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Review Article

Molecular Genetic Analysis and Diagnosis of Albinism Patients in India

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Abstract

Albinism is one of the major metabolic disorders due to tyrosinase deficiency in the body, thus leads to defect in the production of melanin biosynthesis and leads to lack of pigmentation in ocular & cutaneous region is called as oculo cutaneous albinism and lack of melanin in ocular region alone is known as ocular albinism. In this genetic study, performed the candidate gene analysis for TYR, P, MC1R, TYRP1, MATP1 and GPR143 genes in familial and sporadic cases by sequencing analysis. Based on this screening analysis the molecular diagnosis was carried out especially for carrier detection, those families are under risk condition because of the presence of this diseases in their previous generation.

INTRODUCTION

Albinism is a form of hypopigmentary congenital metabolic disorder characterized by partial or total lack of melanin pigment. Approximately one in 17,000 people of all races were affected by albinism [1]. The major ophthalmological risk in albinism patients includes, iris transillumination, congenital nystagmus, hypopigmentation of iris, foveal hypoplasia, reduced visual acuity, astigmatism, photophobia, misrouting of the optic nerves, depigmentation in the retina, especially peripheral to the posterior pole. The severity of the visual defects tends to be proportionate to the degree of hypopigmentation and abnormally large number of crossed fibers appears in the optic chiasm of patients with albinism. The morbidity for the most forms of albinism is ocular region. In different parts of the world, people with albinism not only suffer for health problems but also from social challenges. They may be ridiculed or discriminated against.

The biochemical basis of pigmentation includes a series of candidate genes *TYR, P, MC1R, TYRP1,* and *SLC45A2* for OC1-4 and *GPCR143* for OA1. Any mutation or abnormalities in these candidate genes leads to alterations in the melanin biosynthesis pathway and thus leads to lack of pigmentation in ocular and cutaneous regions. To address these genetic problems, there is more important to develop a program that will evaluate the genes implicated within the melanin bio-synthesis. Analysis of mutations associated with albinism will help for better understands to the complexity of melanin pigment formation. There are some individuals with albinism who do not have mutations in any of the genes and may represent other types of albinism associated with mutations in genes that have yet to be identified. All forms of albinism are heritable and the severity of the disease also may get intensified in future generation.

To avoid this circumstances the genetic counselling is important to determine the chances of further reoccurrence of the condition especially in familial cases, in order to protect next generations in their families. Finally these kinds of analysis will address for the personalised gene-therapeutic research in future. This thesis covers five years of intensive work on general mutation screening of albinism patients from southern and western parts of India, molecular analyses by performing carrier detection and prenatal diagnosis and also computational analysis of structure-functional effects of a pathogenic *TYR* mutation-R239W which was observed in the prenatal case.

The specific objectives in this manuscript are as follows, to screen for exonic mutations in all the known candidate genes of oculo cutaneous albinism type1-4 and ocular albinism to identify the disease-causing mutations in Indian albinism patients especially in the sporadic cases. To develop a basic rapid diagnostic method for early carrier detection in families at risk condition.

An attempt was performed to predict and compare the three-dimensional structure of wild and mutant-R239W form of TYR protein to explore the putative effects of structural changes specifically for the change observed in a family involved in prenatal diagnosis [2].

Over the past several years of progress has been made to

identify a few of the candidate genes like TYR, OCA2 (P, MC1R), TYRP1, MATP and GPR143. In India several mutations were reported in TYR gene and studies on functional aspect is still going on. Next to this TYR gene the most leading type of albinism is OCA2. There is no report for P and MC1R genes responsible for OCA type 2 disease, we are the first group reported mutation in P and MC1R genes.

Socio-Clinical importance of this work

The morbidity for the most forms of albinism is ocular region and there is currently no treatment or therapy for albinism. Development of the optical system is highly dependent on the presence of melanin, and the reduction or absence of this pigment in albinotic individuals leads to visual problems with other ocular defects associated with albinism arise from a poorly developed retinal pigment epithelium (RPE) due to the lack of melanin. There are a number of genetic mutations that can cause melanin-related abnormalities; each mutation presents with distinct phenotypic features. Each candidate gene, when expressed normally, functions as normal and produce melanin. Individuals with mutations to these genes can't synthesize melanin normally and present with the hypopigmentation. This hypopigmentation will vary according to the severity of the mutations, thus leads to different types of albinism. Persons with albinism in Tanzania face several major challenges due to long standing and widespread lack of public awareness of albinism. To avoid these myths and circumstances there is a social need to create a scientific way of awareness based on the genetic research to prevent these kinds of entry in to India.

Characteristic features of genes involved in Albinism

TYR: OCA type I is caused by mutations in the tyrosinase gene located at 11q14-q21 [3]. The gene consists of 5 exons spanning about 65 kb of genomic DNA and encoding a protein of 529 amino acids (Kwon et al 1987). TYR (EC 1.14.18.1) is a copper-containing enzyme catalyzing the first two steps in the melanin biosynthetic pathway, converting tyrosine to L-dihydroxy-phenylalanine (DOPA) and subsequently to DOPA quinone. Mutations completely abolishing tyrosinase activity result in OCA1A, while mutations rendering some enzyme activity result in OCA1B

P gene: Mutations in the *OCA2* gene (formerly known as the P-gene) cause the OCA2 phenotype [4]. The gene consists of 24 exons (23 coding), spanning almost 345 kb of genomic DNA in the region 15q11.2-q12, and encoding a protein of 838 amino acids [5]. The OCA2 protein is a 110 kDa integral melanosomal protein with12 predicted transmembrane domains [4], important for normal biogenesis of melanosomes and transport of melanosomal proteins [6,7].

MC1R gene: MC1R is the "melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor-α-MSH)"gene, also responsible for OCA2. This MC1R is a member of the G protein-coupled receptors super family and contains seven-transmembrane receptor, is the major contributor to normal pigment variation in humans [8-10]. This transcript contains one exon (intron less coding region) with 2.00 kb of genomic DNA, located at the telomeric end of chromosome 16q 24.3 [11,12] and it highly polymorphic in the white population [13] and *MC1R* gene variants have been found to be associated with fair skin and red hair [14-18]. The MC1R gene provides instructions for making the protein melanocortin 1 receptor. The receptor is primarily located on the surface of melanocytes where it determines the relative production of eumelanin and pheomelanin in the melanosome.

TYRP1 gene: OCA3 is caused by mutations in tyrosinase-related protein 1 (*TYRP1*) and located in 9p23 [19], 17 kb genomic DNA, and consists of 8 exons encoding a protein of 536 amino acids [20] catalyzing the oxidation of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) monomers into melanin.

MATP gene: Mutations in the membrane-associated transporter protein gene (*MATP*, also known as *SLC45A2*, MIM 606202) cause OCA4 and *MATP* consists of 7 exons spanning approximately 40 kb of genomic DNA, mapping to chromosomal position 5p13.3 [19-21]. The MATP protein of 530 amino acids contains 12 putative transmembrane domains and shows sequence and structural similarity to plant sucrose transporters; it is expressed in melanosomal cell lines [22,23]. The function of MATP is still unknown, but studies from Medaka fish show that the MATP protein plays an important role in pigmentation and probably functions as a membrane transporter in melanosomes [22].

Ocular Albinism: Ocular Albinism is caused by mutation in OA1 gene (GPR143) is an X-linked gene, located on Xp22.3-22.2, consist of 9 exons of 40 Kb in size codes for 424 amino acids and is thought to be melanosomal transmembrane protein containing six putative transmembrane regions [24,25].

Methodology

Study Subjects:

Inclusion Criteria: Individuals having clinically confirmed OCA and OA with or without (familial/sporadic respectively) family history were recruited for this study.

Exclusion Criteria: Albinism with Syndromes

The subjects collected from,

- Paediatric Clinic, Aravind Eye Hospital, Madurai, Tamil Nadu, India
- Netra Niramay Niketan, Vivekananda Mission Ashram, Chaitanyapur, West Bengal, India
- Mediscan Systems, Chennai, Tamil Nadu, India
- Amrita Institute of Medical Sciences and Research Centre, Cochin, Kerala, India
- Navi Mumbai Institute of Research in Mental and Neurological Handicap, Mumbai, Maharashtra, India.

In addition, sample collection includes 100 normal controls from Aravind Eye Hospital, Madurai, Tamil Nadu, and India.

Enrolments of study cases and clinical examination

The study adhered to the Declaration of Helsinki criteria and was approved by the institutional review board and ethics

committee of Aravind Eye Hospital, Madurai, India. An informed consent form was obtained from each patient following an explanation of the nature of study. All patients were clinically diagnosed by ophthalmologic examinations.

The following molecular techniques were employed in this study

- Pedigree construction by crylic program
- Sample collection from peripheral blood with EDTA coated tube
- Genomic DNA extraction salting out method
- DNA quantification by Nanodrop
- Primer selection based on literature
- PCR amplification and purification
- DNA sequencing and data analysis by Chromas software
- Computational analysis of WT-TYR and R239W mutant

RESULTS AND DISCUSSION

The rationale of this study is to identify the spectrum of genetic variations in Indian albinism patients and to perform early molecular diagnosis for the most predominant oculo cutaneous albinism (OCA) types. In this study, 80 unrelated albinism families were analyzed for all the candidate genes and varieties of mutations were observed in 52 families and there were no mutations/SNPs in the remaining 28 families. OCA genetic testing for carrier detection and prenatal diagnosis were performed with few families under risk. Moreover, the model of human tyrosinase structure was predicted and compared for wild type and a specific mutant by computational approach.

OCA 1

OCA1 is the most frequent inheritable type of albinism in Indian populations. Bi-directional DNA sequence analysis of the 80 families revealed, eight missense mutations p.Arg239Trp, p.Asp383Asn, p.Met370Ile, p.Gly419Arg, p.Lys28Asn, p.Arg299His, p.Glu328Lys, p.Glu203Lys; four nonsense p.Trp108X, p.Arg402X, p.Gln326X, p.Arg278X; one deletion c.1379_1380delTT; two novel p.Ser82Ser, p.Ile222Val1 and two reported p.Ser192Tyr, p.Arg402Gln polymorphisms in (OCA type I) TYR gene.

OCA2

The second most predominant type is OCA2 in Indian populations. Among all the study subjects two novel missense mutations c.1453G > A (p.G485R), c.1055G > C (p.R352T); Two novel SNPs, c.2121A > G (p.Q707Q) and IVSXX + 4 A/G in *P* gene were reported [2]. Human Genetics 2009; 125: 340 [PMID: 19309806] Genbank/HM080076

One novel homozygous missense c.803C > G (p.P268R) mutation in *MC1R* was identified in one of the proband and his affected younger brother. In the same proband one novel heterozygous mutation c.1055G > C (p.R352T) and one novel heterozygous synonymous SNP c.2121A > G (p.Q707Q) in OCA2/P gene were also observed. In addition, one novel heterozygous mutation c.670C > T (p.L224F), two novel polymorphisms c.466G > A (p.V156M), c.444C > T (p.Y148Y) and three reported polymorphisms c.488G > A (p.R163Q), (c.699G > A) p.Q233Q, c.942A > G (p.T314T) were identified in MC1R gene (Figure 1).

There were no mutation reports in OCA3 and OC.A4 in Indian populations, only few reported polymorphisms were identified in OCA3, 4 and OA1 genes, *TYRP1* - p.Arg87Arg *MATP* - p.Thr329Thr, p.Leu374Phe, rs45552240 *GPR143* - IVS6 + 10C/G.

Molecular Diagnosis

Carrier detection: For this preliminary study, the predominant types of OCA (I & II) were analyzed in probands of different families. This study provides the need for genetic testing, especially for the affected individuals from familial cases, to avoid the occurrence of OCA diseases in future generations. This kind of molecular testing is newly emerging procedure for early carrier detections to develop the prior diagnosis of OCA types (I & II) in Indian population. The majority of affected individuals have been

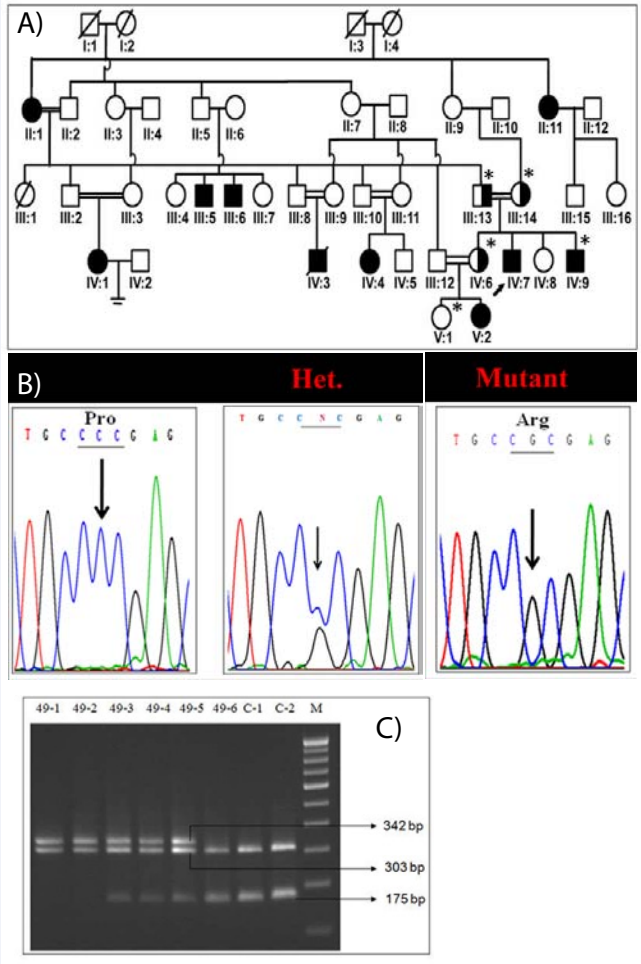
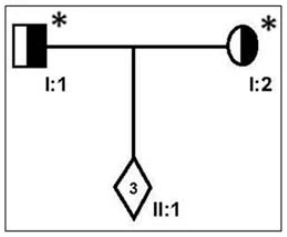
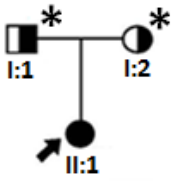
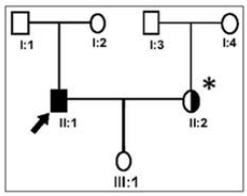
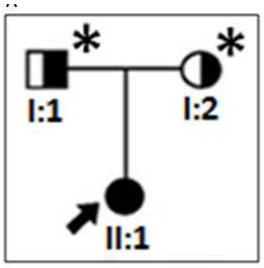
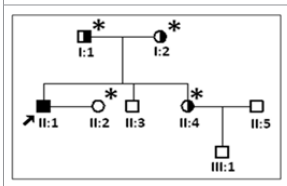
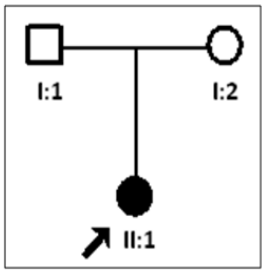
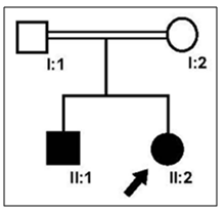
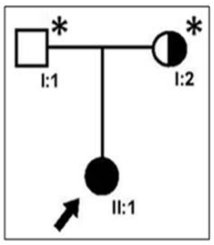
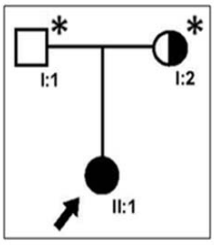


Figure 1 A-Pedigree of 49-1. B-Chromatogram showing Novel mutation c.803C>G (p.P268R) in OCA2 *(MC1R gene). C-* RFLP-*AvrII.* C-Control, M-100bp Marker, 49-1-Proband, 49-2-Proband's affected brother, 49-3- Normal Mother, 49-4-Normal Father, 49-5- Normal Sister,49-6-Siter's Normal daughter, C-1-Control sample 1, C-2-Control sample 2.

compound heterozygotes with different maternal and paternal alleles. This broad investigation of carrier diagnosis should, in principle, make prenatal diagnosis a reality in the future. Prenatal care and screening are important because early diagnosis allows families to take decisions and plan for healthy future. For a recessive genetic disease, the only prevention involves carrier detection with the parent samples and also with the first affected baby sample. In this genetic analysis, few novel mutations as homozygous as well as compound heterozygous conditions were also reported (Table 1).

At present, approximately over 231 mutations of the tyrosinase gene associated with OCA I have been described in the human albinism database (http://albinismdb.med.umn.edu/oca1mut.html) in various ethnic groups. Recently, there has been increased awareness and attention paid to prevent genetic diseases. This finding reiterates the need for increased awareness of molecular diagnosis and public health intervention in order to better address the medical, psychological and social needs of these albinism populations in worldwide.

Table 1: Molecular diagnosis of OCA 1 & OCA 2 genes in carrier family.

Families diagnosed for OCA 1	Result observed
	**Both of the parent samples:** ❖ **c.168G>A (p.Gln56Gln)** @ (H) ❖ **c.324G>A (p.Trp108X)** @ (H) **Mother's DNA alone :** Two reported polymorphisms **c.-301C>T; c.-199C>A** (H)
	**Proband:** ❖ **c.-301C>T & c.-199C>A (h)** **Both of the parent samples:** **c.-301C>T & c.-199C>A** (H)
	**Second Generation couple (II:1, II:2):** ❖ **c.-301C>T** (rs4547091) (H) ❖ **c.-199C>A** (rs1799989) (H)
	**Proband:** ❖ **c.-33 G>T @** (H) (5' UTR) ❖ **c.1205G>A (p.Arg402Gln)** (H) **Both of the parent samples:** **Mother: c.-33 G>T @** (H) (5' UTR) Normal- **c.1205G>A (p.Arg402Gln)** **Father: c.1205G>A (p.Arg402Gln)** (H) Normal- **c.-33 G>T @** (H) (5' UTR)
	**Proband: Exon 1** ❖ c.715C>T (p.Arg239Trp) (h) **Mother:** c.715C>T (p.Arg239Trp) (H) **Father:** c.715C>T (p.Arg239Trp) (H) **Wife: Normal** **Sister:** c.715C>T (p.Arg239Trp) (H)
	**Proband:** ❖ c.832C>T (p.Arg278 Stop codon) (h)
Families diagnosed for OCA 1 (P & MC1R genes)	Result observed
	**(P gene) Proband: Exon 10 & 12** ❖ **c.1**064G>A (p.**Ala355Ala)** (h) ❖ IVS12-4A>G @ (h) ❖ IVS10-58C>T @ (H)
	**(P gene) Proband:** ❖ **c.460G>A (p.Glu154Lys)** @ (H) Father 's DNA - **c.460G>A** (WT) Mother's DNA - **c.460G>A** (H)
	**(MC1R gene) Proband: Exon 10 & 12 Proband:** ❖ **c.0488G>A (p.Arg163Gln) (H)** **Father 's DNA - c.0488G>A (WT)** **Mother's DNA - c.0488G>A (h)** This SNP also associated with Vitiligo Syndrome. A kind of depigmentation of skin due to non-functional melanocytes, autoimmune, genetic, oxidative stress, neural, or viral causes (Halder 2009)
@-Novel; H-Heterozygous, h-homozygous	

Prenatal Diagnosis

In this study, the *TYR* (OCA-I) coding region was analyzed for previously reported (proband and maternal grandmother) mutation in the DNA of Chorionic Villus sample collected from the proband's mother during the third month of pregnancy. This CVS was performed in Mediscan Systems is registered under prenatal diagnostic techniques under the Regulation & Prevention of Misuse Act 1994. A certificate was issued by the Government of Tamil Nadu (Reg. No: PNA/364/99 DT. 15.09.1999). This CVS procedure for the analysis of tyrosinase of

fetal genomic DNA is a rapid and reliable approach to the prenatal diagnosis of oculocutaneous albinism at a relatively early stage of pregnancy, and is safer and less invasive than other methods such as fetal skin biopsy. This mutation, which results in an arginine-tryptophan substitution at codon 239 of the tyrosinase polypeptide (EC1.14.18.1), is highly conserved among related mammalian species. This replacement in the conserved region (239) may be sufficient to change the secondary structure of the protein and resulting pathogenic effects. The SIFT score is 0.00 which meant that the variant (TYR: p.R239W) was predicted as pathogenic. The recent elucidation of the specific gene mutation of tyrosinase in the affected individual revelled DNA-based prenatal diagnosis of tyrosinase-negative oculocutaneous albinism in the first trimester of next pregnancy. Supporting these molecular findings, the woman delivered a baby boy without any features of albinism [26] (Figure 2).

This basic diagnostic molecular method reveals towards creating a healthy society particularly in specific group or geographical cohort. Our research in prenatal screening, expose rapid development of a molecular diagnostic tool to improve the implementation of genetic testing. This is the first successful report revealed the profile of biological information by genetics as well as computational based approach for R239W mutant in the fetus of a familial case.

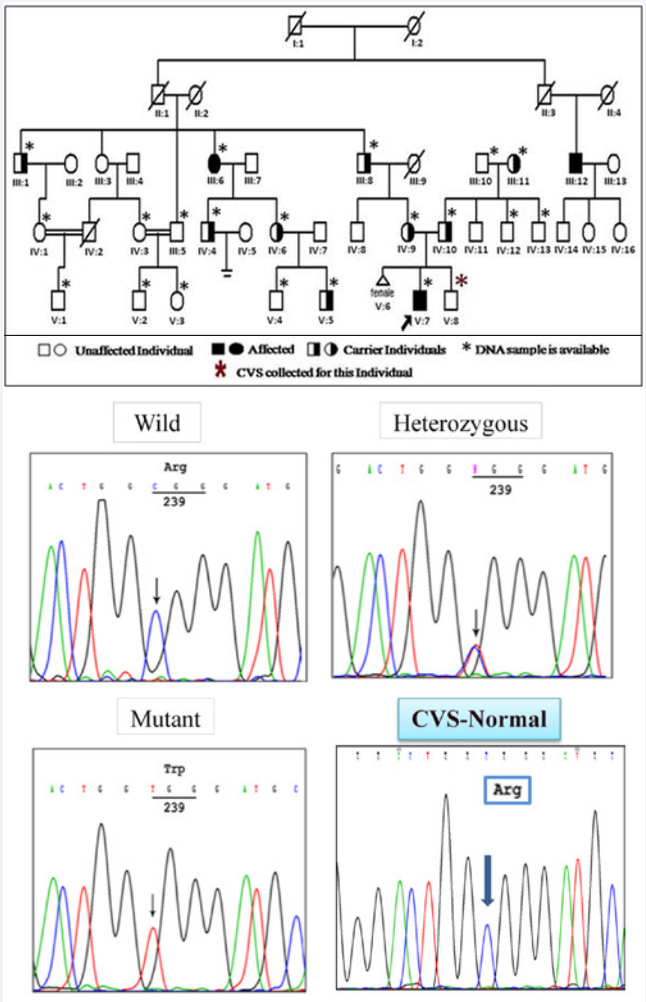


Figure 2 A- Pedigree involved in prenatal diagnosis of R239W Mutant in TYR. B-chromatogram withTYR normal and mutant-R239W.

Structure Prediction and Analysis of Human Tyrosinase for Wild and Arginine 239

Tryptophan Mutant: The tyrosinase structure was predicted with IWX2 as template and further used as template for R239W construction. Both the predicted model was refined and validated by Ramachandran plot analysis. The structure of WT-TYR and R239W mutant models predicted by Schrödinger methods were compared for general physiological features and structural properties. The tyrosinase structure prediction; structural studies of its interactions with copper atoms, molecular surface analysis and the methodologies implemented provides structural data exposing insights into the molecular mechanism of tyrosinase and may provide grounds for structural and molecular phenomenon. In this work an attempt was performed to gain the 3D structure of human tyrosinase from its sequence comparison by homology modelling method and improved the predicted results by validation process. The predicted structures were analysed by comparison to conclude the pathogenic effects of p.R239W mutation in TYR gene [26].

Outcome of the project: This genetic analysis addressed towards creating a novel method to understand the genetic background, subsequent disease mechanism and diagnostic tool that can be clinically applied to identify the risk groups and forewarn themes, so that they can follow preventive strategies which could reduce the metabolic diseases in their next progeny atleast to the specific race in particular geographical location (Figure 3).

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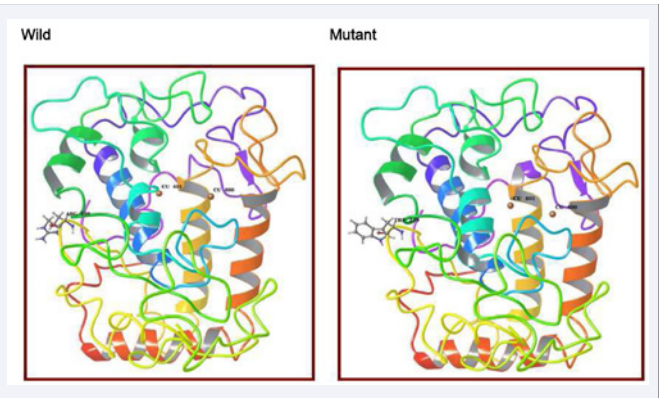

Figure 3 Predicted 3D model of human tyrosinase (hT). The protein structure was refined by energy minimization using OPLS 2005 force field. The energy of the model is 0.443 kcal/mol. The RMSD is 1.8Å between the template and predicted model. The modelled structure was validated by PROCHECK and Ramachandran plot. In both structures the CuA and CuB Domains were shown by brown color balls.

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