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# Genetic association of apolipoprotein E with optic disc size

**Anselm G.M. Jünemann[1, 2], Udo Reulbach[3], Stefan Bleich[4], Johannes Kornhuber[5], Katarzyna Nowomiejska[2], Joanna Moneta-Wielgos[2], Robert Rejdak[2]**

*[1]Department of Ophthalmology, University Medicine, University Rostock, Rostock, Germany*
*[2]Department of General Ophthalmology, Medical University, Lublin, Poland*
*[3]Department of Child & Adolescent Psychiatry, Our Lady's Children's Hospital, Dublin, Ireland*
*[4]Department of Psychiatry, Social Psychiatry, and Psychotherapy, Hannover Medical School, Germany*
*[5]Department of Psychiatry and Psychotherapy, University of Erlangen-Nürnberg, Germany*

## ABSTRACT

**INTRODUCTION.** The purpose of this clinical non-interventional cross-sectional study was to evaluate the role of apolipoprotein E (ApoE) gene alleles ($\varepsilon 2$, $\varepsilon 3$, $\varepsilon 4$) in the determination of optic disc size.
**MATERIALS AND METHODS.** In 32 normal controls, 54 patients with ocular hypertension (OHT), and 96 patients with primary open-angle the optic disc size was determined by planimetry using 15° colour stereo photographs. In all individuals ApoE genotyping was performed.
**RESULTS.** The size of the optic disc was significantly different between subjects with $\varepsilon 3\varepsilon 2$, $\varepsilon 3\varepsilon 3$, and $\varepsilon 4\varepsilon 3$ allele (Kruskal-Wallis-test, Chi-Square: 6.95, p = 0.031; 2.39, 2.77, and 2.78 $mm^2$, respectively).
**CONCLUSIONS.** The results suggest that ApoE gene alleles are associated with optic disc size. ApoE may act as a modulator gene for optic disc morphogenesis.

**KEY WORDS:** apolipoprotein E, optic disc size, ApoE gene alleles

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## INTRODUCTION

The genetic architecture of the optic disk has become the focus of some attention in recent years. Several genome-wide association studies have identified different loci influencing the optic disc morphology, including optic disk size, cup, and rim area [1–3]. In addition, to examine the roles of genetic and environmental factors in the optic disc classic twin studies were performed, indicating that genetic factors were important in the determination of optic disc parameters like optic disk size, cup, and rim area [4, 5].

Apolipoprotein E (ApoE), a lipid transporting protein produced in the liver and brain, is unique among apolipoproteins regarding its special relevance to nervous tissue. It is involved in mobilisation and redistribution of cholesterol in the repair, growth, and maintenance of myelin and neuronal membranes during development or after injury. There are isoform-specific influences on metabolism, growth, and degenerative and regenerative behaviour of nerve tissue. ApoE $\varepsilon 4$-positive carriers show a higher incidence of Alzheimer's disease as well as a reduced regenerative capacity of the brain after traumatic head injuries, and are a risk factor for brain shrinkage in alcoholism [6]. Recently it has been shown that ApoE plays a role in gliogenesis, myelination, and axonal outgrowth during optic nerve morphogenesis [7]. The present study was, therefore, undertaken to investigate whether ApoE isoforms ($\varepsilon 2$, $\varepsilon 3$, $\varepsilon 4$) are associated with optic disc size.

**CORRESPONDING AUTHOR:**
Univ.-Prof. Dr. med. Anselm G.M. Jünemann, F.E.B.O. Direktor der Augenklinik, Universitätsmedizin Rostock, Doberaner Straße 140, 18057 Rostock, e-mail: anselm.juenemann@med.uni-rostock.de

## PATIENTS AND METHODS

This study included 96 patients with primary open-angle glaucoma (POAG, IOP > 21 mm Hg, glaucomatous optic disc, visual field defects), 54 patients with ocular hypertension (OHT, IOP > 21 mm Hg, normal optic disc, normal visual field), and 32 controls (IOP < 22 mm Hg, normal optic disc, normal visual field). All individuals included in the study were unrelated Caucasians and had open anterior chamber angles, clear optic media, and a visual acuity of 20/25 or better. Exclusion criteria were all eye diseases other than glaucoma, diabetes mellitus, and myopic refractive error exceeding –8 dioptres. The study followed the tenets of the declaration of Helsinki for research involving human subjects, and informed consent was obtained from all participants of the study. For all eyes, 15° colour stereo optic disc photographs had been taken with a telecentric fundus camera (30° fundus camera equipped with a 15° converter, Carl Zeiss, Oberkochen, Germany). The disc slides were projected in a scale of 1 to 15. The outlines of the optic disc, optic cup, and peripapillary scleral ring were plotted on paper and morphometrically analysed. To obtain values in absolute size units (i.e. millimetre or square millimetre), the ocular and photographic magnification was corrected by the Littmann method. For ApoE genotyping, genomic DNA was extracted from anticoagulated blood after isolation of peripheral lymphocytes following the "salting out" method. As allele $\varepsilon 3$ is considered to be the ancestral allele, and $\varepsilon 2$ and $\varepsilon 4$ are considered as variants on the basis of single point mutations, the $\varepsilon 3\varepsilon 3$ genotype was used as a reference. As the frequency of the genotypes $\varepsilon 2\varepsilon 2$, $\varepsilon 2\varepsilon 4$, and $\varepsilon 4\varepsilon 4$ was less than or equal to seven, these genotypes were excluded from the analysis.

## RESULTS

The size of the optic disc differed significantly between subjects with $\varepsilon 3\varepsilon 2$, $\varepsilon 3\varepsilon 3$, and $\varepsilon 4\varepsilon 3$ allele (Kruskal-Wallis-test, Chi-Square: 6.95, p = 0.031; 2.39 (SD 0.56) vs. 2.77 [SD 0.69) vs. 2.78 (SD 0.88) mm$^2$] (Fig. 1). Regarding the differences between the possible pairs ($\varepsilon 3\varepsilon 2$,$\varepsilon 3\varepsilon 3$; $\varepsilon 3\varepsilon 2$,$\varepsilon 4\varepsilon 3$; $\varepsilon 3\varepsilon 3$,$\varepsilon 4\varepsilon 3$), only subjects with $\varepsilon 3\varepsilon 2$ allele had a significantly smaller size of the optic disc than subjects with the reference genotype $\varepsilon 3\varepsilon 3$ (Mann–Whitney U, Z = –2.74, p = 0.018, Bonferroni corrected for multiple testing). There was an ascending neuroretinal rim area from subjects with $\varepsilon 3\varepsilon 2$ (1.22 mm$^2$, SD 0.47) to $\varepsilon 3\varepsilon 3$ (1.27 mm$^2$, SD 0.46), and to $\varepsilon 4\varepsilon 3$ (1.31 mm$^2$, SD 0.43) allele; however, this difference was not significant.

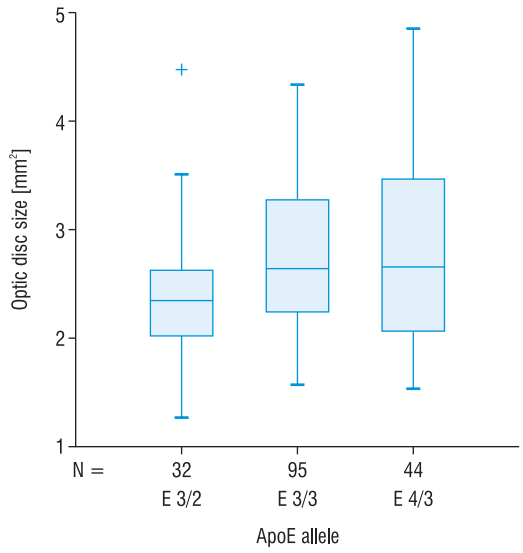


**FIGURE 1.** Optic disc size [mm$^2$] of 171 individuals (normal controls, OHT, preOAG and OAG); + case with more than 1.5 box lengths from the upper or lower edge of the box. The box length is the interquartile range; *significant [Kruskal-Wallis-test, Chi-Square: 6.95, p = 0.031; 2.39 (SD 0.56) vs. 2.77 (SD 0.69) vs. 2.78 (SD 0.88) mm$^2$]; ApoE — apolipoprotein E; OHT — ocular hypertension; preOAG — primary open-angle glaucoma; OAG — open-angle glaucoma

## DISCUSSION

The data from this study indicate that ApoE gene alleles are associated with optic disc size. Small optic disc size is associated with ApoE $\varepsilon 2$ allele carrier, and large optic disc size with ApoE $\varepsilon 4$ allele carrier. This was also true for the neuroretinal rim area, probably due to the correlation between optic disc size and neuroretinal size. These results may reflect the protective effects of ApoE $\varepsilon 4$ allele during human embryogenesis.

In addition, the significant reduction of glial cell and optic axons density, as well as the myelin thickness and the number of lamella in ApoE knockout mice, in parallel with a significantly higher optic nerve cross-sectional area, support a possible role of ApoE in optic nerve morphogenesis [2].

The result of this study are interesting because both ApoE gene allele and optic disc size are thought to act as risk factors for glaucoma. Although no association was found between open-angle glaucoma and ApoE alleles [8, 9], inheritance of ApoE $\varepsilon 4$ allele was associated with elevated risk for glaucomatous changes that are not related to increased intraocular pressure, i.e. normal tension glaucoma [9]. Interestingly, ApoE $\varepsilon 2$ allele was found to be associated with intraocular pressure [8]. The association between glaucoma and optic disc size is discussed controversially in the literature. Studies have

reported larger discs in normal-tension glaucoma but not in high-tension glaucoma compared with normal individuals [10]. Thus ApoE *ε4* allele carrier may have larger optic discs and may be more vulnerable to glaucomatous damage. Further studies are necessary to elucidate the interrelationship between optic disc size, apolipoprotein E, and risk for glaucoma.

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