Monaldi Arch Chest Dis
2007; 67: 4, 176-178

EDITORIAL

Alpha-1 antitrypsin deficiency: from Italy to the world

B. Balbi[1], M. Luisetti[2], L. Corda[3], N. Gatta[4]

Monaldi Arch Chest Dis 2007; 67: 4, 176-178.

Keywords: Alpha-1 antitrypsin deficiency, Italy, population screening, replacement therapy, genotyping.

[1] Divisione di Pneumologia Riabilitativa, IRCCS Fondazione Salvatore Maugeri, Veruno (Novara),
[2] Centro di Diagnosi del Deficit Ereditario di Alfa1-antitripsina, Clinica di Malattie dell'Apparato Respiratorio, Fondazione IRCCS Policlinico San Matteo, Università di Pavia,
[3] Cattedra di malattie dell'Apparato Respiratorio, Università di Brescia, Prima Divisione di Medicina Interna, Spedali Civili, Brescia,
[4] Associazione Nazionale alfa-1 AT, ONLUS, Sarezzo (Brescia), Italy.

Correspondence: Bruno Balbi, M.D., Ph.D., Divisione di Pneumologia Riabilitativa, IRCCS Fondazione Salvatore Maugeri, Via Revislate 13, 28010 Veruno (Novara), Itlay; e-mail:bruno.balbi@fsm.it

In this issue of Monaldi Archives for Chest Disease - Pulmonary series, we publish an original article from the group of Frederick de Serres [1]. As for the previous papers from this group [2-4], this manuscript covers the topic of the worldwide distribution of the alpha-1 antitrypsin (AAT) coding genes, including those carrying deficiency status for this important proteinase inhibitor.

As with the various articles on the same topic from the de Serres group which have previously been published in many respected journals, including Monaldi, this particular article can be criticised for the methodology, as it aims at giving an overall picture of the allelic frequencies even in communities or countries where the available data is really scant or may poorly represent the general population. Although this is obviously understandable, as AAT deficiency was and still is not a priority in the vast majority of the countries examined, the limitation of such an approach has to be taken into account when interpreting the reported data.

Thus, it is accepted that despite the great amount of data examined by the authors a degree of uncertainty still exists on the real allelic frequencies in many areas of the world.

This article together with all the others published by the same authors does have two great merits. First, they gathered in essence all of the data published worldwide on allelic frequencies of AAT genes, regardless of how difficult it was on many occasions to obtain rather old publications, published in local languages and when they were secured in dusty libraries or archives in various cities around the world. With reference to the Italian situation, for instance when some of us had to collect all the manuscripts about the Italian allelic frequencies, it took a great effort to collect the original publications from the seventies, some of them were published in obscure journals and of course not available on the net which meant they were only obtainable by making time-consuming journeys to University Libraries around the country.

The second great merit of the de Serres group is that it attracts the attention of the readers of important Journals such as CHEST, ERJ and others, to this condition, in its attempt to demonstrate that this is one of the most frequent genetic abnormalities that can be found in the general population. This point is crucial for any other development in this field. As AAT deficiency is so frequent, although of course varying from country to country, it goes without saying that research on AAT is needed, and thus that those pursuing the research should be supported as their work is of importance to the scientific community.

This is, or it maybe, the starting point for a "Renaissance" of the interest in AAT in the scientific community. After the "golden age" of the eighties during which the scientific bases for the understanding of the lung disease were settled and through this the concept of the exogenous replacement therapy was put forward, we must admit that over recent years the progress in AAT field has not been so rewarding. However, as is the situation with friends during a mid-life crisis, this rather difficult (and poorly funded) time frame has resulted in a consolidation of true friends of AAT deficiency, i.e. only those really motivated and devoted to this fascinating topic could bear this not exciting moment and keep up with the work.

In this global scenario, one might question the current situation in Italy. As can be seen from the de Serres data and also through consideration of other important authors who dealt with allelic frequencies [5], Italy is somehow at the centre of the crossroad for the frequencies of S and Z genes, as they have respectively a West → East and a North → South gradient across Europe. In addition, recent data [6] has shown that Italy probably holds

the world record for the presence of rare allelic variants, as it was shown that these could represent a substantial part (11%) of the AAT variants observed in our National Registry.

AAT deficiency was considered to have a low incidence in Southern Europe until few years ago. In Italy, the identification of an AAT deficient patients warranted publication also in the mid nineties [7]. However, this belief was not supported by early genetic epidemiological studies, which were mostly conducted on cord blood samples or on the general population in different areas of the country [8-12]. Those studies estimated that in Italy the frequency of the Z gene, for instance, was not significantly different from the one observed in other European countries, at least in the northern part of the country. To address this discrepancy, starting from 1993 a National Programme for detection of AAT deficiency was launched in our country. The results of this Programme were rewarding and a National Registry for AAT deficiency was established in 1997. When updated in December 2006, a total of 2.127 samples had been submitted for diagnosis of AAT deficiency at the Centre for Diagnosis of Inherited AAT deficiency in Pavia, and 276 subjects with severe AAT deficiency were identified and enrolled in the Italian Registry [13, 14]. The rate of diagnosis is quite high (12%), and testifies that the so called "targeted detection" is a winning strategy to identify AAT deficient individuals. Moreover, with 212 out of 276 subjects enrolled perspectively in the AlphaOne International Registry (AIR, www.aatregistry.org), Italy is a major contributor of such multinational, four-continent based registry for individuals affecetd by this genetic condition [15].

In addition from the analysis of the Registry and from the work carried out in the last 15 years, it is evident that AAT deficiency is distributed variably in our country. Thus it is not surprising that in some areas the combination of a higher presence of AAT deficient individuals and patients and the presence of dedicated clinical and basic scientists in the field has resulted in the creation of important reference centres for this condition. One such example, and maybe at least from a quantitative point of view the most important one, is the University Hospital of Brescia, a city located in Northern Italy where there are currently 484 subjects with alpha1-antitrypsin deficiency undergoing follow- up. 90 of the subjects are affected by severe deficiency (i.e. homozygous or double heterozygous) and 394 with intermediate deficiency (i.e. heterozygous). Many subjects among this cohort have resulted as carriers of rare variants (19 with severe deficiency and 49 with intermediate deficiency). Some of these rare variants have never previously been described and a complete characterisation has been undertaken from the clinical, genetic and biochemical point of view. In the Brescia Centre a comprehensive approach to individuals with AAT deficiency (genetic, clinical, functional, imaging and therapeutic) is available and routinely performed.

Another important point is that replacement therapy has been available in Italy for the last 11 years. This has together with the fact that there is a great number of patients in the same area around the city of Brescia has been the soil that generated and has subsequently sustained the growth of the Italian Association of Patients with Alpha-1 Antitrypsin Deficiency (Associazione Nazionale ALFA1-AT - Onlus, www.alfa1at.com). Founded in 2001 by a group of patients, the Association is recognised as a Charity and currently has 486 members. Over the last few years the role and relevance of the Association has steadily grown in the Italian scenario and is also favoured by the Italian Law on Rare Disorders that is encouraging such initiatives. The Association has been very active in promoting awareness of the condition, with participation in National and International Respiratory Meetings and with a thorough contact activity devoted to all the relevant players in our Health System, and has made strong connections with other Patients' Associations for different rare disorders in Italy. In addition, the Association is among the founders of Alfa-Europe, a federation of European Patients Association. Nuccia Gatta, currently President of the Italian Association, is Vice-President of Alfa-Europe, whose last Congress was organised in Rome (September 2007). This Congress gathered representatives of the Patients' Association not only from Europe but from across the globe, including our friends from North-America, South America, Australia, New Zealand. Moreover, the Italian association is working inside the Italian Health System to raise visibility of the condition and to help provide equivalent and appropriate levels of assistance to all patients throughout the Country. From a Scientific point of view, the Association comprises a Scientific Committee (of which currently Dr. B. Balbi is in charge) composed of distinguished Italian and International researchers, and through the Committee it also promotes scientific studies on the condition. The most important is the population screening for AAT genes performed in an Alp Valley (Val Trompia) near Brescia in Northern Italy. This area was chosen because of the preliminary data showing a high incidence of the condition in individuals whose family was originally from that rather isolated area. The data collected in collaboration of the Diagnostic Genetic Centre of the Brescia University (Prof. Facchetti and Dr. Medicina) in more than 2,000 residents confirms this hypothesis, with a higher than expected prevalence of AAT deficiency carrier genes, not only Z and S, but also, as always in Italy, rare variants, some of which had never previously been described [16].

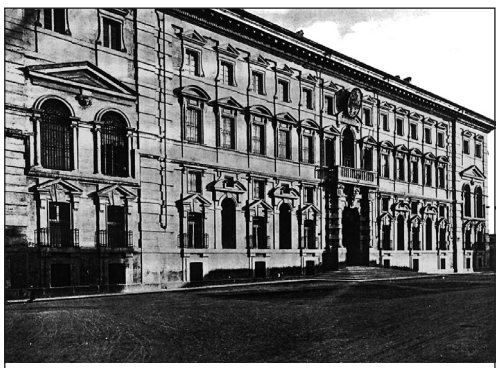
In conclusion, Italy is today a laboratory for a new perspective in AAT deficiency. The different components for a successful enterprise are all present: from a selected group of dedicated researchers, to facilities for genetic diagnosis, from reference clinical centres, mostly in northern Italy where the condition seems more prevalent in the general population, to a patient association leading the role of advocacy for this condition. Furthermore, recently there was a change in the industry distributing replacement therapy, from Talecris to an Italian Company, Kedrion.

Thus, we hope in the near future to have a number of important advancements in this field in our Country, and we would encourange the Italian Alpa-1 community to keep up with good work.

Buon lavoro a tutti!

References

1. de Serres FJ, Blanco I, Fernandez-Bustillo E. PIS and PIZ alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data. *Monaldi Arch Chest Dis* 2007; 67: 184-208.
2. de Serres FJ. Worldwide racial and ethnic distribution of alpha-1 antitrypsin deficiency. Summary of an analysis of published genetic epidemiologic surveys. *Chest* 2002; 122: 1818-1829.
3. de Serres FJ, Luisetti M, Ferrarotti I, Blanco I, Fernandez-Bustillo E. Alpha-1 antitrypsin deficiency in Italy: regional differences of the PIS and PIZ deficiency alleles. Monaldi Arch Chest Dis 2005: 63: 133-141.
4. Blanco I, de Serres FJ, Fernandez-Bustillo E, Lara B, Miravitlles M. Estimated numbers and prevalence of PIS and PIZ of alpha-1 antitrypsin deficiency in European Countries. Eur Respir J 2006; 27: 77-84.
5. Hutchinson DC. Alpha-1 antitrypsin deficiency in Europe: geographical distribution of Pi types S and Z. Respir Med 1998; 92: 367-377.
6. Ferrarotti I, Baccheschi J, Zorzetto M, *et al*. Prevalence and phenotype of subjects carrying rare variants in the Italian registry for alpha-1 antitrypsin deficiency. J Med Genetic 2005; 42: 377-382.
7. Balbi B, Fiasella F, Fabiano F. Deficit di alfa-1-antitripsina. Un caso di fenotipo ZZ con bronchiettasie come principale manifestazione clinica. Rassegna di Patologia dell'Apparato Respiratorio 1994; 9: 254-257.
8. Klasen EC, D'Andrea F, Bernini LF. Phenotype and gene distribution of alpha-1-antitrypsin in a North Italian population. Hum Hered 1978; 28: 474-478.
9. Massi G, Fabiano A, Ragusa D, *et al*. Alpha 1-antitrypsin phenotypes and Pi M subtypes in Italy. Bull Europ Physiopath Resp 1980; 16 (suppl): 301-306.
10. Li Volti S, Musumeci S, Vanella A, Mattina T, La Rosa M, Rizza V. Cartterizzazione dell'alfa-1-antitrispina nel neonato della Sicilia orientale. Med Chir (Med Surg Ped) 1980; 2: 397-400.
11. Klasen EC. α1-antitrypsin phenotype and gene distribution in Southern Italy. Hum Hered 1981; 31: 180-182.
12. Klasen EC, Bos A, Simmelink HD. PI (α1-antitrypsin) subtypes: frequency of PIM4 in several populations. Hum Genet 1982; 62: 139-141.
13. Ferrarotti I, Gorrini M, Scabini R, *et al*. Secondary outputs of alpha1-antitrypsin deficiency targeted detection programme. Respir Med 2007 (in press).
14. Corda L, Bertella E, Pini L, *et al*. Diagnostic flow chart for targeted detection of alpha-1 antitrypsin deficiency. *Respir Med* 2006; 100: 463-70.
15. Stockley RA, Luisetti M, Miravitlles M, Piituilanen E, Fernandez P on behalf of the Alpha One International Registry (AIR). Ongoing reserach in Europe: Alpha One International Registry (AIR) objective and development. Eur Respir J 2007; 29: 582-586.
16. Gatta N, Corda L, Medicina D, *et al*. Frequency of alpha-1 antitrypsin deficiency in a population screening in a high risk area (Val Trompia, Italy). Eur Respir J 2006; 28 (Suppl. 50): 453S.



Pavia - Almo Collegio Borromeo