1/40), and Stargardt disease type 1 (1/85). The top three disorders among Caucasian individuals (excluding CF and SMA) were: deafness autosomal recessive 1A (1/26), Stargardt disease type 1 (1/29), and Pompe disease (1/71). The top three disorders among African American individuals (excluding CF and SMA) were: beta hemoglobinopathies (1/8), galactosemia (1/113), and Pompe disease (1/113). The top three disorders among Asian individuals (excluding CF and SMA) were: deafness autosomal recessive 1A (1/10), beta hemoglobinopathies (1/29), and Stargardt disease type 1 (1/87). Combining expected carrier frequencies for CF and SMA and observed frequencies for all other diseases on the expanded panel, 1 in 2 Caucasians and 1 in 5 individuals of other backgrounds would be expected to be positive. If strictly following current guidelines by screening for CF and SMA alone, an expanded carrier screen increased the probability of identifying carriers by 10-, 7-, 9-, and 9-fold, respectively, for Hispanic, Caucasian, African American, and Asian individuals (Table 6).

Table 2 Diseases and Carrier Frequencies Identified in Hispanic Individuals

Disease *(Gene)*	Observed Carrier Frequency (n=2468)
Beta Hemoglobinopathies *(HBB)*	1/36
Deafness, autosomal recessive 1A *(GJB2)*	1/40
Stargardt disease, type 1 *(ABCA4)*	1/85
Smith-Lemli-Opitz Syndrome *(DHCR7)*	1/130
Pompe Disease *(GAA)*	1/165
Congenital Disorder of Glycosylation, Type Ia *(PMM2)*	1/176
Galactosemia *(GALT)*	1/190
Gaucher Disease *(GBA)*	1/206
Homocystinuria (CBS Deficiency) *(CBS)*	1/224
Sulfate Transporter-Related Osteochondrodysplasia *(SLC26A2)*	1/274
Phenylketonuria (PKU) *(PAH)*	1/274
Methylmalonic Aciduria and Homocystinuria, Cobalamin C (cblC) type *(MMACHC)*	1/274
Carnitine Palmitoyltransferase Deficiency, Type 2 *(CPT2)*	1/309
Glycogen Storage Disease, Type V (GSDV) *(PYGM)*	1/309
Polycystic Kidney Disease, Autosomal Recessive (ARPKD) *(PKHD1)*	1/309
Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency *(ACADVL)*	1/353

Table 3 Diseases and Carrier Frequencies Identified in Caucasian Individuals

Disease *(Gene)*	Observed Carrier Frequency (n=921)
Deafness, autosomal recessive 1A *(GJB2)*	1/26
Stargardt disease, type 1 *(ABCA4)*	1/29
Pompe Disease *(GAA)*	1/71
Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency *(ACADM)*	1/77
Smith-Lemli-Opitz Syndrome *(DHCR7)*	1/84
Familial Mediterranean Fever *(MEFV)*	1/92
Congenital Disorder of Glycosylation, Type Ia *(PMM2)*	1/102
Phenylketonuria (PKU) *(PAH)*	1/102
Congenital Myasthenic Syndrome, RAPSN-associated *(RAPSN)*	1/115
Dihydropyrimidine Dehydrogenase Deficiency *(DPYD)*	1/115
Glycogen Storage Disease, Type V (GSDV) *(PYGM)*	1/115
Gaucher Disease *(GBA)*	1/115
Beta Hemoglobinopathies *(HBB)*	1/115
Homocystinuria (CBS Deficiency) *(CBS)*	1/115
Achromatopsia, CNGB3-associated *(CNGB3)*	1/132
Sulfate Transporter-Related Osteochondrodysplasia *(SLC26A2)*	1/132
Galactosemia *(GALT)*	1/154
Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency *(ACADVL)*	1/184
Usher Syndrome, Type 2A *(USH2A)*	1/184
Carnitine Palmitoyltransferase Deficiency, Type 2 *(CPT2)*	1/184
Factor XI Deficiency (Hemophilia C) *(F11)*	1/184
Tay-Sachs Disease *(HEXA)*	1/184
Primary Hyperoxaluria, Type 1 *(AGXT)*	1/230
Mucopolysaccharidosis type I (MPS I) *(IDUA)*	1/230
Spastic tetraplegia, thin corpus callosum, and progressive microcephaly *(SLC1A4)*	1/230
Carpenter Syndrome *(RAB23)*	1/307
Glycogen Storage Disease, Type Ia (GSDIa) *(G6PC)*	1/307
Bardet-Biedl Syndrome 1 *(BBS1)*	1/307
Long-Chain 3-Hydroxyacyl-Coenzyme A Dehydrogenase (LCHAD) Deficiency *(HADHA)*	1/307
Nijmegen Breakage Syndrome *(NBN)*	1/307
Pseudoxanthoma Elasticum *(ABCC6)*	1/307
Limb-Girdle Muscular Dystrophy, Type 2A *(CAPN3)*	1/307

Table 4 Diseases and Carrier Frequencies Identified in African American Individuals

Disease *(Gene)*	Observed Carrier Frequency (n=339)
Beta Hemoglobinopathies *(HBB)*	1/8
Galactosemia *(GALT)*	1/113
Pompe Disease *(GAA)*	1/113
Deafness, autosomal recessive 1A *(GJB2)*	1/170
Rhizomelic Chondrodysplasia Punctata, Type 1 *(PEX7)*	1/339
Junctional Epidermolysis Bullosa, Herlitz type, LAMB3-associated *(LAMB3)*	1/339
Odonto-onycho-dermal dysplasia/Schopf-Schulz-Passarge Syndrome *(WNT10A)*	1/339
Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency *(ADA)*	1/339
Meckel-Gruber Syndrome, Type 1 *(MKS1)*	1/339
Stargardt disease, type 1 *(ABCA4)*	1/339
Congenital Disorder of Glycosylation, Type Ia *(PMM2)*	1/339
Tyrosinemia, Type I *(FAH)*	1/339
Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency *(ACADM)*	1/339
Mucopolysaccharidosis type I (MPS I) *(IDUA)*	1/339

Table 5 Diseases and Carrier Frequencies Identified in Asian Individuals

Disease *(Gene)*	Observed Carrier Frequency (n=174)
Deafness, autosomal recessive 1A *(GJB2)*	1/8
Beta Hemoglobinopathies *(HBB)*	1/113
Stargardt disease, type 1 *(ABCA4)*	1/113
Familial Mediterranean Fever *(MEFV)*	1/174
Albinism, Oculocutaneous, Type I *(TYR)*	1/174
Methylmalonic Aciduria and Homocystinuria, Cobalamin C (cblC) type *(MMACHC)*	1/174
Progressive Pseudorheumatoid Dysplasia (PPD) *(WISP3)*	1/174
Pompe Disease *(GAA)*	1/174
Gaucher Disease *(GBA)*	1/174
Long-Chain 3-Hydroxyacyl-Coenzyme A Dehydrogenase (LCHAD) Deficiency *(HADHA)*	1/174

Table 6 Expanded Carrier Screening (ECS) Identifies a Greater Number of Carriers Compared to Current Guidelines

	Hispanic	Caucasian	African American	Asian
Number of Carriers Identified by Current Guidelines*	1/49	1/16	1/47	1/43
Total Number of Diseases Not Identified if Following Guidelines	16	84	13	10
Number of Carriers Identified by ECS	1/6	1/3	1/6	1/5
Number of Carriers Identified by ECS plus CF and SMA	1/5	1/2	1/5	1/5
Performance Improvement with ECS	10-fold	7-fold	9-fold	9-fold

*Based on current detection rates and carrier frequencies for CF and SMA

Conclusion:

Compared to testing for CF and SMA alone, an expanded carrier screen increased the probability of detecting a carrier for a disorder by 7- to 10-fold. Our data demonstrate that expanded carrier screening will identify a substantially greater number of carriers among various ancestries compared to testing according to current guidelines alone.

References:

1. ACOG Committee on Genetics. 2017. Committee Opinion #691: Carrier Screening for Genetic Conditions. Obstetrics and Gynecology 129(3).
2. Edwards, J., et al. 2015. Expanded Carrier Screening in Reproductive Medicine- Points to Consider. Obstetrics and Gyencology 125(3): 653

481 Edward H Ross Drive | Elmwood Park, NJ 07407 | 800 633 4522 tel | 201 345 7152 fax | www.genpath.com