Clinical management of subjects with heterozigosity MZ for Alpha1-antitrypsin deficiency: a systematic review

Francesca Baglivo
Nicola Venturoli
Luciano Corda

Second Division of Internal Medicine, Regional Reference Centre for Alpha1 Antitrypsin Deficit, “Spedali Civili” - Specialization School for Respiratory Diseases, University of Brescia, Brescia, Italy

Address for correspondence:
Luciano Corda
Second Division of Internal Medicine
Regional Reference Centre for Alpha1 Antitrypsin Deficit
“Spedali Civili” - Specialization School for Respiratory Diseases, University of Brescia
Brescia, Italy
E-mail: luciano.corda@asst-spedalicivili.it

Summary

This is a systematic review about clinical management of Alpha1-antitrypsin PiMZ heterozygous individuals. Alpha1-antitrypsin (AAT) is an antiprotease glycoprotein synthesized by the liver cells and then released into the bloodstream. Alpha1-antitrypsin deficiency (AATD) is a rare codominant genetic hereditary disease in which alpha1-antitrypsin is produced in an altered form and at reduced levels respect to PiMM individuals. Although homozygous PIZZ deficiency state is an acclarate risk factor for developing liver and lung disease, about heterozygosity PiMZ is not yet well understood. Smoke and alcohol habit could facilitate the onset of chronic obstructive disease (COPD) and liver damage in PiMZ individuals. Smoking discouragement or cessation and alcohol abolition are the best practice to use in the clinical management and follow up of health PiMZ individuals.

KEY WORDS: Alpha1-antitrypsin, heterozigosity, COPD/emphysema, liver disease, follow-up.

Introduction

Alpha1-antitrypsin (AAT) is a 52kDa protein of the serine proteinase inhibitor family (so called serpins). It is predominantly synthesized and secreted by hepatocytes. A lesser portion is produced in lung macrophages and epithelial cells. It is also an acute-phase protein, thus its synthesis and release are increased under inflammatory conditions. Its main physiological function is the inhibition of proteases, particularly of neutrophil elastase. In addiction it exerts indirect anti-inflammatory effects through the regulation of tumour necrosis factor alpha, interleukin-6, interleukin-8 and interleukin-1beta (1-3).

The SERPINA1 gene that encodes the protein, is localized on chromosomal segment 14q32.1 and it is also known as protease inhibitor Pi. Pi locus is highly polymorphic, resulting in different AAT isotypes. The most common allele is the Pi M allele and encodes the normal functioning AAT molecule with normal serum AAT levels. The normal AAT protein has a tertiary structure based on a large central beta sheet, surrounded by two other sheets and a reactive centre loop. At higher temperatures, polymerisation can occur between molecules due to insertion of the loop of one molecule into the large beta-sheet of the other (Figure 1).

AAT deficiency (AATD) is an autosomal codominant disorder. More than 100 different allelic variants have been recognized, often differing by single point mutations. AATD occurs between 1:1800 and 1:5000 live births.

The most frequent and most relevant deficient variant Pi Z is characterized by a single nucleotide substitution of Lys for Glu342 in the AAT gene. It is a combined deficient and dysfunctional allele and occurs in up to 4% of the population in northern Europe.
leads to deficiency of plasma AAT levels and subsequently to a blunt protease inhibitor function resulting in increased risk of pulmonary disease. Furthermore, the point mutation destabilizes the loop-sheet polymerization of the PiZ molecules, resulting in a chain of polymers and their accumulation in the endoplasmic reticulum of hepatocytes. Only 15% of the Z variant of AAT is secreted into the plasma, the other 85% accumulates in the liver, with an increased risk of liver disease.

The variant S allele is characterized by the substitution of Val for Glu264 and results in a protein that undergoes premature intracellular degradation and evokes subtle reduction in serum levels without causing classic clinical liver disease. The S allele has a higher incidence compared with the Z allele (up to 28% in southern Europe).

Less frequently recognized variants are Null alleles resulting in undetectable AAT plasma levels. It is often associated with severe pulmonary disease (Table 1). The real size of this disorder, then, can only be estimated and varies from different regions of the world. It was calculated that approximately 2-3% of caucasian population is Z allele carrier (4).

SS, SZ and ZZ phenotypes are classified as AAT deficiency whereas MS and MZ genotypes are considered as healthy carriers (Table 2).

The heterozygous PiMZ state

Many studies have explored the role of homozygous AATD state in the pathogenesis of lung and liver diseases.

As heterozygous state is more frequent than homozygous state, it is important to know if it can represent an isolated risk factor of lung and liver disease. Unfortunately, there is an existing problem concerning the diagnosis of the heterozygous PiZ state of AATD. It is easily overlooked by clinical exploration and laboratory tests because carriers may have normal serum level of AAT. Even routinely stained liver biopsies and chest X-rays may not recognize first signs of the disease.

Lung function in alpha1-antitrypsin PiMZ heterozygosity

PiZZ homozygosity alpha1-antitrypsin deficiency is a well known hereditary risk factor for emphysematous alterations and early onset of chronic obstructive pulmonary disease (COPD), but regarding PiMZ heterozygosity the published literature is conflicting. Silverman et al. reported that PiMZ patients have an intermediate risk of airflow obstruction, respect to PiMM and PiZZ (4).

Hersh et al. found moderately increased odds of obstructive lung disease in PiMZ patients respect to PiMM. In his systematic review of the medical literature, analyzing the categorical studies, only the case-control studies showed that PiZ heterozygosity increased OR compared to the cross sectional categorical studies that showed only a trend towards increased risk of COPD (5) (Table 3).
Molloy et al. demonstrated the PiMZ heterozygosity is a risk factor for developing pulmonary alterations when associated with cigarette smoke exposure: a family-based study indicated that PiMZ ever smokers have an increased risk of developing COPD compared with PiMM individuals who are ever smokers (6, 7) (Tables 4, 5).

The negative influence of smoking on lung function in PiMZ heterozygotes was further remarked at the end of Swiss SAPALDIA cohort follow-up studying. A systemic low grade inflammation, like that smoke exposure, accelerates lung function decline in PiMZ. Not only cigarette smoke but also obesity can induce negative influence on respiratory system by direct mechanical effect on airways and lung volume, but also producing pro-inflammatory adipokines from adipose tissue that spill over to the blood stream. Obese PiMZ subjects show an increased average annual decline in the forced mid expiratory flow (ΔFEF25-75%) respect to PiMM obese subjects (8) (Figure 2).

Lung function decline is usually evaluated by spirometric measurements, like FEV1 (observed and percentage of predicted) and FEV1/FVC ratio. In PiMZ patients Silva et al. (9) suggested that it is useful to associate diffusing capacity of the lung for carbon monoxide (DLCO) assessment and high resolution CT (HRCT), in order to detect early emphysematous changes and alterations of alveolar-capillary interface, especially in smokers. In particular DLCO is a more sensitive parameter than FEV1 in determining early subclinical effects of intermediate levels of alpha1-antitrypsin. Silva et al. demonstrated that percentage predicted DLCO declines more rapidly in subjects who smoked compared to non smoking subjects.

Contrasting results was described by Sorheim (10): in

<table>
<thead>
<tr>
<th>First Author, Year (Ref.)</th>
<th>n</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Chan-Young, 1978 (204)    | 1,138 | PB | 31 PiMZ individuals from sawmills and grain elevators, all with normal FEVs, despite smoking in 14 individuals.
| Stjernesmyk, 1984 (205)   | 518  | PB | PiMZ gene frequency 12.8% in PiMZ sulite pulp workers with chronic bronchitis versus 8.4% in normal workers (p = NS).
| Horne, 1986 (206)         | 56   | SCS | PiMZ patients.
| Pierre, 1988 (207)        | 871  | PB, longitudinal | No difference in baseline lung function or symptoms in heavily exposed miners with similar smoking history, five-year FEV1/FVC decline greater in PiMZ individuals than in control subjects (p < 0.05).
| Brandstul, 1993 (202)     | 226  | SCS | Same population as Signgaard modeling AAT and endotoxin levels showing additive risk for dysbiosis.
| Sigsgaard, 1994 (203)     | 226  | SCS | PiMZ individuals exposed to cotton dust more likely to develop blysinosis 3/8 (38%) than PiMM individuals 25/187 (13%). OR, 5.8 (CI, 1.1–30) in logistic regression model controlling for endotoxin, tobacco, sex, and age.

**Definition of abbreviations:** CI = confidence interval; OR = odds ratio; PB = population based; SCS = serial cross-sectional.

*All studies to specifically address environmental risk with more than five PiMZ individuals.
the Norway case-control study, compared to PiMM, PiMZ subjects were associated with increased risk of COPD and were more susceptible to emphysematous alterations, although only a low cigarette smoking exposure (< 20 pack-years) but not to high exposure (> 20 pack-years) and Seersholm et al. reported a relative risk of hospitalization for COPD exacerbations in PiMZ patients (4).

In conclusion, we can suggest some key points in the management of AAT PiMZ patients (Figure 3).

An early detection of deficit and genetic AAT phenotyping determination are primarily important, in order to drive patients in a correct life style for preventing pulmonary diseases: the best intervention in preventing obstructive lung disease in PiMZ heterozygotes is abstinence from cigarette smoking (6).

Smoking cessation should be recommended or smoking initiation discouraged. Especially in PiMZ ever smoker individuals, the single breath DLCO test and chest HRCT scan are to be considered very useful screening for detecting early alterations of alveolar-capillary membrane and reduction of lung parenchyma density.

Weight loss is fundamental in order to improve lung function and for reducing the low grade systemic inflammation found in obese patients: PiMZ individuals should be motivated to a regular physical activity and adequate diet regimen.

Table 5 - Results from a family-based study to determine the risk of chronic obstructive pulmonary disease in PiMM and PiMZ individuals (from 7).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PI<em>MM</em></th>
<th>PI<em>MZ</em></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>0.81 (0.75-0.85)</td>
<td>0.77 (0.73-0.83)</td>
<td>NS</td>
</tr>
<tr>
<td>Ever-smoker</td>
<td>0.77 (0.72-0.81)</td>
<td>0.71 (0.58-0.77)</td>
<td>0.0013</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>101.3 (88.7-110.6)</td>
<td>102.2 (88.3-108.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Ever-smoker</td>
<td>94.8 (82.1-102.4)</td>
<td>82.3 (63.1-94.4)</td>
<td>0.0009</td>
</tr>
<tr>
<td>FEF25-75 % predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>84.1 (70.7-100.8)</td>
<td>76.1 (63.6-99.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Ever-smoker</td>
<td>64.8 (52.2-90.2)</td>
<td>47.7 (22.7-66.8)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range). FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF25-75%: forced expiratory flow at 25-75% of FVC; NS: nonsignificant. *n=97; **n=99. Reproduced from [13] with permission from the publisher.

Figure 2 - Linear prediction of % predicted DLco by age for the different ATT phenotypes (from 8).
Asthma and AATD

Knowing that asthma is the most common respiratory diagnosis in patients with AATD prior to the diagnosis of AATD (11) and that atopy is also been reported to be more prevalent in those with AATD (12, 13), some studies were undertaken to establish how AATD is able to determine or modify the course of this disease.

A study conducted by Eden et al. (14) aimed to define prevalence of asthma and atopy in a large group of AATD patients. They submitted an enrolment questionnaire by mail to 2431 patients of the Alpha-1 Foundation Research Registry of the University of South Carolina. The questionnaire was the ATS DLD 78 used in the NHLBI registry. Additional questions were added to know about a physician diagnosis, an atopy and medication history. 757 patients returned the questionnaire. The cohort was divided into three groups: PIZZ phenotypes, PIMZ phenotypes and others (which included PISS, PISS, PISZ, and other rare phenotypes).

44.6% out of them had a medical diagnosis of asthma, 76% reported wheezing and other symptoms when exposed to common triggers (as dust, fumes allergens and activity) and from 20 to 25% reported history of allergies. It is evident that asthma in many patients is not adequately diagnosed.

Patients PIMZ reported asthma as the only diagnosis three time more frequent than patients PIZZ. PIZZ phenotypes reported asthma associated with others respiratory diseases as COPD and enphysema. Probably, other diseases’ symptoms hide asthma symptoms in patients with more severe deficit of AAT, and it is difficult for physician to diagnose asthma because these patients frequently come to medical examination only when their symptoms are already evolved into more severe diseases (Table 6).

Table 6 - Past medical history of wheezing attacks, asthma and smoking by AATD phenotype (from 14).

<table>
<thead>
<tr>
<th>Past history</th>
<th>PIZZ</th>
<th>PIMZ</th>
<th>Other phenotypes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age asthma diagnosed, years (Mean±SD)</td>
<td>39±16</td>
<td>28±18</td>
<td>33±19</td>
<td>0.0017</td>
</tr>
<tr>
<td>Age at 1st attack, years (Mean±SD)</td>
<td>32±15</td>
<td>26±16</td>
<td>31±18</td>
<td></td>
</tr>
<tr>
<td>2 or more attacks?</td>
<td>92%</td>
<td>92%</td>
<td>93%</td>
<td>NS</td>
</tr>
<tr>
<td>Inhaler use to treat attacks?</td>
<td>87%</td>
<td>82%</td>
<td>84%</td>
<td>NS</td>
</tr>
<tr>
<td>Relief of attack within 30 min?</td>
<td>80%</td>
<td>73%</td>
<td>82%</td>
<td>NS</td>
</tr>
<tr>
<td>Are wheezing attacks still present?</td>
<td>69%</td>
<td>60%</td>
<td>84%</td>
<td>0.018</td>
</tr>
<tr>
<td>Age if stopped, years (Mean±SD)</td>
<td>46±14</td>
<td>35±16</td>
<td>51±12</td>
<td>NS†</td>
</tr>
<tr>
<td>Family with asthma?</td>
<td>56%</td>
<td>76%</td>
<td>67%</td>
<td>0.014</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>26%</td>
<td>50%</td>
<td>20%</td>
<td>0.0003</td>
</tr>
</tbody>
</table>
As asthma is a risk factor for an accelerated decline of FEV1 (15, 16), it is important to diagnose it as soon as first symptoms are evident. An allergy evaluation and the avoidance of triggers should be important in the management of AATD patients that report wheezing and other symptoms when exposed to allergens.

Apparently, in subjects with AATD may exist an increased airways hiperresponsiveness, which seems to be negative correlated with alpha1 antitrypsin plasma levels (17).

Liver disease in heterozygous state of alpha1 antitrypsin deficiency

Liver disease consists in the slow but progressive accumulation of mutated AAT proteins, which form polymers and are retained in the endoplasmatic reticulum of hepatocytes. Mutations that have been associated with the retention of mutated AAT are: Z allele, SiiYama and Mmalton. The accumulation can be seen as PAS positive cytoplasmatic inclusion typically found in the periportal zone. Despite the low penetrance of the disease, the association between homozygous state PiZZ and liver disease is well documented (18, 19).

It is, indeed, still debated if the heterozygous state PiZ of AATD could develop chronic liver disease. In the past, many studies have been conducted on this argument, reporting conflicting clinical data. In a large observational study were recognized differences in age at the time of presentation of liver disease correlating with the presence of S and Z alleles: in particular the ZZ phenotype would develop liver disease approximately at 58 years, the SZ phenotype at 66 years and the MZ phenotype at 73 years (20) (Figure 4).

The presence of heterozygous Z allele can modify the progression of other chronic liver diseases. There is a higher incidence of MZ in HCV-related end-stage liver disease (10-13 vs 2.8% in the control group) (1, 21) and in acute liver failure independent of other risk factors (22). Moreover, a study by Fairbanks et al. demonstrated that in MZ carrier phenotypes, the incidence of cryptogenenic cirrhosis is 10 times higher than that in MM phenotypes (3).

In 2000 a study conducted in Bonn (Germany) (23) by Fischer at al. tried to demonstrate that being carrier of the AAT mutation (Pi Z) could increase the risk of chronic liver disease. They analysed the prevalence of immunohistochemical expression of Pi Z in 1847 consecutive liver biopsies and resection specimens and 1030 consecutive autopsy cases. The biopsy series included patient with liver disease (i.e.: cases), the autopsy series constituted the control group. They found AAT deposits in 3.4% of the biopsy series and only 1.8% of them in the autopsy series. The proportion of heterozygous state in the biopsy group was consistent with previous prevalence studies on PiZ- associated liver disease.

Since the prevalence on Pi Z carriers in the biopsy series was significantly more than in the autopsy series they suggested that AAT deficiency of Pi Z type had an influence on the development of liver disease. The Pi Z status may have contributed to the development of pathological serological liver findings or manifest liver disease, which had to be elucidated by liver biopsy or treated by liver resection.

It is known that the extent of Pi Z deposits in liver biopsies correlates well with the inflammatory activity and stage of fibrosis (Figure 5).

The study also found that cirrhotic livers contained globular Pi Z deposits significantly more often than the biopsies with minor fibrosis (Figure 6). This could be explained by the “accumulation theory” according to which exists a direct hepatophatic effect of retained Pi Z (24); supporting this theory there are also experimental studies that demonstrate how the degree of liv-
er cell damage correlate with the number of Pi Z deposits in the mouse liver tissue (25).

However, the exact mechanism by which Pi Z leads to damage of AAT retaining is still unknown.

The Authors of the study then focused on the cases in which AATD was the only causative factor of liver disease. They divided those cases into two groups based to different age: the age group between 20 and 39 years showed only minimal histopathologic changes; the second group (40-82 years) showed significantly higher extent of Pi Z deposits, inflammatory activity and stage of fibrosis. It seems then that even a heterozygous Pi Z state of AATD can cause a slowly progressive liver disease, which in some patients can advance to liver cirrhosis.

Obviously environmental influences have a role in the pathogenesis of the liver disease. An increased state on inflammation might raise levels of Pi Z molecules in hepatocytes and so indirectly initiate a liver cell alteration.

Therefore, we should not to be surprised if the subgroup of the study with a coexistent liver disease (especially alcoholic liver damage and hepatitis C virus infection) presented with more severe inflammation.
and fibrosis, and more Pi Z deposits than the subjects without concurrent liver disease.

The Authors of the study concluded that patients with heterozygous AATD of Pi Z type bear an increased risk for chronic liver disease. If this genetic defect will become clinically relevant, it would be only in middle-aged or old adults. It rare causes liver cirrhosis without concurrent liver disease. It can aggravate or can be aggravated by advanced coexistent chronic liver diseases.

Another study by Regev et al. (26) in 2006 confirmed these data. The study consisted in a large case-control study and aimed to determine the prevalence of AATD carrier state PiZ in liver disease. 1405 patients were enrolled, of which 651 subjects had a well established liver disease and 754 were part of the control group with no liver disease (Figure 7).

They found no difference in PiMZ prevalence between the patients with liver disease and the control group (2.1 vs 1.7%) as it is shown in Figure 7. This suggests that the PiMZ state does not play a role as a cause of de-novo liver disease. They noted, indeed, the PiMZ phenotype was significantly more prevalent in patients with decompensated cirrhosis (5.7%) compared to patients with less severe liver disease (2.1%). The association was particularly evident among HCV (5.6%) and NAFLD (5.0%) patients with more severe disease compared with HCV patients (1.2%) and NAFLD patients (1.9%) with less severe disease.

NAFLD means non-alcoholic fatty liver disease, the most common cause of fatty liver, occurring when fat is deposited (steatosis) in the liver due to causes other than excessive alcohol use. It is related to insulin resistance and metabolic syndrome (Figure 8).

Furthermore, in contrast with previous reports, the
prevalence of PiZ was not increased in patients with cryptogenetic cirrhosis compared with patients with no liver disease or to those with liver disease of known etiologies. They concluded that PiMZ AATD state may have a role in worsening liver disease (especially due to HCV and NAFLD), and may cause a more rapid progression and worse outcome in certain patients.

The role of AAT heterozygosity in HCV affected patients

A more detailed investigation has to be done to clarify the prevalence of heterozygous AATD carriers in HCV affected patients. Previous studies in patients affected by severe liver HCV-related disease showed presence of PiMZ in 10-13% of the patients, compared with 2.8% in controls, suggesting that AAT heterozygosity influenced the development and/or the course of the liver disease (20, 27).

In contrast with these data, the study of Kok et al. (1, 28) published in 2010 found a heterozygosity rate of 0.06 among HCV affected patients (in line with healthy controls in other studies). They also did not find statistically significant increase in the fibrosis degree between Z allele carriers and controls (Table 7). Furthermore, there was similar treatment response against HCV between the two groups of patients (cases and controls) (Figure 9).

Table 7 - Degree of fibrosis in the different AAT groups (N=409) (from 28).

<table>
<thead>
<tr>
<th>Degree of fibrosis in the different A1AT groups (N=409)</th>
<th>Pi MM, n=585 (%)</th>
<th>Pi MM and Pi MS, n=26 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F2</td>
<td>296 (70)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>F3-F4</td>
<td>114 (29)</td>
<td>7 (27)</td>
</tr>
</tbody>
</table>

A1AT, alpha-1 antitrypsin; Pi, protease inhibitor.

Liver transplantation

As many Z allele carriers do not have a liver disease clinically evident, it is probably that livers containing PAS positive accumulation of Z mutated proteins have been used previously for liver transplantation. Roelandt et al. (29) in 2013 studied the incidence of this event in 789 liver transplantation between January 1995 and February 2011. They found that 0.8% of all cases were healthy donor organs containing Z allele for transplantation.

A case report published in 2010 showed the progression of liver disease in a patient who received transplantation by an AAT Z heterozygous liver donor. The patient developed liver function test a normality after 6 years post-transplant even though biopsies revealed only chronic hepatitis with no specific features. Only after 10 years, biopsies could reveal characteristic cytoplasmic inclusions (30).

Cholangiocarcinoma

Alpha1-antitrypsin deficiency may be associated also with tumours even without underlying liver diseases or cirrhosis (19, 20). Recently studies assessing tumoural and non-tumoural liver samples for immunohistochemical Pi Z deposits revealed an unexpectedly high rate of primary cholangiocarcinoma (CCA) (30). In a study lead by Zhou et al., heterozygosity for the allele Z has been linked to intrahepatic CCA (31). It was supposed that the tumour could be arising from bi-potent periportal progenitor cells.

In 2010, another study by Mihalache et al. (32) confirmed the role of alpha1-antitrypsin Z heterozygosity as a potential genetic susceptibility factor for cholangiocarcinoma formation and suggest a contribution of aberrant AAT function in biliary carcinogenesis, although the exact pathophysiologic mechanism remains to be defined.

In conclusion, from this data it is evident that the heterozygous state may be an independent risk factor for development of liver disease. Heterozygosity for the Z allele leads to a 3% risk of developing cirrhosis, whereas homozygosity increases the risk to 30% (33).

The accumulation of AAT in the hepatocytes occurs more profoundly in a disease liver, and consequently it affects the natural course of the liver disease. If associated with other hepatotoxic risk factors (especially HCV and NAFLD) it can accelerate the develop-
Clinical management of subjects with heterozygosity MZ for Alpha1-antitrypsin deficiency: a systematic review

ment of liver disease. Little is known about the development of tumours, but nowadays evidence points to a possible contribution of aberrant AAT proteins to carcinogenesis.

Conclusions and recommendations

In this review we analyzed the scientific literature about alpha1 heterozygotes MZ patients, in order to characterize the risk of developing liver or/and lung disease in this population. We found that MZ heterozygosity represents a known risk factor if associated to previous liver injuries or to smoking habit. Therefore individuals’ life style takes a fundamental role for reducing onset of correlated alpha1-antitrypsin deficiency diseases. MZ young individuals are largely healthy subjects, so an early detection of heterozygosity is the starting point of a good clinical management. Smoking habit has to be avoided and alcohol intake has to be reduced. Referring to our clinical experience, we suggest to perform pulmonary function tests and liver serum enzymes essay every two/three years in healthy MZ individuals and annual follow up visit for patients affected by liver or/and lung pathological alterations. We also consider essential to make subjects aware of what represents PiMZ heterozygosity.

References