PATTERNS OF PROGRESSION IN DIABETIC RETINOPATHY CORRELATION BETWEEN PHENOTYPES AND GENOTYPES

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PURPOSE

To establish a correlation between phenotypes of diabetic retinopathy (DR) progression (phenotypes A, B and C) and genotypes, as identified for 7 candidates genes, i.e. ALR (AKR1B1), RAGE, VEGF, ICAM-1, TNF-a, ACE, and NOS-1 in a population of type 2 diabetic patients with non-proliferative diabetic retinopathy (NPDR).

METHODS

Study Design

348 type 2 diabetic patients with NPDR were included in this study to evaluate the possible correlation between different phenotypes of DR progression identified with non-invasive methods and the different genotypes. From the 348 patients included 236 were considered to genotype analyze until now.

Phenotypes characterization (Non-Invasive Methods)

- Color Fundus Photography was performed for automatic Microaneurysm Turnover assessment (formation and disappearance rates, respectively) (RetmarkerDR, Critical Health, SA)
- Optical Coherence Tomography (Stratus OCT, Carl Zeiss Meditec Inc.) was performed to compute retinal thickness (RT) maps using proprietary software allowing to compute central macular RT values (central 500 µm and 1500 µm in diameter areas). We consider increased RT if we have an area with Increase RT ≥ 10 % or a Maximal RT Increase ≥ 5 %.

Based in the Microaneurysm Turnover and Retinal Thickness we classified the patients in 3 phenotypes of DR progression as:

- Phenotype A: MA turnover < 9 and Normal RT;
- Phenotype B: MA turnover < 9 and Increased RT;
- Phenotype C: MA turnover ≥ 9 and variable RT.

Genotype evaluation

Each patient was submitted to genetic evaluation to identify different genes from a list of candidate genes classified based on gene organization and Single Nucleotide Polymorphisms (SNPs) density, as:

- ALR (AKR1B1)
- VEGF
- TNF-a
- NOS-1
- RAGE
- ICAM-1
- ACE

Statistical Analysis

The distribution for each genotype and each allele (computed from the observed number of genotypes) was analyzed for the 3 Phenotypes using the Pearson $\chi 2$ test and the Fisher exact test when few polymorphisms are observed (less than 5). A similar analysis was conducted the CSME and non-CSME eyes.

RESULTS

236 patients (147 male and 89 female) with a mean age of 60.8±8.3 years (Min: 47; Max: 78) and a diabetes duration of 10.1±5.1 years (mean±SD).

Distribution of DR progression Phenotypes

The 236 patients analyzed were classified as:

- Phenotype A: 105 (44.5%)
- Phenotype B: 60 (25.4%)
- Phenotype C: 71 (30.1%)

CSME development

Development of CSME with need for laser photocoagulation during a 2-year follow-up period was:

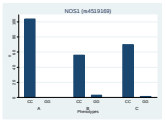
- Non-CSME: 214 eyes/patients (90.7%)
- Development of CSME: 22 eyes/patients (9.3%)

Phenotypes *vs.* Genotypes

The results with the 236 patients showed statistically significant differences:

Between the 3 phenotypes

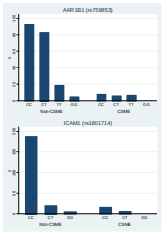
NOS1 (rs4519169) (P=0.031)	CC	GG
Phenotype A (n=105)	100%	---
Phenotype B (n=60)	94.9%	5.1%
Phenotype C (n=71)	98.6%	1.4%



Between CSME and non-CSME eyes

AKR1B1 (rs759853) (P=0.034)	CC	CT	TT	GG
Non-CSME (n=214)	46.5%	41.5%	9.5%	2.5%
CSME (n=22)	38.1%	28.6%	33.3%	---

ICAM1 (rs1801714) (P=0.044)	CC	CT	GG
Non-CSME (n=214)	88.3%	9.4%	2.3%
CSME (n=22)	72.7%	27.3%	---



CONCLUSIONS

In these results we found a statistically significant difference between the 3 phenotypes for NOS1 – rs4519169 (P=0.031) and between CSME and non-CSME eyes for AKR1B1 – rs759853 (P=0.034) and ICAM1 – rs1801714 (P=0.044). These results suggest the possibility that some genes are associated with different rates of progression of diabetic retinopathy in type 2 diabetic patients and with development of CSME, therefore opening new perspectives for the personalized management and treatment of DR.

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