Molecular basis of open-angle glaucoma in Italy

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Abstract

Glaucoma is a group of ocular diseases characterized by an optic neuropathy in which degeneration of retinal ganglion cells leads to a characteristic excavation of the optic nerve head. Primary open-angle glaucoma (POAG) can be subdivided into two groups according to age of onset: –

1. the more common middle- to late-age onset, chronic open-angle glaucoma (COAG) diagnosed after the age of 40 years;
2. the rarer juvenile open-angle glaucoma (JOAG), which is diagnosed between the age of 3 years and early adulthood.

Recently, the gene coding for the trabecular meshwork-induced glucocorticoid response protein (TIGR), located in chromosome 1 (1q23–25), was found mutated in patients affected by POAG. In this work we describe the clinical and molecular genetic features of several Italian families affected by autosomal dominant POAG, collected in various regions of Italy.

Key words: eye protein/genetics – primary open-angle glaucoma (POAG) – trabecular meshwork-induced glucocorticoid response protein (TIGR) gene – haplotypes – mutation.

Introduction

Primary open-angle glaucoma (POAG) is one of the most prevalent causes of irreversible blindness in developed countries, more than 13.5 million people being affected. It produces characteristic optic disk cupping and visual field alterations. Intraocular pressure (IOP) is often a major risk factor (Quigley 1993). The most common form of the disorder is Chronic Open-Angle Glaucoma (COAG), which accounts for almost 50% of all cases of glaucoma. Among Caucasians, this form affects about 2% of the population over 45 years of age (Wilson & Martone 1996).

Classification is traditionally based on age of onset: juvenile glaucoma (JOAG) may appear between the age of 3 and 30 years, adult glaucoma rarely starts before the age of 40 years and is the most prevalent type (Johnson et al. 1996). A number of ocular conditions are also associated with glaucoma with variable expression and degree of penetrance. There is evidence that a family history of this disease is a major risk factor for the development of it. Adult-onset POAG is usually recognized as a complex non-Mendelian disorder with a few families segregating the disease as an autosomal dominant or autosomal recessive trait (Johnson et al. 1996).

Three loci have so far been associated with different forms of glaucoma: GLC1A (1q21–23) (Morrisette et al. 1995) for the juvenile form; GLC1B (2q13) (Stoilova et al. 1996) and GLC1C (3q21–24) (Wirtz et al. 1997) for the adult form. In 1997, Stone and co-workers (Stone et al. 1997) identified the gene associated with the GLC1A locus. This gene encodes for the trabecular meshwork-induced glucocorticoid response protein (TIGR) (Polansky et al. 1997). Preliminary studies show that only 4% of patients studied show linkage with the GLC1A locus.

Materials and methods

We studied 35 autosomal dominant (ad) juvenile and adult POAG families from distinct geographical areas of Italy (Sardinia, the Veneto, Piedmont, Emilia-Romagna, Lombardy and Apulia), collecting 165 patients, who were classified according to the following clinical criteria:

1. Chronic Primary Open-Angle Glaucoma with high pressure.
   (a) IOP>21 mmHg;
   (b) onset age >40 years.
2. Chronic Primary Open-Angle Glaucoma with low pressure.
   (a) IOP <21 mmHg;
   (b) onset age >40 years.
3. Juvenile Primary Open-Angle Glaucoma.
   (a) IOP >21 mmHg;
   (b) onset age <40 years.

Blood samples were collected from affected and unaffected members of the families. Genomic DNA was extracted by standard procedures. Linkage analysis was carried out by using several markers closely linked to the GLC1A locus (D1S194, D1S196, D1S2851, D1S210, D1S2815, D1S218), to the GLC1B locus (D2S161, D2S373, D2S2264, D2S176, D2S1890) and to the GLC1C locus (D3S3637, D3S1535, D3S1569, D3S1744). Direct sequencing of amplified DNA was performed by cycle sequencing.

Results and discussion

Of the 35 families screened, only four POAG families from a single small area of Apulia showed association with the GLC1A locus. The clinical phenotype of these patients is a severe form of POAG. Out of 20 individuals, 16 were affected by glaucoma at a very early age. The average IOP was between 32.3 and 40.6 mmHg. All patients showed an open and normal appearing angle of the anterior chamber but had glaucomatous optic disk damage in one or both eyes. Sixteen patients had had filtration surgery. All the affected members of the four families share the same haplotype at markers D1S210, D1S2815 and D1S2790, clearly suggesting a founder effect. Direct sequencing allowed the identification of a novel mutation in the third exon of the TIGR gene (Angius et al. in press) (1177-GACA→T). This mutation is present in all affected members, including two still asymptomatic young people. A fifth family from the same area, examined later, presented the same mutation at the third exon of the TIGR gene.

We screened affected members of the

other 31 families from other Italian regions (Sardinia, Piedmont, Emilia-Romagna, Lombardy) using markers closely linked to the GLC1B and the GLC1C loci associated with autosomal dominant chronic forms generally less severe than those found associated with the GLC1A locus. No association was found for any of the families analyzed.

In addition, we studied a large family from a village in the Verona district (Veneto) with affected members in three generations.

Every affected subject suffers the most common and mild adult-onset chronic open-angle glaucoma: abnormal appearance of the optic nerve head, loss of visual field and chronic, painless progression with onset after age 50. The condition is associated with moderate IOP elevation. Medical treatment usually gives a satisfactory outcome. The painless progression of the disease is the cause of late diagnosis and this complicates the study of this type of POAG. Analysis of this pedigree clearly suggests an autosomal dominant mode of inheritance with incomplete penetrance.

We have excluded for this family association with the TIGR gene and with the GLC1B and the GLC1C loci. We carried out a genome-wide search for the identification of a new locus or new loci responsible for the disease and are currently making efforts to confirm if one or more loci are responsible for the disease in this family (unpublished data).

Our results are compatible with numerous other genetic studies reported in the literature, which in their turn have failed to link most of the families analyzed to any of the known loci. The mutation we found in the five glaucoma families from Apulia is very important when it comes to the possibility of recognizing asymptomatic carriers and, therefore, of an early detection and therapy of glaucoma.

Considering the high frequency of this disease, the high variability of its clinical manifestations and the results of genetic linkage studies so far, we can expect a large number of loci to be involved in the aetiology of adult-onset POAG.

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The role of class I and class II HLA antigens in primary open angle glaucoma (POAG)

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Summary

Several clinical and epidemiological studies have shown the role of genetic factors in the pathogenesis of primary open angle glaucoma (POAG). In this study, 30 patients affected by this disease were tissue-typed for HLA Class I and Class II antigens. The results pointed up an increased incidence of some antigens and, particularly, a statistically significant association with DQ1 and DR11 alleles.

Key words: glaucoma – HLA typing – genetic factors.

Introduction

The role of hereditary and constitutional factors in the pathogenesis of primary open angle glaucoma (POAG) has been the object of many clincal and epidemiological investigations (Perkins 1974; Armaly 1967; Armaly 1967; Armaly 1967).

It has been hypothesized that certain specific features of the galuacomatous eye, such as the intraocular pressure, the cup/disc ratio and the susceptibility to corticosteroids might be family traits (Armaly 1967; 1967; 1967).

The literature data agree that a predisposition for the disease cannot be fitted into a classical Mendelian schema but there would seem a correlation exists with a multifactorial and/or a polygenic type of transmission difficult to schematize.

There have also been many studies attempting to correlate the glaucomatous disease with an increased incidence of specific alleles of the Major System of Histocompatibility.

An investigation conducted by Gil-Carrasco and co-workers (Gil-Carrasco et al. 1994)) on a Mexican population found a correlation between the allele DR3 and POAG. The authors also found an increased incidence of the alleles A9, B21 and B27.