**Diabetic Retinopathy Detection**

1. **GENE SYMBOL:** APOE

**GENE NAME:** Apolipoprotein E **PMID:** [**11910554**](http://www.ncbi.nlm.nih.gov/pubmed/11910554)

The APOE gene is mapped to chromosome 19 in a cluster with APOC1 and APOC2. Studies have concluded that **epsilon4 allele of the APOE gene is a potential risk factor** for the severity of retinal hard exudates and visual loss in type 2 diabetic Mexican patients. The higher frequency of visual impairment in epsilon-4 carriers makes it a significant indicator for diagnosing Diabetic Retinopathy.

**QUESTION:**

1. Are you a carrier of epsilon-4allele for this gene? (Yes =0.5; No=0)

1.1 Do you belong to the Mexican population? (Yes =0.5; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on Mexican patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR.

1. **GENE SYMBOL:** ALDH2

**GENE NAME:** Aldehyde dehydrogenase 2 family **PMID:** [**24028448**](http://www.ncbi.nlm.nih.gov/pubmed/24028448)

 Aldehyde dehydrogenase is the second enzyme of the major oxidative pathway of alcohol metabolism. Mitochondrial aldehyde dehydrogenase 2 (ALDH2) detoxifies reactive aldehydes in the micro- and macrovasculature. Studies and evidences indicate that **The ALDH2\*2 allele carriers had a significantly higher incidence of DR than the non-carriers**. The incidence of DR was significantly **higher in the drinkers** with the ALDH2\*2 allele than in those with the ALDH2\*1/\*1 genotype.

**QUESTIONS:**

1. Are you a carrier of ALDH2\*2 allele? (Yes-1, No-0)

1.1. Do you belong to the Japanese population? (Yes-1, No-0)

1.2. Are you regular drinker/consumer of alcohol? (Yes-1, No-0)

**SCORE ALLOTMENT AND LOGIC:**

The score will be calculated as the sum total of all three, provided first question is true.

* **Score 3:** If the patient answers ‘Yes’ to all the three questions,he/she is at the highest risk of having Diabetic Retinopathy. Hence a score of 3.
* **Score 2:**

**1 is True, either of 1.1 or 1.2 is false**

Since the original studies were conducted on Japanese patients, patients with different ethnicity might not be at the same risk level. Similarly, drinkers with the risk allele are at a higher risk.

* **Score 1:**

**1 is True, both 1.1 or 1.2 are false**

The patient with both other conditions being false, is at a much lower risk for DR. Hence a score of 1 is assigned.

* **Score 0: 1 is False.**  Negligible risk for Diabetic Retinopathy in this case.

1. **GENE SYMBOL:** API5

**GENE NAME:** Apoptosis Inhibitor 5 **PMID:** [**25819896**](http://www.ncbi.nlm.nih.gov/pubmed/25819896)

This gene encodes an apoptosis inhibitory protein whose expression prevents apoptosis after growth factor deprivation. Studies have identified several single-nucleotide polymorphisms (SNPs) in this gene with modest effects on diabetic retinopathy. It was determined that **rs899036 near API5 is associated with severe diabetic retinopathy.**

**QUESTION:**

1. Is rs899036 present near API5 as examined? (Yes =1; No=0)

1.1 Do you belong to the Chinese population? (Yes =1; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 2:** If both 1 and 1.1 are True, the patient confers the highest risk, and that too for severe diabetic retinopathy. Hence a score of 2 is given in this case.
* **Score 1:**  If 1.1 is False. The study was conducted on Chinese patients; hence a different ethnicity might not be at the same risk. Therefore, a score of 1.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR.

1. **GENE SYMBOL:** ADM

**GENE NAME:** adrenomedullin  
**PMID:** [**17557032**](http://www.ncbi.nlm.nih.gov/pubmed/17557032)

The protein encoded by this gene is a preprohormone which is cleaved to form two biologically active peptides, one of which is adrenomedullin (AM). Evidences suggest that **Type 2 diabetic patients with retinopathy have significantly greater AM levels** than those without DR or not suffering from T2DM. Research findings indicate that circulating AM is increased in type 2 diabetic patients and that increase correlates with poor glucose metabolic control and presence of retinopathy.

**QUESTIONS**

1. Have AM levels reported to be significantly greater than normal? (Yes=1; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If condition 1 is True, patient is reasonably susceptible to diabetic retinopathy. Hence a score of 1 is assigned in this case.
* **Score 0:**  If the condition is false, the patient suffers negligible risk. Henec a score of 0 Is assigned in this case.

1. **GENE SYMBOL:** ACE

**GENE NAME:** Angiotensin Converting Enzyme **PMID:** [**2157294**](http://www.ncbi.nlm.nih.gov/pubmed/2157294)

This gene encodes an enzyme involved in catalyzing the conversion of angiotensin I into a physiologically active peptide angiotensin II.

Studies conducted indicate that **serum levels of ACE gene were found to be significantly elevated from normal** (control subjects) in case of people suffering from diabetes, with difference being more pronounced in case of patients suffering from background retinopathy and proliferative retinopathy.

Hence a reported increase in ACE serum levels can serve as an indicator for detection.

Normal Serum levels as reported for control subjects: 250.5 U/L +/-85.5

**QUESTION:**

1. Enter the serum levels of ACE as reported on eye examination.

**SCORE ALLOTMENT AND LOGIC:**

* **Score 0:** If the serum levels lie lower than 243 U/L, the patient has almost negligible chance of having diabetic retinopathy. Hence a score of 0 is assigned in this case.
* **Score 0.5:** If the serum levels lie in the range 243-336 U/L, the patient has a reasonable chance of having diabetic retinopathy. Hence a score of 0.5 is assigned in this case.
* **Score 1:** If the serum levels exceed 336 U/L, the patient has a very high risk of developing Diabetic Retinopathy. Hence a score of 1 is assigned in this case.

1. **GENE SYMBOL:** AKR1B1

**GENE NAME:** Aldo-keto reductase family 1, member B1 (aldose reductase) **PMID:** **19587357**

This gene encodes a member of the aldo/keto reductase superfamily, which catalyzes the reduction of the aldehyde form of glucose, and is thereby implicated in the development of diabetic complications by catalyzing the reduction of glucose to sorbitol. Variations within the AKR1B1 gene are highly significantly associated with diabetic retinopathy development irrespective of ethnicity. The aldose reductase (AKR1B1) gene was found to have the largest number of polymorphisms significantly associated with diabetic retinopathy. **The z-2 microsatellite was found to confer risk in type 2 diabetes and z+2 to confer protection.**

**QUESTION:**

1. Is z-2 microsatellite present for this particular gene? (Yes =1; No=0)
2. Is z+2 microsatellite present for this particular gene? (Yes = -1, No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** Only 1 is True. In this case the patient has the risk allele, which makes it susceptible to DR. Hence a score of 1.
* **Score 0:** Both 1 and 2 are True; or both of them are false. If both the risk allele and protective allele are present; or none of them is present. In this case it can’t be definitely said that the patient is at a risk.
* **Score -1:** Only 2 is True. In this case the patient has the protective allele. Hence it has additional advantage, therefore a score of -1 is assigned.

1. **GENE SYMBOL:** ARHGAP22

**GENE NAME:** Rho GTPase activating protein 22 **PMID:** [**28544509**](http://www.ncbi.nlm.nih.gov/pubmed/28544509)

This gene encodes a member of the GTPase activating protein family, and the encoded protein is insulin-responsive. Research conducted on Han Chinese Population indicated that **two susceptibility SNPs in ARHGAP22 were found** to be associated with an increased risk of DR-rs10491034 and rs3844492.

**QUESTION:**

1. Are these SNP's in ARHGAP22 reported - rs10491034 or rs3844492?

1.1 Do you belong to the Han Chinese population? (Yes =0.5; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on Han Chinese patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR.

1. **GENE SYMBOL:** C5

**GENE NAME:** complement component 5 **PMID:** [**26934706**](https://pubmed.ncbi.nlm.nih.gov/26934706/)

This gene encodes a component of the complement system, a part of the inte immune system that plays an important role in inflammation, host homeostasis, and host defence against pathogens. The association of C5 SNPs with proliferative diabetic retinopathy (PDR) of type 2 diabetes (T2D) was investigated, and it was reported that **C5 rs2269067 GG genotype confers risk for PDR of T2D in Chinese Han population** and is associated with an elevated C5 mRNA expression and an increased IL-6 production.

**QUESTIONS**

1. Are you a carrier of C5 rs2269067 GG genotype? (Yes =0.5; No=0)

1.1 Do you belong to the Han Chinese population? (Yes =0.5; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on Han Chinese patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR.

1. **GENE SYMBOL:** CDKAL1

**GENE NAME:** CDK5 regulatory subunit associated protein 1-like 1 **PMID:** [**28821857**](http://www.ncbi.nlm.nih.gov/pubmed/28821857)

The protein encoded by this gene is a member of the methylthiotransferase family. Studies concluded that **rs7756992** was one of the most commonly reported SNPs in CDKAL1, with the **major G allele conferring a higher risk** while the minor A allele conferred a lower risk. The study was conducted on Chinese patients.

**QUESTIONS**

1. Are you a carrier of the major G allele for CDKAL1 rs7756992? (Yes =0.5; No=0)

1.1 Do you belong to the Chinese population? (Yes =0.5; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on Chinese patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR.

1. **GENE SYMBOL:** CHN2

**GENE NAME:** chimerin 2  
**PMID:** [**21911749**](http://www.ncbi.nlm.nih.gov/pubmed/21911749)

This gene encodes a guanosine triphosphate (GTP)-metabolizing protein, activity of which is important in cell proliferation and migration. Studies aimed at finding association of SNP’s from this gene found **CPVL/CHN2 rs39059 genetic variant to be associated with diabetic retinopathy in the Chinese type 2 diabetic patients**. The rs39059 G allele was found to be frequent in DR patients, with the frequency being higher in those suffering from severe diabetic retinopathy.

**QUESTIONS**

1. Are you a carrier of CHN2 rs39059 variant? (Yes =0.5; No=0)

1.1 Do you belong to the Chinese population? (Yes =0.5; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on Chinese patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR.

1. **GENE SYMBOL:** CNR1

**GENE NAME:** canbinoid receptor 1  
**PMID:** [**24075694**](http://www.ncbi.nlm.nih.gov/pubmed/24075694)

This gene encodes one of two canbinoid receptors, found to be involved in the canbinoid-induced CNS effects (including alterations in mood and cognition). Studies on association of polymorphism in CNR1 gene in type 2 diabetes and its complications revealed that **The A allele carrier genotype was present in 50% of patients with DR** versus 35% of no DR patients. Hence the presence of A allele for this genetic polymorphism can prove to be a significant indicator for Diabetic Retinopathy.

**QUESTIONS**

1. Are you carrier of the A allele for CNR1 G1359A polymorphism? (Yes =1; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** Since A allele is the risk allele for this polymorphism, confirmation of its presence confers the patient with sufficient risk for DR. Hence a score of 1 is assigned in this case.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR.

1. **GENE SYMBOL:** CYP2C19

**GENE NAME:** cytochrome P450 family 2 subfamily C member 19  
**PMID:** [**24113215**](http://www.ncbi.nlm.nih.gov/pubmed/24113215)

This gene encodes a member of the cytochrome P450 superfamily of enzymes. Studies investigated the association between CYP2C19 polymorphisms and an increased risk of diabetic retinopathy (DR). **The CYP2C19 poor metabolizer genotype was found to be an independent risk factor for DR only in women** when patients were stratified by sex.

**QUESTIONS**

1. Are you carrier of The CYP2C19 poor metabolizer genotype?

2. Are you a woman?

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 2 are True. This is because the risk factor (CYP2C19) was only found to be effective in women as per the evidences, and both conditions being satisfied confers the patient with high susceptibility.
* **Score 0:**  If any of the conditions is false. In this case the patients does not suffer any risk for diabetic retinopathy.

1. **GENE SYMBOL:** DPP4

**GENE NAME:** dipeptidyl-peptidase 4  
**PMID:** [**27816666**](http://www.ncbi.nlm.nih.gov/pubmed/27816666)

The protein encoded by this gene is identical to adenosine deaminase complexing protein-2, and to the T-cell activation antigen CD26.Research findings indicated that serum LECT2 level is negatively associated with the presence of DR and suggest that **low circulating LECT2 level is a risk factor for DR**.

**QUESTIONS**

1. Have serum LECT2 levels been lower than normal? (Yes =1; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If 1 is True. This is because in this case, as per the evidences, the patient suffers from reasonable risk for having diabetic retinopathy.
* **Score 0:**  If any of the conditions is false. In this case the patients does not suffer any risk for diabetic retinopathy.

1. **GENE SYMBOL:** XRCC1

**PMID:** [**24621175**](http://www.ncbi.nlm.nih.gov/pubmed/24621175)

The protein encoded by this gene is involved in the efficient repair of D single-strand breaks formed by exposure to ionizing radiation and alkylating agents. Research aimed at exploring the association between DR and polymorphisms in oxidative stress-related genes, revealed that the Arg399Gln polymorphism contributed an elevated to risk for DR in South-Indian T2DM individuals. **The presence of 399Gln allele was associated with an enhanced risk for DR in South Indian T2DM subjects.**

**QUESTIONS**

1. Are you a carrier of 399Gln allele for this gene? (Yes =0.5; No=0)

1.1 Do you belong to the South Indian population? (Yes =0.5; No=0)

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on South Indian patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR

1. **GENE SYMBOL:** TNFRSF11B

**GENE SYMBOL:** tumor necrosis factor receptor superfamily member 11b

**PMID:** [**24228244**](http://www.ncbi.nlm.nih.gov/pubmed/24228244)

The protein encoded by this gene is a member of the TNF-receptor superfamily. Recent studies indicate that this gene acts as an important regulatory molecule in the vasculature. Evidences suggest that the carriers of **the CC genotype (rs2073618) have a 2.2 higher risk for diabetic retinopathy** than those with either the CG genotype or the GG genotype. Hence presence of CC genotype is a good indicator to detect DR.

**QUESTIONS**

1. Are you a carrier of CC Genotype (rs2073618) for this gene?

1.1 Do you belong to the Slovenian population?

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on Slovenian patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR

1. **GENE SYMBOL:**

**GENE SYMBOL:** glutathione S-transferase theta 1

**PMID:** [**24228244**](http://www.ncbi.nlm.nih.gov/pubmed/24228244)

The protein encoded by this gene is a member of a superfamily of proteins that catalyze the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds. Studies have been conducted on Caucasian patients to figure out the association genetic polymorphisms: polymorphic deletions of glutathione S-transferases with diabetic retinopathy. **It was concluded that individuals homozygous for the deletion of GSTT1 are at an ≈ 2-fold-greater risk of DR.**

**QUESTIONS**

1. Are you homozygous for the deletion of GSTT1?

1.1 Do you belong to the Caucasian population?

**SCORE ALLOTMENT AND LOGIC:**

* **Score 1:** If both 1 and 1.1 are True, the patient confers the highest risk for DR. Hence a score of 1 is given in this case.
* **Score 0.5:**  If 1.1 is False. The study was conducted on Caucasian patients originally; hence a different ethnicity might not be at the same risk. Therefore, a score of 0.5.
* **Score 0:**  If First condition is false. In this case the patients suffers negligible risk for DR