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Pharmacogenetics in Jewish populations

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Abstract

Spanning over 2000 years, the Jewish population has a long history of migration, population bottlenecks, expansions, and geographical isolation, which has resulted in a unique genetic architecture among the Jewish people. As such, many Mendelian disease genes and founder mutations for autosomal recessive diseases have been discovered in several Jewish groups, which have prompted recent genomic studies in the Jewish population on common disease susceptibility and other complex traits. Although few studies on the genetic determinants of drug response variability have been reported in the Jewish population, a number of unique pharmacogenetic variants have been discovered that are more common in Jewish populations than in other major racial groups. Notable examples identified in the Ashkenazi Jewish (AJ) population include the vitamin K epoxide reductase complex subunit 1 (*VKORC1*) c.106G>T (p.D36Y) variant associated with high warfarin dosing requirements and the recently reported cytochrome P450 2C19 (*CYP2C19*) allele, *CYP2C19*4B*, that harbors both loss-of-function [**4* (c.1A>G)] and increased-function [**17* (c.-806C>T)] variants on the same haplotype. These data are encouraging in that like other ethnicities and subpopulations, the Jewish population likely harbors numerous pharmacogenetic variants that are uncommon or absent in other larger racial groups and ethnicities. In addition to unique variants, common multi-ethnic variants in key drug metabolism genes (e.g., *ABCB1*, *CYP2C8*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *NAT2*) have also been detected in the AJ and other Jewish groups. This review aims to summarize the currently available pharmacogenetics literature and discuss future directions for related research with this unique population.

Keywords

Ashkenazi Jewish; *CYP2C19*4B*; Jewish genetics; pharmacogenetics; pharmacogenomics; *VKORC1* p.D36Y

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Introduction

The Jewish population can be traced back to the Ancient Near East around the 18th century BCE, which is consistent with modern genetic studies that indicate a Middle East origin [1, 2]. Despite extensive migration over time to regions in Europe, Africa, and Asia [3, 4], the majority of the current Jewish population resides in Israel and the USA. Based on this geographical isolation and a history of significant population bottlenecks followed by rapid expansion, founder mutations for autosomal recessive diseases have become prevalent at appreciable carrier frequencies, particularly among Ashkenazi Jews (AJ), which has resulted in increased risks for several genetic disorders compared to other racial and ethnic groups [5]. Moreover, the unique genetic architecture of the AJ and other Jewish groups [6–11] has been linked to higher frequencies of alleles that confer increased risks for common diseases, such as Parkinson's disease [5] and breast and ovarian cancer [12].

The important role of race and ethnicity in disease and drug response variability is increasingly being recognized [13], which has prompted recent pharmacogenomic studies directed at patient populations of non-European ancestry [14]. Although few studies on the genetic determinants of drug response variability in the Jewish population have been reported, a number of unique pharmacogenetic variants have already been discovered that are more common in Jewish populations than in other major racial groups. These data are encouraging in that like other ethnicities and subpopulations, the Jewish population likely harbors numerous pharmacogenetic variants that are uncommon or absent in other major racial and ethnic groups. This review article aims to summarize the currently available Jewish pharmacogenetics literature and discuss future directions for related research with this unique population.

Literature review

The PubMed database (NCBI) was searched using the keywords (Jewish or Ashkenazi) and (pharmacogenetics or pharmacogenomics) from 1966 to March 2014. In addition, the FINDbase-PGx database [15] was searched for pharmacogenetic alleles identified in Jewish populations.

Jewish genetics

Jewish ethnic diversity

It is generally believed that the Jewish people can be traced back to Semitic tribes that lived in the Middle East approximately 4000 years ago [1], ultimately migrating extensively and establishing communities in Europe, Africa, and Asia over the past 2000 years [4]. Throughout their history of migration, the Jewish population went through several significant population bottlenecks and expansions that over time caused substantial fluctuations in size and distribution. Accurate population size estimates are challenging given that Jewish identity can be defined by both ancestral background and adherence to Judaism without Jewish lineage or ancestry; however, the worldwide Jewish population currently is estimated at ~13 million [16].

There are an estimated 16 Jewish Diaspora due to geographical separation and diversity in cultural evolution, which are often classified into three major geographic subgroups. The largest among them is the AJ, a community originally founded along the Rhine in Germany from the sixth to ninth centuries, later emigrating to Central and Eastern Europe. Currently, the AJ represent ~80% of modern Jewry and are found predominantly in Israel and the USA, with smaller populations in Canada, Russia, Argentina, and other countries [16]. Extensive migration in the 20th century has resulted in an estimated 6 million AJ individuals in the USA (~2% of the total population) [17], representing the largest single population isolate.

Another major Jewish group is the Sephardim whose origins trace back to the Israelite tribes of the Middle East in the Iberian Peninsula until the Spanish Inquisition expulsion in the late 15th century. Although not as large as the Ashkenazim, the majority of Sephardic Jews (SJ) currently reside in Spain and Portugal, with smaller populations in Israel, the USA, and other countries. In addition to the AJ and SJ, the smaller heterogeneous collection of Middle Eastern (or Oriental) Jews lived in contemporary Israel and Palestine, as well as in Iran, Iraq, Central Asia, and the Arabian Peninsula [3]. The majority of Middle Eastern Jews now populate Israel and the USA, with small communities still existing in some Middle East countries.

Jewish population genetics

Although a detailed review of Jewish population structure is beyond the scope of this manuscript (and recently reviewed elsewhere [17]), any discussion on Jewish pharmacogenetics necessitates a brief overview of Jewish population genetics. The continued advances in genome technologies have driven ongoing research on the origins and relatedness of the Jewish people. Initial population studies based on blood groups and serum markers suggested the origin of most Jewish populations to the Middle East and identified greater genetic similarity between Jewish subgroups than between Jewish and non-Jewish populations [6, 18–20]. Subsequent Y chromosome and mitochondrial haplotype studies confirmed founder effects, genetic drift, and a Middle East origin but were limited in resolution to determine the degree of admixture among the tested Jewish populations [7, 9].

Modern genome-wide analyses have vastly improved the understanding of Jewish population structure, identifying patterns of linkage disequilibrium (LD) and providing evidence for shared genetic ancestries among Jewish groups with variation in admixture from local populations [2, 4, 21, 22]. Notably, principal component analyses of seven Jewish groups (Iranian, Iraqi, Syrian, Italian, Turkish, Greek, and AJ) demonstrated distinct population subclusters with shared Middle Eastern ancestry, proximity to contemporary Middle Eastern populations, and variable degrees of European and North African admixture [2]. These important data allow for verification of genetic ancestry and control for admixture effects when studying the Jewish population. For example, a recent genome-wide association study (GWAS) on AJ Crohn's disease identified clustering of AJ patients with HapMap CEPH-Utah and seven other Jewish HapMap populations; however, after removing the Yoruban-Nigeria, Japanese, and Han Chinese, distinct Jewish group subclusters were apparent that could also quantify the degree of AJ ancestry (e.g., 100%, 75%, 50%) among the self-reported patient population [11] (Figure 1).

Jewish founder mutations and Mendelian diseases

A notable characteristic of the Jewish population is the prevalence of founder mutations for autosomal recessive diseases, which has prompted widespread Jewish carrier screening programs in many countries, particularly for the AJ. These programs began with enzyme-based testing for Tay-Sachs disease [23, 24] and have since evolved to multiplexed DNA-based testing as the founder mutations for additional disease genes have been identified. Laboratories often include at least 16 disorders in their AJ panels [25], with new disease genes and founder mutations continually being discovered by modern genomic approaches [26–30]. Although not as prominent as the AJ carrier screening programs, recessive founder mutations have also been identified in the SJ and other Jewish groups [31, 32].

Jewish pharmacogenetics

Given the relatively recent advancement and enthusiasm for pharmacogenetics compared to Mendelian human genetics research, literature on the genetic determinants of drug response variability for many racial and ethnic subpopulations is only now emerging. This is due, in part, to the fact that most notable pharmacogenetic variants have been identified through candidate gene studies and GWAS with cohorts primarily comprised of non-Jewish European individuals. As such, pharmacogenetic studies on other racial and ethnic groups are warranted, particularly given that drug response can vary by ethnicity [33–35].

Consistent with the identification of recessive founder mutations among the AJ, initial pharmacogenetic studies on the Jewish population have identified several unique variants not found at appreciable frequencies in other populations. Additionally, allele frequency surveys have also detected common pharmacogenetic variants in the Jewish population that are prevalent in other racial and ethnic groups. Table 1 summarizes the reported pharmacogenetic variants identified in Jewish populations, with notable genes and variants detailed below.

Unique pharmacogenetic variants in the Jewish population

CYP2C9 and VKORC1: warfarin pharmacogenetics—Warfarin is an anticoagulant commonly prescribed for prevention of thrombotic events among patients with atrial fibrillation and other indications (e.g., deep vein thrombosis, pulmonary embolism, etc.) [44]. Despite its continued use over many decades, it has a narrow therapeutic index and wide interindividual variability in therapeutic dose requirements, resulting in significant risks of bleeding or stroke when over- or under-anticoagulated, respectively. Warfarin dosing is influenced by a number of clinical and genetic variables [45, 46], which have been incorporated into pharmacogenetic warfarin dosing algorithms to predict therapeutic doses [47–55]. Clinical variables implicated in dose variability include age, height/ weight, concomitant medications, and ethnicity, and established genetic variables include variants in the genes encoding cytochrome P450 2C9 (CYP2C9) and VKORC1, enzymes directly involved in warfarin pharmacokinetics and pharmacodynamics, respectively. In addition, pharmacogenomic studies have identified a smaller role for variants in *CYP4F2* and warfarin dosing [56, 57].

Retrospective studies have shown that pharmacogenetic-guided dosing is more accurate than both empiric dosing and the US Food and Drug Administration (FDA)-approved dosing table in the warfarin label [58]. However, recent randomized clinical trials indicate that although pharmacogenetic-guided dosing is more accurate than routine fixed dosing [59], a dosing algorithm with only three *CYP2C9* and *VKORC1* variants common among Caucasians is not superior to a clinical variable dosing algorithm, particularly among individuals of African ancestry [60]. As such, a major issue behind pharmacogenetic-guided warfarin dosing continues to be the appropriate selection of *CYP2C9* and *VKORC1* variants for a given ethnicity and the ongoing debate over clinical utility [61].

Most pharmacogenetic warfarin dosing algorithms have been defined using Caucasian patients and the variants most common in these populations [e.g., *CYP2C9**2 and *3 and *VKORC1* c.-1639G>A (Table 1)]. Given the variability in allele frequencies for these variants across different racial and ethnic groups [38], recent studies have shown that additional variants are important in other populations. For example, *CYP2C9**5, *6, *8, and *11 are more prevalent among individuals of African descent [38, 62], and a recent GWAS identified a novel *CYP2C* variant implicated in warfarin dosing in this racial group [14]. As such, further studies are warranted on other subpopulations to identify the most relevant alleles to include in warfarin dosing algorithms for a given ethnicity.

In addition to these *CYP2C9* and *VKORC1* variants associated with lower warfarin doses, heterozygous *VKORC1* coding region variants result in warfarin ‘resistance’ and much higher dose requirements to achieve a therapeutic level of anticoagulation (e.g., p.V29L, p.A41S, p.V45A, p.R58G, p.V66M, and p.L128R; Figure 2) [63–67]. Although these variants are rare, all act as dominant alleles regardless of *CYP2C9* and *VKORC1* background. Multi-ethnic allele frequencies for these variants are not well established; however, p.V66M has a carrier frequency of ~1 in 100 among African Americans [62], suggesting that including this variant in warfarin genotyping panels may have utility for this population.

The New York AJ population has been screened for the common *CYP2C9* and *VKORC1* variants, which identified comparable allele frequencies with Caucasians [38] (Table 1). Specifically, the AJ *CYP2C9* extensive, intermediate, and poor metabolizer frequencies were 62%, 33%, and 5%, and the *VKORC1* c.-1639 G/G, G/A, and A/A frequencies were 29%, 48%, and 23%, respectively [38]. Related studies have identified distinct *CYP2C9* (*2 and *3) and *VKORC1* c.174-136C>T (1173C>T) frequencies between Israeli Jewish (AJ, Yemenite, Moroccan, and Libyan) and Japanese individuals [68, 69]. Given the paucity of *CYP2C9* full gene sequencing studies among Jewish individuals, it is currently unknown if unique *CYP2C9* variant alleles exist in this population, suggesting further studies are warranted.

In an effort to identify variants associated with warfarin ‘resistance’ in the AJ population, *VKORC1* has been sequenced in AJ patients requiring high therapeutic doses [43]. A novel coding variant, c.106G>T (p.D36Y; Figure 2; Table 1), was found ~50% of resistant patients but not in any of the patients requiring low doses. In a validation cohort, p.D36Y was again detected in patients in the upper dose quartile compared with noncarriers who required only

~40 mg/week. Like the other warfarin resistant variants, patients carrying both p.D36Y and dose-reducing *CYP2C9* and/or *VKORC1* variants still required high warfarin doses, indicating that this variant is also dominant over the known sensitive alleles.

As the most common *VKORC1* variant implicated in warfarin resistance [70], p.D36Y has allele frequencies of ~15% in Ethiopians, ~3–6% in East Africans, ~4% in the AJ, and <1% among North or West African, Yemenite, SJ, Caucasian, Asian, African-American, and Hispanic individuals [38, 39, 43, 71]. Of note, when taken into consideration with other common warfarin variants, ~85% of AJ and ~90% of SJ individuals have at least one ‘sensitive’ (*CYP2C9**2, *3, *VKORC1* c.–1639G>A) or ‘resistant’ (*VKORC1* p.D36Y) allele, indicating that each group has distinctive warfarin pharmacogenetics and could possibly benefit from genotype-based dose prediction [39]. This is further evidenced by the fact that inclusion of p.D36Y in the International Warfarin Pharmacogenetics Consortium dosing algorithm has recently been shown to significantly improve the performance of dose prediction in the AJ population [72], indicating that this allele should be included in any pharmacogenetic-guided dosing strategy for the AJ. In addition to highlighting the importance of p.D36Y in warfarin dosing for the AJ, these data are instructive for other populations and pharmacogenetic contexts by underscoring the concept that low-frequency variants with significant effect sizes can be important contributors to multifactorial drug response phenotypes.

***CYP2C19**4B: clopidogrel pharmacogenetics**—*CYP2C19* is involved in the metabolism of antidepressants, benzodiazepines, mephenytoin, proton pump inhibitors, and the antiplatelet prodrug clopidogrel [73–75]. Like other *CYP450* genes, common and rare *CYP2C19* variants have been identified in various populations, which are catalogued by the Human Cytochrome P450 (CYP) Allele Nomenclature Committee [76]. Many of these encode reduced or complete loss of function, and their frequencies can also differ between racial and ethnic groups [15, 37, 38, 77, 78]. For example, *CYP2C19**2 (c.681G>A) and *3 (p.W212X) are the most commonly studied *CYP2C19* loss-of-function alleles with average multi-ethnic allele frequencies of ~18% and ~2%, respectively; however, *3 is more prevalent in Asian populations (~9%) [34, 37, 79, 80]. In contrast to these and other *CYP2C19* loss-of-function alleles (*4–*8), the *17 promoter variant (c.–806C>T) results in enhanced transcription and increased enzyme activity [81, 82] (Figure 3). Based on *CYP2C19* genotype, individuals are typically categorized into four phenotypes [83–85]: ultrarapid (*1/*17 or *17/*17), extensive (*1/*1), intermediate (loss-of-function allele heterozygote), or poor (loss-of-function allele compound heterozygote or homozygote) metabolizers [75, 86].

Although the *CYP2C19**2–*8 allele frequencies in the AJ are similar to those in other Caucasian populations [40], the *4 (c.1A>G) AJ allele frequency (~2%) is higher than in Caucasians and Asians (~0.6%) [87, 88] (Table 1). The discovery of *CYP2C19**17 prompted a follow-up study with the AJ, which ultimately led to the recent identification of *4B [36] (Figure 3; Table 1). Notably, *CYP2C19**4B is unique in that it harbors both the *4 (c.1A>G) and *17 (c.–806C>T) variants in *cis* on the same haplotype [36]. Allele-specific cloning and sequencing confirmed that all identified *4 carriers had *17 in *cis* among the AJ, which was classified as *4B by the Human Cytochrome P450 (CYP) Allele Nomenclature Committee.

In other populations, both *4 (c.1A>G) and *17 (c.-806C>T) are typically found in *trans* as independent haplotypes, which are referred to as *4A and *17, respectively (Figure 3).

Due to the only recent identification of *4B, it is currently unknown what the global *4A and *4B allele frequencies are; however, available data suggest that the *4B frequency is as high as 2–3% in the AJ population [37]. It has also been identified at lower frequencies in the SJ, Caucasians, and Hispanics [37]. Despite a low multi-ethnic allele frequency, inclusion of *4B in *CYP2C19* testing panels is warranted because targeted genotyping assays cannot determine the phase of the c.1A>G (*4) and c.-806C>T (*17) variants. As such, a *4/*17 genotype result could actually represent either a *4A/*17 or *1/*4B genotype. Moreover, given that the *CYP2C19* assays currently approved by the US FDA include *17 and not *4, some of the *17 carriers identified by these assays will actually be *4B carriers incorrectly classified as ultrarapid metabolizers. Given that *4B is a loss-of-function allele [36, 87], the predicted metabolizer phenotype for these patients is not ultrarapid but intermediate or poor metabolizer depending on the second allele. As detection of *4A and *4B improves genotyping accuracy and metabolizer phenotype classification, an allele-specific PCR assay that can rapidly detect and discriminate the related *CYP2C19**4A, *4B, and *17 has recently been reported [89].

The role of variant *CYP2C19* alleles in drug response variability and adverse events, particularly with respect to clopidogrel response [90–93], is increasingly being recognized. As such, clinical *CYP2C19* genotyping is now broadly available, including point-of-care [94] and preemptive [95] testing programs, as well as practice recommendations for *CYP2C19*-directed antiplatelet therapy [86]. Similar to the ethnic-specific alleles implicated in warfarin dosing, genotyping appropriate *CYP2C19* variants prevalent among targeted patient ethnicities, such as *4B for the AJ, will undoubtedly improve clinical validity and utility when implementing *CYP2C19* testing for clopidogrel and/or other *CYP2C19*-metabolized drugs. However, given the lack of randomized clinical trial data on *CYP2C19*-directed therapy, evidence supporting clinical *CYP2C19* genotyping implementation is commonly derived from alternative study designs, which ultimately results in continued debate over clinical utility.

P450 oxidoreductase (POR) pharmacogenetics—The *POR* gene encodes an endoplasmic reticulum membrane NADPH-P450 oxidoreductase, which is the major electron donor for microsomal CYP450 enzymes [96]. Because POR is required at various steps in the cholesterol and steroid synthesis pathways, individuals with autosomal recessive POR deficiency exhibit characteristic abnormalities in both sterol and steroid metabolism. This condition manifests as a broad phenotypic spectrum that ranges from healthy infants with 21-hydroxylase to the more extreme Antley-Bixler syndrome, which is characterized by severe congenital craniofacial and skeletal anomalies. In addition to these Mendelian disorders of steroidogenesis, the principal role that POR plays in CYP450 function has prompted recent interest in the potential role of *POR* variants in drug response variability.

Despite the paucity of reported clinical studies on *POR* and drug response variability, the biological plausibility of atypical drug oxygenation due to discontinuity of electron flow from POR to CYP450 as a result of *POR* variants has prompted multi-ethnic allele discovery

and *in vitro* POR activity and enzyme conformation studies. For example, gene sequencing has identified common and rare *POR* variants in Caucasians, African Americans, Asians, and Hispanics, including the common *POR**10 (p.A503V). This allele results in decreased catalytic activity and, therefore, is a strong candidate for influencing drug response [97]. This is supported by its association with reduced CYP3A4 and CYP2D6 activities [98, 99] but not that of CYP1A2, CYP2C19, or 21-hydroxylase [100, 101], suggesting CYP-specific effects mediated by *POR* variants.

Regarding the Jewish population, a recent study identified 30 *POR* coding and flanking region variants in AJ and Moroccan Jewish cohorts [42]. Six of these variants were novel (Table 1), suggesting they may be unique to these Jewish populations [42]. Taken together, these data suggest that *POR* is a candidate gene for future clinical pharmacogenetic studies and that similar to *VKORC1* and *CYP2C19*, some Jewish populations likely harbor unique *POR* variants. However, given the only recently hypothesized role of *POR* in drug response variability, the clinical utility of *POR* genotyping is still very much unknown and untested.

Common pharmacogenetic variants in the Jewish population

Cytochrome P450 2D6 (CYP2D6)—CYP2D6 is involved in the metabolism of ~25% of commonly prescribed medications, including codeine, tamoxifen, antidepressants, antipsychotics, antiarrhythmics, opiates, and antiemetics [102]. Given its principal role in drug metabolism and interindividual variability in enzyme activity due to common variant alleles, Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines have been published for *CYP2D6*-guided codeine [103] and tricyclic antidepressant therapies [104]. The *CYP2D6* gene is extremely polymorphic with over 100 reported alleles and is unique among the *CYP450s* due to the occurrence of full gene copy number variants. Many of these variant alleles have known effects on CYP2D6 enzyme activity, which allows for genotype-based prediction of phenotype, typically classified as ultrarapid, extensive, intermediate, or poor metabolizer. Ultrarapid metabolizers possess multiple functional copies of the *CYP2D6* gene, and poor metabolizers have two loss-of-function alleles. Consequently, patients with these predicted phenotypes can be at increased risk for adverse effects or lack of efficacy when taking medications that are predominantly metabolized by CYP2D6. However, given the complexity of the *CYP2D6* gene and its extremely polymorphic nature, phenotype assignment from *CYP2D6* genotype data is challenging and an ongoing area of research [105, 106].

Due to their established effect on enzyme activity, some of the commonly interrogated *CYP2D6* alleles are *2–*10, *14, *17, *36, *41, and the gene duplication. Like other *CYP450* genes, the frequencies of these *CYP2D6* variants also vary among racial and ethnic groups. A considerable amount of the reported *CYP2D6* allele frequency data have recently been reviewed and summarized in the *CYP2D6*/codeine CPIC guideline [103], which underscores the variable frequencies across major worldwide racial and ethnic groups. There is very little *CYP2D6* frequency data reported for the Jewish population; however, one study on the AJ identified *2, *4, *10, *41, and copy number variants *1xN, *2xN, and *41xN as the most common AJ alleles (Table 1) [40]. These *CYP2D6* AJ allele frequencies translated to ultrarapid, extensive, intermediate, and poor metabolizer frequencies of 8.8%, 70.0%,

16.0%, and 5.2%, respectively. Future studies on *CYP2D6* in other Jewish groups are warranted to determine both common and unique allele frequencies in these populations.

Cytochrome P450 2C8 (CYP2C8)—CYP2C8 is involved in the metabolism of several commonly prescribed drugs, including paclitaxel, amodiaquine, troglitazone, amiodarone, verapamil, cerivastatin, and fluvastatin [107]. Although *in vitro* pharmacokinetic studies have suggested an important role for *CYP2C8* variant alleles in drug metabolism variability, additional clinical pharmacogenetic studies are needed as those reported have often been inconsistent in their conclusions [108]. The *CYP2C8* gene shares 74% sequence homology with *CYP2C9* [109], and of the 14 cataloged alleles, the most common reduced function variants are *2, *3, and *4 (Table 1). Targeted genotyping studies have identified significantly different *CYP2C8**2–*4 frequencies between the African-American, Asian, Caucasian, Hispanic, and AJ populations, with *5–*14 being very rare [37]; however, the AJ *CYP2C8* frequencies (Table 1) were consistent with those in the non-Jewish Caucasian population. Sequencing studies are therefore needed in the Jewish population to determine if they harbor unique *CYP2C8* alleles at appreciable frequencies.

N-Acetyltransferase 1 (NAT1) and 2 (NAT2)—NAT1 and NAT2 are N-acetyltransferase isozymes involved in the metabolism of aromatic amine and hydrazine drugs and carcinogens [110]. One of the most notable examples is the widely used anti-tuberculosis agent isoniazid, which is metabolized and inactivated by NAT2 [110, 111]. Interindividual variability in NAT2 enzyme activity segregates individuals into rapid, intermediate, and slow acetylator phenotypes. Importantly, individuals treated with isoniazid who are NAT2 slow acetylators have an increased risk of hepatotoxicity, and those who are rapid acetylators have an increased risk of early treatment failure. The slow acetylator phenotype is associated with *NAT2* reduced activity alleles (e.g., *5, *6, *7, and *14) and the rapid acetylator phenotype with the reference *NAT2**4 allele and other variants with normal activity (e.g., *12, *13) [112]. The *NAT1* reference allele is also *4, and a number of variant alleles have been reported; however, their effects on NAT1 activity and potential role in clinical drug response variability are less clear than those of *NAT2*.

Like the *CYP450* genes, *NAT2* allele frequencies differ across racial and ethnic groups with African populations having more *NAT2* allelic diversity compared to European and Asian populations [113]. There are limited *NAT1* and *NAT2* data available on Jewish populations; however, one study assessing predisposition to acute myeloid leukemia (AML) among Israeli patients genotyped a number of drug metabolism and transporter genes, including *NAT1* and *NAT2* [41]. Given that this study did not clarify the composition of their Israeli Jewish population, determining *NAT* allele frequencies for specific Jewish groups is not possible with these data (Table 1). Although *NAT* status was not associated with AML predisposition or prognosis, *NAT2* genotype data from the Jewish control cohort translated to rapid, intermediate, and slow acetylator frequencies of 6.4%, 30.3%, and 63.3%, respectively [41]. Future studies are therefore needed to determine *NAT1* and *NAT2* allele and acetylator phenotype frequencies among specific Jewish groups.

Other pharmacogenetic gene/drug pairs—Pseudocholinesterase is involved in the metabolism of certain anesthetic drugs, such as novocaine and succinyl choline, and is encoded by *BCHE*. Mutations in *BCHE* result in pseudocholinesterase deficiency, an autosomal recessive condition with an incidence of ~1 in 400 among Persian (Iranian) Jews [114]. Affected individuals cannot efficiently break down a number of anesthetic agents, which upon drug exposure can manifest as difficulty in breathing or muscle weakness post procedurally. Screening for the common *BCHE* mutation (p.D70G) in a US Persian Jewish subpopulation has been reported, which was well received by the community when coupled with proper counseling and recommendations for alternative anesthetic agents as needed [114].

Other more contemporary pharmacogenetic examples with increasing evidence for clinical utility include *TPMT* and thiopurines, *HLA-B* and abacavir/carbamazepine/allopurinol, *SLCO1B1* and simvastatin, *DPYD* and fluoropyrimidines, *CYP3A5* and tacrolimus, and *UGT1A1* and irinotecan. Many of these gene/drug pairs have available or in-progress CPIC practice guidelines detailing therapeutic options when certain genotypes are identified [115]; however, there is a paucity of literature on these genes and drugs reported in the Jewish population. Consequently, future research is necessary to determine if the actionable pharmacogenetic alleles for these drugs are also found in Jewish groups or if other unique variants are more prevalent.

Conclusions and future perspectives

A unique genetic architecture due to a history of population bottlenecks, expansions, and geographical isolation has made the Jewish people, particularly the AJ, a common model for gene mapping for both Mendelian and complex diseases. Initial pharmacogenetic studies on the AJ and other Jewish groups support the hypothesis that the Jewish population harbors unique pharmacogenetic alleles (e.g., *VKORC1* p.D36Y, *CYP2C19*4B*) as well as common drug metabolism variants prevalent in other populations of European ancestry (e.g., *CYP2C9*2*, *CYP2C19*2*, *CYP2D6*4*). These findings are undoubtedly only the beginning of pharmacogenetic variant discovery in the Jewish population. Future research on the AJ and other Jewish groups using whole-exome or genome sequencing is warranted to identify pharmacogenomic variants in this population and to enable studies on drug response phenotype association. In addition, interrogation of the pharmacogenetic genes that have CPIC practice guidelines is necessary to identify Jewish alleles that are potentially actionable for future clinical implementation research.

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Figure 1.

Principal component analysis (PCA) of Jewish and non-Jewish populations from an AJ Crohn's disease GWAS, reprinted from Kenny et al. [11].

(A) PCA showing the first and second eigenvectors plotting study participants, four HapMap reference samples [CEPH-Utah (CEU), Yoruban-Nigeria (YRI), Han Chinese (CHB), and Japanese (JPT)] and seven Jewish HapMap samples [AJ, European (Italian), Middle Eastern (Syrian, Iraqi, and Iranian), and SJ (Turkish and Greek)] [2]. (B) The same analysis excluding the YRI and CHB+JPT reference panels.

VKORC1 (16p11.2) **Figure 2.**

Schematic illustration of the *VKORC1* gene noting the location of common variants associated with warfarin sensitivity (above) and resistance (below).

The p.D36Y allele associated with high therapeutic warfarin doses and prevalent in the AJ population is highlighted by a gray box. Numbered black boxes represent exons, and numbers in parentheses below selected variants represent historical common nomenclature.

Figure 3.

Schematic illustration of the *CYP2C19* gene noting the location of selected star (*) alleles and relevant genotypes of the *17, *4A, and *4B alleles.

(A) The c.-806C>T (*17) and c.1A>G (*4) variants are in *cis* on the *4B haplotype prevalent among the AJ and are highlighted by a gray box. Numbered black boxes represent exons. (B) The *CYP2C19* haplotypes of the related *17 and *4A and *4B alleles.

Table 1

Pharmacogenetic variant alleles identified in Jewish populations.

Gene	Variant allele and major nucleotide substitutions	dbSNP ID ^a	Functional consequence	Jewish group ^b	Minor allele frequency	References
<i>ABCB1</i>	c.3435C>T	rs1045642	p.I1145I	AJ	0.322	Scott et al. [36]
<i>CYP2C8</i>	*2 (c.805A>T)	rs11572103	p.I269F	AJ	0.004	Martis et al. [37]
	*3 (c.[416G>A; 1196A>G])	rs1057910; rs11572080	p.R139K; p.K399R	AJ	0.076	Martis et al. [37]
	*4 (c.792C>G)	rs1058930	p.I264M	AJ	0.020	Martis et al. [37]
<i>CYP2C9</i>	*2 (c.430C>T)	rs1799853	p.R144C	AJ; SJ	0.127; 0.194	Scott et al. [38, 39]
	*3 (c.1075A>C)	rs1057910	p.I359L	AJ; SJ	0.081; 0.144	Scott et al. [38, 39]
	*5 (c.1080C>G)	rs28371686	p.D360E	AJ; SJ	0.001; 0.000	Scott et al. [38, 39]
<i>CYP2C19</i>	*2 (c.681G>A)	rs4244285	Splicing defect	AJ; SJ	0.146; 0.096	Scott et al. [36], Martis et al. [37]
	*4A (c.1A>G)	rs12248560	p.M1V	AJ; SJ	0.000; 0.004	Scott et al. [36], Martis et al. [37]
	*4B (c.[-806C>T; 1A>G])	rs28399504; rs12248560	Increased expression; p.M1V	AJ; SJ	0.020; 0.000	Scott et al. [36], Martis et al. [37]
<i>CYP2D6</i> ^c	*8 (c.358T>C)	rs41291556	p.W120R	AJ; SJ	0.000; 0.004	Scott et al. [36], Martis et al. [37]
	*15 (c.55A>C)	rs17882687	p.I19L	AJ; SJ	0.004; 0.004	Scott et al. [36], Martis et al. [37]
	*17 (c.-806C>T)	rs12248560	Increased expression	AJ; SJ	0.198; 0.159	Scott et al. [36], Martis et al. [37]
	*1xN	–	Increased expression	AJ	0.022	Scott et al. [40]
	*2 (2850C>T; 4180G>C)	rs16947; rs1135840	p.R296C; p.S486T	AJ	0.164	Scott et al. [40]
	*2xN	–	Increased expression	AJ	0.058	Scott et al. [40]
	*3 (2549delA)	rs35742686	p.R259Gfs	AJ	0.008	Scott et al. [40]
	*4 (100C>T; 1846G>A)	rs1065852; rs3892097	p.P34S; splicing defect	AJ	0.226	Scott et al. [40]
	*5 (gene deletion)	–	Gene deletion	AJ	0.008	Scott et al. [40]
	*6 (1707delT)	rs5030655	p.W152Gfs	AJ	0.002	Scott et al. [40]
<i>CYP4F2</i>	*9 (2615_2617delAAG)	rs5030656	p.K281del	AJ	0.008	Scott et al. [40]
	*10 (100C>T)	rs1065852	p.P34S	AJ	0.062	Scott et al. [40]
	*17 (1023C>T)	rs28371706	p.T107I	AJ	0.008	Scott et al. [40]
	*41 (2988G>A)	rs28371725	plicing defect	AJ	0.140	Scott et al. [40]
	*41xN	–	Increased expression with splicing defect	AJ	0.008	Scott et al. [40]
	*3 (c.1297G>A)	rs2108622	p.V433M	AJ	0.328	Scott et al. [38]
	*3 (c.*222A>C)	rs15561	3'UTR variant	Israeli Jewish	0.008	Muller et al. [41]
<i>NAT1</i> ^d						

Gene	Variant allele and major nucleotide substitutions	dbSNP ID ^a	Functional consequence	Jewish group ^b	Minor allele frequency	References
<i>NAT2</i> ^d	*10 (c.[*215A>T; *222A>C])	rs15561; rs1057126	3' UTR variants	Israeli Jewish	0.227	Muller et al. [41]
	*11 (multiple)	Multiple	Multiple variants	Israeli Jewish	0.075	Muller et al. [41]
	*14A (c.[560G>A; *215A>T; *222A>C])	rs4986782; rs1057126; rs15561	p.R187Q; 3' UTR variants	Israeli Jewish	0.008	Muller et al. [41]
	*14B (c.[560G>A])	rs4986782	p.R187Q	Israeli Jewish	0.008	Muller et al. [41]
	*15 (c.[559C>T])	rs030839	p.R187X	Israeli Jewish	0.011	Muller et al. [41]
	*22 (c.[752A>T])	s56172717	p.D251V	Israeli Jewish	0.003	Muller et al. [41]
	*5A (c.[341T>C; 481C>T])	rs1801280; rs1799929	p.I114T; p.L161L	Israeli Jewish	0.049	Muller et al. [41]
	*5B (c.[341T>C; 481C>T; 803A>G])	rs1801280; rs1799929; rs1208	p.I114T; p.L161L; K268R	Israeli Jewish	0.337	Muller et al. [41]
	*5C (c.[341T>C; 803A>G])	rs1801280; rs1208	p.I114T; K268R	Israeli Jewish	0.035	Muller et al. [41]
	*6A (c.[282C>T; 590G>A])	rs1041983; rs1799930	p.Y94Y; p.R197Q	Israeli Jewish	0.326	Muller et al. [41]
<i>POR</i>	*7B (c.[282C>T; 857G>A])	rs1041983; rs1799931	p.Y94Y; p.G286E	Israeli Jewish	0.030	Muller et al. [41]
<i>VKORC1</i>	p.S102P, p.V191M, p.D648N	–	Missense variants	AJ	0.003, 0.003, 0.003	Tomkova et al. [42]
	p.V164M, p.D344N, p.E398A	–	Missense variants	MJ	0.004, 0.004, 0.004	Tomkova et al. [42]
<i>VKORC1</i>	c.–1639G>A	rs9923231	Decreased expression	AJ; SJ	0.467; 0.500	Scott et al. [39]
	c.106G>T	rs61742245	p.D36Y	AJ; SJ	0.042; 0.006	Scott et al. [39], Loebstein et al. [43]

AJ, Ashkenazi Jewish; MJ, Moroccan Jewish; SJ, Sephardi Jewish.

^a rsID numbers as denoted in dbSNP (<http://www.ncbi.nlm.nih.gov/SNP/>).

^b Ethnicity and Jewish group is as defined by the source literature.

^c The CYP2D6 sequence annotation refers to common nucleotide numbering based on GenBank: M33388.1. For comprehensive CYP2D6 haplotype definitions, see the Human Cytochrome P450 Allele Nomenclature Committee website (<http://www.cypalleles.ki.se/cyp2d6.htm>).

^d For comprehensive NAT1 and NAT2 haplotype definitions, see the database of arylamine N-acetyltransferases (NATs) website (<http://nat.mbg.duth.gr/>).