

## Molecular Genetics of Human Cataract



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**Abstract :** Exact molecular mechanism of aging and senile cataract has not yet been fully understood. Some of the genetic defects like alteration in gene sequence, deletions, up or down regulation of genes seems to have role in cataractogenesis. Genetic variation among individuals of the same ethnic group and between different ethnic groups may react differently in different ethnic groups depending on the environmental and genetic conditions. In addition to these genetic factors biochemical changes such as oxidative stress, protein modifications, and depletion of antioxidative enzymes due to aging have also been identified causative factors in cataractogenesis.

Many of the factors mentioned above for cataractogenesis are age related. The thinness of capsule during aging has been reported, which may also be responsible for the ocular disorders. Recent studies (Gupta *et al.*, 2002, 05) have suggested that incidence of cataract in menopausal women is higher than menstruating women. The overall understanding of genetics mechanism of aging may also help in understanding and prevention of senile cataract.

**Key word :** Aging, gene regulation, hormone cycle, antioxidants.

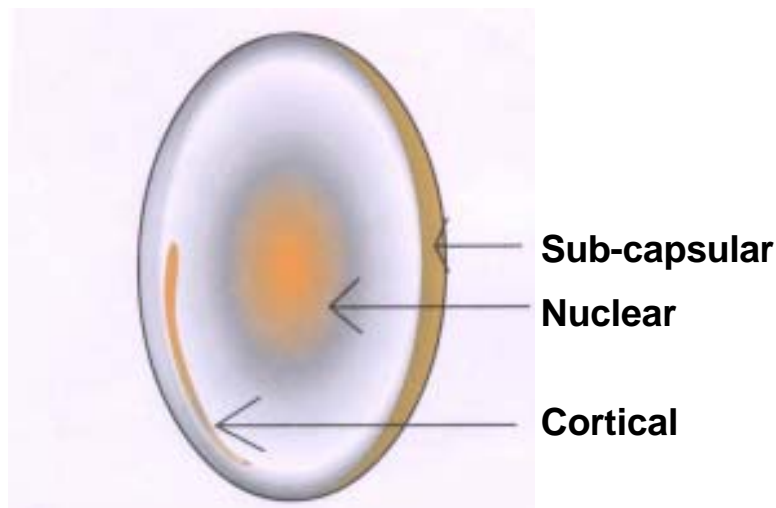
### I. Introduction

Structurally the lens consists of capsule, epithelium and fibre cells (Fig. 1). The lens epithelial cells (LEC) migrate and terminally differentiate into fibers by losing their nucleus. This terminally differentiated lens fiber cells are forced toward the core of the lens. The embryonic fiber that developed and accumulated in the center of the lens in the early embryonic stage is termed as embryonic nucleus, where as the other two layers formed after the embryonic nucleus are known as juvenile and adult nucleus. The outer most part of the lens fibers is termed as cortex and seen as a series of concentric layers (Francis *et al.*, 1999). The whole cortex and epithelium are lodged in the capsule, which is cellular in nature but allows transfer of ions and nutrients across. As no cells are shed, the lens demonstrates cells at varying states of senescence and is remarkable for its ability to preserve its specialised function of transparency throughout the life span. The opaque

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tissue in any part of the clear lens containing transparent crystallin protein in the human eye is identified as cataract. Generally cataract is considered as a multifactorial old age disease; however, it may be present in neonates or may develop at any time in the life span of an individual. Based on the position of the opacity various forms of cataracts have been identified, nevertheless progressive development of opacity covers whole lens and thus results into blindness. Therefore, the study of the lens and cataract also help us to understand the ageing process.

Earlier studies have revealed that the lens undergoes various biochemical and metabolic changes during aging, which lead to the development of cataract. The present knowledge of the effect of aging on lens and particularly on LEC and capsule is poor. Therefore, the effects of aging on LEC, cortex and capsule, all the three components of the lens system has been taken into consideration for aging effects. Finally, suitable example of role of genetics and population genetics in development of cataract is also discussed in this review.



**Fig. 1 :** Schematic drawing of the lens. The lens gradually becomes aged, denatured and opaque without any pathogenic or local causes usually it occurs on both the eyes but onset time may differ. Clinically nuclear SC is common however may be cortical and posterior sub capsular take part in fully developed SC.

## **II. Etiology of Cataract**

Etiological studies revealed that the development of senile cataract (SC) is due to several factors which includes mainly host risk factors such as age, sex, race, and genetics and environmental factors includes smoking, food, ultraviolet radiation (UV), x-ray and steroid drugs (Okano *et al.*, 2001; Katoch *et al.*, 2001). Both long wavelength (UVA, 300-400 nm) and short wave length UV (UV B, 290-320 nm) are found to be associated with SC (Hiller *et al.*, 1983; Jose and Pitts, 1985; Bochow *et al.*, 1989). It is reported that the UV assisted production of N-formyl kynurine (NFK) actively generates various reactive oxygen species (ROS) such as  $H_2O_2$ ,  $O_2^{\cdot-}$ ,  $OH^{\cdot}$ . These ROS have varied effects on lens proteins (Fecundo and Augusteyn, 1983), DNA and RNA synthesis (Kleiman *et al.*, 1990; Sidjanin *et al.*, 1996), cell division and mobility by posing severe oxidative stress. Both intracellular and extracellular oxidative stresses (Andley and Clark, 1989) generated due to ROS also play role in the development of SC (Giblin *et al.*, 1990; Spector, 1995; Spector *et al.*, 1998).

Genetic alterations such as DNA mutations, epigenetic events, up or down regulation of variety of genes in the genome (Kannabiran and Balasubramanian, 2000) also found to play role in cataractogenesis in elderly individuals (Hammond *et al.*, 2000). Recently, molecular biologists have put forth two hypotheses using animal models for the development of SC that,

1. Proteins of the lens are not folded properly and
2. DNA in fiber cells is still not eliminated.

And thus both the phenomena can hinder the pathway of light (Nishimoto *et al.*, 2003).

## **III. Molecular Genetics of Senile Cataract**

Human lens consists of different types of structural and cellular housekeeping proteins, which are framed in a highly ordered arrangement to maintain the lens transparency. The normal functioning of these structural and housekeeping proteins are controlled by the genetic components in the human genome. When the genetic components get disturbed or altered, the whole molecular architecture would be collapsed which can result in opacification of lens. Since these alterations are considered to be age-related phenomena, the normal synthesis of housekeeping proteins would be obstructed as the individual ages.

Collagen, the extracellular glycoprotein (Seland, 1974), forms major constituents of lens capsular bag whose function is to maintain the rigidity. The up or down regulation of this collagen genes are found to play a role in cataractogenesis. Recent experiments on animal models, where the disruption of gene that codes for several different types of glycoprotein result in the formation of cataract.

SPARC (secreted protein, acidic and rich in cysteine) also called osteonectin is another matricellular glycoprotein that regulates cell-cell and cell-matrix interactions, cellular proliferation and differentiation, and the expression of genes encoding extracellular matrix components. SPARC is a key protein regulates the maintenance and structural integrity of the lens capsule, normal cellular homeostasis and the permeability in the lens cells. Norose *et al.* (1998) has developed a SPARC deficient mice model by a targeted disruption of the gene in order to analyze the functional role of SPARC in early onset of opacities in the posterior cortex of the eye. Their results revealed that the inhibition of normal lens fiber cell differentiation, degeneration of fiber cells, formation of vacuole at the equator, and liquefaction of the cortex are the resultant features in SPARC null mice in the early stages of cataractogenesis. Elevated levels of SPARC mRNA and protein have been described in human cataractous lenses and are found to be associated with the process of cataractogenesis (Kantorow *et al.*, 2000). The absence of SPARC proteins alters the structural assembly of type IV collagen in the lens capsule that can also lead to cataractogenesis (Yan *et al.*, 2002).

Lens integral membrane (LIM) protein is the second most abundant protein with in the lens fiber cells. LIM protein considered to be involved in the exchange of ions and metabolites between lens fibers, epithelial cells, and extracellular space. It plays a role in the formation of intercellular channels. Pras *et al.* (2002) has reported a missense mutation in the LIM2 gene of pre-senile cataract, which is segregating in an autosomal recessive mode. This pre-senile cataract was first noticed in human being in the age between 20 and 51. Sequencing of LIM2 revealed a homozygous T→G transversion resulting in a phenylalanine-to- valine substitution at the amino acid position 105 of the protein.

Vimentin is a major component of lenticular cytoskeletal intermediate filament protein and is also an essential pre requisite for the establishment

of filament network in lens fiber cells. The over expression of vimentin in the lenses of transgenic mice interferes with normal differentiation of lens fibers which results in the impairment of cell denucleation and elongation process that leads to cataractogenesis. Normally in the mature lens fiber cells, vimentin are not expressed (Kibbelaar *et al.*, 1979). Thus the over expression of vimentin may lead to the formation of SC (Li *et al.*, 1995).

Presenilin (PS) is a protein responsible for the cleavage of amyloid beta protein (beta APP) in to beta amyloid (Abeta). The Abeta protein is found to be accumulated in most of the age related degenerative diseases. Frederikse and Zigler (1998) analyzed the expression of presenilin gene and post-translational modification of presenilin protein (PSP) in ocular lens. PS protein expression occurs in all age related degenerative diseases Authors have suggested that the expression of PS might contribute to cataractogenesis.

The elderly individuals possess a high frequency of gene coding for glutathione S-transferase (GST), which is involved in the conjugation reactions in phase 2 metabolism of xenobiotics, catalyzing reactions between glutathione and a variety of electrophilic compounds. It is known that most GST substrates are xenobiotics or products of oxidative stress, including some environmental carcinogens. Four GST isoenzyme classes have been identified;  $\alpha$ ,  $\mu$ ,  $\pi$  and  $\theta$ . The genes GSTM1 and GSTT1 code for the cytosolic enzymes GST- $\mu$  and GST- $\theta$  respectively. These two enzymes hold importance because in most of the aged individuals these two genes have been deleted. Tasa *et al.* (1996) studied the possible association between GST polymorphism and the occurrence of SC in Estonian population. In a similar way Pi *et al.* (1996) studied the relationship between GST-  $\mu$  gene mutation and SC susceptibility. The results from both these studies suggested that the GSTM1 positive phenotype and the presence of GSTP1\*A allele and the deletion of GST- $\mu$  may be a genetic risk factor for development of certain types of SC. Moreover, deletion of another isoenzyme gene GST 1 (Sekine *et at.*, 1995) and an age related partial deletion of the C- terminus sequence of the alpha-crystallin are also consider to be the risk factors in the development of SC.

Since oxidative stress contributes much to cataractogenesis, (Spector *et al.*, 1996; Reddy *et al.*, 1997; Yang *et al.*, 1998) the gene amplification of key antioxidative enzymes (super oxide dismutase, catalase, glutathione peroxidase) would provide much information about the mechanism behind cataractogenesis due to defect in antioxidative enzymes.

#### IV. Depletion of Defense System Due to Aging

With the advent of an oxygen rich atmosphere, it is necessary for organisms to develop defenses against the primary oxidative stress components. Thus, enzymes to detoxify the most prevalent oxidants were developed. Superoxide anion ( $O_2^{\cdot-}$ ) is degraded by superoxide dismutase (SOD) in a dismutation reaction yielding  $H_2O_2$  and  $O_2$ . It is interesting that nature choose to eliminate  $O_2^{\cdot-}$  by a reaction in which less reactive but potentially dangerous  $H_2O_2$  is formed. To detoxify  $H_2O_2$ , two different enzyme systems are functioning in cell. Catalase directly metabolizes  $H_2O_2$  to  $H_2O$  and  $O_2$ . It is found in all tissues and its activity is based on the concentration of  $H_2O_2$ . Glutathione peroxidase (GSHPx) takes  $H_2O_2$  to  $H_2O$ , requires GSH as a cofactor and the reaction results in its oxidation to oxidized glutathione (GSSG). This enzyme predominantly found in the cytoplasm of cell and effectively metabolizes  $H_2O_2$  even at lower concentration requires high concentrations of GSH for optimal activity. The GSSG is reduced by glutathione reductase utilizing NADPH as a cofactor and the NADPH is primarily generated by the metabolism of glucose via the hexose monophosphate shunt. Thus the ultimate reductant involved in maintaining the GSH in the reduced form is glucose.

From several studies it is concluded that the oxidative defense mechanism could not cope-up with the increased oxidative stress during the process of aging and cataractogenesis. It is because of the decreased activity of all the necessary antioxidative enzymes (Kaid Johar *et al.*, 2003).

#### V. Effects of Aging on Lens Proteins

Protein synthesis is found to be very active only in outer cuboidal epithelial cell layer. The human lens fiber cells contain majority of house keeping proteins of which 86% comprises of crystallins. Crystallins, the main cytoplasmic proteins, are heterogeneous groups of highly stable, water-soluble molecules. Crystallins are considered to be essential for the maintenance of lens transparency. Normally, every mature lens contains three types of crystallins such as  $\alpha$ ,  $\beta$ , and  $\gamma$  crystallins in the range of 40%, 30% and 25% respectively.  $\alpha$  crystallin is the largest with a molecular weight ranging from 800 to 1000 kDa, depending on the tendency of subunits to aggregate.  $\beta$  and  $\gamma$  crystallins have homologous amino acid sequences and similar structures with each other. The  $\gamma$  crystallins are the smallest of the crystallins, with a molecular weight in the range of 20 kDa. The adult lens cortex contains more of  $\beta$  crystallins whereas the lens nucleus is filled with  $\alpha$

crystallins (Bours *et al.*, 1990).

Terminally differentiated lens fiber cells are metabolically inactive and depend on epithelium to maintain properly balanced intracellular ionic conditions and redox states. A well-developed system of gap junctions and channels connecting lens epithelium and mature lens fiber cells is therefore important in preventing precipitation of cell structural proteins and cataract formation.

The process of lens opacification may be linked to an acceleration of biochemical mechanisms involved in the aging process such as unfolding, cross-linking, leaking, aggregation and autolysis of proteins. In certain circumstances like aging of cells due to oxidative stress the proteins in the lens fiber cells undergo abnormal post-translational modifications that may result in conformational changes which in turn lead to cataractogenesis. These post-translational modifications include deamination, isomerization, racemization, glycosylation, acetylation and carbomylation. Glycation is the process of addition of a glucose residue to the protein molecule. The rate of glycation in  $\alpha$  crystallin increases as a result of aging and diabetes, while it remains constant in  $\beta$  and  $\gamma$  crystallins (Van Boekel and Hoenders, 1992). Low molecular weight (LMW) proteins such as gamma crystallins are responsible for protein aggregation and insolubilization via glycation (Ramalho *et al.*, 1996). Glycosylation is another process similar to glycation. In which the monosaccharide or oligosaccharide residues are added to the protein molecule.  $\beta$ -crystallins undergoes post-translational modification including glycosylation of  $\beta$ B1, phosphorylation of  $\beta$ B2 and  $\beta$ B3. These modified proteins may be the intermediates in the degradation process.

Glutamine and asparagine residues of lens proteins can undergo age dependent nonenzymatic deamidation and converts into glutamic acid and mixture of isoaspartate, and aspartate respectively. During this process the negative charge may alter the structural properties of the protein, resulting in a greater accessibility to the action of endogenous proteases. The same structural changes may lead to the formation of high molecular weight (HMW) aggregates that may directly scatter the light (Takemoto, 1996).

The lens nucleus contains the highest amount of water-insoluble and lowest amount of water-soluble crystallins. It is reported that the level of water-soluble and total protein is decreased whereas the level of urea soluble protein is increased upon aging of lens and cataractogenesis. Another mechanism

is the conversion of soluble LMW cytoplasmic proteins to insoluble HMW aggregates and insoluble membrane protein matrices. The resulting protein changes cause abrupt fluctuations in the refractive index of the lens, scatter light rays and reduce transparency. Relative dehydration of the lens during development and aging has also been observed (Bour *et al.*, 1987) and this decrease in the water may lead to hardening of the lens. Hardness is associated with colouration and advancing age (Tabandeh *et al.*, 1994).

During the process of cataractogenesis decrease in the level of soluble and increase in the level of insoluble sulphhydryl (-SH) groups were observed. The decreased level of soluble SH is due to the formation of disulphide bonds between two proteins or between two SH group of same protein. Altered plasma membrane integrity and increased leakage could be the other reasons for loss of SH groups (Cooper *et al.*, 1986).

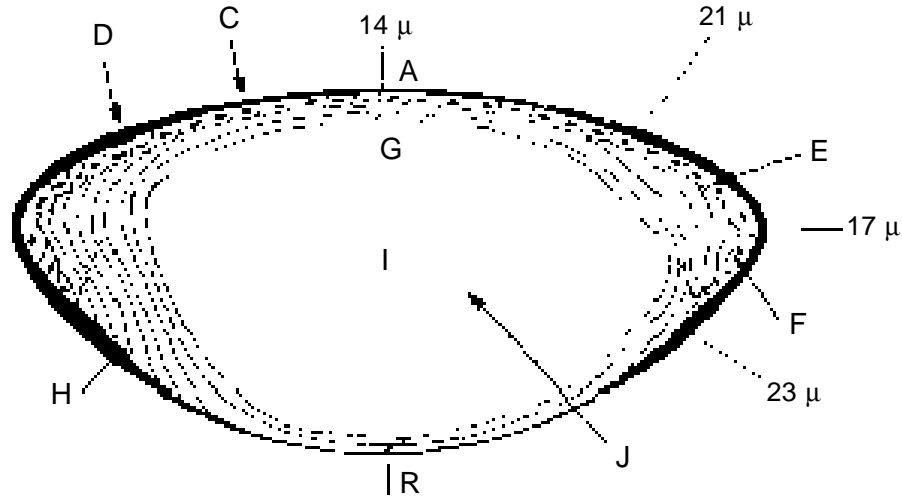
Proteins from the cortex and nucleus of the human lens were studied and changes were detected in their amino acids during SC formation. A progressive oxidation of cysteine and methionine was found in SC lens. In the nucleus of senile cataractous lens, about 90% of the cysteine and 45% of the methionine had been oxidized whereas in the cortical region the incidence of oxidation is comparatively less. This suggested that the oxidation spread from the nucleus to cortex of the cataractous lens (Truscott and Augusteyn, 1977).

In aging process, majority of cells are damaged by the process called lipid peroxidation (LPO). Since the lens epithelial and fiber cells are more primitive than other cellular types, the cells may undergo LPO constantly. From the available data, no quantitative change of free lipids, increased level of cholesterol and phospholipid and decreased level of lipoprotein been observed in the nucleus and cortex of aged and different SC (O'Brien and Little, 1969).

## **VI. Aging Affects Capsule**

The human eye lens is completely enveloped by the capsular bag and is unique in that its cells of origin are completely contained by it. The capsule is the basement membrane of the lens epithelium and is the thickest basement membrane in the body. The anterior side of the capsule is much thicker than posterior side. The capsule receives the insertion of the zonular fibers anteriorly and posteriorly at the lens periphery as well as at the lens equator.

The figure 2 below shows relative thickness of adult human lens capsule in different zones.



**Fig. 2 :** Schematic drawing of adult human lens capsule showing relative thickness of capsule in different zones. (A) Anterior pole (B) Posterior pole (C) Surrounding Capsule (D) Epithelial cells (E) Germinative zone (F) Equatorial zone (G) Cortex (H) Cortical fibers (I) Nuclear (J) Nuclear fiber

The capsule thickness increases with age anteriorly but there is little change at the posterior pole. This reflects that the epithelium, which is the secretory source of the basement membrane, is itself situated anteriorly and is involved in the remodeling of the capsule which occurs with the lens growth. Several studies together indicate that thickness of the human posterior capsule does not increase essentially after birth in contrast to thickness of the anterior capsule. The fact that the capsular lamination, which seems to be a genuine sign of relatively active capsular production, is lost in the human posterior capsule before the age of 6, where as it starts disappearing later in the anterior capsule during middle age (Seland, 1974). The capsular thickness increases up to the age of about 60 and then after become thin (Fischer, 1969).

The lens capsule, which is also called the specialized extracellular matrix, is rich in type IV collagen. It also contains type I, III, V, VI, in addition to a

number of extra cellular matrix components, which include fibronectin, laminin, SPARC, heparin sulphate proteoglycan and enactin.

The collagen fiber, one of the major components of basement membrane, is attributed to epithelium activity and increase with age (Seland, 1974). As a wound healing process, after surgery the collagen accumulation occurs in the posterior capsule due to the residual lens epithelial cell migration, which leads to capsular fibrosis and believed to be one of the reason for formation of secondary cataract. Saika *et al.* (2001) have reported the accumulation of extracellular matrix (ECM) such as collagen types I, III, IV, V and VI in human capsule during capsular opacification. Further ECM has been characterized by immunohistochemistry to localize collagen types XII and XIV (fibril associated collagen with interrupted triple helices -FACITs) in specimens of human capsular opacification and in cultured bovine lens epithelial cells (BLEC). In the absence of injury, human LEC were unstained for FACITs, but 10 days after operation LEC in healing capsules were immunoreactive. FACITs as well as other collagen types were deposited in the ECM in healing injured rat lens, in human capsular opacification and in LEC cultures. This showed that ECM components might regulate LEC behavior during postoperative healing (Saika *et al.*, 2001).

The capsule is freely permeable to water, ions and other small molecules and offers a barrier to protein molecules albumin (70 kDa) and hemoglobin (66.7 kDa). Two kinds of thoughts exist in relation to capsule permeability and the etiology of cataract and it is still unknown. To the first belief the aging capsule becomes insufficiently permeable to allow essential nutrients to reach the lens fibers, while the others believed it becomes too permeable, so that noxious substances, even proteins may enter the lens and damage the fibers (Fisher, 1969)

In the recent study, the mechanical properties of human posterior lens capsule have been studied. They observed the thickness of the posterior lens capsule ranged from 4 to 9  $\mu\text{m}$  and showed no significant changes with age, while the mechanical strength of the posterior lens capsule was found to decrease markedly with age. It shows that the age related loss of mechanical strength seemed to begin earlier in the posterior lens capsule than in the anterior lens capsule (Krag *et al.*, 1997; Krag and Andreassen, 2003). These changes are observed because the young capsule is strong, tough, and highly extensible whereas the older, thicker capsule is less extensible and much more brittle.

Another important function of the lens capsule is to play a role during accommodation, in molding the lens substance into its accommodated form (Krag *et al.*, 1997; Fincham, 1937; Weale, 1963). It was found that the elastic stiffness of the anterior lens capsule decreases with age, indicating that the lens capsule loses its capacity to transmit energy to the lens substance with age. Fischer (1969) showed that 90% of the age related losses in accommodation results from changes in capsular elasticity.

## **VII. Population Genetics : Variation in Cataractogenesis**

Unlike congenital cataracts, which are due to genetic alterations in certain known genes, screening a candidate gene responsible for age-onset cataract is quite difficult, because of the prevailing diverse genetic variants between population and even within group. Since race has been suggested as a possible risk factor for SC (Gibson *et al.*, 1985), genetic homogeneity within the same racial group must play a role in cataractogenesis and other age related diseases. In support of this theory Sommer *et al.* (1991) observed that non-operated cataracts account for a higher percentage of blindness among blacks compared to whites. Cataracts have been identified in patients with heterozygosity in galactokinase (GALK) gene deficiency. GALK deficiency is an autosomal recessive disorder characterized by hypergalactosemia and cataract formation. A novel, prevalent GALK variant, otherwise called “Osaka” was found associated with mongoloid population. The higher incidence was found in Japanese and Koreans, whereas it was lower in Taiwanese and Chinese. No incidence was found in Negritos (black) and Caucasoid (white) (Okano *et al.*, 2001). The authors suggested that “Osaka” variant is the first genetic variant to be identified, probably originated in Japanese and Korean ancestors and that could directly explain the role of genetic factors in the development of cataract in elderly individuals. In continuation of this study, Maraini *et al.* (2003) investigated the possible association between sequence changes or allelic variants in the galactokinase 1 (GALK 1) gene and SC in a homogeneous Northern Italian population (European population). No significant association between these Osaka or GALK1 allele variants and SC was found. These results can be extrapolated to some extent to other European population, but certainly not to African and Asian population groups. Such type of studies has not been done so far in Indian population, which comprise of different ethnic groups. Therefore, this study

should be done extensively in Indian population in order to analyze the possible association of GALK1 allele variants with SC. Considering the Indian scenario, the Indian population consists of mixture of four ethnic groups, Austroloid, Negrito, Mongoloid, and Caucasoid. Several studies based on the classical genetic markers were carried out to understand the genetic variation among the Indian populations. All these studies gave only an outline trend of genetic variations among geographical groups of the country. Kashyap *et al.* (2003) assessed the nature and extend of variations in microsatellite loci and examined genetic diversity and affinity amongst various Indian populations. This study indicated that the Indian populations harbor greater diversity than most of the geographical territories of the world, due to high intra-population variations. The utility of markers in deciphering genetic diversity in population would be helpful to understand population dynamics and diseases specific to population in the present scenario.

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