Diaretinopathy database – A Gene database for diabetic retinopathy

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Abstract:
Diabetic retinopathy, is a microvascular complication of diabetes mellitus and is a major cause of adult blindness. Despite advances in diagnosis and treatment the pathogenesis of diabetic retinopathy is not well understood. Results from epidemiological studies of diabetic patients suggest that there are familial predispositions to diabetes and to diabetic retinopathy. Therefore the main purpose of this database is to help both scientists and doctors in studying the candidate genes responsible for causing diabetic retinopathy. For each candidate gene official symbol, chromosome map, number of exons, GT-AG introns, motif, polymorphic variation and 3D structure are given respectively. In addition to molecular class and function of these genes, this database also provides links to download the corresponding nucleotide and amino acid sequences in FASTA format which may be further used for computational approaches. Therefore this database will increase the understanding of the genetics underlying the development or progression of diabetic retinopathy and will have an impact on future diagnostic, prevention and intervention strategies.

Availability: The database is freely available at http: diaretinopathydatabase.com

Key Words: Diabetic Retinopathy, Genes, SORD, ACE, VEGF, AGTR1

Background:
Diabetic retinopathy, a microvascular complication of diabetes mellitus is a major cause of non-inherited blindness among adults [1]. It is the second leading cause of blindness due to retinal degeneration in the working age group, contributing to an overall 4.8 % blindness across the globe [2]. India, being the diabetic capital of the world, is feared to end up with an alarming 11.4 million type 2 diabetes mellitus individuals developing this sight threatening disease by 2025 if the present trend of 20 % type 2 diabetes mellitus population developing diabetic retinopathy were to continue [3]. Although diabetic retinopathy is a common complication of diabetes, we still know little about the underlying molecular mechanisms. Analyzing the molecular aspects that govern the development of a disease or predisposition to a disease would achieve desirable clinical outcomes by helping physicians to decide specific management of the disease depending upon the patient’s genetic and environmental profile rather than a generalized treatment as laser photocoagulation [4]. Moreover, recognizing an underling genetic susceptibility would help in counseling presymptomatic individuals to adopt preventive and control measures to delay the onset of disease. Therefore this database will help the scientists and doctors in studying the candidate genes responsible for causing diabetic retinopathy and progress faster the diagnostic treatment.

Methodology:
It is found through Literature survey and analysis that many genes play an imperative role in causing the disease. Information on those genes which play active role in diabetic
retinopathy was retrieved from NCBI (National Center for Biotechnology Information) database. The data were normalized to reduce and eliminate redundancy. The protein functional information was extracted from UniProt database which is curated manually. The structures of proteins were extracted from PDB (Protein Data Bank) which is a world-wide repository of information about the three dimensional structures of large biological molecules.

**Figure 1:** The Schema of data collection for Diaretinopathy database

**Data collection:**
Data for this novel database were collected from various literature sources such as PubMed [5], Science Direct [6], Biomed Central [7], Springer link [8], Scirus [9], Wiley journals [10] and also from specific Diabetic journals. The data is provided in alphabetical order and the records are organized to simplify the task of finding any relevant gene. The schema of data collection is given in Figure 1. The database can be accessed alphabetically either using gene name or alternative names for detailed information of the gene.

**Construction of Diaretinopathy database:**
The Diaretinopathy database is a HTML based database and is represented in table format. The home page and the gene page of this database is given as screenshot in Figure 2 and 3. The database is freely available to view and download data at http://diaretinopathydatabase.com/.

**Database features:**
Diaretinopathy database acts as complete web source providing information of 102 potential candidate genes Table 1 (see supplementary material) causing diabetic retinopathy at molecular, biochemical and at structural level. For each candidate genes the database is designed by taking 24 parameters into consideration that comprises official Symbol, alternative names, description, chromosome map showing the location, number of exons and GT-AG introns, motif, polymorphic variation, Enzyme commission (EC) number, catalytic activity, active site, cofactor, biophysicochemical properties, enzyme regulation, induction, molecular pathway, interactors, post translational modification, and 3D structure. In addition to the molecular class and function of these genes, this database also provides links to download the corresponding nucleotide and aminoacid sequences in FASTA format from NCBI and UNIPROT database respectively which may further be used for their computational approaches.

**Software:**
Microsoft windows 95/98/2000/2003/XP operating system was used in the development. HTML was used for the creation of web pages and Javascript was used for the development of database front end.

**Hardware:**
Personal computer with high speed processor with windows 95/98/2000/XP Os was used. We used 10.08 MB memory for running the database.

**Figure 2:** A Screenshot of the database “DIARETINOPATHY DATABASE” home page with links.
Figure 3: A Screenshot of the Gene page in DIARETINOAPTHY DATABASE
Utility

This is however, the first database containing information of susceptibility genes causing diabetic retinopathy. This database finds utility to the scientific community for a quick review on the genetic basis of disease and may serve as a platform for therapeutic treatments.

Future development:

The database will be updated periodically and will be linked to related resources in near future for easy accessing of information so as to ensure that users get latest information on diabetic retinopathy. Additionally, our next prospective goal is to provide drugs that are used in the treatment of diabetic retinopathy treatment.

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## Supplementary material:

### Table 1: Overview of list of genes in DIARETINOPATHY DATABASE

| Candidate Genes | Location   | Function                                                                 |
|-----------------|------------|--------------------------------------------------------------------------|
| ACE             | 17q23.3    | Metallopeptidase activity                                                |
| ADIPOQ          | 3q27       | Angiogenesis                                                             |
| AGER            | 6p21.3     | Inflammation                                                             |
| AGT             | 1q42.2     | Vasoconstrictor                                                          |
| AGTR1           | 3q24       | Transducer                                                               |
| AKR1B1          | 7q35       | Catalytic activity                                                       |
| AKR1B10         | 7q33       | Detoxification of reactive aldehydes                                      |
| AKT3            | 1q44       | Cell survival                                                            |
| ANGPT2          | 8p23.1     | Antagonist                                                               |
| APLN            | Xq25       | Homeostasis                                                              |
| APLNR           | 11q12      | Transducer                                                               |
| APOA1           | 11q23-q24  | Cofactor                                                                 |
| AGHGAP22        | 10q11.22   | angiogenesis,                                                            |
| B4GALT2         | 1p34-p33   | Galactosyltransferase activity                                           |
| BMP4            | 14q22-q23  | Cartilage and bone formation                                             |
| CCDC68          | 8q21       | Unknown                                                                  |
| CCL2            | 17q11.2-q12| Chemotactic factor                                                       |
| CCNL1           | 3q25.31    | Transcription regulator                                                  |
| CORT            | 1p36.22    | Neuropeptide                                                             |
| CREB5           | 7p15.1     | Activates transcription                                                  |
| CRP             | 1q21-q23   | Host defense                                                             |
| CTGF            | 6q23.1     | Chondrocyte proliferation and differentiation,                           |
| EDN1            | 6p24.1     | Vasoconstrictor                                                          |
| ENG             | 9q33-q34.1 | Binding of endothelial cells to integrins                                |
| ENO2            | 12p13      | Catalytic activity                                                       |
| EPO             | 7q22       | Erythroid differentiation                                                |
| FABP2           | 4q28-q31   | Lipid sensor                                                             |
| FGF2            | 4q26       | Neurotrophic factor                                                      |
| GDNF            | 5p13.1-p12 | Growth factor                                                            |
| GRAMD3          | 5q23.2     | Unknown                                                                  |
| GSTM1           | 1p31.3     | Detoxification                                                           |
| H1F1A           | 14q23.2    | Embryonic vascularization                                                |
| HP              | 16q22.2    |                                                                         |
| HS6ST3          | 13q32.1    | Catalytic activity                                                       |
| ICAM1           | 19p13.3-p13| Mammalian growth and development                                         |
| IGF1            | 12q23.2    |                                                                         |
| IGSF21          | 1p36.13    | Unknown                                                                  |
| IL6             | 7p21       | Immunoregulatory function                                                |
| INSR            | 19p13.3-p13| Tyrosine-protein kinase activity.                                        |
| IRF8            | 16q24.1    | Transcription factor                                                    |
| ITGA2           | 5q11.2     |                                                                         |
| KCNK1           | 1q42-q43   | Potassium rectifier channel                                              |
| KIAA0825        | 5q15       | Unknown                                                                  |
| KIAA1804        | 1q42       | Unknown                                                                  |
| KIT             | 4q11-q12   | Mast cell growth factor                                                  |
| KITLG           | 12q22      | Mediates cell-cell adhesion                                              |
| KLLHDC7A        | 1p36.13    | Cytoskeletal associated protein                                           |
| LEKR1           | 3q25.31    | Unknown                                                                  |
| LIPG            | 18q21.1    | Binds heparin                                                            |
| MAPK3           | 16p11.2    | Regulation of postmitotic functions                                       |
| MME             | 3q25.1-q25.2| Hydrolase activity                                                       |
| MMP2            | 16q13-q21  | Cell proliferation                                                       |
| MMP9            | 20q11.2-q13.1| Angiogenesis                                                           |
| MPRIP           | 17p11.2    | Cytoskeleton                                                             |
| MRPS15          | 1p34.3     | Ribonucleoprotein                                                        |
| MTHFR           | 1p36.3     | Catalytic activity                                                       |
| Gene   | Chromosome   | Function                                                                 |
|--------|--------------|--------------------------------------------------------------------------|
| MYSM1  | 1p32.1       | Chromatin regulator                                                      |
| MYT1L  | 2p25.3       | CNS developmental protein                                                |
| NFkB1  | 4q24         | Pleiotropic transcription factor                                          |
| NOS3   | 7q36         | Reactive free radical                                                    |
| ODZ2   | 5q34         | Transcription regulator activity                                          |
| OSCP1  | 1p34.3       | Involved in drug clearance in the placenta                               |
| PGF    | 14q24.3      | Mitogen growth factor                                                    |
| PLXDC1 | 17q21.1      | Endothelial cell capillary morphogenesis                                 |
| PLXDC2 | 10p12.31     | Tumor angiogenesis                                                       |
| PON1   | 10p12.31     | Protect against development of atherosclerosis                           |
| POSTN  | 13q13.3      | Cell adhesion                                                            |
| PPARG  | 3p25         | Key regulator of adipocyte differentiation                                |
| PRKCB  | 16p11.2      | Chromatin regulator                                                      |
| PRKCD  | 3p21.31      | Tumor promoter                                                           |
| PRL    | 6p22.2-p21.3 | Promotes lactation                                                       |
| PTGS2  | 1q25.2-q25.3 | Inflammation                                                             |
| RBF0X1 | 16p13.3      |                                                                         |
| RBP4   | 10q23-q24    | Cargo protein                                                            |
| ROBO4  | 11q24.2      | Developmental protein                                                    |
| ROCK2  | 2p24         | Centrosome duplication                                                   |
| SELE   | 1q22-q25     | Capillary morphogenesis                                                  |
| SELL   | 1q23-q25     | Cell adhesion                                                            |
| SERPINE1| 7q21.3-q22   | 'Bait' for tissue urokinase                                               |
| SERPINF1| 17p13.3     | Inhibitor of angiogenesis                                                |
| SOD1   | 21q22.1; 21q22.11 | Free radical                                                        |
| SOD2   | 6q25.3       | Free radical                                                             |
| SORD   | 15q15.3      | Polyol pathway                                                           |
| SP1    | 12q13.1      | Transcription factor                                                     |
| SPARC  | 5q31.3-q32   | Inhibits cell-cycle progression                                           |
| SST    | 3q28         | Peptide hormone                                                          |
| SUMO4  | 6q25         | Ubiquitin-specific protease activity                                     |
| TAB2   | 6q25.1       | Phosphorylation                                                          |
| TCF4   | 18q21.1      | Transcription factor                                                     |
| TIMP3  | 22q12.1-q13.2| Catalytic zinc cofactor                                                  |
|        | 22q12.3      |                                                                         |
| TLR4   | 9q33.1       | Receptor activity                                                        |
| TNC    | 9q33         | Cell adhesion                                                            |
| TNF    | 6p21.3       | Cell proliferation                                                       |
| TNFRSF13B| 17p11.2    | Humoral immunity                                                         |
| TNFSF4 | 1q25         | Cytokine production                                                      |
| VASH1  | 14q24.3      | Angiogenesis inhibitor                                                   |
| VCAM1  | 1p21.2       | Cell-cell recognition                                                    |
| VDR    | 12q13.11     | Translation regulator                                                    |
| VEGFA  | 6p12         | Vascuogenesis                                                            |
| VEPH1  | 3q24-q25     | Unknown                                                                  |
| VSTM2B | 19q12        | Unknown                                                                  |
| ZNF238 | 1q44-pter    | Transcription factor                                                     |