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5.8 IFN-γ +874 A>T POLYMORPHISM

Exposure to UV light is the major risk factor in the development of age-related cataract (ARC). UV filters produced during tryptophan catabolism maintain the transparency of the lens and protect lens from photo damage. Indoleamine 2,3-dioxygenase (IDO), the first rate-limiting enzyme in the tryptophan catabolism, is up regulated by interferon-gamma (IFN-γ) which harbors single nucleotide polymorphisms (SNPs; A>T) and CA repeat (Pravica et al, 1999; Rossouw et al, 2003). The T allele of SNP at +874 position of the IFN-γ is known to be associated with the up regulation of IDO than the allele A (Raitala et al, 2005). Hence, in the present study it was attempted to assess the contribution of IFN-γ+874 A>T polymorphism in the development of different types of cataracts. DNA isolated from a total of 680 cataract cases [199 nuclear (NC), 175 cortical (CC), 174 posterior sub capsular (PSC), and 132 mixed type (MT)] and 210 healthy, normal individuals were genotyped for IFN-γ +874(A>T) polymorphism by using ARMS PCR technique (Figure-5.26).

![Image of genotypes of IFN-γ +874 A>T polymorphism](image)

**Figure-5.26:** Genotypes of IFN-γ +874 A>T polymorphism studied by ARMS-PCR analysis.

5.8.1 Genotype distribution of IFN-γ +874 A>T polymorphism

The genotype distribution of +874 A>T polymorphism in general did not differ significantly between the patients and controls. Considering different types of cataracts, the genotype distribution of +874 A>T polymorphism in cases of NC was more or less similar
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to that found in the controls, while the frequency of AA genotype was higher in patients of CC (44.6%) and PSC (40.8%) with corresponding decrease in the frequency of TT (CC: 13.1% and PSC: 13.2%) when compared with controls (AA: 38.1% and TT: 17.1%). In cases with PSC, the frequency of AT (46.0%) genotype was also found to be higher when compared with controls (44.8%). In MT type, the frequency of AT (48.5%) and TT (19.7%) was higher and that of AA (31.8%) lesser when compared with controls (AT: 44.8%; TT: 17.1%, and AA: 38.1%). The allele frequencies, in general, in all types of cataracts and controls remained in Hardy–Weinberg equilibrium (Table-15).

Considering the gender wise distribution of +874 A>T polymorphism, no statistically significant difference was found between male patients and male controls. But female patients in total (41.5%) and in different types of cataracts [NC (42.3%); CC (49.4%) and PSC (43.1%)] showed a significant increase in the frequency of AA genotype with corresponding decrease in the frequency of TT (Total: 16.5%; CC: 13.5% and PSC: 9.8%) genotype when compared with female controls (AA: 29.5%; TT: 24.4%). Between the cataract types, females with NC showed high frequency of TT (22.1%) genotype compared with females of CC (13.5%) and PSC (9.8%) types. Allele frequencies in female patients of different types of cataracts and female controls remained in Hardy–Weinberg equilibrium except for NC and total female cases. Genotype distribution of IFN-γ +874 A>T among male smokers and male alcoholics are given in Table-15.

The OR estimates did not show any significant results in the distribution of +874 A>T polymorphism in cataract patients in general, and when each type was compared with the controls. However, female cataract patients with AA genotype showed 2 fold risk for developing ARCs (AA/TT: OR=2.07; 95% CI=1.01–4.29; p=0.03). Risk estimates under dominant model showed significant risk for AA genotype at 5% level (OR=1.69; 95% CI=0.97–2.97; p=0.05). Observation of allele frequencies also revealed one and half times risk for female cases with allele ‘A’ (OR=1.50; 95% CI=1.04–2.15; p=0.02; Table-16).

Considering different types of cataracts there was also 2 to 3 folds increase in the risk for developing CC (AA/AT: OR=2.1, 95% CI=1.1–4.4; p=0.03; AA/TT: OR=3.0, 95%
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CI=1.1–8.1; \( p=0.01 \) and PSC (AA/TT: OR=3.6, 95% CI=1.3–10.1; \( p=0.005 \)) for female patients with AA genotype. Further computations for risk estimates made under dominant and recessive model showed a significantly high risk for AA females with CC at 1% (OR=2.3, 95% CI=1.2–4.6; \( P=0.009 \)); with PSC at 6% (OR=1.8, 95% CI=0.9–3.5; \( P=0.06 \)); and with NC at 7% level of significance (OR=1.7, 95% CI=0.9–3.4; \( P=0.07 \)). Under recessive model, ORs showed significantly high risk for AA and AT individuals for developing PSC (OR=2.9, 95% CI=1.2–7.4; \( P=0.008 \)), while for other cataracts the results were insignificant. Female with TT genotype when compared with other two genotypes (AA+AT) among cases and controls showed significant protection for PSC cataract (OR=0.33, 95% CI=0.13-0.83; \( P=0.008 \)). Considering allele frequencies, similar results were obtained showing nearly 2 folds increased risk for A allele in female patients with CC (OR=1.9, 95% CI=1.2–3.1; \( P=0.004 \)) and PSC (OR=1.8, 95% CI=1.1–2.8; \( P=0.004 \); Table-17).

Patients with the habits like smoking, and alcohol consumption didn’t show association with the \( IFN^-\gamma +874 A>T \) polymorphism for developing ARCs.

The present results indicated that female patients with AA genotype showed risk for developing ARCs specially in cases with CC, PSC and NC, whereas TT genotype offered protection for PSC.

The two polymorphisms, 12 CA repeat and+874 A>T of \( IFN^-\gamma \), have been associated with risk for certain conditions such as acute kidney rejection, aplastic anemia, tuberculosis, symptomatic parovirus infection, and recurrent pregnancy loss (Asderakis et al, 2001; Lio et al, 2002; Kerr et al, 2003; Daher et al, 2003; López-Maderuelo et al, 2003; Rossouw et al, 2003; Dufour et al,2004). For the first time studies by Mamata et al, (2012) showed the association of \( IFN^-\gamma +874 A>T \) polymorphism with ARCs. \( IFN^-\gamma +874 A>T \) polymorphism lies within the transcription factor binding site of NF-kB, which shows an allele-specific binding pattern. NF-kB site induces \( IFN^-\gamma \) expression and the presence of T and A allele of +874 A>T polymorphisms are related to high and low \( IFN^-\gamma \) expression,
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respectively, which in turn influences the *IDO* activity proportionally. This observation was found in females without any clinical condition by Raitala et al, (2005).

Studies have confirmed that opacity of the ocular lens is caused by the elevation of free radicals in the lenticular tissue with increasing age and accumulation of noxious factors. *IDO* enzyme is also involved in $O_2^-$ radical scavenging (Taylor and Feng, 1991), thus helping in the prevention of cataract formation. Hence, the study of this enzyme and its association with genes that mediate its induction like *IFN*-γ seems pertinent to understand in more detail the mechanism of cataract formation. A high risk was observed in this study for AA genotype in female patients with CC and PSC showing significant protection for TT genotypes. Keeping in view the high induction of *IDO* gene by allele T of +874 A>T polymorphism by Raitala et al, (2005) the reduced frequency of genotype TT found in the present cases of PSC may indicate upregulation of IDO facilitating increase in the production of UV filters and also efficient scavenging of free radicals together playing a role in delaying the onset of lens opacification in females. The high risk found for allele A carriers of +874 A>T polymorphism in the CC cases of this study may be associated with low IDO activity affecting the formation of UV filters required for the maintenance of lens transparency.

The study appears to be the first of its kind to be reported with reference to ARCs. Estimation of IDO levels along with genotyping will throw more light on understanding the functional aspects of the association found.