Antitrypsin and Chronic Obstructive Pulmonary Disease among Japanese-American Men


A total of 161 patients with chronic obstructive pulmonary disease (COPD) plus 100 control subjects (identified during a study of heart disease in 6,860 Japanese-American men aged 52 to 75 years who were residing in Hawaii) were analyzed for phenotype in search of the antitrypsin gene Z, which has been shown to be associated with pulmonary emphysema in other racial groups. No carriers of the Z gene were found, and the question of whether the rarity or absence of this gene relates to a low frequency of COPD among Japanese-Americans is reviewed.

The relationship of inherited variations in serum α1-antitrypsin and disease has been a topic of increasing interest since Eriksson1,2 reported in 1964 and 1965 a definite link between severely deficient levels of that chief serum protease inhibitor (Pi) and pulmonary emphysema. Subsequent development of techniques to identify the genetic makeup of individual Pi variants3,4 led to the description of more than 20 different phenotypes, of which only those bearing the Pi Z allele (and to a much lesser extent the Pi S allele, and quite probably the still-to-be-assessed null Pi [-] allele) seem to have clinical significance.5-8

It is now accepted that individuals of homozygous phenotype ZZ (representing the severe deficiency of α1-antitrypsin originally reported by Laurell and Eriksson9) are especially susceptible to pulmonary emphysema. By a logical extension, it has been postulated that, other factors being equal, heterozygotes with phenotypes exhibiting one Z allele are at greater risk of developing the disease than are people of non-Z phenotypes; however, the results of studies to confirm that proposition have not been conclusive thus far, albeit they are generally pointing in that direction.6

A series of reports published during the last decade have shown clear dissimilarity in the frequency of the variant S and Z genes among different racial groups. The "normal" M gene is universally predominant. The S gene is very common in Spaniards while probably absent in Africans and Hindus. The Z gene, already implicated in pulmonary disease, occurs in most populations studied, particularly Swedes and other Europeans; but it is rare and perhaps even absent in others, such as the Japanese.10

It should be noted that in their comprehensive "state-of-the-art" review on antitrypsin, Kueppers and Black3 recorded a frequency for the Z gene of 0.0015 in Japan. This figure was based on the report by Nomiyama and colleagues,11 who, in a study of 960 subjects, found three subjects with heterozygous levels of α1-antitrypsin, as determined by means of a semiquantitative technique using gelatin film. Since the method of crossed electrophoresis necessary to identify the Z allele in heterozygotes was not employed, one must wonder if the low levels of α1-antitrypsin observed in those three subjects might have been due to another variant, such as the S gene (found by Harada and Omoto12 with a frequency of 0.003 in Japan) or even the then unsuspected null allele. Two other reports by Tahara and colleagues13 and by Kozuru and associates14 described a family in Kyushu, Japan, in which several
members revealed heterozygous levels of $\alpha_1$-antitrypsin and in which two siblings showed the extremely low levels of $\alpha_1$-antitrypsin usually seen in ZZ homozygotes, possibly the first time that the $Z$ gene has been found in Japanese subjects. Unfortunately, crossed electrophoresis was not performed on those samples of serum, thus leaving open to question whether the true phenotypes involved the $Z$ gene or not. To our knowledge the unequivocal presence of the $Z$ gene in a sample of pure Japanese blood has yet to be demonstrated.

Because of the association of the $Z$ gene with pulmonary emphysema, the probability of finding this elusive gene in the Japanese would be expected to be increased if it were sought among individuals with chronic obstructive pulmonary disease (COPD). Admittedly, COPD is the rubric for a disease complex that includes, besides emphysema, other conditions with indistinguishable ventilatory features (eminently, chronic bronchitis). The use of the term, COPD, is justified by the difficulty in clinically separating its main components and their usual coexistence.\textsuperscript{15,16} In our series, we have sought the $Z$ gene in the serum of Japanese-American men with spiographic evidence of moderate or severe COPD.

**Materials and Methods**

The Honolulu Heart Study is a prospective epidemiologic project initiated in 1965 by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health as part of a study of men of Japanese descent living in Japan, Hawaii, and California, in order to evaluate the causes and extent of cardiovascular diseases in men of Japanese ancestry.\textsuperscript{17-19} Of the estimated 14,426 Japanese-American men born in the years from 1900 to 1919 who resided on the island of Oahu, Hawaii, at the time, 8,006 were examined by this study in the period of 1965 to 1968, and 7,498 of these were examined again during the years from 1967 to 1970. A third examination of 8,860 members of the original cohort who were still available for study began in 1971 and ended in the early months of 1975.

During this last round of examinations, 6,792 subjects underwent spirometric tests. Spiromograms obtained on a recording spirometer (Collins Vitalometer P-600) were initially measured by trained personnel of the Honolulu Heart Study and were regularly monitored at the NHLBI in Bethesda, Md. Subjects were classified as COPD-positive if the best of three satisfactory spiromograms showed a forced expiratory volume in one second ($\text{FEV}_1$) lower than 60 percent of the forced vital capacity ($\text{FVC}$) and were classified as COPD-negative if the $\text{FEV}_1$ was greater than 70 percent of the $\text{FVC}$. Men whose best value for $\text{FEV}_1$ was in the range of 60 to 70 percent of the $\text{FVC}$ were excluded from the series as a borderline group.

Samples of serum from every COPD-positive subject found during this third examination and from 100 COPD-negative subjects randomly selected to serve as controls were shipped frozen to the NHLBI's antitrypsin reference laboratory at Washington University School of Medicine, St. Louis, with-Out any indication of the subjects' spirometric findings. All of those samples of serum were analyzed for phenotype at that laboratory by previously described standardized techniques,\textsuperscript{10} which included discontinuous acid starch-gel electrophoresis followed by crossed immunoelectrophoresis.

**Results and Discussion**

Out of 6,792 subjects who were tested by spirometry, a total of 161 subjects (2.4 percent) were identified as COPD-positive. There were 144 subjects (2.1 percent) who had moderate COPD, and 17 subjects (0.3 percent) had severe COPD: two of the latter 17 subjects had an $\text{FEV}_1$ of less than 30 percent of the FVC. Each of these COPD-positive, as well as each of the 100 control subjects, was found to be of Pi M phenotype.

These results indicate, in the first place, that the prevalence of COPD in our sample of Japanese-American men between the ages of 52 and 75 years who were living on Oahu is remarkably low. In terms of the severity of COPD, we found that most of our subjects who were COPD-positive had an $\text{FEV}_1$ greater than 40 percent of the FVC, which is a moderate degree of obstructive impairment according to the criteria of Gaensler and Wright.\textsuperscript{20} Only 17 men were in the severely obstructive category ($\text{FEV}_1$ lower than 40 percent of FVC). In contrast, Ferris and associates,\textsuperscript{21} in a subsample of their 1967 survey in Berlin, NH, found a prevalence of COPD of nearly 20 percent among 172 men aged 51 to 70 years; however, the diagnoses of COPD by Ferris et al\textsuperscript{21} were at variance with ours, being based on personal histories of persistent wheezing, dyspnea while walking on the level, and an $\text{FEV}_1$ of less than 60 percent of the FVC, occurring singly or in combination.

The absence of any antitrypsin phenotypes other than the universally normal Pi M phenotype in all of our subjects, both those with COPD and controls, illustrates the rarity of variant $\alpha_1$-antitrypsin genes among the Japanese. Also, it is at least intriguing that not one single $Z$ allele could be found, even by analyzing the phenotype of every individual with overt COPD within a large population sample; nor, for that matter, did we encounter in any of our subjects the S or the F variants previously reported by Harada and Omoto\textsuperscript{12} (which serves to illustrate the need for analysis of phenotypes in many hundreds of members of a given population if one is to arrive at a representative profile of the frequencies of specific genes; our total of 281 subjects was obviously too restricted for such a generalized purpose).

The questions of whether the interesting $Z$ gene occurs in the Japanese and, if it does, what clinical significance may be attached to it in that country can

49O ROBERTS ET AL.

CHEST, 72: 4, OCTOBER, 1977
not be answered categorically at this point. A possibility must be considered that the premature mortality of individuals carrying the Z gene might have excluded their presence in a population aged over 50 years, such as ours. The fact that Nomiyama's group found their three heterozygotes among their younger subjects (less than 25 years old) and found no heterozygotes in the older subjects (over 40 years) in their series is suggestive. To rule out that possibility, a study of a large enough number of Japanese subjects of every age group, with proper phenotyping, would seem desirable.

REFERENCES