Genetic studies of age-related macular degeneration
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CHAPTER 1: GENERAL INTRODUCTION

Figure 1. Normal Macular Anatomy (left) and Normal Macular Fundus Appearance (right). Reprinted with permission from The Macular Degeneration Research, a program of the American Health Assistance Foundation © 2012. http://www.ahaf.org/macular.
**CHAPTER 1: GENERAL INTRODUCTION**

<table>
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<th>Stage</th>
<th>Definition</th>
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| 0     | - No signs of AMD  
|       | - Hard drusen (<63 μm) only |
| 1     | - Soft distinct drusen (≤63 μm) only  
|       | - Pigmentary abnormalities only, no soft drusen (≤63 μm) |
| 2     | - Soft indistinct drusen (≤125 μm) or reticular drusen only  
|       | - Soft distinct drusen (≤63 μm) with pigmentary abnormalities |
| 3     | Soft indistinct drusen (≤125 μm) or reticular drusen with pigmentary abnormalities |
| 4     | Geographic atrophy or choroidal neovascularization |

Figure 2. Fundus Photographs Illustrating The Signs of AMD Graded According To The International Classification and Grading System for AMD.  
(A). Stage 0; (B). Stage 1; (C). Stage 2; (D). Stage 3; (E). Stage 4 (geographic atrophy); (F). Stage 4 (choroidal neovascularization). Definitions of the stages are given in the text. Fundus photographs reprinted with permission from Redmer van Leeuwen et al. [17].
CHAPTER 7: THE DYNAMIC NATURE OF BRUCH’S MEMBRANE

Figure 1. Schematic Drawing of Proteins Present in Bruch’s Membrane and the Corresponding Genes Expressed in Adjacent Cells.

We identified three genes (COL4A3, FNDC5, TIMP3) with higher expression levels in the RPE than in the choroid, and 17 genes (remainder) with higher expression levels in the choroid than in the RPE. A qualitative impression of the gene expression is given. Gene expression levels were determined by RNA microarray study comparing gene expression levels from two adjacent tissue types from the same donor. Experiments were performed in triplicate (on three different healthy older human donor eyes)[24]. bm RPE: basement membrane of the RPE, bm choroid: basement membrane of the choroid. The abbreviation for basement membrane is not used in the accompanying text.
CHAPTER 7: THE DYNAMIC NATURE OF BRUCH’S MEMBRANE

Figure 2. Schematic Drawing Showing the Normal Structure and Functions of Bruch’s Membrane.
Transmission Electron Microscopic image of BM courtesy of Prof. J. Marshall. BM allows for the transport of biomolecules across the membrane, it attaches RPE cells to the membrane and it acts as a physical barrier to prevent the migration of RPE cells and choroidal cells across the membrane.
CHAPTER 7: THE DYNAMIC NATURE OF BRUCH’S MEMBRANE

Figure 5. Overlap in Protein Content of Alzheimer Plaques, AMD Drusen, and Atherosclerotic Plaques.
We analyzed 121 proteins based on the article by Crabb et al. [6] and additional literature searches. We obtained NM numbers for 85 of the proteins characterized by Crabb, and an additional 36 proteins were added based on the recent literature [167]. Note that drusen share 20% of their protein content with AD plaques and less than 10% with atherosclerotic plaques.
We could annotate 113 genes with genbank codes (using Ingenuity) which correspond to drusen proteins identified by Crabb et al. We could annotate 113 genes with genbank codes (using Ingenuity) which correspond to drusen proteins identified by Crabb et al. Thirty six of these genes had higher expression levels in choroid compared to RPE (chor>RPE). Thirteen genes had higher expression levels in RPE than in choroid (RPE>chor) and only three genes had higher expression levels in photoreceptors than RPE (phot>RPE). Gene expression levels were determined by RNA microarray study comparing gene expression levels from two adjacent tissue types from the same donor. Experiments were performed in triplicate (on three different healthy older human donor eyes) [24]. Details of the 113 genes can be found in Table 1.
CHAPTER 8: REDUCED SECRETION OF FIBULIN 5 IN AMD AND CUTIS LAXA

Figure 2. Retinal Photographs of Three Patients.
(A) and (B). Retinal Photographs of Patient 1 (p.Q124P). Small round (cuticular) drusen are symmetrically present. (C). Optical coherence tomogram of patient 1 demonstrates nodular thickening of the retinal pigment epithelium (*). (D) and (E). Fluorescein angiograms of patient 2 (p.G267S) demonstrate choroidal neovascularization in one eye only. (F). and (G). Fluorescein angiogram photographs of patient 3 (p.G267S) demonstrate cuticular drusen with central areas of focal retinal pigment epithelial detachment (*).
CHAPTER 9: GENERAL DISCUSSION

Figure 1. The complement pathway.
The components of the complement system that have been genetically associated with increased or decreased risk of drusen, geographic atrophy (GA), and choroidal neovascularization (CNV), are circled. Reprinted with permission from Donoso et al. [65].