British Journal of Medicine & Medical Research
5(7): 880-888, 2015, Article no.BJMMR.2015.095
ISSN: 2231-0614

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Hypertension Prevalence in the US Population Varies with Differences in Alpha-1 Antitrypsin Genotype: A Cross Sectional Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SK and CS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author LS provided data quality control. Statistical analysis was performed by authors SK, KJH and PJN. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/13447
Editor(s):
(1) Gaetano Santulli, College of Physicians and Surgeons Columbia University Medical Center New York, NY, USA.
Reviewers:
(1) Nilda Espinola-Zavaleta, Department of Echocardiography in Out Patients Clinic, National Institute of Cardiology Ignacio Chavez, Mexico City, Mexico.
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(3) Anonymous, University of Monastir, Monastir, Tunisia.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=709&id=12&aid=6447

Original Research Article

Received 18th August 2014
Accepted 25th September 2014
Published 10th October 2014

ABSTRACT

Background: The prevalence of hypertension (HTN) associated with alpha-1 antitrypsin deficiency (AATD) has been studied with indeterminate results. The aim of the study was to prospectively compare the prevalence of HTN before testing in 3 groups of individuals with subsequently normal, moderately deficient, and severely deficient genotypes of AATD with adjustment for differences in demographics and clinical variables.
Methods: We performed a cross sectional study using data from the Alpha-1 Coded Testing (ACT) study. The univariate demographic and clinical factors associated with HTN were further analyzed by logistic regression analysis.
Results: The prevalence of HTN was 27.2%, 20.6%, and 27.9% for individuals with normal, moderate and severe AATD, respectively ($p<0.02$). The prevalence of HTN increased with age and

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an interaction between age, alpha-1 antitrypsin deficiency genotype and HTN was identified. The relative risk of HTN among young moderately deficient individuals was 0.53 (95% CI 0.37-0.76) the risk of young PiMM and PiMS (normal genotype) individuals. There was no significant difference in the risk in older moderately deficient individuals 1.02 (95% CI 0.76-1.37) and individuals with severe AATD 1.10 (95% CI 0.71-1.68) when compared to normal genotypes.

Conclusion: Moderate deficiency genotypes (PiMZ, PiSS, PiMNull) have less HTN than normal or severe deficiency genotypes, particularly in young individuals. We speculate that protease inhibitor deficiency over a lifetime allows unopposed proteolysis of vascular connective tissue.Measured comorbidities do not explain these findings. Validation of this data should occur in other AATD cohorts.

Keywords: Hypertension; COPD; alpha-1 antitrypsin; AATD; genotype; protease inhibitor.

Clinical Trial Registration: NCT00500123

ABBREVIATIONS

AATD: Alpha-1 antitrypsin deficiency; COPD: Chronic obstructive pulmonary disease; HTN: Hypertension; AAT: Alpha-1 antitrypsin; ACT study: Alpha-1 Coded Testing study; MUSC: Medical University of South Carolina.

1. INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a genetic condition that leads to premature COPD with a prominent panacinar emphysema presentation [1,2]. Lung destruction is a result of an excess of neutrophil elastase, seen predominantly in cigarette smokers, and a deficiency of alpha-1 antitrypsin (AAT). AAT confers protection from proteolytic injury from a variety of serine proteases in the lung and various other organs [3]. Therefore, the effects of the deficiency state are likely expressed in multiple organs.

Few other organs besides lungs are known to be affected by AATD. Hepatic insufficiency in children and adults occurs predominantly in individuals with mutations at the PiZ locus. The mechanism of liver disease is the topic of ongoing research but results from accumulation of misfolded protein in hepatocytes. Other extra-pulmonary manifestations such as panniculitis (skin and fat inflammation) [4,5], and granulomatosis with polyangiitis [6,7] have been noted but are very rare. The association of AATD and cardiovascular disease has been inadequately studied. Cardiovascular disease accounts for 30% of total deaths and hypertension is among top three risk factor for global disease burden [8]. Individuals with AATD also have cardiovascular and cerebrovascular mortality although it is not known if this is differentially expressed in individuals with different SERPINA1 gene polymorphisms [9] or different than age matched populations [10]. Therefore, the objective of this study is to investigate the association between hypertension and AATD. If AATD affected individuals have less vascular elastin, blood pressure and downstream cardiovascular risks might be less than other populations.

2. MATERIALS AND METHODS

2.1 Study Design and Population

We performed a cross sectional study using data from the ACT Study, an ongoing research project (NCT00500123) conducted at the Medical University of South Carolina (MUSC) and funded by the Alpha-1 Foundation. The ACT Study is a home genetic testing study for those at risk for AATD because of COPD or because of AATD in their family members. ACT participants who sign consent and complete a questionnaire are mailed a bloodspot card for home blood collection. Questionnaire data is recorded and collected prior to determination of AAT genotype. The ACT database contains self-reported data on clinical conditions using uniform definitions and coding that are described elsewhere [11]. Alpha-1 genotypes are performed on home acquired blood spots through the Alpha-1 Foundation testing laboratory at the University of Florida. PCR primers for the Z and S alleles were used to define the number of copies of these genes present. Blood spots were eluted to measure an

AAT concentration by nephelometry as described elsewhere [12].

The study sample consisted of 4501 adult participants who expressed interest in the study from June 2010 to October 2012. 1208 participants did not complete consent and 411 participants with age less than 18 years were excluded as they were not screened for the presence of hypertension. Participants with incomplete or missing data (n=7) were also excluded.

We analyzed common variables associated with hypertension including demographics, environmental risks such as smoking, and comorbidities of COPD, sleep apnea, and cardiovascular disease, to determine the relationship between AATD and self- reported hypertension. An AAT level was measured in all subjects. Smoking was defined by $\geq$ 100 cigarettes in a lifetime. The variables included in the study are shown in Tables 1 and 2. The factors with a significant p value <0.10 characterized in univariate analysis with alpha-1 antitrypsin genotype were further analyzed by multiple logistic regression.

Cases were defined as participants self-reporting as hypertensive and who completed genotype testing in the ACT study. The participants were further stratified into three groups based on their AAT genotypes. The moderately deficient group included PiMZ, PiSS, and PiMNull genotypes (AAT concentration range 9.7-43.0 μM) while the severely deficient group included PiZZ, PiSZ, PiZNull and PiSNull genotypes(AAT concentration 3.6-27.7 μM). Normal genotypes were defined by participants with normal AAT concentrations and absence of a Z gene by PCR (PiMM and PiMS genotypes, AAT concentration 16.7-53.0 μM).

2.2 Data Analysis

The primary outcome of the study was to determine if a lifetime of living with deficiency genotypes of AAT alters the risk for hypertension. Baseline characteristics (i.e., arithmetic means and standard deviations) of the study population were stratified by alpha-1 antitrypsin deficiency status. Logistic regression analysis was used to calculate the odds ratios (OR) for the association between AAT genotypes and hypertension status while controlling for covariates of interest. Covariates of interest included demographic variables, cigarette smoking as an environmental risk, and comorbidities of COPD, diabetes, obstructive sleep apnea syndrome, and cardiovascular disease. A χ^2 test was performed to define categorical variables and ANOVA was used to define continuous variables correlated with hypertension. The variables associated with hypertension with a significant p value<0.10 were used to develop a model by multiple logistic regression analysis.

The data was also tested for interaction between variables by different methods. One method involved testing all significant (p<0.10) variables along with all interactions in the full model and the second method involved searching for interactions across each variable then adding significant interactions into full model. If significant interaction was found, then the variable would be split by the median and further tested with the reduced model within those two groups. The results for the reduced model developed by multiple logistic regression analysis are shown by the odds ratios (OR) for the association with AAT genotype. Statistical analysis was performed using statistical package SAS 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

Data was collected from 4501 participants, of whom 2,875 met the inclusion criteria. The genotypes were grouped into normal, moderately deficient and severely deficient genotypes based on the risk of AATD which included 1763, 958 and 154 individuals respectively Table 1.

The mean age for normal, moderately deficient and severely deficient genotyped individuals was 45.3±15.0, 43.4±15.7 and 46.5±15.7 years respectively (p=0.003). Males made up 34.26%, 35.8% and 43.51% of the population in normal, moderately deficient and severely deficient genotype groups respectively (p=0.045). There were more than 90% Caucasians in each group; however, Caucasian individuals were more often found in the moderately (97%) and severely deficient group (98%) due to the racial associations with AATD Z alleles (P=0.0001). Those testing because of a family history of AATD were more frequently found in moderately and severely deficient cohorts (p<0.0001). Severely deficient individuals were also less likely to be testing for the first test for AATD (p<0.0001). The demographics did not significantly vary by marital status or educational

level Table 1. Clinical features of the three groups were also different. Severely deficient individuals had lower rates of heart disease (p<0.006) while moderately deficient individuals had less COPD (p<0.0001) Table 2. Blood spot AAT levels were not different within groups for hypertensive and non-hypertensive cohorts.

The prevalence of hypertension was less in moderately deficient genotypes (20.6%) as compared to normal (27.2%) and severely deficient genotypes (27.9%) Fig. 1.

Table 1. Demographic characteristics of study cohort (N=2875)

Variables	Normal genotype N = 1763		Moderately deficient N =958		Severely deficient N=154		p value
Age*	45.32	(15.01)	43.43	(15.69)	46.48	(15.70)	0.0031
BMI*	28.81	(7.44)	28.38	(7.93)	28.13	(6.54)	0.2565
Family history	1171	(66.42)	879	(91.75)	134	(87.01)	<0.0001
First test for Alpha-1	1687	(95.69)	850	(88.73)	104	(67.53)	<0.0001
Male gender	604	(34.26)	343	(35.8)	67	(43.51)	0.0454
White race	1657	(93.99)	930	(97.08)	151	(98.05)	0.0001
Marital status							
Married	1167	(66.19)	612	(63.88)	105	(68.18)	0.6153
Single	596	(33.81)	346	(36.12)	49	(31.82)	
Education							
Less than high school	968	(54.91)	566	(59.08)	88	(57.14)	0.0792
High school equivalent	795	(45.09)	392	(40.92)	66	(42.86)	

** Values for age and BMI are given as mean with standard deviation*

Table 2. Clinical characteristics from and comorbidities of the study cohort (N=2875)

Variables	Normal genotype N = 1763		Moderately deficient N =958		Severely deficient N=154		p value
COPD	610	(34.6)	193	(20.15)	49	(31.82)	<0.0001
Liver disease	88	(4.99)	34	(3.55)	8	(5.19)	0.2742
Lung or liver disease present	629	(35.68)	209	(21.82)	51	(33.12)	<0.0001
Past or present smokers	868	(49.66)	459	(49.35)	77	(50.99)	0.9207
Diabetes	143	(8.4)	58	(6.26)	11	(7.19)	0.0957
Heart disease	123	(6.98)	48	(5.01)	4	(2.6)	0.0057
Obstructive sleep apnea	144	(8.17)	69	(7.2)	8	(5.19)	0.1471
Hypertension	479	(27.17)	197	(20.56)	43	(27.92)	0.0149

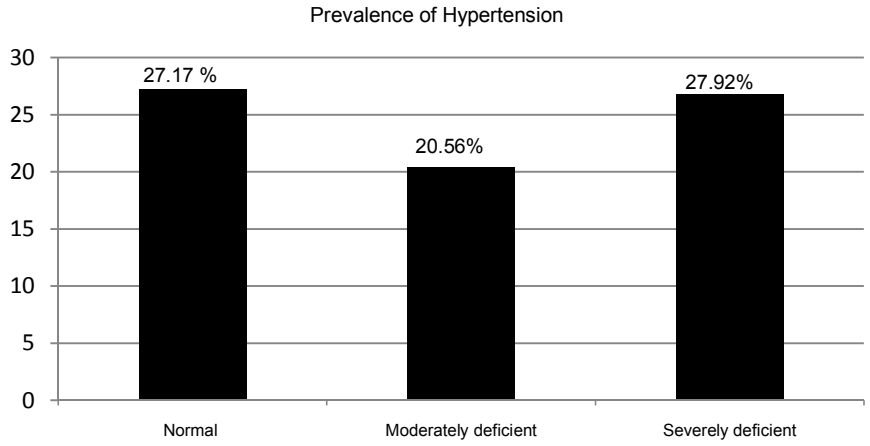

Fig. 1. Graph showing prevalence of hypertension across all genotypes

According to the model, the odds of the participants with moderately deficient genotypes having hypertension were less (OR=0.76; CI 0.60-0.95) when compared to the odds of those with normal genotypes when adjusted for age, gender, family history of AATD, race, presence of symptoms of COPD or liver disease diagnosed by a physician, diabetes, and heart disease. There was no significant difference in the presence of hypertension between participants with severe deficiency and normal genotypes (Fig. 2).

No interaction was found between variables except for the interaction between genotype and participant age. We tried several methods to model and further define the age interaction. Fig. 3 divides participants at the median of ≤ 48 and > 48 years to explore this interaction. The results show that young individuals with moderately deficient genotypes have less hypertension (OR=0.53; CI 0.37-0.76) when compared to those with a normal genotype adjusted for other variables. There was no significant difference in hypertension prevalence between individuals with severely deficient and with normal genotypes in the age group ≥ 48 years when adjusted for other variables (OR=1.29; CI 0.68-2.43). The odds ratio for the population stratified by age is given in Fig. 3.

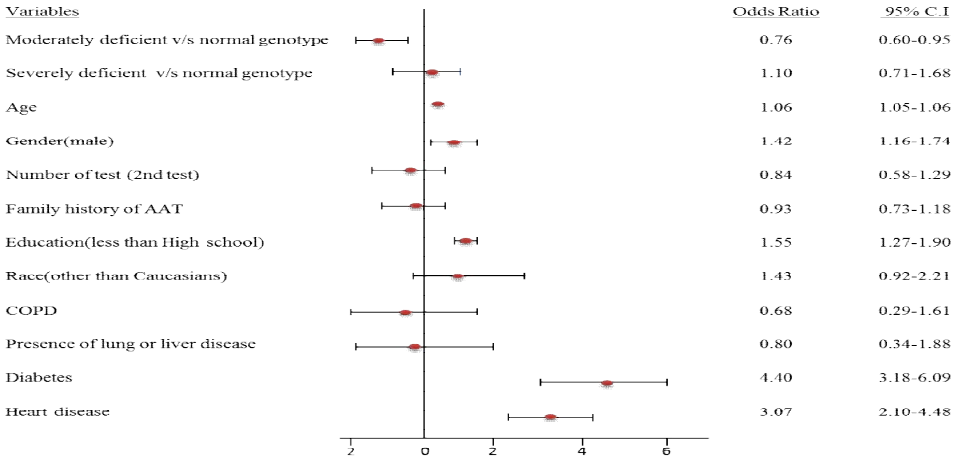

Fig. 2. Forest plot of all variables found to have P<0.10 in multivariate analysis with hypertension as the outcome

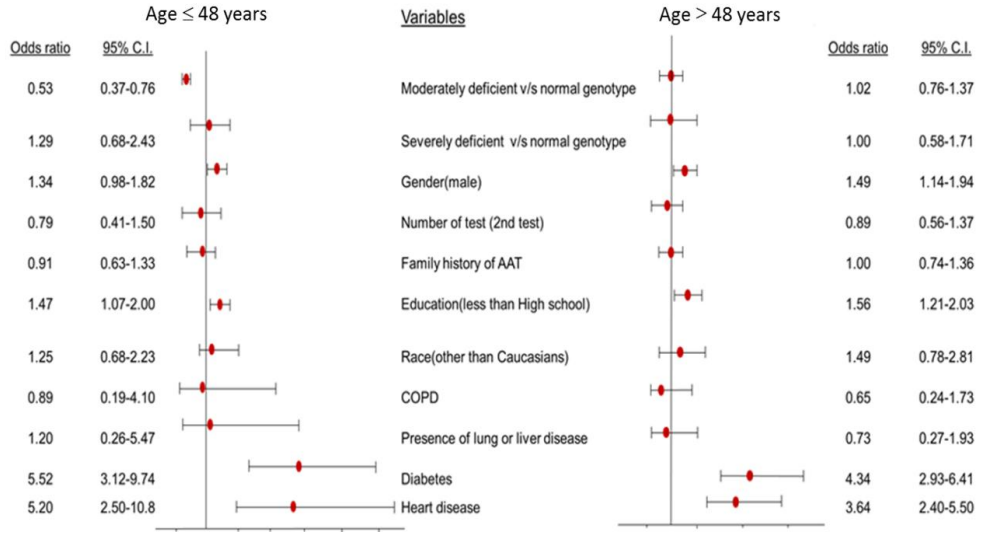

Fig. 3. Forest plot of all variables found to have P<0.10 in multivariate analysis stratified by age group with hypertension as the outcome

For the age group >48 years, there was no significant difference in hypertension prevalence between individuals with moderately deficient and normal genotypes (OR=1.02; CI 0.76-1.37) or between severely deficient and normal genotypes (OR=1.00; CI 0.58-1.71).

We further explored the data for individuals without COPD, liver disease, diabetes, and heart disease, to assess whether these co-morbidities explain the higher prevalence of hypertension in severely deficient compared to moderately deficient individuals. The analysis shows that young (age < median of 48 years) moderately deficient genotypes still have lower blood pressure when compared to normal genotypes for all comorbidities (diabetes data not shown) Table 3.

4. DISCUSSION

The genetic epidemiology of hypertension has generated a large number of candidate genes that associate with systolic or diastolic blood pressure [13]. Although these studies are robust, the clinical outcomes associated with the presence of these GWAS signals has been less impressive[13]. For example, a study of 17,000 Swedish individuals were examined for the presence of 29single nucleotide polymorphisms (SNPs) associated with HTN finding an odds ratio for HTN incidence of 1.192 (95% CI 1.140-1.245) [14]. This low rate suggests that the majority of hypertensive individuals do not have known polymorphisms associated with their disease while some other genes will be found [15,16]. The alternative explanation for the tendency for essential HTN to track in families is that there are many rare polymorphisms that would never be found in population cohort studies. Our study shows the effect of one such rare polymorphism that affects only 3% of the US population and is interactive with age.

Our study suggests that young individuals (<48 years) with moderately deficient AAT genotypes (PiMZ, PiSS, and PiMNull) have less hypertension compared to young individuals with normal genotypes (PiMM or PiMS). Individuals with severely deficient AAT genotypes and older individuals with moderately deficient genotypes do not have a reduced risk of hypertension. Comorbidities of cardiac disease other than hypertension, diabetes, lung or liver disease do not explain these observations.

Table 3. Prevalence of hypertension in cohorts without co-morbidities

Without heart disease				
	Normal	**Moderate**	**Severe**	**p value**
All (2700)				
TP	1640	910	150	
BP	392(23.9)	171(18.8)	40(26.7)	0.005
≤48 years (1651)				
TP	980	592	79	
BP	141(14.4)	47(7.9)	14(17.7)	0.002
>48 years (1049)				
TP	660	318	71	
BP	251(38.0)	124(38.9)	26(36.6)	0.919
Without COPD and liver disease				
	Normal	**Moderate**	**Severe**	**p value**
All (1986)				
TP	1134	749	103	
BP	264(23.3%)	136(18.2%)	24(23.3%)	0.026
≤48 years (1281)				
TP	723	500	58	
BP	102(14.1%)	38(7.6%)	7(12.1%)	0.002
>48 years (705)				
TP	411	249	45	
BP	162(39.4%)	98(38.3%)	17(37.9%)	0.977

The importance of this finding is twofold. From the perspective of pathogenesis, a genetic condition that causes lower blood pressure could be important to focus future research in hypertension. Since the AAT carrier state is associated with lower levels of AAT protein than individuals with PiMM normal alleles, the most likely cause of lower blood pressure is less systemic vascular resistance from lower levels of elastin in the vascular wall. AAT is a serine protease inhibitor that competitively binds neutrophil elastase and other proteases. A mild deficiency state could therefore influence vascular elastin during development or throughout early life.

If the above finding can be confirmed, the conundrum is to explain the recurrence of hypertension with aging in the moderately deficient population and the complete absence of any difference in hypertension prevalence in individuals with severely deficient AATD genotypes.

Two earlier studies are partially consistent with our results. The Dutch twin study in 160 twins aged 14-20 years and their parents reported that MZ's had lower systolic blood pressure than those with MM genotype in males and no difference in hypertension in females. This study did not take into account environmental and genetic risk affecting blood pressure [17]. The Copenhagen City Heart Study reported a reduced risk of hypertension in the subjects of moderately (n=39) and severely deficient (n=6) genotypes as compared to those with normal genotypes (N=7918) [10]. These correlated with a lower risk for ischemic cardiovascular disease (OR=0.77, CI 0.61-0.98) compared to normal genotypes and a lower risk for ischemic cerebrovascular disease (OR=0.7, CI 0.51-0.96) compared to normal genotypes) [10]. In addition, the Z allele frequency increased between ages of 20 and 93 years suggesting that the lower blood pressures carried a survival advantage.

In contrast, a smaller Australian cohort with 314 subjects (258MM, 43 MS, 13 MZ and no SS, SZ, ZZ) reported no difference in risk of hypertension for individuals with deficient S and Z alleles [18].

Many vascular pathophysiological factors have been implicated in the genesis of hypertension including increased sympathetic nervous system tone, over-production of vasoconstrictor substances in the renin-angiotensin-aldosterone axis, deficiency of vasodilator substances, altered expression of kallikrein–kinin system proteins, increased activity of vascular growth factors, and changes in adrenergic receptors influencing heart and vascular tone [19]. These alterations are likely additive to other as yet undefined genetic components to explain the higher prevalence of hypertension in some families.

At first glance, elastin deficiency might be thought to make vasculature less distensible and more prone to hypertension. However, elastin is a component of the connective tissue matrix. In the lung, the loss of lung elastin increases lung compliance. However, the biochemical impact of AATD on vasculature is incompletely known. AAT is actively involved in atherogenesis as an important regulator that protects elastic tissue from the damage by elastase secreted from neutrophils in the arterial wall [20]. One study from Cardiff demonstrated that the patients with AATD related COPD have increased aortic stiffness [21,22]. Whether this observation is unique to COPD or severe AATD is not known; yet, may help explain the higher prevalence of hypertension in our cohort with severe AAT deficiencies who are mostly COPD patients.

There are limitations to our study. Study participants to the ACT study join to determine their AAT genotypes and therefore are a highly selected population. The ACT study is comprised largely of two types of participants interested in their AAT genotypes, those with lung or liver disease and those who have abnormal family genetics. A second limitation of the study is the reliance on self- report data for medical conditions including hypertension which may be subject to recall bias given the high prevalence of COPD in the study population.

5. CONCLUSION

In conclusion, individuals less than age 48 with moderately deficient AAT genotypes have less hypertension than those with normal or severely deficient AAT genotypes independent of heart and lung disease. Validation of this observation and understanding the physiologic mechanisms behind this association require further study in a prospectively identified cohort enriched for AAT deficiency genotypes. If confirmed, marked differences in the prevalence of hypertension in carriers of one abnormal AAT gene are of sufficient magnitude to potentially impact

lifespan. Since hypertension is common and is associated with mortality, our observation could explain persistence of the PiZ allele in the population.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Eriksson S. Pulmonary emphysema and Alpha-1 antitrypsin deficiency. Acta Med Scand. 1964;175:197-205.
2. Stoller JK, et al. Physical and social impact of alpha 1-antitrypsin deficiency: Results of a survey. Cleve Clin J Med. 1994;61(6):461-7.
3. Belorgey D, et al. Protein misfolding and the serpinopathies. Prion. 2007;1(1):15-20.
4. Edmonds BK, Hodge JA, Rietschel RL, Alpha 1-antitrypsin deficiency-associated panniculitis: case report and review of the literature. Pediatr Dermatol. 1991;8(4):296-9.
5. Korver G, Liu C, Petersen M. Alpha1-antitrypsin deficiency presenting with panniculitis and incidental discovery of chronic obstructive pulmonary disease. Int J Dermatol. 2007;46(10):1078-80.
6. Klapa S, et al. Lower numbers of FoxP3 and CCR4 co-expressing cells in an elevated subpopulation of CD4+CD25high regulatory T cells from Wegener's granulomatosis. Clin Exp Rheumatol. 2010;28(1 Suppl 57):72-80.
7. Mota A, et al. Alpha 1-antitrypsin activity is markedly decreased in Wegener's granulomatosis. Rheumatol Int; 2013.
8. Santulli G. Epidemiology of cardiovascular disease in the 21st century: Updated numbers and updated facts. JCvD, 2013;1(1):1-2.
9. Dawkins P, et al. Mortality in alpha-1-antitrypsin deficiency in the United Kingdom. Respir Med. 2009;103(10):1540-7.
10. Dahl M, Tybjaerg-Hansen A, Nordestgaard BG. Risk of ischemic heart and ischemic cerebrovascular disease is not increased in S, Z, and 11478A alpha1-antitrypsin carriers of the Copenhagen City Heart Study. Arterioscler Thromb Vasc Biol. 2003;23(11):55.
11. Strange C, et al. Genetic testing for alpha1-antitrypsin deficiency. Genet Med. 2004;6(4):204-10.
12. Bals R, et al. Identification of individuals with alpha-1-antitrypsin deficiency by a targeted screening program. Respiratory Medicine. 2007;101(8):1708-1714.
13. Lind JM, Chiu CL. Genetic discoveries in hypertension: Steps on the road to therapeutic translation. Heart. 2013;99(22):1645-51.
14. Fava C, et al. Prediction of blood pressure changes over time and incidence of hypertension by a genetic risk score in Swedes. Hypertension. 2013;61(2):319-26.
15. Santulli G, et al. CaMK4 gene deletion induces hypertension. J Am Heart Assoc. 2012;1(4):001081.
16. Santulli G, Trimarco B, Iaccarino G. G-protein-coupled receptor kinase 2 and hypertension: molecular insights and pathophysiological mechanisms. High Blood Press Cardiovasc Prev. 2013;20(1):5-12.
17. Boomsma DI, et al. Alpha-1-antitrypsin and blood pressure. Lancet. 1991;337(8756):1547.
18. Huggard PR, West MJ, Summers KM. Alpha 1-antitrypsin deficiency alleles and blood pressure in an Australian population. Clin Exp Pharmacol Physiol. 1996;23(6-7):600-1.
19. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med. 2003;139(9):761-76.
20. Stakisaitis D, Basys V, Bentis R. Does alpha-1 proteinase inhibitor play a protective role in coronary atherosclerosis? Med Sci Monit. 2001;7(4):701-11.

21. Duckers JM, et al. Cardiovascular and musculskeletal co-morbidities in patients with alpha 1 antitrypsin deficiency. Respir Res. 2010;11:173.

22. Ahlgren AR, et al. Changes in aortic wall stiffness in men with alpha 1-antitrypsin deficiency. Eur J Vasc Endovasc Surg. 1997;14(4):252-7.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=709&id=12&aid=6447