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ScienceDirect
NeuroToxicology 28 (2007) 899–914
NeuroToxicology

Art, alpha-1-antitrypsin polymorphisms and intense creative energy: Blessing or curse?

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Received 1 February 2007; accepted 21 May 2007
Available online 14 June 2007

Abstract

Persons heterozygous for Z, S and rare alpha-1-antitrypsin (AAT, SERPIN1A) polymorphisms (ca. 9% of population) are often considered 'silent' carriers with increased vulnerability to environmentally modulated liver and lung disease. They may have significantly more anxiety and bipolar spectrum disorders, nutritional compromise, and white matter disease [Schmechel DE, Browndyke J, Ghio A. Strategies for the dissection of genetic–environmental interactions in neurodegenerative disorders. Neurotoxicology 2006;27:637–57]. Given association of art and mood disorders, we examined occupation and artistic vocation from this same series. One thousand five hundred and thirty-seven consecutive persons aged 16–90 years old received comprehensive work-up including testing for AAT 'phenotype' and level, nutritional factors, and inflammatory, iron and copper indices. Occupations were grouped by Bureau of Labor Standards classification and information gathered on artistic activities. Proportion of reactive airway disease, obstructive pulmonary disease, and pre-existing anxiety disorder or bipolar disorder were significantly increased in persons carrying AAT non-M polymorphisms compared to normal MM genotype (respectively, 10, 20, 21, and 33% compared to 8, 12, 11, and 9%; contingency table, pulmonary: χ^2 =37, $p = 0.0001$; affective disorder: $\chi^2 = 171$, $p = 0.0001$). In persons with artistic avocation ($n = 189$) or occupation ($n = 57$), AAT non-M polymorphisms are significantly increased (respectively, proportions of 44 and 40% compared to background rate of 9%; contingency table, avocation: $\chi^2 = 172$, $p = 0.0001$; occupation: $\chi^2 = 57$, $p = 0.0007$). Artistic ability and 'anxiety/bipolar spectrum' mood disorders may represent phenotypic attributes that had selective advantage during recent human evolution, an '*intensive creative energy*' (*ICE*) behavioral phenotype. Background proportion of *ICE* of 7% consists of 49 of 1312 persons with AAT MM genotype (4%), and 58 of 225 persons with non-MM genotypes (26%) (contingency table, $\chi^2 = 222$, $p = 0.0001$). Penetrance of *ICE* increases in genotypes with lower AAT levels: PiMS, 18%; PiMZ, 44%; PiSS and PiZZ, 100% (five cases). At all ages, persons with non-MM genotype had significantly higher proportion of thiamine deficiency (50% in PiMZ), reactive hypoglycemia (20% in PiMZ), and possibly fatty liver (thiamine: $\chi^2 = 28$, $p = 0.0001$; hypoglycemia: $\chi^2 = 92$, $p = 0.0001$). In older persons, PiMZ genotype had significantly increased proportion (46%) of brain MRI T2 white matter abnormalities ($\chi^2 = 49$, $p = 0.003$).

Persons with *ICE* and MM genotype showed increased prevalence of pulmonary disorders and same signature as S and Z carriers and homozygotes (see above). Z polymorphism was associated with delayed age of onset (average 7 years) for persons with toxic environmental or occupational exposures (log rank, $p = 0.0001$) and more stable cognitive change in persons with neurodegenerative illness ($p < 0.05$). At all ages, *ICE* phenotype and Z polymorphism were associated with altered copper homeostasis with low or absent non-ceruloplasmin bound copper ($p < 0.05$). AAT polymorphisms which affect iron, lipid and copper metabolism may affect early events in nervous system development, function and response to environmental exposures. AAT may also be a 'switch' for copper metabolism and low 'free' copper would be theorized to provide protection for lipid oxidation and favorably affect beta-amyloid and other aggregation, but possibly alter early 'critical' period of CNS development. AAT polymorphisms may define an important and treatable subset of persons presenting with CNS disorders. This new *proposed* phenotype for AAT transcends classic pattern of strictly liver and lung disease, and should be considered for proper evaluation and management of patients presenting with classic AAT-related disorders, affective disorders, persons with *ICE*, white matter disease or multisystem disorders of memory.

Keywords: Alpha-1-antitrypsin or AAT; Art; Anxiety and bipolar disorders; Copper homeostasis; Neurodegeneration; Toxic exposures

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0161-813X/$ – see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.neuro.2007.05.011

1. Introduction

Alpha-1-antitrypsin (SERPIN1A, AAT, proteinase inhibitor or Pi, chromosome 14q32.1) is a secreted serine protease inhibitor involved in neutrophil elastase inhibition, macrophage activation, and regulation of iron and lipid metabolism (Schroeder et al., 1985; Billingsley et al., 1993; Byth et al., 1994; Graziadei et al., 1993, 1994, 1997, 1998; Moraga et al., 2001; Moraga and Janciauskiene, 2000; Janciauskiene et al., 2001; Mashiba et al., 2001). AAT has many genetic polymorphisms, some of which result in impaired release and diminished or deficient levels of serum AAT. Most persons have combinations of various M polymorphisms (M, M1, M2, . . . ca. 90% of population; e.g. genotype PiMM). In persons of Caucasian origin, next most common genotype is single point mutations of AAT: S (6%) or Z (3%), found in ca. 9% of persons in SE United States (Blanco et al., 2001; de Serres, 2002), combined with various M alleles as heterozygotes (e.g., PiMS, PiMZ). Origin of S and Z mutations dates back to Neolithic times: 110–135 generations for Z (3300–4050 years) and 280–470 generations for S (8400–13100 years) (Seixas et al., 2001). Numerous other polymorphisms exist in persons of African origin, but are less well studied (Hayes, 2003; de Serres et al., 2005). Rare persons homozygous for S or Z or compound heterozygotes such as PiSZ have significant risk of severe liver dysfunction and/or obstructive pulmonary disease sometimes early in life, related to tissue injury through unchecked elastase activity, tendency for intracellular aggregation, and/or polymerization/deposition along vessels (Ikebe et al., 2000; Perlmutter (2002, 2003); Teckman et al., 2002, 2004; Teckman and Perlmutter, 2000; Aldonyte et al., 2004; Mulgrew et al., 2004; Strange et al., 2006). The numerous set of persons heterozygous for S or Z may be more susceptible to cirrhosis with ''2nd hit'' such as hepatitis C infection or alcoholic liver disease, and to chronic obstructive pulmonary disease with smoking (Parfrey et al., 2003). Presence of the S AAT polymorphism may be associated with more rapid progression of coronary artery disease, but the Z polymorphism paradoxically may be protective (Talmud et al., 2003; Dahl et al., 2003). However, the literature generally maintains that persons heterozygous for S and Z polymorphisms or 'carriers' are clinically ''silent''. Most carriers accordingly are never genotyped.

In this report, we further extend the phenotype for S and Z polymorphisms from vulnerability to liver and lung disease to brain function and vulnerability to CNS disorders. Discovery of this extended phenotype was based on a strategy of comprehensive analysis of persons presenting with cognitive disorders, prompted by an informative index case with history of mild liver abnormalities and bipolar disorder (Schmechel et al., 2006). The index case presented with early onset neurocognitive disorder at age 55 with outside diagnosis of Alzheimer Disease, mood disorder ultimately diagnosed as bipolar disorder I and liver enzyme abnormalities. This person was heterozygous for AAT Z polymorphism and also had significant reactive hypoglycemia, hepatosteatosis, thiamine deficiency, and obstructive sleep apnea. After treatment for the above conditions, the patient improved and has been stable for 7 years.

This strategy resulted in the report that persons presenting with cognitive complaints or disorders *and* pre-existing anxiety disorder or bipolar spectrum disorder have a significantly increased proportion of S and Z polymorphisms and a significantly higher likelihood of thiamine deficiency (Schmechel et al., 2006). Given the strong association of bipolar mood disorder and artistic vocation reported in the literature (e.g., *Touched with fire: manic-depressive illness and artistic temperament*, Dr. Kay Jamieson, 1993), one would expect that AAT polymorphisms might also be associated with phenotype of artistic ability or vocation.

To test this hypothesis, we examined the relationship of AAT polymorphisms with pre-existing treated mood disorder, occupation, and artistic vocation or avocation in a consecutive series of 1537 persons ages 16–90 years old presenting to Duke University Memory Disorders Clinic (previously reported 1149 cases, Schmechel et al., 2006, with 388 additional patients). We applied practice guidelines for MCI and dementia evaluation, and investigated liver function including testing for AAT polymorphisms. As part of a larger research effort on cognitive disorders, we tracked occupation, the common instance of potential toxic environmental or occupational exposures, inquired about artistic avocations and hobbies, as well as gathering information on general health conditions.

We confirm the expected aggregation of pulmonary disease and the newer association with anxiety and bipolar disorders (Schmechel et al., 2006), and now report that artistic vocation is also significantly increased in persons with AAT polymorphisms S, Z and non-M rare alleles. We propose merging these two partially overlapping phenotypes of mood disorder and artistic ability into a new phenotype of 'intense creative energy' or *ICE*. We present information that AAT may influence not only iron and lipid metabolism but also copper and zinc metabolism. Persons with S and Z polymorphisms had significantly lower non-ceruloplasmin bound copper and altered iron, copper and zinc homeostasis. This observation of lower 'free copper' may explain finding that Z polymorphism is also associated with delayed age of onset for chronic toxic environmental or occupational exposures and slower progression rate in neurodegenerative disorders.

The frequent association of abnormalities in cerebral white matter, glucose metabolism, and thiamine levels together with the background prevalence of non-M AAT polymorphisms (15%) should motivate clinicians to search diligently for preventable or correctable conditions in persons with these polymorphisms. This proposed new AAT behavioral phenotype of intense creative energy should be tested by researchers in other clinical populations for validation. We provide evidence that a specific behavioral signature of non-M AAT polymorphisms is common and presumably arises early in development during the critical period of brain development including myelination. Non-M AAT polymorphisms may also exert significant long-term effects on CNS function and vulnerability after the critical period. Thus, these polymorphisms may not be 'silent'. The pleiomorphic character of AAT polymorphisms

may represent an important selective advantage for the recent emergence of S and Z mutations, and for the numerous alleles present in other non-European populations.

2. Methods

One thousand five hundred and thirty-seven consecutive patients over the age of 16 years old were examined one or more times over a 6 year period in the Memory Disorders Clinic of the Joseph and Kathleen Bryan Alzheimer Disease Research Center (ADRC) at Duke University. Presentation to our referral clinic was usually 2–4 years after onset of symptoms. Age of onset was taken as patient and/or informant reported onset of clinical symptoms sufficient that resulted in or would have warranted medical evaluation. Clinical evaluation was performed using practice guidelines for mild cognitive impairment (MCI) and dementia syndromes (Knopman et al., 2001; Petersen et al., 2001), in a two-visit model with diagnosis confirmed at second visit after medical history, full physical and neurological/psychiatric examination, and appropriate neuropsychometric screens. Guidelines call for complete blood count, measures of renal and liver function, B12 and thyroid determinations, and anatomical neuroimaging. Clinical indication for additional genetic and laboratory tests of liver function included: high prevalence of abnormal iron indices, low or deficient thiamine levels, and palmar telangectasia. We tested for plasma homocysteine levels, thiamine (B1) deficiency using serum and red cell thiamine levels, and for iron indices (serum iron, transferrin, and ferritin) (Schmechel et al., 2006). Evaluation of vascular risk included lipid profile and inflammatory markers: serum ceruloplasmin (ferroxidase) activity (Cp), serum copper, zinc, and high sensitivity assay for C-reactive protein (Crp). Non-ceruloplasmin bound copper ('free' copper) and % free copper was calculated by assuming fully charged ceruloplasmin molecule with six copper atoms (Schmechel et al., 1996a,b).

Apolipoprotein E (APOE) genotypes were obtained in 1017 patients (66%), hemochromatosis gene testing in 913 patients (60%) for C282Y, H63D and S35C mutations, methylene tetrahydrofolate reductase (MTHFR) in 963 persons, and alpha-1-antitrypsin phenotyping in all 1537. These genetic tests were used for counseling and treatment selection, but were not used to change the *clinically based* primary neuropsychiatric diagnosis established at first or second visit. Half of the persons (51%) had neuroimaging film scans that were available for actual review (as opposed to written interpretative reports). These were characterized into groups based on presence and severity of ischemic microvascular disease of white matter (none, mild, moderate or severe), demyelinating-like lesions (MS), or presence of vascular infarcts (lacunes or infarcts).

Primary neuropsychiatric diagnoses were based on established and published guidelines (Knopman et al., 2001; Petersen et al., 2001). Commonly encountered diagnoses included: normal, cognitively impaired non-demented (CIND), mild cognitive impairment (MCI), possible or probable Alzheimer disease (AD), AD with Parkinsonism (ADPD), AD with vascular disease (ADVD), frontal lobe dementia, frontotemporal dementia (FTD, often with motor findings such as Parkinsonism), Lewy body dementia (LBD), primary progressive aphasia (PPA), progressive supranuclear palsy (PSP), vascular dementia (VD), and other minor categories. MCI was employed for persons in mini-mental status examination (MMSE) range 24–30 and categorized as amnesic (aMCI) (history of memory problems, missing one to three recall items on MMSE and/or with intrusions) and multi-domain or 'non-amnesic' (naMCI) (history of behavioral, personality change and/or language problems, difficulty with executive function, relatively retained recall compared to deficits in registration, processing, language, executive function). Larger diagnostic groups were created from persons with CIND and MCI syndromes (group 1), with AD and AD-related diagnoses (group 2), and with FLD/FTD, PPA, and other non-AD related diagnoses (group 3).

An important category for secondary neuropsychiatic diagnoses was history of previously diagnosed and treated depression (11%), anxiety disorder (12%), and bipolar disorder or mixed mood disorder treated with mood stabilizers (13% of all cases). Persons were also categorized by medical history, medication use, and physical examination into history of treated coronary artery disease (CAD) and categories of prior treated or clinically evident pulmonary disorder: reactive airway disease or asthma (RAD), chronic obstructive pulmonary disease (COPD), and no apparent pulmonary disorder. RAD often was present in persons with COPD, and such persons were assigned to COPD category (Eden et al., 2006).

Occupational history was available using informant history and intake forms, and confirmed by examiner. Occupations were characterized by 23 categories of standard occupational classification system of US Bureau of Labor Standards (BLS) with additional categories of sports (removed from artist class), homemaker, and unemployed/disabled. An alternative more flexible definition of 'artist' was listed as positive when the person had taken substantial artistic training and/or created or designed works of art or participated in performances even though a homemaker or employed in another category. These included music performances, acting, drawing or painting, substantial original crafts, creative writing, landscape design, and professional decorating. Not included as positive were routine participation in church choirs, artwork in kit form, simple seasonal crafts, regular high school or undergraduate school activities. Assignment of BLS category and rating of artistic vocation was done independently in batch analysis and without knowledge of clinical and laboratory information. In addition, artists were divided into six categories used by Markusen (2004): actor/director, dancing, music, photography, visual arts, and writing. Where several categories were possible for a person, the most frequent or dominant category was noted.

Environmental and toxic exposure information was available and dichotomized into potential environmental or occupational exposure or no apparent exposure. Legacy pesticide exposures were assumed for persons working on farms up through teen-age years on tobacco or cotton farms or with significant pesticide/herbicide exposure in youth. Many of our subjects had potential legacy pesticide exposures in their youth prior to age 20 associated with agricultural work (36%). We considered adult occupations such as auto mechanic or

tobacco farming to represent possible occupational and environmental exposures (respectively, volatile organic solvents and pesticide/herbicides). Most frequent occupations for 333 persons with positive history were: industrial production, industrial installation, farming or agriculture, and life sciences (BLS categories). In terms of potential exposures, most frequent categories were: volatile organic compounds ($n = 157$), pesticides/herbicides ($n = 75$), and electromagnetic field or emf exposures ($n = 33$), and organic compounds ($n = 31$). In this paper, we will concentrate on two most numerous exposure categories of volatile organic compounds (VOC) and pesticides/herbicides.

All testing except lipids was on non-fasted specimens of opportunity with APOE genotyping (Athena Laboratories), AAT phenotyping (Mayo Laboratories), hemochromatosis genotyping (Duke University Laboratories) and other routine laboratory tests were conducted in CLIA-approved facilities of Duke University Medical Center or Mayo Laboratories. Assay for APOE polymorphisms uses the serial invasive signal amplification reaction method (the Invader DNA assay) for the detection of six possible genotypes (4/4, 3/3, 2/2, 4/3, 4/2 and 3/2) in the APOE gene. Hemochromatosis (HFE) gene regions of interest were amplified by polymerase chain reaction (PCR) then digested with restriction enzymes; DpnII for H63D; HinfI for S65C; and RsaI for C282Y mutations. Resultant fragments were resolved by agarose gel electrophoresis and analyzed. Alpha-1-antitrypsin (AAT) phenotyping involves agarose gel electrophoresis with identification of different isoforms: M, M1, M2, S, Z, and rare alleles. Although based on biochemical assay, phenotypic analysis for AAT is commonly used for assigning genetic allelic status and is highly accurate (Blanco et al., 2001; de Serres, 2002; Dahl et al., 2003). The assay also provides mass information on serum levels of AAT (normal range 100–190 mg/dL). We will refer to these phenotypes as PiMM, PiMS, PiMZ and so forth without distinction of M subtypes for ease of communication.

The results were analyzed using Statgraphics package on anonymized spreadsheet of patient data without identifying characteristics and with ages over 90 reported as 90 or above. Usual analysis for categorical variables was by contingency table with chi-square analysis. Analysis was done both for individual AAT genotypes and also for larger groupings of PiMM and all non-MM categories to avoid small cell size. ANOVA was performed on numerical data with age, gender, or other adjustment where appropriate. IRB exemption was granted for retrospective anonymized analysis of clinical database.

3. Results

3.1. Demographics

Demographic information on the 1537 consecutive persons in this clinical series is presented in Table 1. Proportion of non-M AAT polymorphisms was slightly higher than expected for Southeastern United States (14% compared to 9%), but background rates vary considerably in different regions of US (Blanco et al., 2001). Gender proportion, educational level, and MMSE did not vary significantly across different main AAT phenotypes. Eighty-seven percent of persons were Caucasian and 11% African-American. These particular polymorphisms (S and Z) were significantly less frequent in black persons (4%) compared to Caucasians (16%) as expected from literature (de Serres et al., 2005; de Serres, 2002). There are presumptively other AAT polymorphisms that affect AAT function and levels in persons of African and non-Caucasian origin (de Serres, 2002; Hayes, 2003). For all diagnoses grouped together, age of onset was slightly lower for Z polymorphism carriers: 59 ± 2 years old for Z compared to 64 ± 0.4 years old for M and 64 ± 1 years old for S carriers ($\chi^2 = 6.6$, $p = 0.036$, log-rank). There was no significant association of AAT polymorphisms with three broad diagnostic

Table 1
Proportion of AAT polymorphisms and associated demographics

	ALL	PiMM	Non-M	PiMS	PiMZ	PiM{X}[a]	Pi{ZZ,SS,...}[b]
Number (%)	1537	1312 (85.4%)	225 (14.6%)	140 (9.1%)	52 (3.4%)	24 (1.6%)	9 (0.6%)
Age of onset (years)	62.4 ± 0.4	64.4 ± 0.4	62.7 ± 0.9	64.2 ± 1.2	59.4 ± 1.8	61.7 ± 2.7	62.2 ± 4.4
Gender (% female)	56.8	56.4	58.9	57.1	55.8	79.2	55.6
Race (%)							
Caucasian	88.5	87.0	96.4	97.1	96.2	95.8	100.0
Black	9.8	11.1	3.1	2.1	3.8	4.2	–
Other	1.7	1.9	0.5	0.8	–	–	–
Education (years)	14.2 ± 0.1	14.0 ± 0.1	14.4 ± 0.2	14.4 ± 0.3	14.7 ± 0.4	13.5 ± 0.6	15.2 ± 1.0
MMSE score	23.9 ± 0.2	24.1 ± 0.2	23.7 ± 0.4	22.9 ± 0.5	24.1 ± 0.8	26.1 ± 1.3	27.3 ± 1.9
MMSE change/year	−1.3 ± 0.2	−1.6 ± 0.2	−1.5 ± 0.5	−2.1 ± 0.6	−0.6 ± 0.9	−1.6 ± 1.2	−1.2 ± 2.2
Toxic exposure							
All (%)	333 (21.7%)	282 (21.5%)	51 (22.7%)	35 (25.0%)	10 (19.2%)	3 (12.5%)	3 (33.3%)
Pesticide (%)	75 (4.9%)	59 (4.5%)	16 (7.2%)	9 (7.2%)	6 (11.5%)	0 (–)	1 (11.1%)
VOC (%)	159 (9.9%)	135 (9.8%)	24 (11.2%)	19 (13.7%)	3 (5.8%)	2 (8.3%)	0 (–)

Age of onset vs. AAT polymorphism, log-rank, $\chi^2 = 6.65$, $p = 0.036$. MMSE difference, ANOVA, adjusted for gender, education, initial MMSE score, interval, M vs. S, M vs. Z, $p < 0.05$, Fisher least significant difference.

[a] Rare alleles: 10 PiIM, 7 PiGM, 2 PiPM, 2 PiVM, one each PiFM, PiEM, Pi{unknown allele}M.

[b] Homozygotes and compound heterozygotes: 2 PiZZ, 3 PiSS, 2 PiSZ, 1 PiIZ, 1 PiIS.

groups: CIND/MCI, AD-related dementias, and non-AD dementias or group of 19 normal persons. In CIND/MCI group, there was a trend towards increased proportion of Z polymorphisms with CIND diagnosis. There was no significant association with specific primary diagnoses in AD group (data not shown). In CIND/MCI and AD groups, proportion of persons with aMCI compared to naMCI and with ADVD compared to AD was approximately 2:1 (Schmechel et al., 2006). In non-AD diagnostic group, there was significantly higher proportion of persons with non-M polymorphisms presenting with demyelinating disease (38%, 6 of 16 total cases, contingency table, $\chi^2 = 49$, $p = 0.0003$). In persons with normal pressure hydrocephalus, there was likewise significantly higher proportion of non-M polymorphisms (25%, 8 of 32 total cases, contingency table, $\chi^2 = 16.0$, $p = 0.003$). There were trends towards increased proportion of persons with AAT polymorphisms and non-vascular diagnoses with focal neurological findings: 2 of 5 cases of CBDG, 6 of 35 cases of ADPD, and 18 of 91 cases of PPA. Toxic environmental or occupational exposures (Table 1) and significant smoking (34%) and alcohol use (23%) were common across all AAT genotypes.

Since this series represents persons *coming to clinic* with neurological symptoms and signs, we examined whether there was any aggregation of APOE, Hfe or MTHFR genotypes with AAT polymorphisms. We found no relationship with exception of tendency for persons homozygous for Hfe C282Y polymorphism to have S or Z AAT polymorphism (two of six persons). Proportion of APOE4 in the large subset genotyped for APOE was increased, consistent with E4 as vulnerability factor for onset of aMCI and AD (allele frequency 0.33 or 54% of persons carried one or two E4 alleles, compared to expected background population rate of 0.15 or ca. 30% carrier rate). Overall proportion of persons with Hfe C282Y polymorphism was ca. 12% similar to expected background rate (Barton et al., 1998), and MTHFR C677T (''VV'') homozygous state ca. 12% slightly above background rate of 7% (Kawashiri et al., 2000).

3.2. AAT polymorphisms and classic phenotype of vulnerability to pulmonary disorders

There was a significant increase in pre-existing history or physical examination evidence of reactive airway disease (RAD) and chronic obstructive pulmonary disease (COPD) with S and Z polymorphisms. Combined prevalence of RAD and COPD was 20% in persons with $PiMM_i$ genotype compared to 42% for persons with PiMZ genotype and 78% for persons with two non-M alleles (Table 2) (contingency table, $\chi^2 = 37$, $p = 0.0001$). When there is a positive smoking history (present in ca. 30% of persons), the respective proportions for combined RAD and COPD prevalence were: 30% for persons with $PiMM_i$ and 55% for persons with PiMZ genotype. The AAT enhancement of pulmonary disorders is most striking for COPD prevalence in non-smokers: 7% for persons with $PiMM_i$ and 24% for persons with PiMZ genotype. MS genotype was intermediate. Increased pulmonary disease for S and Z carriers is reported in literature, although not observed in all studies (Hersh et al., 2004; Dahl et al., 2005). Relationship for reactive airway disease was less pronounced than COPD. There was no significant correlation of prior coronary artery disease (CAD) and AAT polymorphisms, although proportion of CAD was 2–3-fold less in persons with PiMZ compared to PiMS or $PiMM_i$ genotypes. When CAD is compared to quartiles of serum AAT levels, there is significant

Table 2
AAT polymorphisms and associated clinical phenotypes of pre-existing pulmonary or mood disorder

	ALL	PiMM	Non-M	PiMS	PiMZ	PiM{X}[a]	Pi{ZZ,SS,...}[b]
Total number	1537	1312	225	140	52	24	9
AAT level	129 ± 0.7 (n = 1531)	**142 ± 0.7** (n = 1311)	**115 ± 1.7** (n = 220)	**122 ± 2** (n = 136)	**95 ± 3** (n = 51)	**131 ± 5** (n = 24)	**75 ± 8** (n = 7)
Pulmonary disorder							
None	1206 (78.5)	1051 (80.2)	**155 (68.9)**	103 (73.6)	**30 (57.7)**	20 (83.3)	**2 (22.2)**
Asthma (RAD)	125 (8.1)	101 (7.7)	24 (10.7)	12 (8.6)	**7 (13.5)**	2 (8.3)	**3 (33.3)**
COPD	205 (13.4)	159 (12.1)	**46 (20.4)**	**25 (17.9)**	**15 (28.9)**	2 (8.3)	**4 (44.4)**
Affective disorder							
None	980 (63.8)	**887 (67.7)**	**93 (41.3)**	**69 (49.3)**	**12 (23.1)**	**9 (37.5)**	**2 (22.2)**
Depression	166 (10.8)	156 (11.9)	**10 (4.4)**	**7 (5.0)**	**1 (1.9)**	1 (4.2)	1 (11.1)
Anxiety	189 (12.3)	**141 (10.8)**	**48 (21.3)**	**32 (22.9)**	**13 (25.0)**	2 (8.3)	1 (11.1)
Bipolar spectrum	197 (12.8)	**123 (9.4)**	**74 (32.9)**	**32 (22.9)**	**26 (50.0)**	**12 (50.0)**	**5 (55.5)**
Bipolar subtypes:							
BP I	47 (3.0)	33 (2.4)	**14 (6.3)**	5 (3.6)	**6 (11.5)**	1 (–)	2 (–)
BP II	25 (2.4)	20 (2.0)	5 (4.5)	5 (5.8)	2 (3.9)	0 (–)	0 (–)
Mixed disorder	113 (6.6)	**61 (4.1)**	**52 (21.1)**	**21 (12.2)**	**17 (32.7)**	11 (–)	2 (–)
Others	12 (0.7)	9 (0.8)	3 (0.3)	1 (0.9)	1 (1.9)	0 (–)	1 (–)

Numbers and column proportions (% in parentheses) of each AAT genotype for separately for each clinical phenotype category—pre-existing pulmonary disorder, pre-existing mood disorder, and bipolar spectrum subtypes (% sums to original subcategory of bipolar spectrum in affective disorder grouping). AAT level vs. AAT genotype, one-way ANOVA, $F = 76.0$, $p = 0.0001$; values ± standard error. AAT vs. pulmonary disorder, MM vs. non-M, contingency table, $\chi^2 = 15.1$, $p = 0.0005$; AAT genotypes; $\chi^2 = 36.6$, $p = 0.0001$ (some cells <5). AAT vs. affect, MM vs. non-M, contingency table, $\chi^2 = 135.1$, $p = 0.0001$; AAT genotypes, $\chi^2 = 177.1$, $p = 0.0001$ (some cells <5). AAT vs. bipolar subtypes, MM vs. non-MM, contingency table, $\chi^2 = 23.8$, $p = 0.0001$. Bold values are for cells with $\chi^2 > 2.0$.

[a] Rare alleles: 10 PiIM, 7 PiGM, 2 PiPM, 2 PiVM, one each PiFM, PiEM, Pi{unknown allele}M.

[b] Homozygotes and compound heterozygotes: 2 PiZZ, 3 PiSS, 2 PiSZ, 1 PiIZ, 1 PiIS.

relationship of increasing CAD with higher quartiles (contingency table, $\chi^2 = 23$, $p = 0.0001$).

3.3. AAT polymorphisms and phenotype of anxiety and bipolar spectrum disorders

AAT levels are significantly different across the various AAT genotypes (Table 2). They provide obvious clinical clue that a person may be an AAT polymorphism carrier (82% of persons with AAT <100 mg/dL are non-MM). However, 28% of persons with Z polymorphism were above this clinical cut-off limit. As previously reported (Schmechel et al., 2006), proportion of persons with pre-existing treated anxiety and bipolar disorders was significantly increased with PiMS, PiMZ and rare AAT genotypes (Table 2) compared to persons with MM_i genotypes or to persons in categories of pre-existing depression or no affective disorder (contingency table, $\chi^2 = 171, p < 0.0001$). This effect is prominent: ca. 40–50% of persons with PiMS or rare AAT genotypes and 73% of persons with PiMZ genotype have either pre-existing anxiety disorder or bipolar spectrum disorder compared to 20% of persons with $PiMM_i$. Specific diagnosis, level of cognitive impairment, as well as APOE, Hfe or MTHFR genotypes showed no relationship to affective disorder. Many persons with anxiety disorder or bipolar disorder presented with mild cognitive impairment, and significantly fewer were genotyped for APOE and Hfe, but the above relationships of AAT genotype held in both genotyped and non-genotyped subsets, regardless of 'intent' to genotype for these other markers (data not shown).

In this extension of the previously reported series, we subdivided bipolar spectrum disorders into bipolar type I (BPI), bipolar type II (BPII) or clinically diagnosed mixed disorders with anxiety-hypomania. The significant association of AAT polymorphisms observed for the broad category of bipolar spectrum disorders held for each of these clinical subtypes (Table 2), although particularly marked for persons with clinical 'mixed disorders'.

In a given individual *without* acute inflammatory or infectious illness, serum AAT levels were very stable over periods of 6–18 months ($n = 302$, $r^2 = 44\%$, F-ratio = 237, $p = 0.0001$). In fact, AAT levels are slightly lower for persons with pre-existing anxiety or bipolar disorder compared to persons with depression or no affective disorder (ANOVA, 134 ± 2, 131 ± 2, 141 ± 2 and 140 ± 1 mg/dL, respectively, F-ratio = 6.5, $p = 0.0001$). This difference is presumably secondary to different proportions of non-M AAT genotypes and their associated lower expression levels. There is no significant difference in AAT levels across affective diagnostic categories for any single AAT genotype including $PiMM_i$. Thus, AAT levels do not distinguish affective categories other than by being a rough guide to likelihood of non-M polymorphisms for persons with very low or high levels.

3.4. AAT polymorphisms: extended phenotype of artistic vocation and intense creative energy

The index case of PiMZ-associated cognitive disorder, liver abnormalities and bipolar spectrum disorder was a brilliant and highly successful professional who, in fact, had a major avocation as a woodworker and craftsperson designing and creating large model railroad layouts. This first person proved to be typical of the frequent concurrence of artistic vocation or avocation and AAT polymorphisms. Given the observed relation of artistic ability and bipolar spectrum disorder reported in the literature and the proposed relation of AAT polymorphisms and mood disorders (Schmechel et al., 2006; Table 2 of this paper), we then examined systematically the relationship of AAT polymorphisms to artistic occupation according to Bureau of Labor Standards (BLS) criteria (Table 3). Fifty-seven vocational artists are present in the 1537 persons of our series and 40% of these 57 persons are carriers for non-M AAT polymorphisms (contingency table, $\chi^2 = 152$, $p = 0.0037$). For the entire group, AAT levels adjusted for age and gender were slightly, but significantly lower for artists compared to non-artists (127 ± 2 mg/dL for artistic vocation/avocation, 122 ± 4 mg/dL for stricter BLS-artist category, compared to 140 ± 1 mg/dL for non-artists, ANOVA, $p < 0.00001$). For persons with $PiMM_i$ genotype, AAT levels are not significantly different for artistic vocation/avocation.

Using the more expanded definition of artistic vocation or avocation (see Section 2), 189 or 12% of the 1537 persons were characterized as artists including the index case. Of this subgroup of artists, 44% or 84 of these 189 persons were carriers for S, Z or rare AAT polymorphisms compared to observed 8% carrier rate for non-artists (contingency table, $\chi^2 = 195$, $p = 0.0001$). Conversely, proportion of artists was 12.3% for all persons combined and 8.0% in persons with $PiMM_i$ genotype whereas proportion in AAT carrier group (S, Z, other rare polymorphisms, and homozygotes/compound heterozygotes) ranged from 27 to 75% (Table 3). Of note is all of the three persons with PiSS genotype and both of the persons with PiZZ genotype in this series are artists (100%!!).

Pre-existing anxiety or bipolar disorder and artistic classification categories overlap, but are not coincident. Overlap of persons with anxiety or bipolar spectrum disorders to expanded artistic classification is 47/105 (45%) for persons with $PiMM_i$ genotypes, 26/38 (68%) for persons with PiMS genotype, 23/29 (79%) for persons with PiMZ genotypes and 6/7 (86%) for persons with Pi{ZZ,SS,...} homozygous or compound heterozygous combinations. The above proportions compare to 18% of persons having anxiety or bipolar disorder in group of persons *without* artistic vocation/avocation and with $PiMM_i$ genotypes. Thus, overlap of artistic vocation and mood disorder is observed for all AAT genotypes, but is enhanced in non-M carriers.

Two of the self-reported attributes of persons with AAT polymorphisms and artistic avocation and/or anxiety/bipolar spectrum disorders are heightened non-verbal intuitive awareness of their surroundings and periods of focused intense creative energy. Given the observed overlap of art and mood disorders and the above clinical attributes, we created an overall phenotype of intense creative energy (ICE) composed of artists with mood disorder, comparing them to artists without reported anxiety or bipolar spectrum disorders, and to persons with these mood disorders but no apparent artistic vocation or

Table 3
AAT polymorphisms and associated behavioral traits of art, intense creative energy (ICE), and mood disorder

	ALL	PiMM	Non-M	PiMS	PiMZ	PiM{X}[a]	Pi{ZZ,SS,...}[b]
Total number	1537	1312	225	140	52	24	9
BLS occupation							
Other categories	1480 (96.3)	**1378 (97.4)**	**202 (89.8)**	134 (95.6)	**42 (80.8)**	**20 (83.3)**	**6 (66.7)**
Professional artist	57 (3.7)	**34 (2.6)**	**23 (10.2)**	6 (4.3)	**10 (19.2)**	**4 (16.7)**	**3 (33.3)**
All artistic activity							
None	1347 (87.6)	**1207 (92.0)**	**140 (62.2)**	**102 (72.9)**	**23 (44.2)**	**13 (54.2)**	**2 (22.2)**
Artistic	190 (12.4)	**105 (8.0)**	**85 (37.8)**	**38 (27.1)**	**29 (55.8)**	**11 (45.8)**	**7 (77.8)**
Artistic categories							
Acting	8 (0.5)	7 (0.5)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Dancing	4 (0.3)	1 (0.1)	**3 (0.9)**	**2 (1.4)**	**1 (1.9)**	0 (–)	0 (–)
Music	42 (2.7)	**23 (1.8)**	**19 (7.2)**	**12 (8.6)**	**3 (5.8)**	**3 (12.5)**	**1 (11.1)**
Photography	7 (0.5)	3 (0.2)	**4 (1.3)**	1 (0.7)	**1 (1.9)**	0 (–)	**2 (22.2)**
Visual arts	100 (6.5)	**52 (4.0)**	**48 (22.6)**	**19 (13.6)**	**17 (32.7)**	**8 (33.3)**	**4 (44.4)**
Writing	29 (1.9)	19 (1.5)	**10 (4.5)**	4 (2.9)	**7 (13.5)**	0 (–)	0 (–)
Art/mood							
Non-artist/normal	1069 (69.6)	**992 (75.6)**	**77 (34.2)**	**63 (45.0)**	**7 (13.5)**	**5 (20.8)**	**2 (22.2)**
All subtypes	468 (30.4)	**320 (24.4)**	**148 (65.8)**	**77 (55.0)**	**45 (86.5)**	**19 (79.2)**	**7 (77.8)**
Subtypes							
(1) Artist only	81 (5.3)	**57 (4.3)**	**24 (10.7)**	**12 (8.6)**	**6 (11.5)**	**5 (20.8)**	1 (11.1)
(2) ICE	110 (7.2)	**49 (3.7)**	**61 (27.1)**	**26 (18.3)**	**23 (44.2)**	**6 (25.0)**	**6 (66.7)**
(3) Mood only	277 (18.0)	**214 (16.3)**	**63 (28.0)**	**39 (27.9)**	**16 (30.8)**	**8 (33.3)**	0 (–)

Numbers and proportions (% in parentheses) of each AAT genotype separately for BLS-artist occupation category and artistic activity and its subcategories. AAT vs. BLS-artistic occupation, MM vs. non-M, contingency table, $\chi^2 = 56.7$, $p = 0.0007$; AAT vs. BLS-artistic occupation, $\chi^2 = 151.5$, $p = 0.0037$ (some cells <5). AAT vs. art, MM vs. non-M, contingency table, $\chi^2 = 157.2$, $p = 0.0001$; AAT genotypes; $\chi^2 = 202.1$, $p = 0.0001$ (some cells <5). AAT vs. artist category, MM vs. non-M, contingency table, $\chi^2 = 171.5$, $p = 0.0001$; AAT genotypes, $\chi^2 = 336.5$, $p = 0.0001$ (some cells <5). AAT vs. ICE phenotype, contingency table, MM vs. non-M, $\chi^2 = 227.2$, $p = 0.0001$; AAT genotypes vs. ICE subtypes, $\chi^2 = 295.3$, $p = 0.0001$ (some cells <5). ICE phenotype for AAT genotypes: PiMM: 4%; PiMS: 18%; PiMZ: 44%; PiIM: 20% ($n = 11$); PiGM: 14% ($n = 7$); PiSS: 100% ($n = 3$); PiZZ: 100% ($n = 2$). Bold values are for cells with $\chi^2 > 2.0$.

[a] Rare alleles: 10 PiIM, 7 PiGM, 2 PiPM, 2 PiVM, one each PiFM, PiEM, Pi{unknown allele}M.

[b] Homozygotes and compound heterozygotes: 2 PiZZ, 3 PiSS, 2 PiSZ, 1 PiIZ, 1 PiIS.

avocation, and to persons with neither artistic ability or mood disorder. The ICE phenotype showed no association with APOE4 alleles, MTHFR or Hfe polymorphisms. For APOE2 allele, two out of five total persons with APOE2/2 genotype were artists without mood disorder. As expected from the separate highly significant relationships for AAT with art and mood disorder taken alone, the combined phenotype of intense creative energy is highly related to AAT genotype. The proportion of ICE phenotype is 4% in persons with M polymorphisms (47 of 1312), 19% in PiMS carriers (26 of 140), 25% in persons with other non-M polymorphisms (6 of 24), 44% in PiMZ carriers (23 of 52), and 78% in Pi{ZZ,SS,...} persons (7 of 9) (contingency table, $\chi^2 = 241$, $p = 0.0001$). All three persons with PiSS genotype and both persons with PiZZ genotype had ICE phenotype (100%!!)—artists with mood disorder; this underlines that proportion of ICE phenotype is increased with increasing number or severity of non-M AAT polymorphisms (Fig. 1).

The usual association of AAT polymorphisms with vulnerability to pulmonary disorders followed this same pattern in this clinical series with some increase in already high proportion in non-MM subgroups (Fig. 2). Of interest, persons with AAT MM polymorphisms and ICE phenotype had increased proportion of pulmonary disorders: non-ICE PiMM group with 19% pulmonary disorders compared to ICE PiMM group with 54% pulmonary disorders (contingency table, $\chi^2 = 37$, $p = 0.0001$). The above results support both the AAT locus as a dominant factor for the ICE phenotype as well as suggesting that additional genetic or environmental factors may influence a grouped phenotype of pulmonary vulnerability, artistic ability and mood.

3.5. Possible mechanisms underlying CNS phenotypes of AAT polymorphisms

Given the published literature on the role of AAT as an acute phase reactant and its involvement in iron metabolism and inflammation, we examined laboratory values grouped by AAT polymorphisms. While pulmonary disorders were most highly associated with AAT genotypes with low expression levels (Table 2), the newer AAT phenotypes of mood disorder, artistic ability and intense creative energy (Tables 2 and 3) were also observed with AAT genotypes with relatively normal expression levels such as PiMS and PiGM. This supports an effect of non-M AAT polymorphisms that may be more dependent on other biochemical properties besides release.

We therefore examined other related metabolic and biochemical parameters available in this group of patients. A significant increase in the proportion of persons with reactive hypoglycemia by 5-h oral glucose tolerance test was observed

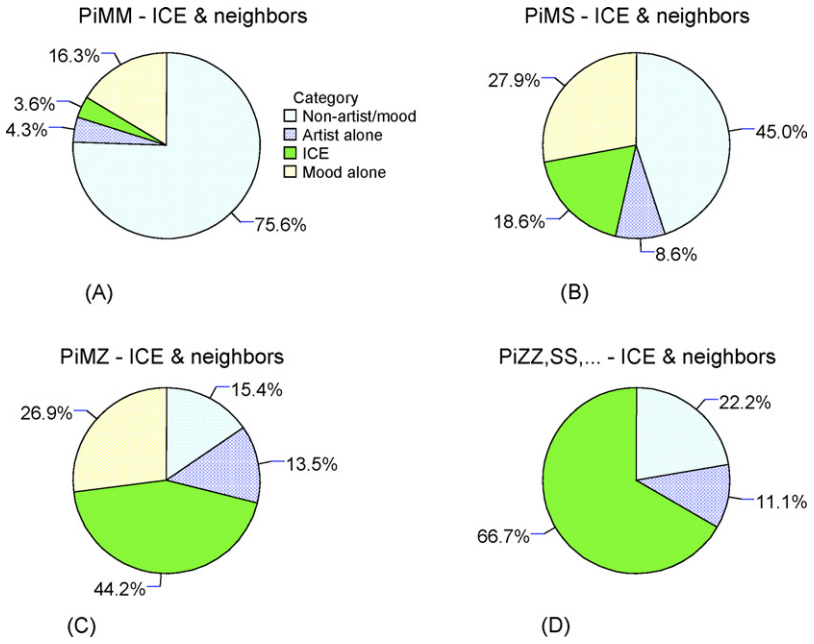

Fig. 1. Prevalence of ICE and its two neighbors (artist alone, mood disorder alone) compared to non artist/non mood disorder persons for different AAT genotypes. (A) PiMM. (B) PiMS. (C) PiMZ. (D) PiZZ, PiSS and compound heterozygotes.

(Table 4), particularly in persons with anxiety disorder. Many persons (50%) with AAT Z polymorphism were B1 deficient at time of presentation with either low plasma thiamine or red cell thiamine levels or both (Table 4). Persons with ICE phenotype, heavily represented by non-M AAT polymorphisms, also showed significant increased proportions of B1 deficiency, reactive hypoglycemia, and lower serum B1 levels. C-reactive protein (Crp) showed non-significant trend to lower values in persons with non-MM polymorphisms, but was significantly decreased in persons with ICE phenotype (Table 4).

Since AAT modulates iron metabolism and inflammatory response, we examined peripheral markers of iron and trace mineral metabolism. There was trend towards increased iron saturation with non-MM AAT polymorphisms and significantly increased serum iron and iron saturation only for persons with Pi{ZZ,SS,...} polymorphisms. There was no significant difference in behavioral phenotype groups of ICE and mood disorder alone. We are currently examining response of iron indices to inflammatory stress in this series (work in progress).

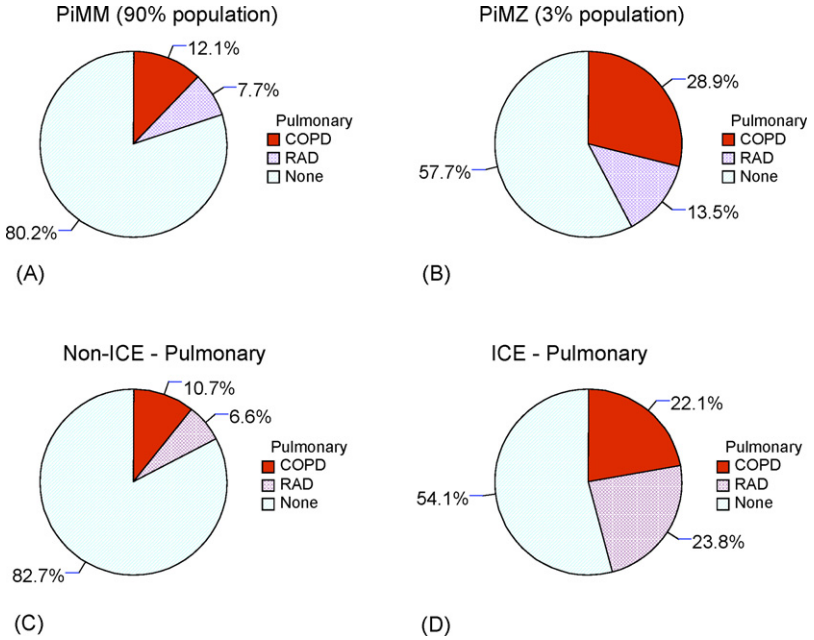

Fig. 2. Comparison of prevalence of pulmonary disorders for AAT genotypes PiMM and PiMZ compared to non-ICE and ICE phenotypes. (A) PiMM. (B) PiMZ. (C) Non-ICE phenotype. (D) ICE phenotype.

Table 4
AAT polymorphisms, ICE, and associated laboratory values

	PiMM	PiMS	PiMZ	Pi{ZZ,SS,...}[a]	Non-ICE	ICE	Mood
Metabolic							
Biphasic GTT	**4.4%**	**12.9%**	**19.2%**	**25.0%**	**5.4%**	**10.2%**	**8.7%**
B1 deficiency	20.0%	18.3%	**48.0%**	**50.0%**	**19.3%**	**43.0%**	**25.9%**
Serum B1 (ng/mL)	**3.71 ± .18**	**3.61 ± .54**	**2.30 ± .69**	1.19 ± 2.08	**2.72 ± 0.09**	**1.86 ± 0.26**	**2.61 ± 0.19**
Inflammatory							
Crp (mg/dL)	0.36 ± .02	0.34 ± .06	0.29 ± .11	0.20 ± .25	**0.36 ± 0.02**	**0.24 ± 0.08**	**0.40 ± 0.05**
Iron indices							
Fe (mcg/dL)	78 ± 1	77 ± 3	81 ± 4	**94 ± 11**	78 ± 1	80 ± 3	78 ± 2
Tf (mg/dL)	260 ± 1	264 ± 4	255 ± 7	266 ± 17	260 ± 1	263 ± 5	267 ± 3
Ferritin (mg/mL)	135 ± 6	137 ± 18	146 ± 29	130 ± 76	136 ± 6	134 ± 22	132 ± 13
Transferrin index	0.44 ± .01	0.43 ± .02	0.46 ± .03	**0.51 ± .07**	0.44 ± 0.01	0.45 ± 0.02	0.43 ± 0.01
Copper/zinc							
Cu/Zn ratio	1.50 ± 0.02	1.49 ± 0.04	1.44 ± 0.07	**1.34 ± 0.20**	**1.50 ± 0.01**	**1.41 ± 0.05**	1.45 ± 0.03
Cu (mcg/dL)	119 ± 1	121 ± 3	120 ± 4	123 ± 11	**119 ± 1**	**115 ± 3**	**119 ± 2**
Zn (mcg/dL)	81 ± 1	85 ± 2	86 ± 2	94 ± 7	**82 ± 1**	**84 ± 2**	**85 ± 1**
Cp (mg/dL)	38.6 ± 0.3	38.6 ± 0.9	39.4 ± 1.3	37.7 ± 4.5	38.5 ± 0.3	38.7 ± 1.1	38.2 ± 0.7
Cu/Cp	3.10 ± 0.01	3.18 ± 0.04	3.07 ± 0.06	3.05 ± 0.20	**3.12 ± 0.01**	**2.99 ± 0.05**	**3.12 ± 0.03**
Free Cu (%)	5.43 ± 0.46	7.50 ± 1.31	4.36 ± 1.95	4.67 ± 6.47	5.83 ± 0.43	2.29 ± 1.61	6.03 ± 0.97
Free Cu (%) $E4_{adj}$	**4.77 ± 0.72**	**6.86 ± 1.74**	**0.97 ± 2.65**	−1.81 ± 13.87	**4.96 ± 0.72**	**1.14 ± 3.12**	**6.11 ± 1.37**

Contingency table: biphasic GTT vs. AAT, $\chi^2 = 91.9$, $p = 0.0001$ (some cells <5); biphasic GTT vs. ICE categories, $\chi^2 = 49.8$, $p = 0.0001$ (some cells <5). B1 deficiency vs. AAT: $\chi^2 = 28.1$, $p = 0.0005$ (some cells <5); B1 deficiency vs. ICE categories: $\chi^2 = 35.7$, $p = 0.0001$ (some cells <5). B1 and AAT, M–Z, S–Z difference; ICE vs. non-ICE or mood, ANOVA, significant by Fisher's least significant difference; ICE vs. non-ICE or mood, Crp, copper, zinc, Cu/Zn ratio, transferring, ferritin not significant w/r AAT genotype; Fe and AAT, transferrin index, Cu/ZN ratio, M and S difference compared to Pi{ZZ,SS,...}; ANOVA, significant by Fisher's least significant difference; Cu/Zn ratio, copper, zinc, copper/ceruloplasmin and ICE categories; differences significant by Fisher's least significant difference; Freecu% and AAT and ICE, adjusted for APOE4 status, M–Z and S–Z differences significant by Fisher's least significant difference; bold values are for cells with $\chi^2 > 2.0$.

[a] Homozygotes and compound heterozygotes: 2 PiZZ, 3 PiSS, 2 PiSZ, 1 PiIZ, 1 PiIS.

Given the occurrence of possible pancreatic or insulin response dysfunction (reactive hypoglycemia) and the fact that the cuproenzyme ferroxidase (e.g., ceruloplasmin) is involved in iron metabolism, we examined peripheral indices of copper and zinc metabolism. There was a trend towards higher serum zinc in persons with non-MM AAT polymorphisms, and a significantly depressed copper/zinc ratio in persons with Pi{ZZ,SS,...} (Table 4). Non-ceruloplasmin bound 'free copper' was significantly lower in PiMZ persons and trended towards higher values in PiMS persons (Table 4). When behavioral phenotypes of non-ICE, ICE and mood disorder were examined, there were significant differences were observed in serum copper, zinc, copper/ceruloplasmin ratio and derived % free copper (Table 4). The % 'free' copper is a number estimated from ceruloplasmin activity and serum copper. Assuming fully charged holoceruloplasmin (six copper atoms/molecule), many patients did not apparently have enough serum copper to account for observed enzymatic activity. The magnitude of the observed deficit could be accounted for in most cases (75%) by either reduced copper loading of one copper for all ceruloplasmin molecules or presence of approximately 5–10% apoceruloplasmin. These data do not exclude increased ceruloplasmin activity per molecule (increased specific activity) as an alternative reason for apparent mismatch of observed serum copper and ceruloplasmin activity. The relationship of AAT levels to other acute phase proteins such as c-reactive protein, ceruloplasmin, and transferrin and acute phase reactants such as serum iron, copper and zinc were examined. *Only* serum copper and to a lesser degree ceruloplasmin levels were strongly related to serum AAT levels. This relationship was specific to each AAT genotype including M subtypes and is illustrated for persons with MS genotype where 25% of the variance in serum copper levels is accounted for by serum AAT level. In summary, persons with PiMZ and Pi{ZZ,SS,...} polymorphisms and the group with ICE behavioral phenotype had significantly different copper and zinc indices and apparent free copper, supportive of a potential disorder of copper metabolism (Fig. 3).

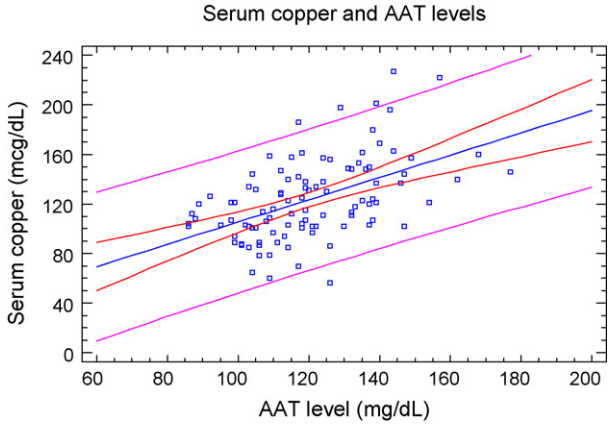

Fig. 3. Correlation of serum copper and AAT levels is high (25% of variance).

3.6. Relationship of AAT polymorphisms to abnormalities of central white matter

White matter T2 changes have been associated with bipolar disorder (Ahn et al., 2004; Brambilla et al., 2005) and one reference links AAT polymorphisms to demyelinating disease (Lolin and Ward, 1995). We found that there was a significant increase in brain MRI scans with qualitative rating of severe white matter T2 or Flair changes in persons with AAT polymorphism Z. Some typical neuroimaging examples are illustrated in Fig. 4. Severe white matter changes were found in 14.3% of 666 persons with PiMM compared to 45.7% of 35 persons with PiMZ genotype (contingency table, $\chi^2 = 49$, $p = 0.0003$). Severely abnormal scans were slightly more common in artists, but not in persons with general group of bipolar disorders. Demyelinating disease was significantly more common in carriers of Z and rare AAT polymorphisms (38% of total cases) noting low over-all numbers in this category. Two of these cases (genotype PiMZ) were post-immunization reactions in military personnel. One of three persons with AAT PiSS genotype had neurological illness c/w corticobasal degeneration after multiple desensitization injections for allergies (normal MRI). Thus, 3 of the 54 persons with PiMZ or PiSS AAT polymorphisms had significant post-immunization neurological syndromes, but none of the other 1537 persons in this series. Twenty-five percent of persons with vascular lacunes had adult onset diabetes (twice proportion of other groups) and vascular lacunes were markedly less common in MZ group. Distribution of neuroimaging results is illustrated for PiMM and PiMZ in Fig. 5.

3.7. Copper homeostasis and white matter abnormalities

The association of Z polymorphism with low % 'free' copper and with severe white matter disease raises the question of whether low free copper is by itself associated with severe white matter disease. In fact, severe white matter disease was most accentuated in lowest quartile of % free copper whereas vascular lacunes were most accentuated in highest quartile of % free copper (contingency table, $\chi^2 = 10.9$, $p = 0.012$). Copper

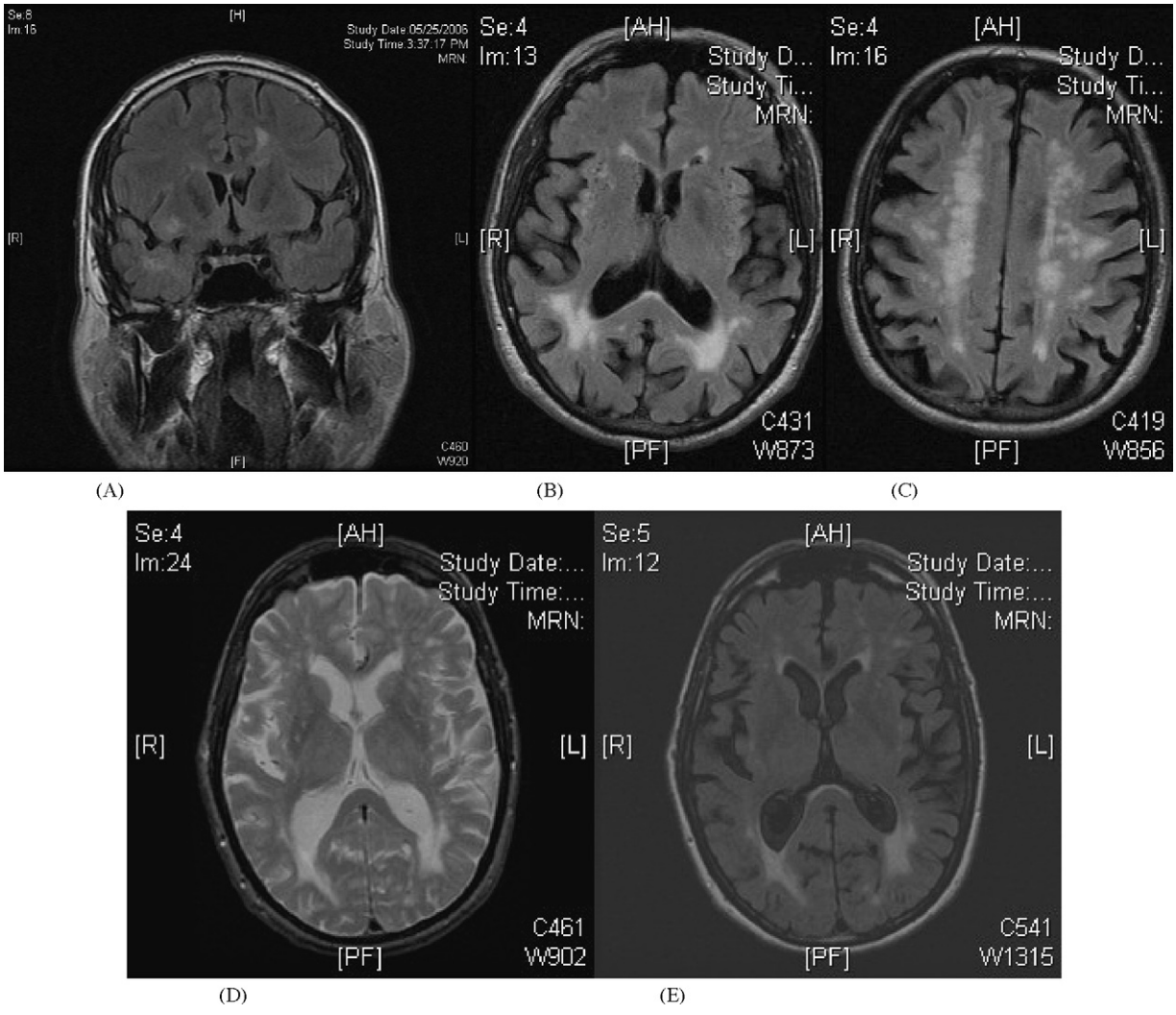

Fig. 4. Brain MRI scans. (A) Flair sequence, MZ patient with demyelinating disease post-immunization with abnormal areas next to corpus callosum—left hemisphere and in right temporal lobe. (B) Flair sequence MZ patient with confluent white matter lesions in posterior white matter and (C) multiple other lesions throughout deep white matter in same patient as (B). Another MZ patient with severe white matter lesions visualized on T2 imaging (D) and Flair sequences (E).

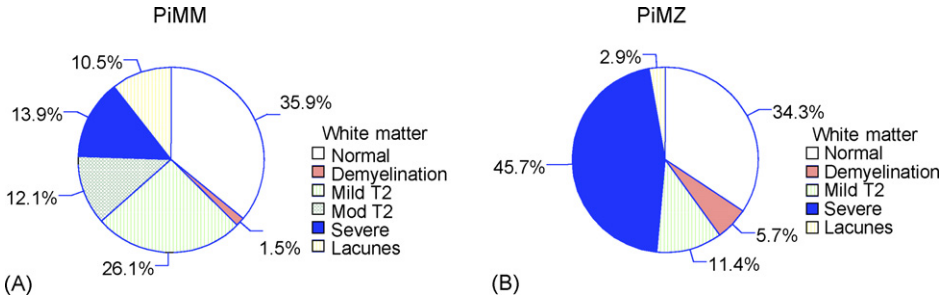

Fig. 5. Distribution of brain MRI abnormalities in persons with AAT PiMM genotype (A) compared to PiMZ genotype (B), showing increased proportion of persons with severe white matter T2 abnormalities (solid dark blue), and persons with demyelinating-'multiple sclerosis' lesions (solid light red), and decrease in vascular lacunes (2.9 vs. 10.5%) for PiMZ compared to PiMM (see text).

deficiency is associated with dysmyelination or hypomyelination (Schmechel et al., 1996a,b).

3.8. Relationship of toxic exposures, AAT polymorphisms, age of onset and % free copper

There was no significant relationship between chronic environmental or occupational toxic exposures and artistic vocation/avocation or between toxic exposure and AAT genotype. There was significant increase in alcohol use and slight increase in smoking among group of artistic vocation/avocation. The proportion of persons with chronic environmental or occupational toxic exposures in this over-all series was approximately 20% over-all and 34% in males. As previously presented (Schmechel et al., 2006) and now in this larger extended series, AAT polymorphisms are associated with significantly different age of onset in 1192 *non-exposed* persons: PiMZ (mean age of onset 59 ± 2.9 years) $\gg$ PiMS (66 ± 1.8 years) $\sim$ PiMM$_i$ (67 ± 0.5 years) [$\chi^2 = 18.0$, $p = 0.00012$, log-rank]. However, in 328 chronic toxic exposure persons (all exposures grouped together), the series is significantly inverted: PiMM$_i$ (mean age of onset 61 ± 1.2 years) $<$ PiMS (65 ± 4.1 years); PiMZ (66 ± 10.3 years) [non-significant differences for AAT genotypes]. The difference in age of onset for PiMZ is significant [$\chi^2 = 7.1$, $p = 0.0075$, log-rank] as is the difference for PiMM [$\chi^2 = 22.5$, $p = 0.00002$, log-rank], but not for PiMS. Thus, chronic toxic exposures of a variety of causes are associated with ca. 5 year earlier age of onset for PiMM$_i$ persons, with little or no effect for MS persons, and delayed onset for PiMZ persons. This implies possible neuroprotective effect for *chronic* toxic occupational or environmental exposures in S and Z polymorphism carriers.

Copper status tracks this differential effect of AAT polymorphisms. For persons with PiMM$_i$ genotype, % free copper (unadjusted) is essentially the same for non-exposed ($n = 595$) and all toxic exposure cases ($n = 208$): 5.5 ± 0.5% and 5.3 ± 0.9%. In contrast, for persons with PiMZ genotype, % free copper is markedly different for non-exposed ($n = 35$) and all toxic exposure cases ($n = 9$): 6.0 ± 2.2 and '-2.5 ± 4.3%' [ANOVA, significant by Fisher least significant difference]. This suggests possibility that low % free copper is generally associated with delayed age of onset. We again underline that negative % free copper is a theoretical construct, but must denote altered copper homeostasis with either a proportion of circulating apoceruloplasmin, generalized undercharge of holoceruloplasmin by one to two copper atoms per molecule, and/or change in specific activity relationships of ceruloplasmin.

To speak further to this possibility, we examined age of onset for two large groups of occupational exposures: volatile organic solvents (VOC) ($n = 154$), no exposure ($n = 1193$) and pesticide exposures ($n = 76$). Age of onset is earlier for VOC exposed persons (62 ± 2.0 years), compared to non-exposed (67 ± 0.5 years), compared to pesticide (72 ± 1.6 years) [$\chi^2 = 25.2$, $p = 0.00001$, log-rank]. We then carried out analysis by ANOVA of effects of AAT phenotype and toxic exposure on % 'free' copper. % Free copper was significantly different for VOC exposed persons (6.8 ± 0.9%), non-exposed (5.3 ± 2.7%), and pesticide exposed persons (-4.0 ± 2.8%). The above results support a relationship of later age of onset in subgroups with lower % 'free' copper.

There was no significant relationship of % free copper and APOE4 alleles or C282Y carrier state. However, % free copper was significantly higher in persons with MTHFR VV genotype, and significantly lower in 15 persons homozygous for H63D Hfe polymorphism and for 6 persons homozygous for C282Y (note one each AAT PiMS and PiMZ carriers). There was significantly increased proportion of AAT S and Z carriers in pesticide exposed group compared to VOC and non-exposures (20% carrier rate, 15 of 75 pesticide exposed persons compared to 12%; contingency table, $\chi^2 = 11.1$, $p = 0.023$).

3.9. Stability of cognitive scores and AAT polymorphisms

We analyzed the current expanded series for change in MMSE scores for 547 persons presenting with MMSE > 19 and followed for more than 6 months. The change scores were adjusted for gender, education, initial MMSE score, and test–retest interval (Table 1). This analysis confirmed previous finding that while PiMZ persons have earlier age of presentation, PiMZ persons have significantly more stable cognitive course (Schmechel et al., 2006). MMSE change per year was -1.6 ± 0.2 (485 persons with PiMM$_i$ genotype), -2.1 ± 0.6 (42 persons with PiMS genotype) and -0.6 ± 0.9 (20 persons with PiMZ genotype) [Table 1, mean follow-up 2 years, ANOVA, $p < 0.05$, Fisher's least significant difference].

In this over-all series of MCI, AD and non-AD, E4 status was not significant predictor. In subset of persons with ultimate diagnosis of pure AD, E4 was significant for increased decline with number of E4 alleles and same AAT relationship was observed.

Artist vocation/avocation status alone was not significantly associated with different amount of cognitive change although trend was to more stability for artists (as expected for high proportion of Z polymorphism). Presence of pre-existing affective disorder was associated with significantly different MMSE cognitive change per year: none > anxiety > depression > bipolar spectrum, respectively $-1.7 \pm 0.2 > -1.2 \pm 0.4 \sim -1.3 \pm 0.5 > -0.1 \pm 0.5$ [ANOVA, significant by Fisher least significant difference]. Toxic environmental or occupational exposure alone was associated with significantly greater decrease in MMSE scores [−2.1 for all exposures compared to −1.5 for non-exposed, ANOVA, significant by Fisher least significant difference]. When AAT polymorphism and toxic exposure status were considered together, the stabilizing effect of Z polymorphism was again observed with S > M > Z with regard to MMSE change (data not shown).

Similar to paradoxical effect of Z polymorphism on age of onset with toxic exposures, rate of change was actually less for exposure cases compared to non-exposed persons in PiMZ persons. When VOC exposures are compared to pesticide exposure cases, there is a clear association of lower '% free copper indices' associated with pesticide exposure and/or Z polymorphism with more stable rate of cognitive change. The largest decrease in MMSE was observed in persons with S polymorphism and VOC exposure which showed largest average % free copper value. This implies that some carriers for Z polymorphism have both delayed 'onset' of neurodegenerative disorders related to chronic occupational or environmental toxic exposures and a more generalized protection with apparently slower cognitive decline once neurodegenerative disorder begins. There is a further more general implication that high % free copper, associated with more vasculopathic changes on MRI scans (see above), is a negative factor for both age of onset and for apparent rate of cognitive decline.

4. Interpretation

The classic phenotype of AAT polymorphisms is increased vulnerability to environmentally modulated liver and lung disease (de Serres, 2003; Hersh et al., 2004; Scott and Egner, 2006; Perlmutter, 2006). Clinicians faced with persons presenting with liver or lung disease sometimes consider and test for the potentially adverse contributing role of S and Z alpha-1-antitrypsin (AAT) polymorphisms. The literature on liver and lung disease also mentions the frequent occurrence of anxiety in these persons, often ascribing anxiety to medication side effect and reaction to the stress of poor health (e.g., asthma or reactive airway disease) (e.g., Lehrer et al., 2002). We now examine an entirely different clinical group: persons presenting with complaints of memory, cognition or behavior to a University-based neurological clinic. In this comprehensive series, 15% of persons carry S, Z or other rare AAT polymorphisms, possibly enriched above background rate of ca. 9% for SE United States (Blanco et al., 2001). The AAT mutation subgroup in our series indeed demonstrates classic phenotype with significantly higher prevalence of lung disorders: pre-existing reactive airway disease or chronic obstructive pulmonary disease, and also potentially GI-related disorders: B1 deficiency, hepatosteatosis, and reactive hypoglycemia. However, persons with AAT polymorphisms also demonstrate a unique behavioral phenotype – intense creative energy or ICE – potentially related to nervous system development, function and response to injury.

We have previously reported that AAT carriers for S, Z and other rare polymorphisms have a high prevalence of pre-existing mood disorders: specifically anxiety disorder and bipolar disorders (Schmechel et al., 2006). Of note is the linkage of anxiety disorder to 14q32.1 near the AAT locus (Zandi et al., 2003). In light of the literature on co-existence of bipolar disorders and artistic vocation or occupation (e.g., Jamison, 1993), we have now performed an internal 'replication' by examining in this same patient series the potential relationship of AAT polymorphisms to an ''artistic'' phenotype or disposition. AAT polymorphisms are, in fact, significantly increased in both professional artists (Bureau of Labor Standards categories) and persons with artistic avocation. As predicted, there is significant overlap with bipolar spectrum disorders or anxiety disorder. These findings now support the conclusion that ''silent'' AAT polymorphisms associated with abnormal AAT and/or lower serum levels of AAT are associated with two overlapping behavioral traits or phenotypes of long-standing mood or affective disorder (anxiety and bipolar spectrum) and of artistic occupation or avocation. The higher prevalence of COPD and reactive airway disease in these same subsets supports that the AAT gene itself is responsible and not a segregating gene or region nearby, This may provide one genetic basis for the observation that pulmonary disease is increased in persons with bipolar disorder (Goodwin et al., 2003; Beyer et al., 2005).

These AAT mutations are pleiomorphic in their manifestations since there is only a 50% overlap of pre-existing bipolar/anxiety disorder and persons with artistic disposition. However, we noted that many carriers were extremely energetic, high-functioning individuals who expressed their artistic disposition as ''creative energy'' subject to depression when this energy was thwarted or repressed. While some artists had clinically treated bipolar I or II disorders, many had mixed disorder with anxiety and tendency to periods of controlled 'hypomania' yet productive and creative. A common, more inclusive behavioral phenotype is proposed of '*intense creative energy*' or ICE which may manifest in artistic skills and talent, business or religious acumen, and/or significant mood disorder (see also Jamison, 1993; Karlsson, 1978). These persons are also commonly extremely intuitive and 'prophetic' in their approach to the analysis of situations and taking of decisions. This behavioral phenotype would be advantageous in many settings, but in certain historical periods, may have exposed the person to social ostracization or even religious persecution. *Intense creative*

energy or ICE is significantly associated with AAT mutations, but transcends this single gene since a similar significant aggregation of artistic drive, pulmonary vulnerability and mood disorder is observed in the group with normal AAT polymorphisms. Despite the dominant influence of AAT polymorphisms, ICE is obviously multifactorial with other genetic, environmental and behavioral factors. This confirms the behavioral studies associating 'art and madness' (reviewed in Jamison, 1993) and illustrates a strategy of genetic association with a behavioral trait which then should be recursively studied and expanded for further refining 'eigen' traits and the search for other genetic and environmental factors. Nucleating out from the subgroup with ICE, for example, studies could examine the artist subgroup for possible unreported or undetected mood characteristics or the mood disorder group for possible latent artistic ability or talent. AAT genetic typing offers an ordered approach to developing further the ICE phenotype and transcending purely behavioral 'DSM' classification.

In terms of the classic AAT phenotype, many persons in our series had previously clinically unrecognized histories of otitis media into late childhood, frequently bronchitis or reactive airway disease (asthma) after upper respiratory infection, drug reactions, or mild elevations in liver enzymes (Table 5). Persons with ICE phenotype, with or without AAT polymorphisms, had increased prevalence of pulmonary disorders. Thus, there may be a more significant and unified biological signature to AAT polymorphisms that escapes current clinical categories. On an immediate practical level, this means that the co-existence of anxiety/bipolar disorders in the setting of liver or pulmonary illness may not be secondary, but be directly related in many persons to common biochemical factors—low or variant AAT expression. Likewise, the frequent occurrence of hepatosteatosis, reactive hypoglycemia and nutritional deficiency (B1) may offer both treatment options and direct attention to potential mechanisms of illness and aggravating factors in overall health whether the initial presentation or recognition is 'neuropsychiatric' or 'medical'. Other genes affecting metal and lipid metabolism or inflammatory response may also influence these traits.

Since this new extended AAT phenotype involves pre-existing behavioral attributes dating in many cases to childhood, another hypothesis is AAT mutations must have potentially fundamental and early effects on nervous system function or integrity (Table 5). This raises the possibility that AAT mutations may modulate the 'critical' pre- and postnatal period of neurological development, including myelination which extends to age 30. AAT is not widely expressed in normal

Table 5
Summary table

A. Proportion of AAT carriers for different clinical presentations	
Clues to presence to AAT carrier state	New proposed clues
History of otitis media	*History of reactive hypoglycemia*
History of asthma, frequent bronchitis, COPD (21% are carriers)[a]	*Thiamine deficiency (19% are carriers)*
History of intermittent elevated liver enzymes	*Anxiety or bipolar spectrum mood disorder*
Palmar telangectasia	*(25% and 38% are AAT carriers, respectively)*
	Extensive white matter disease (25% are carriers)
	Artist or intense creative energy (57% are carriers)

B. Proposed expansion of AAT phenotype	
Traditional AAT phenotype	Hypothesis of extended AAT phenotype: ICE
Vulnerability to reactive airway disease	Early
Vulnerability to COPD	B1 deficiency
Vulnerability to hepatic disease	Reactive hypoglycemia
	Non-alcoholic fatty liver (NAFLD)
	Copper metabolism disorder
	Intense creative energy (ICE)
	Mood disorder – anxiety/bipolar
	Attention deficit disorder/dyslexia
	Autoimmune CNS disease
	Late
	Vulnerability to cognitive disorder (? size of effect)
	White matter disease (up to 50% of MZ carriers)
	Later onset to toxic exposure-related CNS disease
	More stable course in neurodegenerative disease

C. Comparison of ICE phenotype–PiMM and non-MM AAT genotypes	
ICE: Normal PiMM AAT genotype	ICE: Non-MM AAT polymorphisms
Asthma, COPD (53%)—compared to 15%[b]	Asthma, COPD (47%)
Thiamine deficiency (35%)—18%[b]	Thiamine deficiency (48%)
Reactive hypoglycemia (4%)—4%[b]	Reactive hypoglycemia (16%)
Extensive white matter disease (26%)—14%[b]	Extensive white matter disease (13%, enhanced in Z)
Copper metabolism disorder	Copper metabolism disorder

[a] Compared to 9% background carrier rate.
[b] Comparison %, non-art/ICE/mood, PiMM.

nervous tissue (see review, Schmechel et al., 2006). Thus, additional questions are whether the association of AAT mutations with mood disorders and artistic disposition emerges from AAT expression in peripheral organs or tissues, in central nervous system tissues, or in both, and whether AAT interacts with single stochastic events or continuous factors such as environmental exposures, diet, antigenic challenge, or infection. This series represents largely older persons presenting with mid-late life cognitive problems and demonstrates an increased proportion of APOE4 carriers compared to general population. In addition, the clinic population is from a rural state with significant farming, electronics, and furniture manufacturing as potential sources of toxic occupational or environmental exposures (Helmer et al., 2001).

We did, however, identify pedigrees with younger carriers and young persons with AAT mutations and the above associations of art, mood and biochemical abnormalities such as B1 deficiency and hepatosteatosis. Some of these younger persons presented as attention deficit or learning disability, emphasizing the potentially pleiomorphic character of AAT mutations. If indeed AAT S and Z polymorphisms are associated with altered iron and copper homeostasis, particularly low or marginal iron or free copper available to nervous tissue, then there might be delayed myelination rates and longer critical period resulting in different outcome for nervous system development. This might result in behavioral phenotype at cost of white matter vulnerability to other insults such as dysmyelination or vascular injury. Another possibility is compromise of copper containing enzymes such as dopamine-beta-hydroxylase or peptidyl-glycine-amidating enzyme and lead to abnormalities of monoamine or other subcortical pathways (Schmechel et al., 1996a,b). Abnormalities in subcortical structures have been suggested for bipolar disorders (Berns et al., 2002; Malhi et al., 2004; Haznedar et al., 2005). These changes may result in anatomical differences (Beyer et al., 2004) and acquired conditions or lesions could also result in this same phenotype of intense creative energy (Miller et al., 1996, 2000). Studies in primates underline the possibility of subclinical 'silent' injury related to disordered iron/copper homeostasis and associated abnormalities in monoaminergic and ascending reticular activating system pathways (Schmechel et al., 1996a,b; Schmechel, 2001).

A significant finding is that age of presentation for memory or cognitive disorder is earlier in persons carrying Z polymorphism (Schmechel et al., 2006). However, in the considerable subgroup of persons with chronic toxic environmental or occupational exposures, there is opposite effect with later age of onset for carriers for S and Z polymorphisms compared to common M polymorphisms. This implies potential paradoxical neuroprotective value of AAT polymorphisms at least for *chronic* toxic exposures. In addition, carriers of Z polymorphism had more stable clinical course of all neurodegenerative categories compared to persons with normal AAT genotypes (Schmechel et al., 2006). This stabilizing effect was present for all cases regardless of environmental exposure factors.

AAT has multiple effects on inflammatory response involving iron and lipid metabolism in macrophages, and is considered an 'iron' switch involved in the anemia of chronic inflammation (Weiss et al., 1996; Graziadei et al., 1993, 1994, 1997, 1998). The above effects of AAT mutations on onset and progression rate of neurodegenerative illness, mood and artistic disposition, and response to toxic exposures raised questions of possible mechanisms. These effects might be due in part to the effects of AAT on inflammation and trace mineral homeostasis. In this report, we present data that AAT polymorphism Z is associated with abnormal copper homeostasis with low 'free' copper signifying possibly copper deficiency or altered copper distribution, implying AAT may also be a 'copper' switch. The low serum copper levels compared to measured ceruloplasmin (ferroxidase) activity (low 'free copper') implies reduced copper charge of ceruloplasmin, some circulating apoceruloplasmin, and/or increased specific activity of ceruloplasmin. This apparent effect on activity or copper charge of a secreted hepatic cuproenzyme could result from changes in copper homeostasis such as diversion of copper into other tissues through induction of copper, zinc superoxide dismutase (SOD1) during response to oxidative stress.

Low non-ceruloplasmin bound copper and/or possible increased specific activity of ceruloplasmin (ferroxidase) implied by our results could be advantageous for the periphery resulting in diminished lipid peroxidation and/or reduction of circulating, pro-oxidative diferrous iron (Fe^{2+}). These peripheral 'adaptive' changes in iron and copper metabolism could have, however, potentially adverse CNS effects since the nervous system and other tissues such as pancreas are sensitive to even mild copper deficiency (Schmechel et al., 1996a,b) and may depend on uptake of unbound or 'free' copper. Low CNS copper stores could affect mitochondrial function, myelination, and result in CNS injury or diminished response to injury (e.g., low SOD1). However, this potentially adverse effect of low 'free' copper must be balanced against the association of high serum copper levels with lipid peroxidation and potential interaction and vasculopathy of high serum copper and dyslipidemia. Moreover, copper binding sites are present on beta-amyloid, synuclein and prion-associated protein. For these aggregating and potentially neurotoxic oligopeptides and oligomers involved respectively in Alzheimer disease (AD), Parkinson disease (PD), and Creutzfeldt–Jakob disease (CJD, 'mad cow' disease), high copper might catalyze aggregation and lowering serum copper and tissue copper stores has been advanced as therapeutic strategies (e.g., Barnham et al., 2003). Thus, the observed 'neuroprotective' effect for chronic toxic exposures and more stable progression rate associated with Z carriers may be related to the 'naturally' occurring difference in copper homeostasis with low 'free' copper. Thus, Z and possibly S carriers might have long-term selective genetic advantage for resistance to chronic toxic exposures or some forms of neurodegeneration.

Central nervous system mechanisms are supported by the finding that abnormal white matter and thiamine deficiency were significantly more common in *older* persons with PiMZ genotype. This is consistent with previous reports of white matter abnormalities in persons with bipolar disorder, particularly bipolar II (Ahn et al., 2004; Brambilla et al., 2005). Peripheral mechanisms could result from significant differences in liver and pancreas function (reactive hypogly-

cemia), metabolic liver dysfunction such as hepatosteatosis and abnormalities of trace minerals. In particular, low free copper associated with S and Z polymorphisms might indicate marginal copper stores that might affect central myelination or mitochondrial integrity. Other actions of AAT as a normal 'acute phase' reactant on vascular injury, apoptosis, and macrophage function may alter the outcome from CNS remodeling during development and from 'normal' environmental factors such as diet, viral or bacterial infection.

Thus, AAT polymorphisms may define a new distinctive clinical phenotype of artistic vocation and affective disorders – ICE or *intense creative energy* – in addition to well-known phenotype of vulnerability to liver and lung disorders. One would expect that personal decisions, other modifying genes, and environmental factors including infections and diet might play a role in the development of this phenotype. This potential effect of AAT polymorphisms may represent a positive selective advantage given the high societal impact of artists and the high energy and intellectual potential of many persons with bipolar spectrum disorders. From a practical clinical perspective, persons presenting with affective disorders and/or with liver/lung disorders should potentially be screened for these polymorphisms given the potential interaction of behavioral patterns and medical illness (pointing to affective disorder in someone with liver/lung disease, or alternatively liver/lung vulnerability in someone with affective disorder). In many cases, detecting these treatable AAT polymorphisms may provide a potentially unifying biochemical explanation for illness or behavioral traits. In this series, the resultant information and genetic counseling for the affected persons and families was well received and appreciated. Likewise, persons with these polymorphisms may present with CNS injury (white matter disease) and metabolic problems (hepatosteatosis, hypoglycemia, B1 deficiency). From a research perspective, these findings need validation and extension through further studies in normals and other clinical populations with thorough assessment of the subtypes of affective disorder and through basic research on the effects of AAT polymorphisms on intermediate metabolism and trace mineral homeostasis. The *intense creative energy* phenotype proposed from this clinical series is dominated by the apparent influence of AAT polymorphisms, but may also define a larger group of persons defined by pulmonary and physical frailty, intense creative energy and mood disorder. Other genes and environmental factors influencing this *ICE* phenotype may relate to inflammation, trace mineral metabolism or intermediate metabolism. From a personal perspective, the possible 'curse' of increased vulnerability to pulmonary and liver disorders of AAT polymorphisms may be balanced by the 'blessing' to oneself and others of intense creative energy and its fruits.

Acknowledgements

Research supported by NIA Grant AG-05128, BINH Foundation, and many private gifts to the Joseph and Kathleen Bryan ADRC. I gratefully acknowledge the support and contributions of clinical personnel, Sandra Dawson RN, Roberta Wallace MSW, and Ronald Nelson. Daniele and Stefanie Schmechel assisted in selection of title and the term 'ICE'. Thanks to the many patients and artists, especially the index case. Financial considerations. US Patent issued for relationship of AAT polymorphisms and affective disorders/AD.

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