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Comprehensive population screening in the Ashkenazi Jewish population for recurrent disease-causing variants

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Abstract

The Ashkenazi Jewish (AJ) population has an increased risk for a variety of recessive diseases due to historical founder effects and genetic drift. For some, the disease-causing founder mutations have been identified and well-characterized, but for others, further study is necessary. The purpose of this study is to assess the carrier frequencies of 85 pathogenic variants causative of 29 recessive conditions in the AJ population. Up to 3000 AJ individuals were genotyped by Luminex MagPlex®-TAG™ bead array or Agena Bioscience™ MassARRAY assays. We identified seven conditions with carrier frequencies higher than 1 in 100, nine between 1 in 100 and 1 in 200, and four between 1 in 200 and 1 in 500. Variants in nine conditions had a detected carrier rate of less than 1 in 500 or were not identified in approximately 2000 AJ individuals. We assessed the combined AJ carrier frequency for 18 relatively prevalent diseases to be 1 in 6, and the risk of AJ individuals to be a carrier couple for one of these 18 diseases as 1 in 441. We note additional recessive genetic conditions should be considered for AJ carrier screening panels.

Keywords

Ashkenazi Jewish; founder mutation; genetic counseling; prenatal carrier screening

Introduction

The highly shared genetic background of Ashkenazi Jewish (AJ) individuals has enabled the identification of population-specific founder mutations for a variety of Mendelian diseases. Founder mutations for severe, recessive conditions have been included in prenatal carrier screening programs, which have been adopted by the AJ community. Practice guidelines published by the American College of Medical Genetics and Genomics (ACMGG) in 2008 recommend that all individuals of AJ ancestry who are pregnant or considering pregnancy

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Conflict of interest

All authors declare no conflict of interest.

Supporting Information

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receive testing for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay–Sachs disease, and be offered testing for Fanconi anemia, complementation group C, Niemann–Pick disease type A, Bloom syndrome, mucolipidosis IV, and Gaucher disease (1). Many laboratories, including our own, also screen for additional targeted mutations on expanded carrier panels (2). More recently, the ACMGG has published a policy statement regarding the incorporation of additional targeted mutations in expanded carrier screening panel testing (3).

Here, we present the carrier frequencies of 85 pathogenic variants causative of 29 recessive conditions in the AJ population. We also compared the AJ carrier frequencies of 18 conditions that may be appropriate for genetic screening in the AJ population to frequencies identified in a general population excluding 100% self-reported AJ individuals.

Materials and methods

Study population

Peripheral blood samples were obtained with informed consent from 2252 individuals who self-reported 100% AJ ancestry undergoing carrier screening at The Mount Sinai Genetic Testing Laboratory. DNAs were genotyped for 85 variants causative of 29 conditions (Tables S1, S2, Supporting information). An additional 1390 individuals of AJ ethnicity and at least 6813 individuals of ethnicities excluding 100% AJ ancestry received carrier screening for 18 of these conditions as part of our expanded carrier screening. This research was carried out using preexisting, anonymized DNAs, and this human subjects research met criteria for exemption by the Mount Sinai Institutional Review Board (Exemption 4 category).

Carrier screening assays

In the pilot screening, 84 variants were genotyped using Luminex MagPlex®-TAG™ bead array (Luminex, Austin, TX) and/or the Agena Bioscience™ MassARRAY system (Agena Bioscience™, San Diego, CA) (Tables S3–S5). One variant, *MAK* p.K433*fs*, was genotyped by PCR followed by gel electrophoresis. A minimum of 1494 DNA samples were genotyped.

Subsequently, an expanded AJ carrier screening clinical test was developed based on Agena Bioscience™ technology and included assessment of 67 variants causative of 18 conditions (Table S6). A minimum of 1390 individuals and 6813 individuals from a general population sample that excluded individuals with 100% self-reported AJ ancestry were tested (Table 1).

Results

Variant selection and panel design

In an effort to better characterize additional genetic diseases in the AJ population, we reviewed the literature and our internal laboratory database to compile a list of pathogenic variants to be further investigated. Pathogenic variants causative of recessive conditions with significant morbidity and early childhood-onset presentations were considered. Two pathogenic variants (*PKHD1* c.3761_3762delCCinsG and *SUMF1* c.463T>C, p.S155P) were recommended by geneticists in our Clinical Genetics Program for inclusion after

identifying disease-causing mutations in individuals of AJ descent (Supplementary Methods); one of these variants, *PKHD1* c.3761_3762delCCinsG, has since been reported (4). Pathogenic variants already included as part of our carrier screening panel were excluded from this study (2). In total, 85 pathogenic variants causative of 29 recessive disorders were further studied (Tables S1 and S2). Conditions included 10 metabolic diseases (CPT2, CDG1A, GALT, HHH, MSD, PHGDHD, TYRSN1, WD, PBD1A, and PBD5A), 5 neurological conditions (AMRS, HYC1, LS-*NDUFS4*, LS-*NDUFAF5*, and PCH1A), 3 developmental disorders (BBS2, DC, and SLOS), 3 hematologic diseases (ABL, CAMT, and SCN3), 1 connective tissue disorder (EDSVIIC), 1 dermatologic disorder (JEB-H), 3 ocular diseases (RP59, RP62, and GLC3A), and 3 renal diseases (ATS-*COL4A3*, ATS-*COL4A5*, and ARPKD) (Figure S1).

Allele and carrier frequencies

The allele frequencies of the 85 variants assessed in 100% AJ individuals ranged from 0 to 0.0190 (Table S7). A total of 37 out of 85 variants were detected in this population, and 24 out of 37 variants had allele frequencies higher than 0.1%. Six variants had frequencies higher than 0.5% and three alleles had frequencies higher than 1%. Three homozygous individuals were identified (*MTTP* c.2593G>T, p. G865*, $n = 1$, Hardy–Weinberg equilibrium $p < 0.01$; *CYP1B1* c.1103G>A, p.R368H, $n = 2$, Hardy–Weinberg equilibrium $p = 0.18$). Allele frequencies for these variants in the AJ population were compared to those in the Exome Aggregation Consortium (ExAC) non-Finnish Caucasian dataset (Figure S2). Most variants showed enrichment in the AJ population, suggesting possible founder effect.

We did not identify any carriers for four conditions (ATS-*COL4A5*, HHH, HYC1, and LS-*NDUFAF5*). Two eye conditions, GLC3A and RP62, had carrier frequencies of 1 in 26 and 1 in 29, respectively, and were therefore excluded from further analysis. The carrier frequencies for 18 remaining relatively common diseases ranged from 0.028 (1 in 36) to 0.003 (1 in 373), which resulted in a cumulative carrier frequency of 0.166 (1 in 6) (Table 1, Figure S3). The likelihood of two AJ individuals being a carrier couple for one of these 18 diseases is 0.0023 (1 in 441). When the 18 relatively common AJ conditions identified in this study are added to 18 conditions commonly tested in the AJ population for a total assessment of 36 conditions, the cumulative AJ carrier frequency is 1 in 2 (Table S8).

Discussion

In an effort to ascertain whether additional AJ conditions should be considered for extended AJ prenatal carrier screening panels, the literature was reviewed and the carrier frequency of 85 pathogenic variants causative of 29 recessive conditions in approximately 2000 individuals who self-reported 100% AJ ancestry was assessed. Thirty-seven variants were detected in this AJ population with allele frequencies ranging from 0.01% to 1.90%. Many of these variants trended towards enrichment in the AJ population, supporting the existence of founder effects. Additionally, almost all (35 of 37) of these variants are rare in the general Caucasian population with allele frequencies ≤0.5%. The exceptions were *DHCR7* c.964-1G>C and *PMM2* p.R141H. *DHCR7* c.964-1G>C is the most common causative variant for SLOS with allele frequencies of 1.27% in the ESP European American

population, 1.06% in the 1000 Genomes Project European population, and 0.68% in ExAC Caucasian population. Despite its high frequency, this variant has rarely been reported as homozygous in SLOS patients, and the few reported homozygotes have all manifested the most severe end of the phenotypic spectrum (5, 6). Additionally, epidemiological studies suggest that the prevalence of SLOS is much lower than expected given the high carrier frequency of this variant (6–8). This discrepancy may be explained by either embryonic lethality or early fetal demise caused by homozygosity of this null allele. Similarly, *PMM2* p.R141H has a high carrier frequency (0.54% in ESP European Americans, 1.2% in the 1000 Genomes Project European population, and 1.1% in the ExAC Caucasian population) and the observed disease prevalence of 1:40,000–80,000 is much lower than expected given this frequency (9). This pathogenic variant has not been reported in a homozygous state in CDG1A patients and may cause embryonic lethality (9). However, this population incidence discrepancy could be explained by either under diagnosis of CDG due to its highly variable clinical presentation, or due to reproductive advantage at the stage of gametogenesis, fertilization, implantation, or embryogenesis, rather than resistance to environmental factors during infant or adult life (10). Hence, considering the complexity of both SLOS and CDG1A, caution should be taken when providing genetic counseling for these two conditions.

The carrier frequencies determined from genotyping approximately 2000 AJ individuals were compared to frequency data available in the literature. Of note, one limitation of this study is that the ancestry was self-reported. Except for one variant (*SLC25A15* p.F188del), our calculated carrier frequencies correlated with published data. The *SLC25A15* p.F188del variant is common in French-Canadians with an extremely high carrier rate of 1 in 19 in an isolated northern Saskatchewan region (11). This variant is almost exclusively reported in French-Canadian HHH patients and had not been reported in AJ individuals except for a 1 in 94 carrier rate in a small control group with less than 300 self-reported AJ individuals. The high occurrence of this mutation in the French Canadian population, the low incidence in other ethnic groups, and the absence of this variant in more than 2000 AJ individuals in the present study suggest that this variant is less likely to be an AJ founder mutation.

Presently, variants in 25 genes were detected in a population of approximately 2000 individuals of self-reported 100% AJ ancestry; however, not all of these variants are proper candidates for reproductive genetic testing. Five conditions (JEB-H, LS-*NDUFS4*, PCH1A, SCN3 and PBD1A) had carrier frequencies of less than 1 in 500, and therefore were not included in our clinical testing panel. The missense variant *CYP1B1* p.R368H for primary congenital glaucoma had the highest carrier frequency at 1 in 26. Surprisingly, two homozygotes were identified by genotyping 2148 healthy AJ individuals. The allele frequency of this variant was 1.9% in this AJ population, which was much higher than that reported for general European Caucasians (ExAC Caucasian population, minor allele frequency 0.29%). Obligate homozygous carriers without clinical manifestations have been reported for this variant, suggesting incomplete penetrance of this disease allele (12). *MAK* p.K433*fs* had the second highest AJ carrier frequency (1 in 29) in our screening. A large number of persons homozygous for this variant has been reported, all of whom manifested late-onset disease with slow progression (age at diagnosis ranged from mid-30s to 70s) (13). Hence, we did not include these variants in our clinical AJ carrier screening panel.

We also evaluated variants causative of several diseases that may be considered less severe genetic conditions. For example, the age at presentation of WD varies from early childhood to late adulthood, and symptoms are highly variable, even within families. Two additional conditions (GALT and TYRSN1) may be diagnosed via newborn screening and so reproductive testing for these diseases may not be recommended. However, given the high AJ population carrier frequencies and significantly reduced quality of life associated with these conditions, knowledge of disease status prior to clinical manifestations may benefit patients. Additionally, establishing early diagnosis of a metabolic condition and providing intervention may prevent metabolic decompensation and result in a more favorable prognosis.

For most disorders we analyzed, a limited number of pathogenic variants account for the vast majority of mutant alleles, enabling highly sensitive targeted molecular genetic testing in the AJ population. This testing may be more cost-effective, faster, and simpler to analyze than tests involving full gene sequencing. However, limitations to performing targeted molecular testing in AJ carrier screening include a reduced detection rate in individuals of mixed ethnicity and the diminished ability to identify novel mutations. When the partner of a known carrier is negative by genotyping or is not of AJ descent, full gene sequencing may be recommended as a second-tier choice.

Here we assess the frequency of 85 pathogenic variants in the AJ population, and the results suggest that additional diseases should be considered for AJ carrier screening panels. These findings may serve as a reference for future genetic education and counseling in AJ communities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Gross SJ, Pletcher BA, Monaghan KG, et al. Carrier screening in individuals of Ashkenazi Jewish descent. Genet Med. 2008; 10:54–56. [PubMed: 18197057]
2. Scott SA, Edelmann L, Liu L, et al. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Hum Mutat. 2010; 31:1240–1250. [PubMed: 20672374]
3. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. 2013; 15:482–483. [PubMed: 23619275]
4. Quint A, Sagi M, Carmi S, et al. An Ashkenazi founder mutation in the PKHD1 gene. Eur J Med Genet. 2016; 59:86–90. [PubMed: 26721323]
5. Jira PE, Wanders RJ, Smeitink JA, et al. Novel mutations in the 7-dehydrocholesterol reductase gene of 13 patients with Smith--Lemli--Opitz syndrome. Ann Hum Genet. 2001; 65:229–236. [PubMed: 11427181]
6. Nowaczyk MJ, Farrell SA, Sirkin WL, et al. Smith-Lemli-Opitz (RHS) syndrome: holoprosencephaly and homozygous IVS8-1G-->C genotype. Am J Med Genet. 2001; 103:75–80. [PubMed: 11562938]

7. Tint GS, Irons M, Elias ER, et al. Defective cholesterol biosynthesis associated with the Smith-Lemli-Opitz syndrome. N Engl J Med. 1994; 330:107–113. [PubMed: 8259166]
8. Nowaczyk MJ, Zeesman S, Waye JS, Douketis JD. Incidence of Smith-Lemli-Opitz syndrome in Canada: results of three-year population surveillance. J Pediatr. 2004; 145:530–535. [PubMed: 15480380]
9. Schollen E, Kjaergaard S, Legius E, Schwartz M, Matthijs G. Lack of Hardy-Weinberg equilibrium for the most prevalent PMM2 mutation in CDG-Ia (congenital disorders of glycosylation type Ia). Eur J Hum Genet. 2000; 8:367–371. [PubMed: 10854097]
10. Schollen E, Kjaergaard S, Martinsson T, et al. Increased recurrence risk in congenital disorders of glycosylation type Ia (CDG-Ia) due to a transmission ratio distortion. J Med Genet. 2004; 41:877–880. [PubMed: 15520415]
11. Sokoro AA, Lepage J, Antonishyn N, et al. Diagnosis and high incidence of hyperornithinemia-hyperammonemia-homocitrullinemia (HHH) syndrome in northern Saskatchewan. J Inherit Metab Dis. 2010; 33(Suppl 3):S275–S281. [PubMed: 20574716]
12. Bejjani BA, Stockton DW, Lewis RA, et al. Multiple CYP1B1 mutations and incomplete penetrance in an inbred population segregating primary congenital glaucoma suggest frequent de novo events and a dominant modifier locus. Hum Mol Genet. 2000; 9:367–374. [PubMed: 10655546]
13. Stone EM, Luo X, Heon E, et al. Autosomal recessive retinitis pigmentosa caused by mutations in the MAK gene. Invest Ophthalmol Vis Sci. 2011; 52:9665–9673. [PubMed: 22110072]

Table 1

Allele and carrier frequencies for 18 conditions that have been screened in current study

		AJ population						non-AJ population		
Disease-gene	**Mutation**	**Sample size**	**Allele frequency (95% CIs)**	**Carrier frequency (95% CIs)**	**Detection rate[a]**	**Residual risk[b]**	**Chance for being a carrier couple**	**Sample size**	**Allele frequency (95% CIs)**	**Carrier frequency (95% CIs)**
Abetalipoproteinemia (ABL)-*MTTP*	p.G865*	3347	0.0025 (0.0015–0.0042)	1/185 (1/301–1/115)	95%	1/3671	1/34041	7071	0.0004 (0.0001–0.0009)	1/1414 (1/3841–1/571)
	p.S738fs	2954	0.0002 (0–0.0011)					7071	0 (0–0.0003)	
Alport syndrome (ATS)-*COL4A3*	p.L14_L21del	3639	0.0026 (0.0016–0.0042)	1/192 (1/309–1/120)	95%	1/3812	1/36685	7240	0.0001 (0–0.0006)	1/3620 (1/20899–1/898)
Arthrogryposis, mental retardation, and seizures (AMRS)-*SLC35A3*	p.S296G	3622	0.0011 (0.0005–0.0023)	1/453 (1/973–1/221)	95%	1/9035	1/204931	7239	0.0001 (0–0.0006)	1/3620 (1/20896–1/898)
	p.Q172*	3617	0 (0–0.0007)					7239	0 (0–0.0003)	
Bardet–Biedl syndrome 2 (BBS2)-*BBS2*	p.D104A	3627	0.0014 (0.0007–0.0026)	1/139 (1/209–1/94)	95%	1/2770	1/19452	7232	0.0001 (0–0.0006)	1/723 (1/1423–1/380)
	p.R632P	3626	0.0022 (0.0013–0.0037)					7232	0.0006 (0.0003–0.0011)	
Carnitine palmitoyltransferase II deficiency (CPT2)-*CPT2*	p.S113L	3587	0.0061 (0.0045–0.0083)	1/51 (1/65–1/40)	95%	1/1006	1/2625	6815	0.0031 (0.0022–0.0042)	1/131 (1/174–1/99)
	p.Q413fs	3586	0.0036 (0.0024–0.0054)					6815	0.0007 (0.0003–0.0013)	
	p.R124*	3590	0 (0–0.0007)					6815	0 (0–0.0004)	
	p.S38fs	3573	0 (0–0.0007)					6815	0.0001 (0–0.0005)	
Congenital amegakaryocytic thrombocytopenia (CAMT)-*MPL*	c.79+2T>A	3617	0.0088 (0.0069–0.0114)	1/57 (1/73–1/44)	95%	1/1111	1/3194	7069	0.001 (0.0006–0.0017)	1/505 (1/887–1/293)
Congenital disorder of glycosylation Ia (CDG1a)-*PMM2*	p.P113L	3575	0 (0–0.0007)	1/61 (1/79–1/47)	90%	1/597	1/3678	6813	0.0001 (0–0.0005)	1/106 (1/137–1/83)
	p.F119L	3579	0 (0–0.0007)					6813	0 (0–0.0004)	
	p.R141H	3578	0.0082 (0.0063–0.0107)					6813	0.0046 (0.0035–0.0059)	
	p.V231M	3575	0 (0–0.0007)					6813	0.0001 (0–0.0005)	
Dyskeratosis congenita, autosomal recessive (DC)-*RTEL1*	p.R1264H	3627	0.0026 (0.0016–0.0042)	1/165 (1/256–1/107)	95%	1/3279	1/27186	7239	0.0008 (0.0004–0.0014)	1/517 (1/908–1/300)
	p.M516I	3630	0.0004 (0.0001–0.0013)					7239	0 (0–0.0003)	
	p.R981W	3627	0 (0–0.0007)					7239	0.0001 (0–0.0004)	
	p.R998*	3627	0 (0–0.0007)					7239	0.0001 (0–0.0006)	
	p.G763V	3619	0 (0–0.0007)					7239	0 (0–0.0003)	
Ehlers–Danlos syndrome, type VIIC (EDS7C)-*ADAMTS2*	p.Q225*	3367	0.0027 (0.0016–0.0043)	1/187 (1/306–1/116)	95%	1/3722	1/34990	7235	0.0005 (0.0002–0.001)	1/1034 (1/2358–1/479)
	p.W795*	3367	0 (0–0.0007)					7235	0 (0–0.0003)	
Galactosemia (GALT)-*GALT*	c.-1039_+789del5573ins129	3582	0.0025 (0.0015–0.0041)	1/156 (1/240–1/102)	90%	1/1548	1/24240	6815	0.0012 (0.0007–0.002)	1/162 (1/222–1/119)
	c.253-2A>G	3581	0 (0–0.0007)					6815	0.0001 (0–0.0005)	
	p.S135L	3576	0.0001 (0–0.0009)					6815	0.0004 (0.0001–0.0009)	

Disease-gene	Mutation	AJ population						non-AJ population		
		Sample size	Allele frequency (95% CIs)	Carrier frequency (95% CIs)	Detection rate[a]	Residual risk[b]	Chance for being a carrier couple	Sample size	Allele frequency (95% CIs)	Carrier frequency (95% CIs)
	p.Q188R	3576	0.0003 (0–0.0011)					6815	0.001 (0.0005–0.0017)	
	p.T138M	3575	0 (0–0.0007)					6815	0.0001 (0–0.0005)	
	p.F171S	3582	0 (0–0.0007)					6815	0 (0–0.0004)	
	p.L195P	3575	0 (0–0.0007)					6815	0 (0–0.0004)	
	p.Y209C	3573	0 (0–0.0007)					6815	0.0001 (0–0.0005)	
	p.K285N	3581	0.0003 (0–0.0011)					6815	0.0004 (0.0001–0.0009)	
Multiple sulphatase deficiency (MSD)-*SUMF1*	p.S155P	3625	0.0018 (0.001–0.0032)	1/279 (1/501–1/159)	95%	1/5558	1/77764	7238	0.0006 (0.0003–0.0011)	1/905 (1/3841–1/571)
3-Phosphoglycerate dehydrogenase deficiency (PHGDHD)-*PHGDH*	p.V490M	3625	0.0011 (0.0005–0.0023)	1/453 (1/974–1/221)	95%	1/9043	1/205303	7242	0.0002 (0.0001–0.0007)	1/2414 (1/3841–1/571)
Polycystic kidney disease, autosomal recessive (ARPKD)-*PKHD1*	p.A1254fs	3578	0.0046 (0.0032–0.0066)	1/105 (1/149–1/75)	90%	1/1043	1/11076	6815	0.0018 (0.0012–0.0028)	1/227 (1/3841–1/571)
	p.T36M	3587	0.0001 (0–0.0009)					6815	0.0002 (0.0001–0.0007)	
	p.R496*	3581	0 (0–0.0007)					6815	0.0001 (0–0.0006)	
	p.L1966fs	3581	0 (0–0.0007)					6815	0 (0–0.0004)	
	p.V3471G	3583	0 (0–0.0007)					6815	0 (0–0.0004)	
	p.D3230fs	3581	0 (0–0.0007)					6815	0 (0–0.0004)	
Retinitis pigmentosa (RP59)-*DHDDS*	p.K42E	3621	0.0043 (0.003–0.0062)	1/117 (1/169–1/81)	95%	1/2317	1/13644	7238	0.0013 (0.0008–0.0021)	1/381 (1/614–1/239)
Smith–Lemli–Opitz syndrome (SLOS)-*DHCR7*	c.964-1G>C	3604	0.0119 (0.0096–0.0148)	1/40 (1/50–1/33)	95%	1/791	1/1640	15369	0.003 (0.0024–0.0037)	1/122 (1/146–1/102)
	p.W151* (c.452G>A)	3612	0.0004 (0.0001–0.0013)					15369	0.0009 (0.0006–0.0013)	
	p.W151* (c.453G>A)	3614	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.M1V	3615	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.V326L	3602	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.T93M	3612	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.R352Q	3601	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.R352W	3602	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.R404C	3602	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.S169L	3615	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.R242C	3614	0 (0–0.0007)					15369	0.0001 (0–0.0003)	
	p.R242H	3613	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.F302L	3613	0 (0–0.0007)					15369	0 (0–0.0002)	
	p.G410S	3602	0 (0–0.0007)					15369	0 (0–0.0002)	

Disease-gene	Mutation	AJ population						non-AJ population		
		Sample size	Allele frequency (95% CIs)	Carrier frequency (95% CIs)	Detection rate[a]	Residual risk[b]	Chance for being a carrier couple	Sample size	Allele frequency (95% CIs)	Carrier frequency (95% CIs)
	p.E448K	3606	0 (0–0.0007)					15369	0.0001 (0–0.0003)	
Tyrosinemia type 1 (TYRSN1)-*FAH*	p.P261L	3581	0.0034 (0.0022–0.0051)	1/143 (1/216–1/96)	95%	1/2846	1/20514	6813	0.0005 (0.0002–0.0011)	1/619 (1/1177–1/335)
	c.554-1G>T	3571	0 (0–0.0007)					6813	0 (0–0.0004)	
	c.1062+5G>A	3578	0.0001 (0–0.0009)					6813	0.0003 (0.0001–0.0008)	
	p.Q64H	3577	0 (0–0.0007)					6813	0 (0–0.0004)	
	p.W262*	3574	0 (0–0.0007)					6813	0 (0–0.0004)	
	p.E357*	3566	0 (0–0.0007)					6813	0 (0–0.0004)	
Wilson disease (WD)-*ATP7B*	p.E1064A	3572	0.0028 (0.0018–0.0044)	1/67 (1/89–1/51)	85%	1/443	1/4530	6813	0.0004 (0.0002–0.001)	1/189 (1/266–1/135)
	p.H1069Q	3565	0.0035 (0.0023–0.0053)					6813	0.0017 (0.0011–0.0026)	
	p.R778L	3578	0 (0–0.0007)					6813	0 (0–0.0004)	
	p.M645R	3563	0.0011 (0.0005–0.0023)					6813	0.0005 (0.0002–0.0011)	
Peroxisomal biogenesis disorder 5A (PBD5A)-*PEX2*	p.R119*	3626	0.0022	1/227 (1/383–1/136)	95%	1/4513	1/51349	7232	0.0003 (0.0001–0.0009)	1/1446 (1/3928–1/583)

[a]Detection rate was determined by calculating percentage of chromosomes representing all mutation(s) listed.

[b]Refers to the risk of being a carrier of the disease after testing negative for listed mutations.