American Journal of Medical Genetics 99:70–75 (2001)

Tay-Sachs Screening in the Jewish Ashkenazi Population: DNA Testing Is the Preferred Procedure

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A unique screening program for the identification of Tay-Sachs Disease (TSD) heterozygotes has been performed in the traditional Orthodox Ashkenazi Jewish (AJ) community since 1983. In recent years the program has utilized the biochemical assay for the determination of hexosaminidase A levels by the heat inactivation technique as well as by direct DNA analysis. The three mutations which were analyzed were those that have been shown to be prevalent among AJ TSD patients and carriers, namely the four nucleotide insertion mutation in exon 11 (1278+TATC), the splice mutation at the 5′ end of intron 12 (1421+1g→c), and the adult mutation, a Gly^{269}→Ser substitution in exon 5 (G269S). A total of 103,133 individuals were tested by biochemical analysis, and 38,197 of them were also assayed by DNA testing. Furthermore, 151 chromosomes from TSD patients or obligate heterozygotes were subjected to DNA analysis for one of the three mutations. DNA testing of the latter identified one of the three AJ mutations in every case, predicting a very high detection rate of heterozygotes in this community by this method. By contrast, the sensitivity of the enzyme assay ranged from 93.1% to 99.1% depending on the exclusion (inclusion) of inconclusive results as positive, while the specificity ranged from 88.1% to 98.8% depending on the inclusion (exclusion) of inconclusive results as positive. Our results strongly support the use of DNA testing alone as the most cost-effective and efficient approach to carrier screening for TSD in individuals of confirmed Ashkenazi Jewish ancestry.

KEY WORDS: Tay-Sachs Disease; Ashkenazi Jews; population screening; DNA testing; hexosaminidase A

INTRODUCTION

Tay-Sachs Disease (TSD, GM2 gangliosidosis type B, MIM# 272800) is a recessive neurodegenerative lysosomal storage disease caused by the deficiency of α chains of the hexosaminidase A (hex A) isozyme [Gravel et al., 1995]. TSD is found at relatively high frequency in the Ashkenazi Jewish (AJ) population with an incidence of 1:3,600 vs. 1:360,000 in the general non-Jewish population [Gravel et al., 1995; Kaback et al., 1997]. The identification of the deficient enzyme opened the door for screening programs in this population for the detection of heterozygotes with the goal of ascertaining high-risk couples (in which both spouses are heterozygotes) before the birth of the first affected offspring.

The preferred technique for the determination of hex A in the screening programs is the heat inactivation procedure which enables mass screening and is considered accurate [O'Brien et al., 1990; Kaback et al., 1997]. This screening was initiated in 1971 in the US [Kaback et al., 1997] and later was established in Israel and other countries with high concentrations of Ashkenazi Jews. These programs have been responsible for the reduction by more than 90% in the birth of TSD affected children in this population [Kaback et al., 1993], an impressive success, which was later applied as a model for similar projects for the prevention of prevalent genetic disorders in other populations.

The genes for the α and β chains of the hex A isozyme were cloned [Proia and Soravia, 1987; Proia, 1998], which enabled the identification of TSD-causing mutations. Three mutations were identified among AJ TSD patients, namely 1278+TATC, 1421+1g→c and G269S.

Abbreviations used: ES, enzyme serum assay; EL, enzyme leukocyte/platelet assay; DNA, DNA testing; IAP, including inconclusive results as positive; IAN, including inconclusive results as negative.

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Received 4 August 2000; Accepted 6 November 2000

Published online 16 January 2001

Homozygosity and compound heterozygosity for either of the first two mutations cause the infantile type while the third mutation is found in the adult form in compound heterozygosity with one of the first two mutations [Arpaia et al., 1988; Myerowitz and Costigan, 1988; Navon and Proia, 1989; Paw et al., 1989; Myerowitz, 1997].

Despite the success of the TSD screening programs in the AJ population, the traditional Orthodox AJ community, which comprises about 10% of the AJ population, did not initially participate in these programs as it was not suitable for their requirements stemming from their religious and moral beliefs. Like many people of various religious or philosophical perspectives, observant Jews view having children as the most fundamental expression of their humanity, and consider birth control and abortion as impermissible according to Jewish law. However, individuals may seek special dispensation from their rabbi in extreme circumstances on a case-by-case basis. Consideration of this basic value on the absolute sanctity of human life was a founding principle of the Dor Yeshorim screening program.

In 1983 a not-for-profit organization, Dor Yeshorim, was established. It provides confidential and anonymous screening for TSD and other diseases which addressed the requirements of this community. Because abortion is generally not accepted as an option, it is a premarital program for individuals before their engagement or earlier in a relationship [Broide et al., 1993].

Dor Yeshorim has developed a novel system that provides anonymous testing in an effort to prevent the disease and at the same time avoid the potential stigma, discrimination, and/or burden of knowledge that could be attached to divulging an individual's carrier status. As these concerns are being discussed by the genetics community, the Dor Yeshorim program is one that could be studied for new ideas about minimizing the risks associated with finding out about our genetic constitution. The program does not record any names. All information is stored by a confidential ID number and birth date. Reporting is based on compatibility of couples. If at least one party is a non-carrier, the couple will be told they are compatible for the specific disease tested. Only couples where both members are carriers of the same disease are informed of their results and offered counseling. The couple maintains the autonomy and privacy to make their own decision regarding whether or not to pursue an at-risk marriage.

Dor Yeshorim has identified over 250 prospective couples where both members were found to be carriers of the same disease. Given this information, the prospective couples were afforded the opportunity to choose another marriage partner who would not pose a risk for an affected child. The program was first operated in the U.S., and later applied in Canada, Europe, and Israel. At present the program tests, in addition to TSD, cystic fibrosis [Abeliovich et al., 1996], Canavan disease, and Fanconi anemia Type C, all of which are relatively prevalent in the AJ population.

Initially, TSD screening was done using biochemical assay. From 1992–1998, a portion of Dor Yeshorim's specimens were tested by both the enzyme determination procedure as well as DNA analysis for the three AJ mutations. This has enabled us to compare the accuracy and reliability of the two procedures for carrier identification. The data presented here clearly demonstrate the advantage of DNA analysis versus the biochemical test as an accurate, consistent, rapid, and cost-effective procedure for heterozygote identification in the AJ population.

MATERIALS AND METHODS

Enzyme Determination

Hex A was determined in serum, leukocyte, or platelet extracts by the heat inactivation technique as previously described [Broide et al., 1993]. Four different testing centers performed these determinations. Each is a quality controlled laboratory undergoing regular certification for performing these enzyme assays. Three labs perform serum tests with follow-up based on analysis of white blood cells (leukocytes). One lab performs serum tests with follow-up based on platelet analysis. Each laboratory uses its own cutoff points for carrier and inconclusive status, based on its own operating procedures. For this analysis, for each tested individual we used the status (carrier, inconclusive, or non-carrier) reported to us by the laboratory. Hex A determinations in leukocytes or platelet extracts, in the Dor Yeshorim program, were performed only if both partners were in the carrier/inconclusive range by serum analysis. As for the serum tests, each laboratory specifies its own cutoffs for carrier or inconclusive status based on leukocyte/platelet analysis. Again, when such tests were performed, we used the carrier status results reported to us by the laboratory.

Mutation Analysis

DNA was extracted from lymphocytes by conventional methods and the three AJ mutations (1278+TATC, 1421+1g→c and G269S) were determined as described [Triggs-Raine et al., 1990].

Subjects

Information regarding family heritage and country of origin are required to be accurately completed at the time of testing. According to information supplied, the individuals tested in the Dor Yeshorim screening program described here were Ashkenazi Jews. This was defined as having all four grandparents of Jewish origin deriving from Central or Eastern Europe. A total of 103,133 non-patients were analyzed by the serum assay; of these, 1,228 were further evaluated by leukocyte/platelet assay. A total of 38,197 were tested by both DNA analysis and serum assay, while 1,035 of these were also subjected to the leukocyte/platelet analysis. In addition to screening non-patients, we also evaluated 151 chromosomes from TSD patients or

obligate carriers by DNA analysis for the three AJ mutations.

Statistical Analysis

The different testing procedures were evaluated by calculating the sensitivity (1 — false negative rate) and specificity (1 — false positive rate). To address the question of which TSD screening approach is optimal for the AJ population — enzyme assay, DNA testing, or some combination of the two — we compared the sensitivity and specificity of several possible testing scenarios, as follows: (I) Enzyme serum assay alone, including inconclusive test results as positive (abbreviated ES-IAP); (II) Enzyme serum assay alone, including inconclusive test results as negative (abbreviated ES-IAN); (III) Enzyme serum assay, followed up by leukocyte/platelet analysis for those with positive or inconclusive serum results, including inconclusive leukocyte/platelet results as positive (ES+ELP-IAP); (IV) The same as III, except inconclusives by leukocyte/platelet analysis are considered negative (ES+ELP-IAN); (V) DNA analysis alone (DNA); (VI) DNA and enzyme serum analysis, including DNA-negative but serum inconclusive results as negative (DNA+ES-IAN); (VII) DNA and enzyme serum analysis, following up DNA negative and serum assay positive and inconclusives with the leukocyte/platelet assay, counting leukocyte/platelet inconclusives as negative (DNA+ES+ELP-IAN). For the last two scenarios, we do not include the case of counting inconclusives as positive because the increase in sensitivity by that approach was modest compared to a larger decrease in specificity. Although most labs ultimately consider inconclusives as positive, we also included in our analysis the disposition of such individuals as negative to evaluate the impact on false positive and false negative rates.

Because testing is couple-based, we considered sensitivity and specificity for couples as well as individuals. A couple is considered at risk if both members carry a TSD mutation but not at risk if at least one member does not. Sensitivity is calculated as the square of the individual sensitivities (i.e. the probability that both carriers are detected as such). Specificity is calculated for each not-at-risk mating type (i.e. non-carrier x non-carrier and carrier x non-carrier) as the probability that at least one member is considered a non-carrier, with the final specificity calculated as the weighted average across the two mating types. Assuming a true TSD carrier frequency of 4.3% (as observed in this study), the proportion of not-at-risk matings that are carrier x non-carrier is 8.25%, versus 91.75% that are non-carrier x non-carrier. Couple-based sensitivities and specificities were calculated using the individual sensitivities we obtained from DNA analysis of obligate TSD chromosomes (plus previous literature reports) and the enzyme analyses compared with DNA testing results described above. Because at-risk couples are expected to be infrequent (.043x.043 = .00185, or 1 in 541 couples), it is also important to consider the actual expected number of false negative and false positive results from each of these screening paradigms. To do so, we considered the testing of 100,000 couples and determined how many of the expected 185 at-risk couples (100,000/541) would be called not-at-risk (i.e. false negatives), and how many of the expected 99,815 not-at-risk couples would be called at-risk.

RESULTS

DNA Analysis of TSD/Carrier Chromosomes

The results of DNA analysis performed on unrelated TSD patients and obligate heterozygotes (parents of TSD patients), a total of 151 chromosomes, are presented in Table I. All the TSD alleles in this analysis were identified as one of the three AJ mutations. It was unambiguously verified that all the tested individuals were Ashkenazi Jews by origin. The data obtained by the DNA analysis for the three TSD mutations clearly indicate that heterozygotes will be detected by the analysis of the three AJ mutations with high accuracy. Previous data reported a detection rate (sensitivity) of obligate heterozygotes ranging from 92% to 100% by testing for these three mutations [Triggs-Raine et al., 1990; Grebner and Tomczak, 1991; Landels et al., 1993]. Combining the results of these three studies with the current data gives a sensitivity of 251/254 = 98.8% for carrier detection by DNA analysis.

Enzyme and DNA Analysis of Non-Patients

From 1983–1998, a total of 103,133 individuals were tested for hex A levels by the serum assay. Of these, 4,877 (1:21) were in the carrier range and 7,976 (1:13) were inconclusive. Some 1,228 individuals who were found in the carrier/inconclusive range in serum were retested by enzyme assay in leukocytes or platelets and 513 were found to be in the carrier/inconclusive range. Thus, of the 1,228 specimens that underwent further analysis, only 41.8% of the carriers/inconclusives by serum were confirmed as carriers or inconclusives by leukocytes or platelets.

A total of 38,197 individuals was analyzed by DNA testing in addition to the enzyme determination. Of these, 1,634 were positive for one of the three AJ mutations, a carrier frequency of 4.28%, while 36,563 did not carry one of the three mutations. Table II summarizes the results of the enzyme determinations as compared to DNA analysis. Using the mutation results as the gold standard, the comparison from the general screening yielded the following. Of the 36,563 individuals without mutations, 422 were found to be carriers by serum assay, yielding a false positive rate of

TABLE I. Mutation Analysis for Common Ashkenazi Jewish TSD Mutations in Obligate Heterozygotes and Affected Patients

Mutation	Number (%)
1278+TATC	136(90.1%)
1421+1g→c	13(8.1%)
G269S	2(1.3%)
Other	0(0.0%)
Total	151(100.0%)

TABLE II. Comparison of Biochemical Determinations With DNA Analysis

Status (by the biochemical test)	No of individuals	Positive: mutation identifed	Negative: no. of mutation identified
Carriers by serum	1,944	1,522	422[b]
Inconclusive by serum	4,040	97	3943
Normal by serum	32,213	15[a]	32,198
Carriers by leukocyte/platelet	234	220	14[b]
Inconclusive by leukocyte/platelet	61	8	53[c]
Normal by leukocyte/platelet	740	0	740

[a]One person had a bone marrow transplant.
[b]Including 5 individuals in whom the pseudodeficiency mutation was identified.
[c]Including 2 individuals with the pseudodeficiency mutation.

422/36,563 = 1.2%, or a specificity of 98.8%. Among the same 36,563 individuals, 3,943 had serum enzyme results in the inconclusive range. Including these individuals as carriers increases the false positive rate to 4,365/36,563 = 11.9%, or reduces the specificity to 88.1%. Out of a total of 1,634 mutation carriers, 15 were considered to be normal by the serum enzyme assay, yielding a false negative rate of 15/1,634 = 0.9%, or a sensitivity of 99.1%. An additional 97 were determined to be inconclusive by serum test; including these as negative would result in a false negative rate of 112/1,634 = 6.9%, or a sensitivity of 93.1%. Thus, including the inconclusives as positive yields an unacceptable false positive rate, while including them as negative yields an unacceptable false negative rate.

Even the more sensitive platelet and leukocyte method, typically used for follow up of inconclusive results by serum assay, still demonstrated poor operating characteristics. A total of 1,035 individuals was tested by both leukocyte/platelet assay and mutation analysis. In this group were 228 identified with one of the three mutations, while 807 were non-carriers. Among the non-carriers, 14 were identified as carriers by leukocyte/platelet analysis, yielding a false positive rate of 14/807 = 1.7%, or a specificity of 98.3%. In this group were 53 inconclusive individuals. Including them as positive yields a false positive rate of 67/807 = 8.3%, or specificity of 91.7%. Among the 228 mutation carriers, none was found to be normal by leukocyte/platelet assay, yielding a false negative rate of 0.0% or sensitivity of 100%. In this same group, eight individuals were found to be inconclusive; including these subjects as normal gives a false negative rate of 8/228 = 3.5%, or sensitivity of 96.5%. Again, including inconclusives as carriers yields an unacceptable false positive rate, while including them as non-carriers gives an unacceptable false negative rate. Out of a total of 1,634 subjects who ultimately were identified with a mutation, 14 individuals (0.9%) tested in various quality controlled centers had serum enzyme values in the normal range. These 14 false negatives by serum assay occurred despite the fact that the range of carrier/inconclusive was broadened in the present work as compared to previous screening programs [Lowden and Davidson, 1977; Padeh et al., 1977].

During 1999, Dor Yeshorim conducted further research to address the issue of enzyme assay specificity. Some 478 samples that were found to be positive/inconclusive by serum enzyme analysis and negative for the three common TSD mutations (1278+TATC, 1421+1g→c, G269S) were analyzed for a total of 10 rare TSD/pseudodeficiency mutations (ΔTTC910–912 or 913–915; C540G; C509A; G1444A; Δ1039–1056; G1176A; C739G; C745T; G748A). Five carriers of a pseudodeficiency mutation were found as well as one carrier of the C509A mutation. Ten of the 14 specimens that were also positive/inconclusive by leukocyte/platelet, and negative for the three common TSD mutations, were analyzed for the 10 above mentioned mutations. Two were found to be carriers of pseudodeficiency mutations [Tomczak et al., 1993]. The remaining eight underwent gene sequencing with no TSD mutation detected.

Evaluation of Screening Paradigms

The results of our analysis of sensitivity and specificity of seven different approaches to screening (see Methods) are given in Table III. We focus on the

TABLE III. Individual and Couple-Based Sensitivity and Specificity For Seven Different Screening Paradigms Plus Expected Number of False Negatives and False Positives From Screening 100,000 Couples*

	Individual		Couple		100,000 couples	
Paradigm	Sensitivity	Specificity	Sensitivity	Specificity	False pos	False neg
ES-IAP	99.08%	88.06%	98.17%	97.72%	2,276	3
ES-IAN	93.15%	98.85%	86.77%	99.90%	100	24
ES+EL-IAP	99.08%	99.01%	98.17%	99.92%	80	3
ES+EL-IAN	95.60%	99.79%	91.39%	99.98%	20	16
DNA	98.82%	100.0%	97.65%	100.0%	0	4
DNA+ES	99.92%	98.85%	99.84%	99.89%	110	0.3
DNA+ES+EL	99.88%	99.79%	99.76%	99.98%	20	0.4

*ES, enzyme serum assay; EL, enzyme leukocyte/platelet assay; DNA, DNA testing; IAP, including inconclusive results as positive; IAN, including inconclusive results as negative.

number of incorrect results out of 100,000 couples screened. Enzyme serum assay alone, counting inconclusives as negative, yields an unacceptable number of false negatives (24); although counting inconclusives as positive yields an acceptable number of false negatives (three), it provides an unacceptable number of false positives (2,276). Following up serum assay positives and inconclusives by the leukocyte/platelet assay does reduce the number of false positives dramatically (to 80) while maintaining an acceptable false negative number (three). However, the added precision in this case comes at significant increased expense/effort, due to the large number of subjects that will need to be evaluated by the more difficult test.

By contrast, the numbers in Table III demonstrate that DNA testing alone provides extremely reliable results, with only four false negatives expected and no false positives. Adding enzyme assay to DNA testing can eliminate the expected four false negatives, but at the expense of producing 110 false positives (for serum analysis alone) or 20 false positives (if follow-up by leukocyte/platelet is employed), not to mention the additional time and financial expense required. Considering that DNA testing is now less expensive than enzyme serum assay, these results argue strongly for DNA analysis alone.

DISCUSSION

Serum analysis has been the method of choice for TSD screening programs for a number of reasons. Serum analysis is financially economical, can be done on a mass scale due to automation, and can even be done from frozen specimens. However, serum analysis can also be affected by pregnancy, diabetes, or use of medications. Having the subject undergo additional analysis may present a challenge in logistics when additional blood samples are required, as well as creating anxiety for testees, especially in a prenatal scenario or when a prospective couple is emotionally involved.

The more reliable platelet and leukocyte methods also have significant drawbacks and are therefore not suitable for general screening programs. They require fresh samples, and therefore can only be processed in a limited time frame. They are also more expensive and labor intensive.

The major problem with the enzyme assay can be viewed as the overlap in enzyme activity distributions between TSD carriers and non-carriers. False negatives can be minimized by setting a high threshold for enzyme activity, but at the expense of increasing the false positive rate. Similarly, setting a low threshold minimizes false positives at the expense of increasing false negatives. The solution to this problem has been to characterize subjects with values in the overlap region as inconclusive, requiring additional testing, which also leads to additional anxiety and expense. Even then, there still remains a false positive and false negative rate of about 1%.

By contrast, DNA testing offers a highly specific approach to screening in the AJ population. At question is the sensitivity of using DNA analysis alone. In our study of 151 chromosomes, all TSD affected and obligate carriers possessed one of the three AJ TSD mutations. Our study contains, by far, the largest number of such subjects. The next largest study, that of Triggs-Raine et al. [1990], found that one subject out of 62 did not carry a classic AJ mutation. The study of Landels et al. [1993] found no such cases out of 15. It was only the small study of Grebner and Tomczak [1991] that found two out of 26 cases not to carry one of the AJ mutations. From the four studies combined, the sensitivity of DNA analysis is 98.8%. However, in practice, the sensitivity might even be higher if high assurance of AJ descent of tested subjects is provided.

Although much attention has been paid to the impact of false negatives (potentially leading to missed affected offspring), false positive assignments, which typically go unconfirmed, can also have significant negative impact and need to be minimized. For example, in the context of the Dor Yeshorim program, couples who are already involved face serious decisions about whether to marry upon finding out that both are TSD carriers.

Screening projects are also evaluated by the financial expenditures. In our recent experience to date, the cost for serum enzyme analysis has been $30 per sample and $50 per sample for leukocyte/platelet testing. Given the proportion of subjects requiring both tests (seeTable II), the average cost of enzyme analysis per individual tested is about $38. By contrast, our DNA analyses have been based on testing for four diseases (and 12 mutations) found in the AJ population: Tay-Sachs disease (three mutations), cystic fibrosis (six mutations), Canavan disease (two mutations) and Fanconi anemia Type C (one mutation). The test for the 12 mutations costs $50 per subject; thus, on a prorated basis, testing for the three Tay-Sachs disease mutations costs $12.50, which is approximately one-third the cost of the enzyme assay. As DNA testing kits become more readily available and automated, we can also anticipate an even greater cost savings, perhaps to one-quarter the expense of enzyme analysis. It has also been suggested [Grebner and Tomczak, 1991; Fernandes et al., 1992; Natowicz and Prence, 1996] that the two procedures can be combined, namely biochemical and DNA analysis, for properly conducting this program, although this might lead to prolonged waiting periods and increased costs. In light of our results as given in Table III, DNA analysis alone appears sufficiently accurate to be completely justified as the analytical procedure of choice for individuals of confirmed AJ heritage. While, in theory, the projected four at-risk couples out of 100,000 to be missed by DNA analysis alone could be identified by enzyme assay, this would come at great additional expense, and still lead to a sizeable number of false positive results. Another way to view this conclusion is that after a negative screening test for the three AJ mutations, an AJ individual would be at the same, or lower risk of being a TSD carrier as non-Jews, who are not routinely screened. A suitable analytical kit which includes the three AJ mutations will facilitate the tests, permit increased numbers of

simultaneous tests, and make it operational for every genetic center.

Previous reports have indicated the presence of a pseudodeficiency allele in carriers [Tomczak et al., 1993]. The allele is involved in reduced serum hex A activity while intracellularly the enzyme levels are normal. It is not associated with a disease either in homozygosity or in compound heterozygosity with a TSD allele. It is apparently in low frequency in the population tested in the Dor Yeshorim program, but it is likely to account for some of the false positive results by serum analysis. Since this mutation is not involved with any clinical abnormalities, it is not essential to include it among the mutations tested in this project.

The data presented here were obtained by the Dor Yeshorim program which includes primarily traditional Orthodox Jews from around the world. The carrier frequency by mutation analysis was found to be 4.29% (1:23), while the carrier frequency in the AJ population at large was previously determined to be 3.57–3.85% (1:26–1:28). Furthermore, the mutation distribution among TSD carriers was also different in the Dor Yeshorim samples versus the AJ population at large. The most frequent mutation, 1278+TATC was found to account for 88.7% of the TSD alleles among the non-patient carriers in this population, and 90.1% among TSD patients and obligate carriers, as compared to approximately 82% in the general AJ population [Paw et al., 1990; Triggs-Raine et al., 1990; Grebner and Tomczak, 1991; Fernandes et al., 1992; Han-Wook et al., 1993; Kaback et al., 1993; Landels et al., 1993; Myerowitz, 1997]. The traditional Orthodox community comprises about 10% of the total AJ population and is mostly isolated from the larger, secular AJ population. The TSD carrier frequency appears higher in this community due to an elevated frequency of the 1278+TATC insertion. A more thorough study of this community is required to determine whether these differences stem from the origin of this group in a defined region in Europe or from secondary founder effects, and whether other genetic disorders prevalent in the AJ population are differently distributed in this group as compared to the general AJ population.

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