α_1 -Antitrypsin and coeliac disease in Spain

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SUMMARY Ninety-three Spanish children suffering from coeliac disease and 103 control subjects from the same area were screened for the amount of α_1 -antitrypsin (α_1 AT) and for any electrophoretic variations in it. In this case-control study no significant differences were detected either in phenotype distribution or amount. The present results indicate that no genetic association exists between α_1 AT and coeliac disease.

α_1 -Antitrypsin (α_1 AT locus Pi)[†] occurs in more than 30 genetic variants of which the ones producing abnormally small amounts of this protease inhibitor are of clinical interest.

Pi Z is the common deficient allele, Pi ZZ individuals having an α_1 AT serum concentration of 10% of the normal value. Some heterozygous phenotypes such as MS, MP, M- exhibit intermediate levels.

α_1 AT deficiency was found to be associated with chronic obstructive lung disease,¹ chronic cirrhosis of the liver,² arthritis,³ uveitis,⁴ and ankylosing spondylitis.⁵

Although several studies have suggested a multifactorial inheritance of coeliac disease, its genetics is still unclear. An association between α_1 AT deficiency and coeliac disease has been reported.⁶⁻⁸ As these studies have not been totally conclusive we studied a population of children with coeliac disease to find out whether α_1 AT is associated with this clinical condition.

Methods

PATIENTS

Ninety-three unrelated children with coeliac disease were studied from the gastrointestinal unit of 'La Paz' Hospital in Madrid. The mean age was 5 years (range 0-15 years). One hundred and three sex and

age-matched unrelated controls came from other departments of the same hospital in Madrid. Blood samples were collected in Madrid and flown immediately to Amsterdam. Serum was separated and kept at -70°C.

Coeliac disease was diagnosed according to the criteria of the ESPGN.⁹ At the time of blood collection most of the patients were on a gluten free diet.

α_1 AT was phenotyped using a combination of the methods of Klasen *et al.* and Frants and Eriksson.^{10 11}

Quantification of the protease inhibitor was performed with the standard radial immunodiffusion technique.¹² The average values of α_1 AT were expressed as percentage of the standard value. The standard serum is a mixture of several sera from healthy blood donors with phenotype M. The amount of this standard serum was compared by Dr M K Fagerhol with his serum pool and found to be the same.¹³

Results

Six different alleles were observed in the coeliac population, whereas only four were found among the controls.

Table 1 shows that the two populations are in Hardy-Weinberg equilibrium. This table does not include the subtyping of the M. The gene frequencies found for the subtypes among the controls are: M1: 0.67476, M2: 0.17476, and M3: 0.06796. The high S frequency is in agreement with the findings in other investigations in the Spanish population coming from the 'central meseta' at Madrid.¹⁴ Two phenotypes (MP and MZ) were detected in the coel-

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[†]The nomenclature used follows the rules laid down by the International Committee of Pi typing.¹³

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Table 1. *Pi* phenotypes and gene frequencies in 93 patients suffering from coeliac disease and 103 controls.

		<i>Pi</i> phenotypes*					Total	<i>Genes</i> *			
		<i>M</i>	<i>MS</i>	<i>MZ</i>	<i>MP</i>	<i>Others</i>		<i>Pi M</i>	<i>Pi S</i>	<i>Pi Z</i>	<i>Pi P</i>
Controls	Obs.	86	17	—	—	—	103	0.91748	0.08252	—	—
	Exp.	86.70	15.60	—	—	0.701	103				
	χ^2_1	0.006	0.126	—	—	0.701	0.833				
Coeliac—patients	Obs.	74	17	1	1	—	93	0.89785	0.09140	0.00538	0.00538
	Exp.	74.97	15.26	0.90	0.90	0.97	93				
	χ^2_1	0.013	0.198	0.012	0.012	0.97	1.205				

*Subtypes of M have been pooled Controls: for 1 degree of freedom: $p=0.36$ Coeliac patients: for 1 degree of freedom: $p=0.27$

Table 2. Distribution of electrophoretic α_1 AT variants among patients and controls.

Phenotype*	Patients ($n=93$)		Controls ($n=103$)		χ^2	<i>P</i>
	no.	%	no.	%		
M	74	79.6	86	83.5	0.50221	0.48
MP	1	1.1	0	0	1.12534	0.29
MS	17	18.3	17	16.5	0.10736	0.74
MZ	1	1.1	0	0	1.12534	0.29

*Subtypes of M have been pooled

Table 3. Quantification of α_1 AT in patients and controls

Phenotype	Patients			Controls			<i>T</i> *	<i>df</i>	<i>P</i>
	no.	Mean %	St. dev. %	no.	Mean %	St. dev. %			
M	74	111.2	28.3	86	113	26.9	0.401	158	0.58
MP	1	76.6	—						
MS	17	94.1	17.3	17	95.9	13.2	0.332	32	0.75
MZ	1	80.9	—						

*Student's *t* test

iac population, which were not found among the controls. As far as the phenotype frequencies are concerned the differences between the two populations were not significant (Table 2). The average values of α_1 AT expressed as % of standard value¹⁴ in different phenotypes are shown in Table 3.

The sera of patients with coeliac disease exhibit the same average amounts as the control sera.

Discussion

In the present study no significant differences in α_1 AT phenotype frequencies and amounts were found between Spanish children suffering from coeliac disease and healthy controls. This finding contrasts with three previously mentioned reports.^{6, 7, 8}

The study of Walker-Smith and Andrews⁶ was performed on a group of 28 treated and untreated coeliac patients and 14 controls. Phenotyping of the two groups was not done. To base an association between α_1 AT, which is an acute phase reactant, and disease only on quantitative data is unjustified.

Ellis⁷ reported a significant excess of intermediate α_1 AT phenotypes compared with controls. However, part of these so-called intermediate phenotypes appeared to be M-. The 'typing' of the null allele was based on the quantitative data and, as far as we know, no family studies were done. It is very likely that the M- individuals in reality had an MM phenotype with decreased α_1 AT levels.

We found 15 M phenotypes with intermediate levels of α_1 AT (ranging from 50% to 80%), seven among the controls and eight among the coeliac patients. Three of these samples were heterozygous for subtypes of M, so they could not be M-; the others were homozygous for M1.

Ellis also found a high number of 'intermediate variants' among the youngest patients. Our data, however, showed a more or less uniform distribution of these phenotypes.

Greenwald *et al.*⁸ described an elderly man with low levels of α_1 AT, hepatic cirrhosis, emphysema, and intestinal mucosal atrophy. As no other similar case has come to our knowledge, neither in the literature nor through our own experience, it is very likely that, in this case, the combination of α_1 AT

deficiency and coeliac disease has happened by chance.

We conclude, that α_1 -antitrypsin is not associated with coeliac disease.

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