

Tay Sachs disease in Australia: reduced disease incidence despite stable carrier frequency in Australian Jews

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Tay Sachs disease (TSD) is an autosomal recessive lysosomal storage disorder caused by mutations of the *HEXA* gene¹ (Mendelian Inheritance in Man [MIM] number, *606869; gene map locus, 15q23-q24)² that cause hexosaminidase A enzyme deficiency.³ It is 100 times more common in Ashkenazi (European) Jews (carrier frequency, 1 in 27) than in general populations (carrier frequency, 1 in 250).⁴ Affected babies appear normal at birth, then experience slow neurological decline and death in infancy (infantile TSD) or early childhood (intermediate TSD). No cure or effective treatment exists.

Preconception genetic screening programs for TSD have been introduced in Jewish communities worldwide to determine individuals' carrier status.^{5–8} Ninety-nine per cent of TSD cases among Jewish people are caused by three known *HEXA* mutations.⁹ Prospective identification of risk allows individuals and couples to make informed decisions about reproduction.

Based on international best-practice principles,^{8,10,11} Australian genetic screening programs for TSD¹² have targeted senior Jewish high school students in Sydney (from 1995 to 2012 through the Australasian Community Genetics Program, Laboratory and Community Genetics Department, Pacific Laboratory Medicine Services [PaLMS], Pathology North) and in Melbourne (from 1998 to 2011 through Victorian Clinical Genetics Services [VCGS]; and in 2012 through Austin Health). Sydney and Melbourne are home to Australia's two largest Jewish communities, where 50%–70% of Jewish high school students attend schools that access screening (Eckstein G. Demography of the Sydney Jewish community: an overview of information from the 2006 Census. Unpublished report commissioned by the Jewish Community Appeal (JCA); copies available on

Abstract

Objectives: To evaluate the outcomes of preconception screening of Jewish Australians for Tay Sachs disease (TSD) carrier status on Jewish TSD-affected births.

Design, participants and setting: Epidemiological observational study involving a complete retrospective audit of infantile and intermediate TSD cases diagnosed in Sydney and Melbourne between 1 January 1995 and 31 December 2011 (Royal Children's Hospital Melbourne; Pacific Laboratory Medicine Services, Pathology North, NSW Health Pathology, Sydney; Victorian Clinical Genetics Services, Melbourne; and SA Pathology, Adelaide), and carrier frequency among Jewish high school students attending schools participating in TSD screening programs over the same period.

Main outcome measures: Jewish TSD carrier frequency; and expected versus observed Jewish TSD-affected births.

Results: The 2006 Census indicated that most of the total 88 826 Jewish Australians live in Melbourne (46%) and Sydney (40%). The 7756 Jewish high school students screened for TSD in Sydney and Melbourne during the study period had a carrier frequency of one in 31 (3.26%; 95% CI, 2.89%–3.68%). The estimated expected number of TSD-affected births in Melbourne and Sydney in 1995–2011 was 4.1 for Jewish births and 7.4 for other births (a ratio of Jewish to non-Jewish births of 1:2). The actual number was 12 (four in Sydney and eight in Melbourne), of which two were Jewish (a ratio of Jewish to non-Jewish births of 1:5). This finding of fewer than expected Jewish TSD cases coincided with a period during which screening programs were operating. There have been no Jewish TSD-affected children born to parents who were screened previously.

Conclusion: Community education, appreciation of autosomal recessive inheritance and genetic carrier screening before pregnancy are the likely factors in our finding of fewer than expected Jewish babies with TSD. Ongoing outcome monitoring must continue.

request from <http://www.jca.org.au>). The design of the Sydney program, on which the Melbourne program is based, has previously been described.⁷ Jewish-community-funded screening is free to students and uptake is high (99.6%).¹³ Screening programs offer testing for additional conditions relevant to the target community, including Fanconi anaemia, familial dysautonomia, Canavan disease, Bloom syndrome, glycogen storage disease type 1a, mucopolysaccharidosis type IV, Niemann–Pick disease type A and cystic fibrosis.

An important measure of the success of a genetic screening program is the reduction of target disease incidence over time. Other measures of success include access to and uptake of screening in the target population.¹⁴ Here, we report the outcomes of Jewish screening programs for TSD on the incidence of TSD-affected births in Sydney and Melbourne from 1995 to 2011, inclusive.

Methods

We retrospectively audited all TSD cases diagnosed in Sydney and Melbourne from 1995 through 2011. All samples were processed by one or more of three Australian laboratories (PaLMS, Pathology North, NSW Health Pathology, Sydney; VCGS, Melbourne; and SA Pathology, Adelaide). Laboratory records from these centres pertaining to each case were reviewed. Records of cascade screening (ie, systematic screening of relatives of affected infants) were identified. We audited all laboratory testing for TSD case diagnosis and carrier screening during the study period. This included diagnosis of TSD cases, cascade screening and screening program referrals. Between 50% and 70% of Jewish high school students attend Jewish high schools that participate in TSD screening programs. Within TSD screening programs, there is 99%

1 Summary of results from Tay Sachs disease (TSD) screening programs in Melbourne and Sydney, 1995–2011

TSD screening program	Total students screened	Carriers	Carrier frequency	95% CI
Melbourne	4097	129	1 in 32 (3.15%)	2.66%–3.73%
Sydney	3659	124	1 in 30 (3.39%)	2.85%–4.03%
Total	7756	253	1 in 31 (3.26%)	2.89%–3.68%

2 Summary of Australian Bureau of Statistics births data for Sydney, New South Wales, Melbourne and Victoria, 1995–2010

Year	Sydney	New South Wales	Melbourne	Victoria
1995–1999	Unpublished	433 833	Unpublished	303 833
2000–2004	285 037	430 151	224 458	302 750
2005–2009	303 045	450 887	257 095	340 931
2010	65106	95 918	54 023	70 568
2011	Unpublished	Unpublished	Unpublished	Unpublished
Estimated births 1995–2011	1 009 470	1 499 000	827 700	1 081 700

3 Expected and observed Tay Sachs disease-affected births in Sydney and Melbourne, 1995–2011

	Jewish	Non-Jewish	Total	Overall ratio of Jewish to non-Jewish TSD-affected births
Expected births	4.1	7.4	11.5	1:2
Observed births	2	10	12	1:5
Rate ratio (95% CI)	0.49 (0.06–1.76)	1.35 (0.65–2.49)		

uptake among students offered screening.

Parents of a child with TSD are routinely asked about Jewish heritage, and this information was obtained from laboratory records, medical records and clinical genetics files. Data from testing laboratories and medical records were cross-referenced to eliminate duplication of cases.

We identified all TSD cases diagnosed and obtained the medical and laboratory records for audit. For all TSD cases identified, parental TSD carrier results were on record. We cross-referenced case and cascade screening results with screening program data. Although our audit of laboratory results identified family members of TSD-affected Jewish children who chose to undertake cascade screening and were found to be TSD carriers, no further analysis was performed on the results of extended cascade screening.

Statistical analysis

We obtained summary statistics for births registered in Sydney and Melbourne in 1995–2010.^{15–17} Births for 2011 (Australian Bureau of Statistics

[ABS] unpublished data) were estimated based on consecutive data for the previous 15 years.^{15–17} Jewish births for 1995–2010 were proportionally estimated from the 2006 Australian census report,^{18,19} and we used the number of 0–4-year-olds identified as Jewish as a proxy measure for births during this 5-year census period.

De-identified data relating to all students screened for TSD in Sydney in 1995–2011 and Melbourne in 1998–2011 were used to calculate TSD carrier frequency among Jewish students. This was used to model expected TSD-affected births among Jewish Australians. Carrier frequency for TSD in the general Australian population has not been measured. We used the World Health Organization estimate for TSD carrier frequencies in mixed populations (1 in 250 or 0.4%)²⁰ to model expected TSD-affected births among non-Jewish Australians.

The predicted numbers of infants born with TSD in Jewish and non-Jewish Australians were calculated using the Hardy–Weinberg equation.²¹

All statistical analyses were conducted using SPSS version 15.0 (IBM SPSS Statistics).

Ethics approval

Ethics approval was obtained from the Northern Sydney Local Health District Human Research Ethics Committee (HREC) and the Royal Children's Hospital Melbourne HREC.

Results

In the 2006 census, 88 826 of a total 19 855 288 Australians (0.45%) identified themselves as Jewish; 46% of Jewish Australians lived in Melbourne and 40% in Sydney.

Box 1 shows that the 7756 Jewish high school students screened had a TSD carrier rate of one in 31 (3.26%); rates were similar in Sydney (3.39%) and Melbourne (3.15%).

Box 2 shows ABS births data for Melbourne and Sydney in 1995 through 2011.^{15–17}

The 2006 Australian census recorded 4394 Jewish children aged 0–4 years in Melbourne and Sydney.¹⁸ The census-based estimate of Jewish births in Melbourne and Sydney in 1995–2011 was 14 940. Box 3 shows numbers of observed and predicted TSD-affected babies born in Sydney and Melbourne in 1995–2011; a total of 12 babies with TSD were born in this period — four in Sydney and eight in Melbourne — of whom two were Jewish.

The observed ratio of Jewish to non-Jewish TSD-affected births was 1:5 compared with the expected ratio of 1:2. No Jewish TSD carrier identified through screening has had a TSD-affected child.

Our audit showed that no parents of TSD-affected Jewish children had participated in screening, and no screening program participants were parents of TSD-affected children.

Discussion

Twenty years after the introduction of TSD carrier testing in Australia,¹³ there have been fewer than expected Jewish TSD-affected births (Box 3). Further, no genetic carrier identified through screening has had a TSD-affected child. As many of these individuals, now aged 16–38 years, have not commenced and/or completed their families, the full impact of the screening program is yet to be realised.

During the study period, most extended families of TSD-affected infants underwent cascade genetic screening, and no parents of an infant with TSD had further TSD-affected children. This is a strong demonstration of the effectiveness of community genetic screening for TSD, supported by appropriate laboratory testing infrastructure.

Current Jewish Australian screening program carrier frequencies are comparable to international Jewish carrier frequencies from 1970 to the present.⁵ TSD predominantly affects those of Ashkenazi Jewish ancestry. Of 4105 Australian Jewish high school students screened for TSD in 1995–2007, 78% of participants and 95% of carriers were Ashkenazi.²² TSD carrier frequencies were 1 in 25 for Ashkenazi Jews and 1 in 97 for those of mixed and non-Ashkenazi Jewish heritage.²² No distinction is made in census data between Ashkenazi and other Jewish Australians, so subpopulation analysis was not performed.

The ABS and Jewish community organisations estimate that Jewish Australians underreport their religion in the census, and usually apply a correction factor of 20% (Eckstein G. Unpublished report; copies available on request from <http://www.jca.org.au>) We did not apply any correction factor to estimates of Jewish births or expected numbers of Jewish TSD cases.

Our study has limitations relating to the rarity of TSD, the low disease frequency and the small size of the Australian Jewish population. These factors prevented the reduction in observed Jewish TSD cases reaching statistical significance in our study. To demonstrate a significant reduction in cases, it would take 70 years to observe around 12 Jewish TSD cases, using the Poisson model.²³

TSD testing is now less invasive,²⁴ and the cost of laboratory testing has fallen over the 16-year period

described in this study. Outreach screening strategies to extend the benefits of TSD preconception screening to a wider target population should be considered.

Overall, we found that since TSD screening commenced in Australia, the number of observed TSD cases in Jewish Australians has halved compared with predictions, while carrier frequency remains high (1 in 31). Preconception carrier screening, supported by community education and the appreciation of autosomal recessive inheritance are the likely key factors explaining the fewer than expected Jewish babies born with TSD.

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