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Towards the application of precision medicine in Age-Related Macular Degeneration

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ABSTRACT

The review essentially describes genetic and non-genetic variables contributing to the onset and progression of exudative Age-related Macular Degeneration (AMD) in Italian population. In particular, AMD susceptibility within Italian population is contributed to by genetic variants, accounting for 23% of disease and non-genetic variants, accounting for 10% of AMD. Our data highlighted prominent differences concerning genetic and non-genetic contributors to AMD in our cohort with respect to worldwide populations. Among genetic variables, SNPs of *CFH*, *ARMS2*, *IL-8*, *TIMP3*, *SLC16A8*, *RAD51B*, *VEGFA* and *COL8A1* were significantly associated with the risk of AMD in the Italian cohort. Surprisingly, other susceptibility variants described in European, American and Asiatic populations, did not reach the significance threshold in our cohort. As expected, advanced age, smoking and dietary habits were associated with the disease. In addition, we also describe a number of gene-gene and gene-phenotype interactions. In fact, AMD-associated genes may be involved in the alteration of Bruch's membrane and induction of angiogenesis, contributing to exacerbate the damage caused by aging and environmental factors.

Our review provides an overview of genetic and non-genetic factors characterizing AMD susceptibility in Italian population, outlining the differences with respect to the worldwide populations. Altogether, these data reflect historical, geographic, demographic and lifestyle peculiarities of Italian population. The role of epigenetics, pharmacogenetics, comorbities and genetic counseling in the management of AMD patients have been described, in the perspective of the application of a "population-specific precision medicine" approach addressed to prevent AMD onset and improve patients' quality of life.

1. Age-related Macular Degeneration: state of art

The launching of Precision Medicine Initiative in 2015 represented the starting point for the introduction of a novel approach for treatment and prevention of disease. The project aims to apply the scientific evidence gathered by advanced technologies to the clinical practice and provide a deeper understanding of many diseases (Collins and Varmus, 2015). The knowledge of disease conditions is essential to improve patient's welfare and disease treatment according to individual variability in genes, environment and lifestyle. The realization of the precision medicine initiative is possible thanks to the huge amount of data collected through the deep exploration of the human genome in health and disease conditions (high-throughput DNA sequencing, GWAS, HapMap Project, 1000 Genome Project, Encode). In particular, the

Abbreviations: AMD, Age-Related Macular Degeneration; CNV, Choroidal Neovascularazation; RPE, Retina Pigment Epithelium; BrM, Bruch's membrane; ECM, Extra-Cellular Matrix; GA, Geographic Atrophy; ROS, Reactive Oxigen Species; TF, Transcription Factors; CRX, Cone-Rod Homeobox; miRNAs, micro-RNAs; VA, Visual Acuity; RNFL, Retinal Nerve Fiber Layer; PDT, Photodynamic Therapy; IOP, Increased Intraocular Pressure; CVD, Cardiovascular Diseases; AD, Alzheimer Disease; PD, Parkinson Disease; CRP, C-reactive protein

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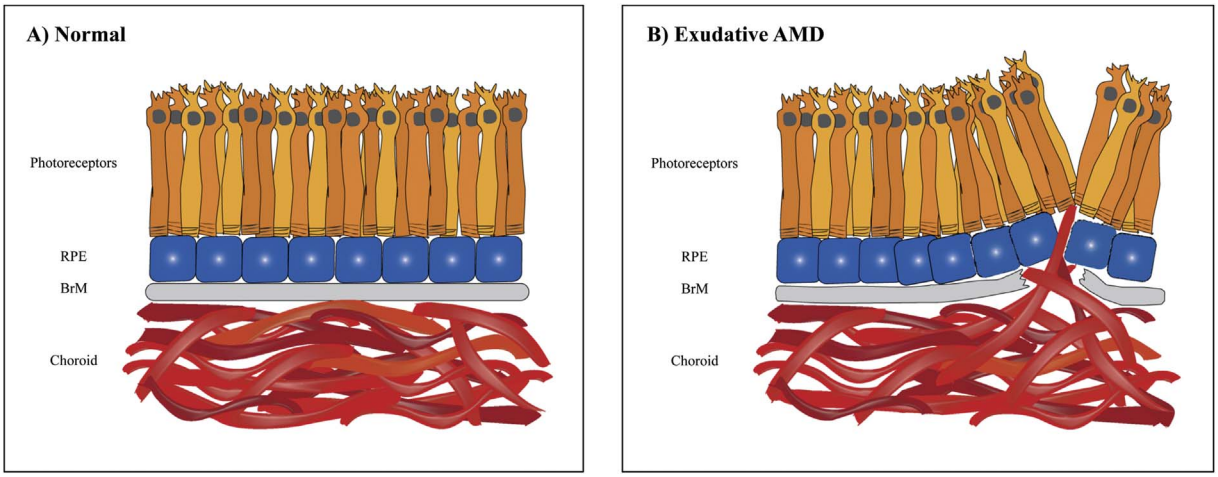

Fig. 1. 1A: Cytoarchitectonics of the central retina in normal condition. 1B: Cytoarchitectonics of the central retina in exudative AMD.

1000 Genome Project uncovered genomic variability within different populations across the world, identifying approximately 10 million Single Nucleotide Polymorphisms (SNPs) with highly variable frequencies among individuals belonging to the same or different populations (1000 Genomes Project Consortium et al., 2015; Ginsburg and Willard, 2013). In addition, the 1000 Genome Project highlighted that genomic diversity between single individuals and/or within populations mainly consists of common and rare SNPs with their own Minor Allele Frequency (MAF). In particular, common SNPs (MAF > 0.05) have usually a wide geographic distribution as a result of their early origin, while rare SNPs (MAF < 0.05) are more restricted to specific geographic areas because of their recent origin (Choudhury et al., 2014). The study of common and rare SNPs can provide useful information about demographic histories of specific populations and ancestral groups. However, the differential distribution of genetic variations across populations depends not only on demographic history, but also on adaptation to the local environment (Choudhury et al., 2014; Ginsburg and Willard, 2013; Shen et al., 2013). For example, the mutational spectrum of the *FLG* gene associated with atopic eczema (AE) shows evidence of population-specific distribution between northern European and Mediterranean subjects (Cascella et al., 2015). The heterogeneous distribution of *FLG* variations (0% in Mediterranean areas vs 10% in northern Europe) suggests a possible relationship between variations in UV radiation due to geographic location and differential susceptibility to AE, which is driven by adaptation to local environments (Cascella et al., 2011, 2015). Therefore, the study of common and population-specific SNPs has become extremely helpful to characterize particular phenotypes or define populations with higher susceptibility/protection to specific diseases. Human phenotypes can be described as monogenic or complex. Monogenic traits are strongly influenced by variations within a single gene, while complex traits are influenced by the interactions among multiple genes, environmental factors and individual lifestyle. Thus, complex traits can be exploited to describe new pathogenic mechanisms, identify individuals at greater risk of disease and set up appropriate preventive or predictive strategies for the management of complex disorders (Grishkevich and Yanai, 2013). However, even beyond next-generation gene sequencing and developing diagnostic tools and targeted therapies, the basic approach to clinical care has to be re-envisioned to fulfill the promise of personalized medicine. In this context, Age-related Macular Degeneration (AMD, OMIM #610149) is one of the investigated complex disease, since the risk or protection of AMD strictly depends on genetic and environmental factors. A large number of population-based studies on AMD have identified several associated genetic factors with differing frequencies and impact on disease outcome (Bailey et al., 2014; Fritsche et al., 2014; Horie-Inoue and Inoue, 2014). Therefore, understanding the prevalence, burden, and population-specific risk factors for AMD is essential for adequate health care planning and provision.

AMD affects approximately 10 million people worldwide, and it is the main cause of low vision among people aged 55 years and older. The number of AMD cases is expected to increase to 11.3 million in 2020, 14.6 million in 2030 and 18.9 million in 2040 (Sobrin and Seddon, 2014; Wong et al., 2014). In Italy, over 1 million individuals manifest with initial symptoms of the disease, and 63000 new AMD cases are estimated each year (Cascella et al., 2014). Patients affected with AMD experience a progressive loss of the central vision and visual acuity, distortion of images and straight lines, blurry and dark central areas, altered perception of colors. As a result, most of the routine activities of these patients are compromised, especially driving and reading. In addition, patients' quality of life is severely impaired; they usually require psychological, visual and caring support which, altogether, contribute to increase the economic and social burden of the disease.

The hallmarks of the disease include the progressive degeneration of the central part of the retina (*macula*) and drusen formation, changes that ultimately disrupt the cytoarchitectonics of the central retina and cause atrophy or abnormal choroidal neovascularization (CNV). According to the clinical phenotype, AMD is classified as non-exudative or exudative (Lambert et al., 2016; Cascella et al., 2014; Fritsche et al., 2014). In the early stage of disease, fundus examination reveals the presence of non-exudative lesions such as drusen, areas of Retinal Pigment Epithelium (RPE) depigmentation or pigment clumping. These drusen typically occur with significant pigment changes and accumulation of pigment in the posterior pole. Morphological characteristics of the drusen (size, coalescence, extension) and the occurrence of pigment changes appear to be correlated with the risk of disease evolution. The late stage of AMD is characterized by either the presence of central retinal atrophy, termed geographic atrophy (GA), or the presence of an exudative neovascular lesion, known as choroidal neovascularization (CNV) (Lambert et al., 2016; Horie-Inoue and Inoue, 2014). In the presence of CNV (Fig. 1), the abnormal blood vessels typically sprout from the choriocapillaris and can penetrate Bruch's membrane (BrM) into the space beneath the RPE (type 1 CNV) or the subretinal space (type 2 CNV). In some cases, neovascularization appears to initiate from the retinal vessels, induces detachment of the pigment epithelium and finally creates anastomosis with choroidal vasculature (Retinal Angiomatous Proliferation-RAP or type 3 CNV).

Concerning the onset and the evolution of the disease, a number of triggering factors have been described up to date. First, aging is responsible for the loss of approximately 30% of rod photoreceptors and has been directly correlated with disease prevalence (Marazita et al., 2016; Fritsche et al., 2014; Cascella et al., 2014; Ehrlich et al., 2008).