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The Prevalence of HLA–B27 in the US: Data From the US National Health and Nutrition Examination Survey, 2009

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Abstract

Objective—To carry out the first large-scale population study of the prevalence of HLA–B27 in the US, which is needed for public health planning purposes because of recent improvements in medical therapy and diagnostic testing for ankylosing spondylitis (AS).

Methods—The national prevalence of HLA–B27 was determined as part of the 2009 US National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey monitoring the health and nutritional status of the US civilian, noninstitutionalized population. DNA polymerase chain reaction analysis was conducted in samples from 2,320 adults ages 20–69 years from this nationally representative sample.

Results—The age-adjusted US prevalence of B27 was 6.1% (95% confidence interval [95% CI] 4.6–8.2). By race/ethnicity, the prevalence of B27 was 7.5% (95% CI 5.3–10.4) among non-Hispanic whites and 3.5% (95% CI 2.5–4.8) among all other US races/ethnicities combined. In Mexican Americans, the prevalence was 4.6% (95% CI 3.4–6.1). The prevalence of B27 could not be reliably estimated for other US racial/ethnic groups because of the low number of B27-positive individuals in those groups. For adults 50–69 years of age, the prevalence of B27 was 3.6% (95% CI 2.2–5.8), which suggested a decrease in B27 with age. These prevalence estimates took into account the NHANES survey design and are reviewed with respect to data from the medical literature.

Conclusion—Our findings provide the first US national prevalence estimates for HLA–B27. A decline in the prevalence of HLA–B27 with age is suggested by these data but must be confirmed by additional studies.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Reveille had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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An association between HLA–B27 and ankylosing spondylitis (AS) was first noted in the medical literature almost 40 years ago, and since that time, HLA–B27 typing has been used as a supplemental clinical diagnostic test for patients in whom AS is suspected. The exact mechanism of a pathogenic role of B27 in AS is still an area of active clinical investigation (1,2). B27 also has been demonstrated to be associated with disorders of the heart valves and conduction system as well as disorders of the immune system (3).

While HLA–B27 has been extensively studied from a clinical perspective, there are currently relatively few large-scale population studies of the prevalence of B27, and none have been performed in the US. A national-level B27 prevalence estimate is needed for public health planning purposes because of recent improvements in medical therapy for AS and particularly because of recent improvements in diagnostic testing for the disorder. This study presents US national prevalence estimates for HLA–B27 based on data from the 2009 US National Health and Nutrition Examination Survey (NHANES).

SUBJECTS AND METHODS

The NHANES is a cross-sectional survey monitoring the health and nutritional status of the civilian, noninstitutionalized population of the US (4,5). Data were collected via household interviews and direct, standardized physical examinations, and biologic specimens were collected in specially equipped mobile examination centers. The NHANES survey samples are selected through a complex, multistage probability design. The survey design involves the selection of primary sampling units (counties), census tract segments within primary sampling units, households within census tract segments, and persons within households, with known probability of selection at each stage. Each annual sample is nationally representative; however, to protect confidentiality and increase statistical reliability, NHANES data are publicly released for 2-year survey periods. For a limited number of survey items, data are only available on a 1-year sample because of funding availability or other reasons, as was the case for HLA–B27 testing. These 1-year data sets are accessible through special requests of the National Center for Health Statistics Research Data Center.

The 2009 NHANES survey oversampled major US demographic subgroups, such as Hispanic persons and non-Hispanic black persons, as well as persons with low income. The target age range for the B27 prevalence study was US adults ages 20–69 years. In 2009, a total of 3,257 persons were screened, 2,495 were interviewed, and 2,320 had laboratory data for HLA–B27, yielding an overall response rate 71.2%. Demographic data were collected in the NHANES household interview and included the respondent’s age and self-designated race/ethnicity. The participant’s sex was recorded as observed by the NHANES interviewers.

HLA–B27 typing was performed by contract with LabCorp. The B27 analysis used a polymerase chain reaction (PCR) to specifically replicate the DNA sequences encoding the HLA loci of interest. DNA was extracted from blood samples obtained from survey participants. Exons 2 and 3 of the HLA–B locus were amplified with locus-specific primers, and the amplified DNA was arrayed onto 7 replicate nylon membranes and immobilized by ultraviolet crosslinking. The crosslinked sample DNA was hybridized with sequence-

specific oligonucleotide probes to identify HLA–B27 allele sequences. A consensus probe was used as a positive control for PCR amplification. Positive probe hits were detected with chromogenic substrate. Duplicate interpretations of positive probe hits were uploaded into a laboratory information system that interpreted the hit pattern to determine if each specimen was B27 positive or B27 negative. All B27-positive specimens and 2.5% of the B27-negative samples were confirmed using a second, independent DNA preparation in order to identify any sample switches made during manual steps. A negative control was included in each amplification run as a quality control check for contamination of the reactions by specimens or amplified product DNA. The oligonucleotide positive control dots were required to be positive for each probe and to be clearly distinguishable from all negative controls. The dots that were expected to be negative for a given probe were required not to show any signal above background.

Sample weights, which account for the unequal selection probabilities of subgroups and adjust for nonresponse and noncoverage, were incorporated in calculating the B27 prevalence estimates and their standard errors. Age adjustment was carried out by the direct method using the year 2000 Census Bureau projections for the US civilian, noninstitutionalized population (5). Standard errors were estimated by the delete 1 jackknife method, which is a replication method and therefore a design-based approach to variance estimation (6). Ninetyfive percent confidence intervals (95% CIs) were constructed using the logit transformation because the B27 prevalence estimates were low (<10%). The polynomial statement in the SUDAAN Proc Descript routine was used to test for linear trends. Both linear trends and the equality of the prevalence of B27 were tested (univariately) at the $\alpha = 0.05$ level using Student's *t*-test with the appropriate degrees of freedom. Multiple logistic regression was applied to control for confounding. In testing statistical hypotheses both univariately and multivariately and in constructing confidence intervals, the complex sample design was incorporated (7) using SUDAAN (release 10.0; Research Triangle Institute) and SAS (release 10.0; SAS Institute) software. The NHANES analytical guidelines were used to set criteria for minimum acceptable sample sizes (based on design effect and specified proportion) and relative standard errors to assess the statistical stability of computed estimates. Estimates with relative standard errors ≥30% and sample sizes less than the recommended levels are designated as potentially unreliable and should be interpreted with caution (5).

RESULTS

Table 1 presents the HLA–B27 prevalence data for the major US demographic subgroups. Overall, 124 of the 2,320 NHANES 2009 adult survey participants ages 20–69 years were positive for B27. Based on these data, the weighted, age-adjusted US national prevalence estimate for B27 in this age range was 6.1% (95% CI 4.6–8.2). Of the 124 B27-positive individuals, 2 came from households where there was another B27-positive family member (a self-reported mother, father, sister, brother, son, or daughter) in the study sample.

Sensitivity analyses were conducted dropping 1 of the B27-positive family members from each of these 2 households, and this did not significantly affect the findings. Therefore, all 124 B27-positive individuals were retained in further analyses. There was no significant

difference between men and women in the estimated prevalence of B27. Among the men who were sampled, 53 of 1,123, or a weighted estimate of 5.8%, were B27 positive, while among the women, 71 of 1,197, or a weighted estimate of 6.5%, were B27 positive.

Among major US race/ethnicity subgroups, the overall age-adjusted B27 prevalence in non-Hispanic white adults was estimated at 7.5% (95% CI 5.3–10.4), and in all other US races/ethnicities combined, the age-adjusted B27 prevalence estimate was 3.5% (95% CI 2.5–4.8). The prevalence of B27 in non-Hispanic white persons was significantly higher than that in the group of all other races/ethnicities combined ($P < 0.01$). Among Mexican Americans, the estimated age-adjusted B27 prevalence was 4.6% (95% CI 3.4–6.1). This prevalence estimate was significantly lower than the estimated B27 prevalence in non-Hispanic white persons ($P < 0.05$). Due to sample size limitations and low prevalence, the B27 prevalence could not be reliably estimated in other US race/ethnic groups.

When the prevalence of B27 was estimated by age group in decades, the prevalence estimates were as follows: 8.0% (4.6–13.4) in 20–29 year olds, 5.6% (3.4–9.2) in 30–39 year olds, 8.1% (5.8–11.2) in 40–49 year olds, 2.9% (1.4–5.8) in 50–59 year olds, and 4.6% (1.9–10.7) among those ages 60–69 years. However, the prevalence estimates for both the 50–59-year and 60–69-year age groups did not meet the criteria for statistical reliability, and these latter 2 age groups were combined, resulting in a prevalence of 3.6% (95% CI 2.2–5.8) in 50–69 year olds. This combined age group was used for further analyses. There was no evidence of a linear trend toward a decreasing prevalence of B27 across the 4 age categories.

Multiple logistic regression was then performed to provide a multivariable analysis of the independent effects of sex, race/ethnicity (non-Hispanic white versus all others), and age group in 4 categories (ages 20–29, 30–39, 40–49, and 50–69 years) on B27 prevalence. This regression model showed 2 significant results: the non-Hispanic white group had a 2.3 (95% CI 1.5–3.5) increased odds of being B27 positive as compared to all other race/ethnic groups combined, and the 50–69-year-old group had significantly lower B27 positivity than the 20–29-year-old reference group (odds ratio 0.4 [95% CI 0.2–0.9]). Also, B27 analysis adjusted for sex and race/ethnicity showed significantly lower B27 prevalence estimates for older, as opposed to younger, US adults (3.6% for those ages 50–69 years versus 7.3% for those ages 20–49 years) and, again, significantly lower B27 positivity among 50–69 year olds as compared to younger adults ages 20–49 years (odds ratio 0.4 [95% CI 0.3–0.8]). There were no significant sex differences in the odds of being B27 positive.

DISCUSSION

Our principal finding is that in 2009, the overall national prevalence of HLA–B27 in US adults ages 20–69 years was 6.1%. By race/ethnicity, the estimated prevalence of B27 among US adults classified as non-Hispanic whites was 7.5% and was more than 2 times higher than the prevalence in all other US races/ethnicities combined (3.5%). Although it was possible to provide a prevalence estimate of B27 in Mexican Americans (4.6%), sample size limitations generally precluded making reliable prevalence estimates of B27 in other US race/ethnicity subgroups. There were no significant sex differences in B27 prevalence.

The B27 prevalence estimates by age were more complicated. For US adults ages 20–49 years, the B27 prevalence was 7.3%, while for those ages 50–69 years, it was 3.6%. A sex- and race/ethnicity-adjusted analysis of B27 by age subgroups also showed significantly lower odds of B27 in older versus younger adults. However, there was variation in B27 prevalence across age categories when considered by decade, and an additional analysis showed no evidence of a decreasing linear trend in B27 prevalence with age. The study findings, therefore, are not completely consistent with respect to whether there is a lower prevalence of B27 at older ages. Unfortunately, in the current medical literature, there are neither large-scale population-based studies of B27 prevalence nor population-based studies of the mortality rates in B27-positive persons that might inform these findings. The existing literature relating to mortality in treated patient populations with B27-related arthritis and cardiac disorders shows a relative increase in mortality rates in some studies, but not in others (8–10).

Additional research therefore seems desirable because of the theoretical possibility of increased mortality rates among those who are B27 positive. Clinically, HLA–B27 has known associations with disorders of the heart valves, the cardiac conduction system, and the immune system. Although B27 conveys increased resistance to viruses, such as human immunodeficiency virus and hepatitis C virus, it is also linked to a decreased immune response to intracellular bacterial pathogens. This latter effect can produce arthritis, but there is also the possibility that persistent subclinical infections may give rise to a state of altered immune regulation, chronic systemic inflammation, and increased atherosclerosis risk (3).

The methodologic strengths of NHANES are its nationally representative sample of both men and women, its high response rates, oversampling of older persons and ethnic subgroups, and its standardized, quality-control protocol for data collection. However, it cannot address any issues of increased mortality with B27 because the current NHANES results are from a cross-sectional survey. Previous NHANES surveys conducted in the 1970s through 2004 are linked to long-term mortality followup; however, the mortality experience of more recent NHANES surveys such as this 2009 study will not be known for many years. Also, the availability of only a single year of NHANES data for B27 resulted in unstable estimates for non-Hispanic black persons and for the 50–59-year-old and 60–69-year-old subgroups. The NHANES cross-sectional survey design is ideal, however, for prevalence estimation, and the prevalence estimates reported here are unlikely to be significantly biased either by selection bias, by familial aggregation of B27, or by selective nonparticipation in the survey. For example, with the availability of modern therapies, it is unlikely that significant numbers of older persons with B27-related health conditions were homebound or in long-term care facilities and, thus, were excluded from the NHANES survey sample. Finally, we cannot entirely exclude the possibility that the current findings may have resulted from chance variation in a single study.

Our findings provide the first US national prevalence estimates for HLA–B27. While these estimates must be interpreted in light of the limitations previously noted for NHANES data, our results appear to generally be similar to previous prevalence estimates based on smaller-scale studies (2,3). A decline in the prevalence of B27 with age might be suggested by these

data, but this relationship has not been demonstrated definitively, so further studies are necessary to confirm these findings. Since HLA–B27 is an important biomarker that may be linked to the pathogenesis of AS and spondylarthritis generally, these 2009 NHANES data may be useful for future public health planning.

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The findings and conclusions contained herein are those of the authors and do not necessarily represent the views of the United States Centers for Disease Control and Prevention.

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Table 1

Prevalence of HLA–B27 in US adults ages 20–69 years, by selected characteristics, NHANES 2009 data*

Selected characteristics	Sample		Prevalence†	
	No. positive for HLA–B27	Total population	% (95% CI)	SE
Overall US prevalence	124	2,320	6.1 (4.6–8.2)	0.8
Sex				
Male	53	1,123	5.8 (3.9–8.4)	1.0
Female	71	1,197	6.5 (4.7–8.9)	1
Race/ethnic group				
Non-Hispanic white	79	1,021	7.5 (5.3–10.4)‡	1.2
Mexican American	27	622	4.6 (3.4–6.1)§	0.6
Non-Hispanic black	4	345	1.1 (0.4–3.1)¶	0.5
Age group				
20–29 years	39	498	8.0 (4.6–13.4)	2.0
30–39 years	26	471	5.6 (3.4–9.2)	1.3
40–49 years	34	508	8.1 (5.8–11.2)	1.2
50–59 years	11	404	2.9 (1.4–5.8)¶	0.9
60–69 years	14	439	4.6 (1.9–10.7)¶	1.9

*For race/ethnicity, only data for the major subgroups in the US are shown, which therefore do not sum to the overall sample size. All race/ethnicities are included in the overall prevalence estimates and in the prevalence estimates by sex and age. NHANES = National Health and Nutrition Examination Survey.

†Estimates for sex and race/ethnicity are age-adjusted to the 2000 US civilian population using age groups 20–29 years, 30–39 years, 40–49 years, 50–59 years, and 60–69 years. The 95% confidence intervals (95% CIs) were constructed using the logit transformation (3).

‡$P < 0.01$ versus all other race/ethnic groups combined.

§$P < 0.05$ versus non-Hispanic white persons.

¶Estimates do not meet criteria for statistical stability.