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Expanded Genetic Screening Panel for the Ashkenazi Jewish Population

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Abstract

Purpose—Carrier screening programs that identify the presence of known mutations have been effective for reducing the incidence of autosomal recessive conditions in the Ashkenazi Jewish population and other populations. Yet, these programs have not realized their full potential. Furthermore, many known autosomal recessive and dominant conditions are not screened for and the molecular basis of other conditions for which screening might be offered is unknown.

Methods—Through literature review and annotation of full sequenced genomes from healthy individuals, we expanded the list of mutations. Mutations were identified in a sample of 128 fully sequenced Ashkenazi Jewish genomes that were filtered through clinical databases and curated manually for clinical validity and utility using the American College of Medical Genetics scoring (ACMG) system. Other known mutations were identified through literature review.

Results—A panel of 203 mutations was identified for 92 autosomal recessive, 24 autosomal dominant, and 4 X-linked disorders.

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Conclusion—Screening for a broader range of disorders could not only further reduce the incidence of autosomal recessive disorders, but could also offer the benefits of early or presymptomatic diagnosis.

Keywords

Ashkenazi Jews; genetic testing; carrier screening; whole genome sequencing; variant annotation

Introduction

Population-based genetic screening is a valuable application of genomic technology that can have significant clinical and public health benefits. Presymptomatic detection of disease and identification of increased disease risk provide the opportunity for early diagnosis, intervention or prevention. The identification of genetic carrier status provides the opportunity for reproductive counseling and family planning, allowing for the prevention of the birth of an affected child or for early diagnosis and intervention.[1] Many population-based screening programs target specific populations, such as newborns, particular ethnic groups, or those deemed to be at increased risk for certain diseases. With the advancement of genetic technologies, such as multiplex testing to conduct high-throughput genotyping of a multitude of variants, there has been an expansion in the number of diseases that can be screened for in the predisposition, presymptomatic, and carrier states. Selecting conditions to include on a population-based screening panel and even selecting the criteria to make this decision remain active questions.

Founder effects, in combination with endogamy and possible selection, have made some Mendelian conditions more prevalent in the Ashkenazi Jewish (AJ) population. Ethnicity-based carrier screening programs in this and other populations have been successful in decreasing the incidence of autosomal recessive conditions.[1] The best-known example is Tay-Sachs disease, a severe, progressive neurodegenerative disorder caused by a defect in hexosaminidase A enzyme activity. Beginning in 1970, Tay-Sachs carrier screening in AJ individuals was the first population-based public health initiative aimed at decreasing the incidence of a lethal genetic disease. This coordinated effort which included education, genetic counseling, and voluntary screening, was adopted throughout the United States as well as internationally. Within 30 years of its inception, the program was successful in decreasing the incidence of Tay-Sachs disease by over 90% in the AJ populations of the United States and Canada.[1] In addition to Tay-Sachs disease, there are many other recessive disorders that occur more commonly in the AJ population and many labs now offer genetic carrier panels aimed at those of AJ ethnicity. The American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) have set forth recommendations for conditions that should be included on an AJ panel.[2] Despite these recommendations, there are differences between what is recommended and what is offered by labs, as well as differences among the various labs. In a multi-ethnic study of screening 23,000 individuals for 400+ Mendelian variants among, including variants found among Ashkenazi Jews, this ethnic group was the most likely to have carriers of serious recessive disorders. Many of these disorders were not included on the ACMG or ACOG lists of recommendations.[2] In addition, the AJ community has generally been supportive of carrier

screening for severe disorders, and expansion beyond what is currently recommended. Therefore, expanding current AJ screening panels to include more conditions appears justified.

In addition to carrier screening panels, there are a growing number of predisposition genetic screening panels that identify those at increased risk of future disease. Currently, the targeted population tends to be those already deemed to be at increased risk due to their family history of disease. Cancer risk assessment represents an application of predisposition screening that provides the opportunity for prevention and early diagnosis to decrease risk.[3] One such example is *BRCA1/2* screening which serves as a paradigm for high-risk, population-based screening. With an increasing number of disease risk variants being discovered, genetic risk assessment for adult-onset conditions will continue to grow.[4] Some who might benefit from genetic risk assessment may escape attention due to incomplete penetrance, sex-limited expression, and lack of or limited personal and/or family history.[5] Extending predisposition screening beyond those who meet standard high-risk criteria should have clinical utility, especially when offered in multiplex format.

As the number of disease variants grows and technological advances improve ease and efficiency of detection, criteria are needed against which to judge the merits of adding new genetic tests. In 1968, Wilson and Jungner delineated the principles of population-based screening which require that the condition in question be an important public health problem, an effective treatment be available that might be applied in the latent phase of disease, a suitable test be available that is acceptable to the population, and cost-benefit be favorable.[6] Originally intended to be applied to newborn screening, these same criteria have been adapted to the assessment of population screening for risk of adult-onset conditions.[4] In the case of carrier screening, the targeted diseases have generally been severe with limited or no intervention available, with the intended goal of decreasing the incidence of such diseases. However, recent expansion of such screening has included diseases that are less severe and for which treatment or prevention is available.[7]

Studies aimed at assessing risk alleles in populations must also deal with interpreting variants with limited support for pathogenicity. The curation of genetic variants has recently received attention from medical societies including the American College of Medical Genetics (ACMG).[8] Factors considered by the ACMG and other groups include type of variant, support in the literature, number of cases and controls with the variant and odds ratio, similarity to known pathogenic variants, results of prediction algorithms, and functional studies. A recent study that performed whole-exome sequencing on 6,517 European and African Americans suggested that 45% of individuals carry at least one mutation in genes included on newborn screens.[9]

We recently sequenced 128 Ashkenazi Jewish individuals (The Ashkenazi Genome Consortium dataset, or “TAGC dataset”) and established a list of previously known and new mutations.[10] Here we address the pathogenicity of the newly identified mutations and the clinical utility of screening for them.

Methods

DNA samples were collected from 128 individuals who were disease-free and were verified by Principal Component Analysis to have Ashkenazi Jewish origin, as we recently described.[10] DNA sequencing was carried out by Complete Genomics (CG) and annotated using the reference genome version hg19. [10]

ClinVar and OMIM, publicly available genetic databases that catalog genotypes and phenotypes, were scanned via a custom web crawler to identify variants associated with phenotypes.[11] Of the 2,434 variants that were identified from sequencing 128 AJ individuals, 80 variants were reported by ClinVar or OMIM as “pathogenic” or “possibly pathogenic.” These variants were curated manually by at least two independent reviewers through literature review and assigned a score based on the American College of Medical Genetics scoring (ACMG) system. An additional 56 variants were scored as “pathogenic, very strong” using the ACMG system. Factors considered were number of patients, number of controls, association with other mutations, and functional studies (Table 1S). [8] Those determined to be pathogenic or likely pathogenic were then further reviewed for individual clinical utility and frequency of the variant.

Calculations of expected prevalence were performed for each variant based on Hardy-Weinberg equilibrium using allele frequencies for our data and carrier frequencies for variants found in the literature (Table 2S). If available, literature frequencies were used as they should be based on a larger number of samples, but for new variants the frequencies from our study was used. However, if the rare mutations had other more common mutations for the same disease, or if they were well-established in the literature in the Ashkenazi population, they were not removed from the panel. Note that this method of estimation does not include consideration of prevalent Jewish/non-Jewish marriages, which would not impact allele frequencies in the current adult population, but would lessen impact to offspring of one non-Jewish parent.

We assessed the clinical utility of screening for each of the diseases. Factors including opportunity to provide reproductive counseling, diagnosis, early detection of disease, and the impact of early intervention on outcomes were all considered in our analysis for inclusion on the panel. Factors pertaining to personal utility, such as increasing knowledge and control, were also considered. Diseases considered to be benign biochemical traits or lacking clinical utility were removed from the panel. Mutations based on PubMed curation that we reported in a previous reviews,[12,13] and on lists from other laboratories that offer Ashkenazi Jewish carrier screening were assessed for clinical validity and clinical utility, then added if they met the same criteria as the variants identified from the sequenced genomes. The different Ashkenazi screening panels currently available are compared in Table 4S, along with the ACMG and ACOG recommendations.

The impact of the additional mutations in the expanded panel was calculated by comparison to the other panels (Table 3S). For new mutations being added, the number of impacted individuals was calculated based on the Hardy-Weinberg equations. To guarantee that our estimate is conservative, we did not consider mutations with frequency above 2% for

dominant mutations and 10% for recessive ones, unless well-established conditions, such as congenital adrenal hyperplasia and familial Mediterranean fever. For genes harboring multiple mutations, we assumed that their effects are independent, and that the effects of different genes are independent.

Results

The final panel included conditions that confer early age of onset risks to offspring and afford the opportunity for reproductive genetic counseling, as well as conditions tested for in the presymptomatic period that inform personal risk of future disease (Table and Table 2S). The 25 conditions that appear on at least one Ashkenazi Jewish panel currently being offered (Table 3S) are all included on this panel. An additional 60 conditions were included based on the criteria of a predicted frequency of at least 1 in 60,000 and clinical utility for the patient, resulting in a total of 203 mutations for 120 conditions. The panel included 92 autosomal recessive, 24 autosomal dominant, and 4 X-linked disorders (Table 3S). Fifteen variants for dominant and X-linked disorders only appeared once in our study samples, and thus require further data on allele frequency before final acceptance for implementation in a screening panel.

Categories of disorders

Many conditions that fall into the category of presymptomatic screening confer future risk of cancer, such as *BRCA1/2* and mismatch repair gene testing, but this group also includes diseases such as obesity and enchanced S cone dystrophy. Diseases that inform primarily risk to offspring are mostly autosomal recessive and range from very severe conditions, such as glycine encephalopathy and Leigh syndrome, to milder conditions, such as hyperoxaluria and icthyosis. Genetic testing may be diagnostic for affected children. Some of the dominant conditions, such as Brugada syndrome, adult-onset diabetes, and hypophosphatemic nephrolithiasis/osteoporosis 2, have variable expressivity, and a screening test would be diagnostic and may offer the opportunity for early diagnosis and intervention in affected offspring. There are also some X-linked conditions for which clinical utility may be offered in a variety of ways. Female carriers of *COL4A5* gene mutations which cause Alport syndrome, can gain information about risks to offspring as well as personal risk of future symptoms, if they are currently asymptomatic.[1] Cornelia de Lange syndrome, an X-linked dominant disorder, may have a mild presentation in parents who have been reported to have more severely affected children.[20]

Clinical utility

This panel was designed to include highly penetrant Mendelian disorders for which clinical utility may be derived from testing. Therefore, some conditions were removed from our clinical panel if they did not provide clinical utility. Cystathianuria and pentosuria are benign biochemical traits and therefore were not included. Cryptorchidism, a readily apparent and correctable trait, and familial candidiasis, typically quite mild for mutation carriers, were removed due to lack of clinical utility. Warfarin resistance was removed also due to the lack of demonstrable clinical utility. Indeed, the American College of Medical Genetics and Genomics (ACMG) has recommended against population-based screening for warfarin

resistance due the current paucity of data supporting suchscreening.[21] Due to uncertain penetrance, *APOE* was removed.

Some previously reported conditions and variants that were not detected in the TAGC dataset were added to our panel. The c.1716+1G>A variant in the *F11* gene causing Factor XI deficiency is considered to be an AJ mutation.[22] Two galactosemia variants in the GALT gene were added, Q188R and K285N, due to their high frequency in Eastern European populations.[23] The E372X variant in the *BCKDHB* gene, which causes Maple Syrup Urine disease, was also added due to its high frequency in the AJ population.[24] Tyrosinemia was added to our panel because the P261L mutation in the *FAH* gene is known to be prevalent in the Ashkenazi Jewish population.[25] Deletion of exon 7 in the *SMN1* gene conferring Spinal Muscular Atrophy was added due to its prevalence in all populations, and the recommendation from the ACMG to screen all couples regardless of race or ethnicity.[26] In addition, the common mutations for congenital adrenal hyperplasia were added; p.P30L, IVS2 13C>G (IVS 2), p.I172N, exon 6 mutation cluster (p.I236N, p.V237E, p.M239K), p.V281L, p.Q318X, p.R356W, and an 8 bp deletion in exon 3.[27]

Varying risk depending on allelic status

Some recessive conditions that confer different phenotypes in the monoallelic and biallelic states can be considered to offer information pertaining to both personal risk as well as risk to offspring. One example is the *GBA* gene in which a mutation carrier has a risk to have a child affected with Gaucher disease if two mutations are inherited, and also has a personal risk of developing Parkinson disease.[14] Another example is the *ATM* gene in which a mutation carrier has a future risk of cancer as well as the risk to have a child with ataxia telangiectasia, if two mutations are inherited.[15] This screening test may also be diagnostic for recessive conditions in adults that can have atypical presentations or later onset. Examples include cystic fibrosis,[16] Gaucher disease,[17] and *GJB2* associated hearing loss.[18] For the newly identified mutations, frequencies may be revised once larger numbers of subjects are tested. Indeed, some of the low-frequency mutations may be private to the individuals sequenced and may not be found among other members of the AJ population.

A conservative estimate suggests that screening of all mutations in our expanded panel is expected to detect medically-relevant dominant mutations in 28% of patients (about 14,000 a year, assuming 50,000 tests a year). Prenatal screening for recessive conditions using our expanded panel is expected to affect 3–4% of the couples (1,800 a year, assuming 50,000 prenatal tests a year).

Discussion

Through our variant analysis we have identified a number of disease variants that are prevalent in the Ashkenazi Jewish population. These variants provide additional genotyping targets that can be included in an expanded AJ screening panel. Traditionally, the goal of carrier screening has been to decrease the occurrence of severe, untreatable genetic disorders, as evidenced in the case of Tay-Sachs. However, with our increasing ability to identify prevalent disease variants in certain populations, we need to reframe our goals of population screening and genetic counseling.

In assessing the utility of a genetic screening test, clinical endpoints such as reduction in morbidity and mortality have traditionally been used. However, there is a move towards broadening this definition of clinical utility to include informational, psychological, and social benefits of undergoing a genetic test.[28] Also referred to as personal utility, learning one's genetic carrier status or future risk of disease can alleviate anxiety, afford the opportunity for future life planning, and satisfy a need for information, which are all valuable benefits of genetic testing irrespective of clinical use or health outcomes.[28] For example, in individuals who chose to undergo susceptibility testing for Alzheimer disease, a disease for which there is no proven cure or prevention, information-seeking was an important motivator for pursuing genetic testing, as were logistical and altruistic factors such as future planning, preparing family members, and contributing to research, emphasizing the importance of considering these other endpoints as measures of the utility of genetic testing.

Gaucher disease serves as a paradigm for conditions that fall outside of the traditional screening criteria but are now part of many AJ panels. Several professional organizations have recommended against AJ population screening for Gaucher disease due to poor genotype/phenotype correlations and lack of data on the efficacy of treatment for mild disease.[29] Screening for Type 1 Gaucher disease, caused by the p.N370S mutation, has been particularly controversial due to its variable expressivity and reduced penetrance. About 90% of those homozygous for this mutation are mildly affected or completely asymptomatic, yet even symptomatic individuals are diagnosed only at the time of the screening test.[7] Conditions that do not have a clear-cut genotype/phenotype correlation present challenges for genetic counseling and prenatal decision-making. In addition, for conditions with reduced penetrance, carrier screening may actually uncover an unexpected diagnosis.[7] An analysis of the Israeli screening program for type 1 Gaucher disease between 1994 and 2005 revealed that most couples did not terminate pregnancies predicted to have mild or asymptomatic disease. In addition, termination was significantly less likely if the couple received genetic counseling or consulted with a Gaucher disease specialist, emphasizing the importance of genetic counseling as an integral part of any screening program.

Non-syndromic deafness is another condition that demonstrates a limited number of AJ mutations, but for which the clinical utility of screening may be minimal. It has been demonstrated that two mutations in the *GJB2* gene yield a carrier frequency of 4.76% among AJ individuals.[30] Although this frequency is similar to that of Gaucher disease and Tay-Sachs, *GJB2* screening is not routinely offered. The identification of carrier risk for hearing would aid in the early diagnosis of an affected child, and could identify cases that might be missed by newborn screening – especially because the hearing loss may not be present at birth. Early diagnosis can also facilitate early intervention which has been shown to be beneficial for language acquisition and learning among deaf and hard of hearing children.[30] Familial Mediterranean Fever (FMF) is another condition that falls outside of traditional population screening criteria, but for which carrier screening is widely available.[31] Since the symptoms of FMF are generally not life-threatening, and over 90% of patients respond to colchicine treatment, FMF has generally not been recommended for population based carrier screening. However, like non-syndromic hearing loss, there are significant benefits from screening for early diagnosis and treatment which has been shown to be beneficial.[32] Non-

classical 21-hydroxylase deficiency, a mild form of congenital adrenal hyperplasia (CAH), is a condition with variable expressivity and an estimated prevalence of 1/100 in the general population, making it the most common autosomal recessive condition. In the Ashkenazi Jewish population, the frequency is estimated to be even higher (1/27).[33] Partial 21-hydroxylase deficiency can lead to precocious puberty, cystic acne, and advanced bone age. Affected males usually do not exhibit symptoms, but may have oligospermia and reduced fertility, whereas women more commonly suffer from menstrual and gonadal dysfunction that can lead to infertility. In both males and females, these symptoms may be reversed with hormonal treatment. Population genetic screening of this frequent yet largely undiagnosed condition, can identify affected individuals and offer the opportunity for treatment.[34]

One advantage to applying predisposition screening to a particular group is that ethnicity-based screening exhibits lower rates of variants of uncertain significance, favorably impacting clinical utility and cost-effectiveness. Expanded population-based *BRCA1/2* screening has been shown to be cost effective in the Ashkenazi Jewish population, because screening would lessen the risk of ovarian cancer.[5] As in the case of *BRCA1/2* screening, risk assessment for other cancer syndromes, such as Lynch syndrome and Cowden syndrome, provides the opportunity for early detection and intervention to reduce, prevent, or diagnose cancers early. Despite discussion about universal screening for Lynch syndrome among colon cancer patients, no such similar discussion of AJ population screening has taken place.[35] For other conditions for which there is no intervention available to decrease risk, such as Parkinson disease and various types of deafness, there may still be some utility in gaining the knowledge of one’s risk for future life planning as well as informing risks for family members.

Opinions conflict about the benefits of expanding carrier screening for the AJ population. Some worry that the number of diseases on the panel precludes the ability to provide adequate counseling to ensure truly informed consent. Others have concerns about increasing anxiety in individuals who are screened for a multitude of conditions, and that given the low frequency of many of these conditions, this harm outweighs the potential benefits.[36] Modifications to the standard informed consent process for single gene tests should be considered when screening for multiple conditions. As providing a detailed discussion about each disease on the panel is not feasible, new models of consent will be needed to explain risks and benefits effectively and to assess patient understanding. Healthcare professionals beyond genetic counselors and medical geneticists should be trained to convey this information in order to meet the growing demand.[37] In a study of pregnant women and their partners regarding informed consent for genetic carrier screening, one significant finding was confusion about the purpose of genetic screening. Individuals associated this screening with gaining information about their offspring and not about themselves.[38] Nonetheless, when explained that personal risks could also be identified, most individuals in another study indicated a preference for screening.[39] Since the diseases on this panel impart both reproductive and personal risks, with some mutations conferring both, it will be important to emphasize the different types of information that may be gleaned from genetic screening. Patients vary in their preferences of a generic consent model, in which general principles of screening are explained with the details of each disease discussed only if the patient tests positive, versus a comprehensive consent model, in which details about

each disease being screened for are given prior to testing. This variability calls for a more personalized approach to the consent process to meet the patient's needs. Of course, with an extensive screening panel, even applying the comprehensive model of consent will have its limitations due to the sheer amount of information that would need to be conveyed for all of the diseases. In addition to a more personalized approach to the consent process, it would be beneficial to allow individuals to choose what they would like to be tested for due to the broad range of diseases offered on our panel and the varying implications for both personal and reproductive risk,. Such an approach will enhance autonomy for the patient by respecting his/her right *not* to know.[40]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table

List of phenotypes by inheritance pattern

Autosomal Dominant (n=25)
Adrenocortical hyperplasia
Arrhythmogenic right ventricular dysplasia/cardiomyopathy
Bone marrow failure, telomere-related, 1
Breast/ovarian cancer predisposition
Brugada syndrome 1
Carcinoid tumors/Cowden disease 3
Cerebral cavernous malformations
Colon cancer predisposition
Corneal dystrophy, hereditary polymorphous posterior
Diabetes mellitus, noninsulin-dependent
Enhanced S-cone syndrome
Familial hypercholesterolemia
Hyperglycinuria
Hyperlipoprotenemia, type III
Long QT syndrome 5
Lynch syndrome
Nephrolithiasis/osteoporosis, hypophosphatemic, 2
Obesity
Paraganglioma 5
Parkinson disease 8
Retinitis pigmentosa 17
Thyroid carcinoma, familial medullary
Timothy syndrome
Vitelliform macular dystrophy, adult onset
Von Willebrand disease, type 2N
Autosomal Recessive (n=93)
Alpha thalassemia
Abetalipoproteinemia
Acyl CoA dehydrogenase deficiency
Albinism, oculocutaneous, type IB
Amegakaryocytic thrombocytopenia
Bartter syndrome type 3
Beta-ureidopropionase deficiency
Bloom syndrome
Bronchiectasis with or without elevated sweat chloride 2
Canavan disease
Candidiasis, familial, 4

Carnitine palmitoyltransferase 2 deficiency
Charcot-Marie-Tooth disease, type 1A
Cockayne syndrome A
Combined hyperlipidemia, familial
Congenital adrenal hyperplasia
Congenital myasthenic syndrome
Cryptorchidism
Cystic Fibrosis
Cystinuria
Deafness, autosomal recessive 1A
Dihydrolipoamide dehydrogenase deficiency
Dihydropyrimidine dehydrogenase deficiency
Dyskeratosis congenita, autosomal recessive, 3
Early-onset myopathy, areflexia, respiratory distress, and dysphagia
Ehlers-Danlos syndrome, type II
Epidermolysis bullosa dystrophica
Factor XI deficiency (PTA)
Familial dysautonomia
Familial hyperinsulinism
Familial Mediterranean Fever
Fanconi anemia, complementation group C
Follicle-stimulating hormone deficiency
Fructose intolerance
Fucosyltransferase 6 deficiency
Galactosemia
Gaucher disease, type 1
Glutathione synthetase deficiency
Glycogen storage disease Ia
Grey platelet syndrome
Haemophagocytic lymphohistiocytosis, familial
Hemochromatosis
Hemolytic anemia, nonspherocytic, due to glucose phosphate isomerase deficiency
Hermansky-Pudlak syndrome 1
Hermasky-Pudlak syndrome 3
Homocystinuria
Hyper IgD syndrome
Hyperoxaluria, primary, type 3
Hyperprolinemia, type I
Hypertrophic osteoarthropathy, primary
Hypocholinesterasaemia

Ichthyosis vulgaris
Ichthyosis, congenital, autosomal recessive 1
Immunodeficiency, centromeric instability & facial anomalies syndrome
Joubert syndrome
Leber congenital amaurosis 2
Leigh Syndrome
Leukoencephalopathy, brain & spine involvement, lactate elevation
Mandibuloacral dysplasia
Maple syrup urine disease
Megalencephalic leukoencephalopathy with subcortical cysts
Megaloblastic anaemia, thiamine responsive
Mitochondrial DNA depletion syndrome 1
Mucolipidosis IV
Muscular dystrophy, limb girdle 2L
Myoadenylate deaminase deficiency, myopathy due to
Nemaline myopathy
Neuronal ceroid lipofuscinosis, infantile
Niemann-Pick disease, type A
Phosphoglycerate dehydrogenase deficiency
Prekallikrein deficiency
Primary ciliary dyskinesia
Propionic acidaemia
Protoporphyria, erythropoietic
Refsum disease
Retinitis pigmentosa 1
Retinitis pigmentosa 28
Retinitis pigmentosa 59
Retinitis pigmentosa 62
Smith-Lemli-Opitz syndrome
Spastic paraplegia
Spinal muscular atrophy 37
Spondylocostal dysostosis
Stargardt disease 1
Tay-Sachs disease
Thrombotic thrombocytopenic purpura, familial
Thyroid dyshormonogenesis 3
Usher syndrome, type 1F
Usher syndrome, type 3A
Vici syndrome
Walker-Warburg syndrome

Xeroderma pigmentosum, group C
X-linked (n=4)
Alport syndrome
Fragile X syndrome
Premature ovarian failure 2B
Premature ovarian failure 4