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Apolipoprotein E ϵ 4 Offers Protection Against Age-Related Macular Degeneration

Duncan A. Friedman, B.S.¹, Walter J. Lukiw, Ph.D.^{1,2}, and James M. Hill, Ph.D.^{1,2,3,4}

¹Department of Ophthalmology, LSU Health Sciences Center, New Orleans, LA

²Department of Neuroscience Center, LSU Health Sciences Center, New Orleans, LA

³Department of Pharmacology, LSU Health Sciences Center, New Orleans, LA

⁴Department of Microbiology, LSU Health Sciences Center, New Orleans, LA

Abstract

Background—In many previous studies, age-related macular degeneration (ARMD) has been linked to a variety of different risk factors. The publications have debated whether apolipoprotein E (apoE) ϵ 4 serves as a potential protective factor in the development of the disease. Other studies have classified the behavior of this protein in different pathologies, including Alzheimer's disease (AD) and cardiovascular disease. The general behavior of the ϵ 4 isoform of ApoE is different than the predominant ϵ 3 isoform.

Hypothesis—We propose that the general characteristics and molecular behavior of apoE ϵ 4 cause it to be a protective factor against the development of ARMD by preventing cumulative effects of oxidative retinal damage.

Evaluation of Hypothesis—Review of the literature related to ARMD and ApoE, using OVID as our main database, led to the development of several theories regarding ApoE ϵ 4's behavior compared to ϵ 3 and potential explanation of its protective characteristics.

Consequences of Hypothesis—We relate these theories to the potential behavior of ApoE ϵ 4 in other situations including choroidal neovascularization, Alzheimer's Disease (AD), cardiovascular disease, herpes simplex virus infection, and smoking.

Discussion—The potential implications of this theory could be used as a branching point for further studies that examine the role of the different apoE isoforms, in relation to the other risk factors for ARMD.

INTRODUCTION

Age-related macular degeneration (ARMD) is the leading cause of blindness in individuals over the age of 65 in the United States. New onset of the disease occurs at a 5 year incidence rate of 315,000 individuals over 75 years old [1]. The Framingham Eye Study (illustrated by

Address correspondence to: James M. Hill, Ph.D., LSU Eye Center/LSU Health Sciences Center, 2020 Gravier Street, Suite B, New Orleans, LA 70112-2234. Phone: (504) 568-2774, FAX: (504) 568-2385, E-mail: E-mail: jhill@lsuhsc.edu.

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Table 1) reported a prevalence of 2% of Americans 52-64 years old, 11% at 65-74 years, and 28% of individuals over 75 years [1]. The Eye Disease Prevalence Research Group found the prevalence to be 2% in individuals 50-64 years old, 5 % in 65-74 years old, and as high as 38% in individuals over 75 years old [2]. The disease affects 1.75 million Americans at any given time [3]. As an individual ages, the chances of acquiring ARMD increase, as age is the leading risk factor for development of the disease. Other risk factors for the disease include nicotine exposure (smokers > nonsmokers) [4], high dietary intake of cholesterol (higher cholesterol > lower cholesterol) [5], hypertension, ethnicity, hypercholesterolemia, and a possible gender bias (women > men) [6]. These and other risk factors are outlined and defined in Table 2. The disease presents in one of two predominant forms: geographic atrophy (also classified as “dry” macular degeneration) or choroidal neovascularization (CNV) (classified as “wet” macular degeneration). The more prevalent (80%) “dry” macular degeneration is characterized by development of deposits within the retina and Bruch’s membrane that contain degradation products of cells, transmembrane, and pro-inflammatory proteins extruded into the area through the local vasculature. These products coalesce and organize into structures known as drusen, characterized by a classic diameter greater than 63nm [7]. Compared to a normal retina (Figure 1a), the two types of ARMD present with very different pathologies and can be easily distinguished by a fundoscopic exam or fluorescein angiography. Figure 1b depicts a retina with choroidal neovascularization, while Figure 1c demonstrates geographic atrophy. Despite all that is known about the manifestations and associations of ARMD development, the specific cause(s) and pathogenesis of the disease have yet to be elucidated.

The pathogenesis of ARMD may be elucidated closely inspecting the macular drusen and its components. Co-localization studies of retinas have shown macular drusen to contain substances such as unusual forms of A-beta peptides, vitronectin, serum amyloid P, immunoglobulin light chains, complement, and apolipoprotein E (ApoE) [8,9]. The drusen-associated cross-linked dimeric forms of A-beta peptides, the pathological hallmark of AD, are highly neurotoxic and may be the principal pathological agent in AD [10]. The deposition of A-beta-peptides may be an important contributor to the local, inflammatory events that contribute to drusen biogenesis, the atrophy of the retinal pigmented epithelium, and the pathogenesis of age-related macular degeneration [11].

Another important, contributory aspect of ARMD pathogenesis is the position of a genetic locus in ARMD patients: 19q13.31. This locus is close to the gene responsible for apoE production [12]. Further, numerous publications have posited the effects of apoE and the influence that this lipoprotein has on development of ARMD [6,13-18]. These substances play a significant role in the pathogenesis of ARMD.

In addition, an interesting controversy surrounds the link between the apoE and the development of ARMD. The polymorphism of the ApoE gene occurs in three predominant isoforms: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, with $\epsilon 3$ being the most prevalent. Individuals have two ApoE ϵ genes, causing a disproportionate distribution of six genotypes, as shown in Table 3. For at least the past five years, different publications have characterized relative susceptibility to ARMD based on the presence of each of these six genotypes. The majority of publications have found a negative correlation between ApoE $\epsilon 4$ and ARMD compared to ApoE $\epsilon 3$, suggesting $\epsilon 4$ as a protective factor in the development of the disease [3,6,14-18]. At the same time, conflicting publications have shown either no correlation or even a positive correlation [16,20]. However, the positive correlations have either been weak positives or the studies themselves have been noted to lack adequate power to assess ApoE $\epsilon 4$ as a risk factor [13,16]. Further, the studies that failed to demonstrate negative correlations have fallen just short of statistical significance and one of these studies examined ApoE $\epsilon 4$ as a risk factor in younger individuals not characteristic of the age group that usually defines ARMD [20]. Despite these discrepancies,

there appears to be a significant and growing argument for ApoE ϵ 4 as a potential protective factor.

ApoE ϵ 4, ϵ 3 and ϵ 2 isoforms differ from each other by single cysteine-arginine substitutions in the amino acid at different positions, as demonstrated in Table 4. The apoE ϵ 4 variant allows conformational changes in the protein that subsequently cause terminal domain interaction, as well as formation of molten-globule geometry [21]. Even more intriguing is the fact that these conformational changes inhibit the normal dimerization of the apolipoprotein E (apoE ϵ 4) that usually occurs with the apoE ϵ 3 and apoE ϵ 2 isoforms. Since the apoE ϵ 4 cannot dimerize, it does not remain intracellular as readily as the other isoforms. Given this change in conformation, different membrane dynamics could be affecting the formation of drusen.

Based on the cumulative data outlined above, we suggest that the information supports the possibility that the apoE ϵ 4 allele offers a reduced risk for onset and/or severity of ARMD.

HYPOTHESIS

The protective effect of the ApoE ϵ 4 gene is mediated by the fact that this isoform is more fluid in nature, allowing for facilitated transport of lipids and cholesterol that would otherwise accumulate and form drusen responsible for ARMD. Retinal apoE may also have a role in the inhibition of the formation of soluble, oligomeric forms of A-beta peptides and the ensuing neurotoxic effects imparted by cross linked and/or dimeric forms A-beta molecules.

EVALUATION OF HYPOTHESIS

By evaluating the potential implications of this hypothesis, we can foresee a potential contribution to ARMD derived from ApoE. Retinal cells are in a continuous state of flux with photoreceptor components continuously extruding into the retinal pigmented epithelium (RPE) for renewal of their light absorbing effects. Bruch's membrane is responsible for dealing with degradation of retinal cells. The Bruch's membrane/RPE interface is also adjacent to the highly vascular choroid, allowing the easy entry of circulating inflammatory products, such as complement proteins and A-beta peptides. Cholesterol accumulation can occur if inflammation arises, altering the characteristics of the vascular barrier at the retina. Beatty et al. [22] specifically notes that the retina is an area susceptible to high oxidative damage which could potentially lead to drusen formation through repetitive inflammatory events. These damaging effects are due to the generation of oxygen free-radicals from the area's high oxygen use, high proportion of polyunsaturated fatty acids, and exposure to visible light. Interstitial accumulation of breakdown components, repetitive inflammation, and extrusion of inflammatory products could account for drusen formation at the Bruch's membrane/retinal pigmented epithelium interface.

Much like atherosclerotic plaque reversal has been demonstrated with increasing amounts of HDL-cholesterol, these inflammatory accumulations could perhaps be reversed by a more mobile transport molecule such as apoE ϵ 4. The fact that the ϵ 4 protein does not dimerize could allow the proteins to more easily navigate the interstitium and travel back to the vascular structures in the area. In fact, the specific structure of the ApoE ϵ 4 isoform could cause the molecule to localize more readily to vascular structures throughout the body than to the interstitium. The apoE ϵ 4 could also carry products via formation of "lipid rafts", a phenomenon that has been suggested to allow easier movement of these products [23]. Compared to ϵ 3 or ϵ 2, the greater mobility of particles offered by these lipid rafts could prevent breakdown product accumulation and subsequent inflammation, which would have a cascading effect, ultimately contributing to decreased formation of drusen and, subsequently, decreased incidence of ARMD development. If the degradation proteins are allowed to accumulate, the drusen would

subsequently form, leading to progressive retinal damage and, ultimately, the development of ARMD. This model is outlined in Figure 2.

EMPIRICAL DATA

Immunohistochemical studies demonstrated the presence of ApoE in the photoreceptor cells, RPE, and choroid, as well as a significant amount of apoE in Müller cells and a minimal amount in retinal ganglion cells [24]. The ApoE is known to be a reactionary protein that has increased synthesis induced by cell damage [25]. A study by Anderson et al. [24] does not specifically place apoE within the drusen themselves, but instead shows the apoE to be adjacent to the retinal accumulations, which may seem to argue against the proposed role of apoE actually forming drusen by coalescence with other material. Instead of ApoE remaining within the drusen, the study demonstrated a concentric ring formation, characteristic of drusen, which may indicate layered deposits of material. Li et al. [26] showed that ApoE is the most prominent apolipoprotein associated with drusen isolated from donor eyes. The Anderson [24] and Li [26] studies demonstrate the important association of apoE in the formation of drusen. Although the drusen themselves may not contain the apoE, it could mediate the deposition of molecules at the periphery of these organized structures, which is reaffirmed by the co-localization studies [9].

Dithmar et al. [27] showed that, in young mice starting at age 2 months, absence of apoE caused a greater accumulation of membrane-bound material. This finding also reaffirms the concept that apoE is responsible for the mediation of cell breakdown products. Complete absence of apoE would remove a potential protective factor and cause more retinal damage. This also shows that there may be differing levels of functionality for each of the ApoE alleles, with ApoE $\epsilon 4$ being a more effective carrier of inflammatory molecules than its $\epsilon 3$ counterpart. This does not deny the fact that $\epsilon 3$ may also be an effective carrier of cholesterol, but suggests that it is not as effective as $\epsilon 4$.

Zarepari et al. [18] reports that subjects with nicotine exposure carrying the $\epsilon 4$ allele were less susceptible to ARMD than those with the $\epsilon 3$ or $\epsilon 2$ alleles. Nicotine may promote oxidative retinal damage, which would lead to cellular breakdown and inflammation. If $\epsilon 4$ could transport the breakdown products away easier than $\epsilon 3$, there should be a decreased incidence of drusen formation in ApoE $\epsilon 4$ individuals. The decreased ability of $\epsilon 3$ individuals to carry away damage products would ultimately lead to greater accumulation of products and subsequent drusen formation.

Lukiw [28] addresses the transport issue from an alternate perspective; although the main emphasis of the publication deals with cholesterol, A-beta trafficking, and apoE's influence in Alzheimer's disease, it is possible to draw a few deductions. Importantly, cholesterol intrinsic to the brain cannot cross an intact blood-brain barrier, however the more polar cholesterol oxide 24S-hydroxycholesterol (24S-HC) can readily traverse this barrier. Mahley et al. [21] points out that the ApoE $\epsilon 4$ isomer's conformation and interaction causes greater oxidative damage. If this "damage" were instead considered beneficial because of the potential for increasing cholesterol mobility, this combination of observations could subsequently explain another potential mechanism of ApoE $\epsilon 4$'s effects. This theory would necessitate further investigation of how the retinal vasculature behaves compared to a blood-brain barrier in an undamaged state, but still provides a possible means of supporting decreased inflammation in the retina.

The relative solubility of the apoE $\epsilon 4$ molecule and its ability to carry cholesterol and lipids appears to play some role in preventing drusen formation. Whether that mechanism is through oxidative transport or simple membrane fluidity, there are multiple explanations that point to the fact that the $\epsilon 4$ allele's increased solubility could account for a decreased formation of drusen.

CONSEQUENCES OF HYPOTHESIS

Choroidal Neovascularization (CNV)

The other predominant form of ARMD involves the formation of new vessels that penetrate Bruch's membrane and invade under the RPE. CNV accounts for ARMD only 20% of the time compared to geographic atrophy, but is responsible for approximately 21% of legal blindness in the United States [1]. No previous studies have specifically looked at the development of CNV-type ARMD in relation to ApoE isoforms. A question now arises as to how our proposed model of ApoE could cause or prevent CNV.

Langheinrich et al. [29] point out that mice deficient in ApoE and LDL develop increased peri-aortic vasa vasorum by micro-CT. They attribute this development to increased metabolic demand and intravascular plaque formation. Areas of the retina experiencing increased photoreceptor damage and cell death could possibly require an increase in metabolic mediation of the degradation products. If this is the case, the ApoE ϵ 4 molecule could prevent neovascularization by decreasing relative metabolic demand in the area. ApoE ϵ 3 status may be sufficient to mediate metabolic demand and prevent CNV, but it would be important to examine the relative neovascular formation in the choroid based on overall presence of ApoE, prior to examining the influence of the apoE isoforms.

Despite the potential effect that ApoE may have on CNV, it is also important to consider the fact that CNV could manifest independent of ApoE as a factor. Although ApoE may contribute to the process, the formation of new vascular structures may be due to other factors, such as production of vascular endothelial growth factor (VEGF) or other paracrine effects and local mediation. With age as the leading risk factor in the development of ARMD, it is possible that vascular senility and increasing cell death could be the leading cause for increased oxygen demand. Thornton et al. [4] points out that nicotine exposure causes relative hypoxia in the area of RPE and retina. Again, nicotine's damaging effects could be the predominant cause of CNV. It appears that more sophisticated studies regarding the effects of the different risk factors on CNV-type ARMD need to be conducted. ApoE could possibly be a cause, a contributory factor, or a ancillary contributory factor to this type of ARMD pathology.

Atherosclerosis

A major dilemma is justifying the effects of apoE ϵ 4 as a protective factor in the retina while previous studies have shown the ϵ 4 isoform to be a risk factor in the development of atherosclerosis [30]. ApoE ϵ 4 is associated with an increase in the formation of intravascular plaques, which can subsequently lead to heart disease and other vascular effects. These damaging effects seem to be in direct contrast to the possible protective benefits proposed.

One potential means of rationalizing this discrepancy is the fact that apoE ϵ 4 may specifically localize to the vasculature instead of the interstitium. This could be due to the fact that ϵ 4 is relatively more soluble and migrates more easily through the interstitium into the vasculature. Within the vasculature, the ϵ 4 molecule could continue its primary role in carrying cholesterol and other lipids, thus depositing more of these products in intravascular plaques elsewhere in the circulation, especially areas of endothelial damage. ApoE ϵ 4 has also been shown to cause oxidative effects, which may change the cholesterol to an oxidized state, causing more intravascular plaque deposition. The question then arises, where does this oxidative effect take place? Do local factors within the vasculature predispose to greater oxidation versus the local factors in the retinal interstitium? The apoE ϵ 3 or ϵ 2 molecules are considered protective factors in plaque development. This phenomenon can be justified by the fact that these isoforms would remain interstitial and avoid intravascular deposition. These theories require that the fluidity

model of ApoE isoforms be supported by other studies, but the theory is in accord with the hypothesis.

Herpes Simplex Virus

We have previously proposed a potential increase in Herpes Simplex Virus Type 1 (HSV-1) susceptibility based on the type of ApoE allele (Figure 3). The model posits increased viral uptake, activity, oxidative damage, viral load, and reactivation in individuals with apoE ϵ 4 compared to those with apoE ϵ 3 or ϵ 2. This could be, in part, due to the increased formation of lipid rafts associated with apoE ϵ 4. If ApoE ϵ 4 actually causes a relative increase in the amount or mobilization of lipid rafts, the virus could travel more readily from the primary site of infection to the trigeminal ganglion. Lipid raft endocytosis could be increased in individuals with apoE ϵ 4, causing a greater chance of establishing latency [23]. Stimuli that would cause viral reactivation would ultimately lead to recrudescence because the virus would travel more easily or more rapidly. Another hypothesis made by this group stated that use of statins should decrease viral mobility by limiting the formation of these apoE4-containing lipid raft domains [23]. The relative mobility of the ApoE isoforms could ultimately explain the development of HSV-1 pathology and further support the hypothesis for ARMD development.

Alzheimer's Disease

A recent study has demonstrated an increased development of Alzheimer's Disease (AD) associated with the presence of ApoE ϵ 4 [21]. This association has been attributed to the potential oxidative damage of apoE ϵ 4 caused by its conformation. The study further argues that apoE ϵ 3 and ϵ 2 are more stable isoforms that prevent damage. Although it may appear that this relationship should also exist in the retina, there are many differences between these two environments. Primarily, the relative blood flow between the two areas is significantly different. The highly vascular choroid approximates the retina via Bruch's without significant impedance to transport. The area primarily responsible for development of AD, the nucleus basalis, must negotiate a blood-brain barrier (BBB) for transport of any cell degradation products. These cell degradation products could viably be "locked" into the interstitium of the brain more readily than the interstitium of the retina due to the effects of the BBB. There is also a different composition to brain material when compared to the interstitium surrounding the retina. The aggregated A-beta peptides, forming the neuritic plaques that are characteristic of AD, contain many different accessory proteins (such as tau protein) and lipids from those found in drusen. One previous study points out that the A-beta found in neuritic plaques appear ultrastructurally different from the A-beta of drusen [9]. Given the two different environments, it is hard to equate damage associated with ARMD to damage associated with AD. Still, there may be a relation based on the behavior of ApoE molecules and their interaction with their immediate environments.

Nicotine

Nicotine also has a significant role in the pathology of these two diseases. Although it may be a completely independent mechanism in both diseases, nicotine has opposite effects on ARMD versus AD, much like that of ApoE ϵ 4. While nicotine is considered to be a risk factor for the development of ARMD, it is a potentially protective factor for development of AD [4]. In contrast, ApoE ϵ 4 appears to be a risk factor for AD while it is protective against ARMD. How these two environmental factors interact is a topic for future study, including the potential synergistic effect that they may have in relation to either disease. It will also be necessary to keep these relationships in mind when trying to modify the effect that one isoform exerts on a specific disease. Mahley et al. [21] suggests that a potential chemotherapy for AD would be the specific manipulation of apoE ϵ 4 molecules to assume a more apoE ϵ 3 type conformation

through the use of protein interaction inhibitors. However, modifications to alleviate one pathology could possibly result in an increased development of another disease.

DISCUSSION

ApoE is, in part, responsible for A-beta peptide, cholesterol and other lipid transport throughout the systemic circulation [28]. Absence of lipoprotein ApoE ϵ 4 has been shown to induce the development of ARMD in mouse models. The different apoE ϵ 2, ϵ 3, and ϵ 4 isoforms have different structural conformations and biophysical and biochemical properties, which influence the way they behave *in vivo*. ApoE ϵ 4 is known not to dimerize like the other isoforms and this may contribute to its higher solubility and easier mobilization throughout the cell, through the interstitium, and into the local and systematic circulation. ApoE ϵ 4 may even specifically localize to the cerebral vasculature, which would account for its association with atherosclerotic plaque formation in the brain. Indeed, increased fluidity could account for a number of pathologies associated with the apoE ϵ 4 isotype.

As for ApoE status being a specific risk factor for the formation of ARMD, it is important to remember that ApoE is only one of a number of potential risk factors. Other factors contribute to the development of the disease in a multi-factorial fashion, and the effects could be considered additive. By our definition, an individual with the apoE ϵ 4 isoform that smokes should be less susceptible than an apoE ϵ 4 individual who does not smoke. Likewise, a smoker with an apoE ϵ 3/ ϵ 3 genotype would be more susceptible to ARMD than a smoker with an apoE ϵ 3/ ϵ 4 genotype. Given the risk factors listed in Table 2, any one factor could contribute to onset development and severity of the disease. Multiple factors could synergistically increase or decrease the overall risk for ARMD.

Subsequent studies derived from this hypothesis could include examination of the risk factors in relation to the different isoforms of ApoE and the development of ARMD. Further co-localization studies could demonstrate the specific location of the different isotypes. This would require a mouse model with knock-in genes compared to the already known mouse models, but they are feasible for long-term studies. Finally, experiments to test the “fluidity” model of ApoE would help support the hypothesis. While much research still needs to be conducted to adequately evaluate the *in vivo* function of the various ApoE alleles, our hopes are that our hypothesis will influence the experimental design, focus, and direction of future experiments on ARMD.

Abbreviations Used in this Paper

24S-HC, 24S-hydroxycholesterol
 A-beta, Beta amyloid
 AD, Alzheimer’s Disease
 AF-Am, African-American (Table2)
 ApoE, Apolipoprotein E (gene)
 apoE, Apolipoprotein E (protein)
 AREDS, Age-related eye disease study
 ARMD, Age-related macular degeneration
 BBB, Blood brain barrier
 CNV, Choroidal neovascularization
 CSF, Cerebrospinal fluid
 CT, Computed tomography
 EDPRG, Eye disease prevalence research group (Table 1)
 FES, Framingham Eye Study (Table 1)
 HDL, High-density lipoprotein

HSV-1, Herpes simplex virus type 1
 LDL, Low-density lipoprotein
 NML, Normal (Table2)
 Pk-yrs, Pack years-needs definition
 RPE, Retinal pigmented epithelium
 VEGF, Vascular endothelial growth factor

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Figure 1.

A) Normal retinal fundus (grayscale)-notice clearly defined foveola without signs of edema or RPE changes. Vessels are clearly defined leading to macula. B) Wet ARMD (grayscale)-exudative age related macular degeneration with subretinal hemorrhage from choroidal neovascularization. C) Dry ARMD (grayscale)-Advanced nonexudative, age-related macular degeneration demonstrating geographic atrophy.

Figure 2.
The predicted actions and consequences following any initial insult relative to ApoE alleles.

Figure 3.

The predicted actions and consequences following an insult from exposure to HSV-1 relative to ApoE alleles.

Table 1

Prevalence of individuals with ARMD by age group

Age (years)	FES Prevalence (1977)	EDPRG (2004)	Population (people) (N = 30,000,000)
52-64	2%	2%	600,000
65-74	11%	5%	1,500,000
75+	28%	38%	11,400,000

Table 2
ARMD Risk factors (RF)/Protective factors (PF) in Humans

	Description	High Risk	Protective
1.	Age	Age >65	Age <65
2.	Retinal ischemia	+	-
3.	Genetics	+	?
4.	Complement Factor H	Dysfunctional	Functional
5.	ApoE allele	ε2, ε3	ε4
6.	Hypercholesterolemia	+	-
7.	Smoking	>10 pk-yrs	<10 pk-yrs
8.	Smoking cessation	?	>2 years
9.	Atherosclerosis/arteriosclerosis	+	-
10.	Light exposure/oxidative damage	+/-	+/-
11.	Race	Caucasian (AREDS)	Af-Am
12.	Hypertension	+	-
13.	Vitamin A intake	-	+
14.	Genetic link	+	-
15.	BMI	Obese	NML

Table 3

Estimated Human Genotype Frequency of ApoE*

e3/e3	e3/e4	e3/e2	e4/e4	e2/e2	e4/e2
~55%	~25%	~15%	~1-2%	~1-2%	~1-2%

* These frequencies are generally accepted for most populations, especially with regard to the USA.

Table 4

Structural differences between different isoforms of apoE

	$\epsilon 2/\epsilon 2$	$\epsilon 3/\epsilon 3$	$\epsilon 4/\epsilon 4$
Residue 112	Cys	Cys	Arg
Residue 158	Cys	Arg	Arg
Relative Charge	0	+1	+2