

## The Molecular Basis of Alpha-Thalassaemias in India: A Review

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### INTRODUCTION

Alpha-thalassaemia is a common hereditary condition caused by deletion of one or more  $\alpha$ -globin genes leading to decreased or absence of  $\alpha$ -globin chain production. The excess  $\beta$ -globin chains in a three alpha globin gene deletion case produce HbH disease who have moderate anaemia, and are generally thought to be asymptomatic (Sen et al., 2004). However where four  $\alpha$ -globin genes are deleted (homozygous  $\alpha$ -thalassaemia) severe anaemia results, which may cause fetal death or hydrops fetalis. In both HbH disease and hydrops fetalis (Hb Bart's) the detection is by electrophoresis or peripheral blood studies. The phenotypic diversity of HbH disease is well known and carriers are rarely detected. The study of the  $\alpha$ -globin gene is comparatively difficult and requires molecular studies. Our study has been directed to this effort to detect  $\alpha$ -globin defects in normal, tribal and nontribal populations of Eastern India. The presence of the defect has been correlated with the phenotypic expression and prenatal detection carried out when required. Two of the  $\alpha$ -globin gene deletional mutants studied (-3.7 and -4.2) appeared to be present in tribal as well as nontribal population along with  $\beta$ -globin gene defects.

### DELETION CAUSES $\alpha$ -THALASSAEMIA

$\alpha$ -globin genes and its two pseudo genes are embedded within two highly homologous 4 kb duplication units. Single gene deletions are either the leftward type involving the X homology blocks and deletion of 4.2 kb DNA, or the rightward type, involving the Z homology blocks and deletion of 3.7 Kb of DNA. Both types of single alpha gene deletions occur due to mispairing of homologous sequences within Z or X homology blocks. Unequal crossing over results in the deletion of one alpha gene on one chromosome ( $-\alpha$ ) and triplicated alpha genes on the other ( $\alpha\alpha\alpha$ ) (Higgs et al., 1989).

Alpha thalassaemia has been documented in different areas of India (Brittenham et al., 1980) (see Table 1). The large Indian population is multi-ethnic and divided into subgroups, which practise

caste endogamy and clan exogamy. Various evolutionary forces such as natural selection, mutation and recombination, migration and genetic drift play an important role to regulate the frequency of the mutation. Common  $\alpha$ -thalassaemia determinant ( $-\alpha$ ) has been characterized by RFLP (Restriction enzyme length polymorphism, PCR (Polymerase Chain Reaction) and DNA sequencing analysis of DNA isolated from blood in subjects from some regions of India (Kar et al., 1986; Agrawal et al., 2002; Gajra et al., 2003; Sen et al., 2004; Sen et al., 2005 a, b).

### Incidence of $\alpha$ -Thalassaemias among the Tribal Population in India

Our present study has shown that alpha thalassaemia mutations -3.7del and -4.2 del occur throughout Eastern India. However it appears to be lower in Arunachal Pradesh and Assam and higher tribals of Bolpur, West Bengal. It thus appears to be not related to the genetic drift from the Southeast Asian countries and could be due to de novo mutation. Further studies are needed.

### The Origin of Tribes

In Eastern India mainly in the northeast region the majority of population is comprised of tribes mostly of Tibeto-Mongoloid stock

The origin of the tribes is also heterogenous and the Santhal, Oraon, Mundas of West Bengal and Orissa are anthropologically distinct from the Tripuris of Tripura. Arunachal Pradesh has twenty-four major tribal groups (Adi, Aka, Apatani, Bangni, Khamba, Khampti, Khowa, Memba, Miji, Hill Miri, Mishng, Monpa, Na, Nishi, Nocte, Sherdukpen, Sulung, Singpho, Tagin, Tangsa, Wancho, Yobin, Zakhring etc.) and forty-seven subgroups. These constitute about 70.0% of the total population. They all are genetically distinct while tribes living in the states of Assam are categorized in to fourteen hill tribes (Chakma, Dimasa, Ahom, Garo, Hajong, Hmar, Khasi, Kuki, Laker, Man, Mizo, Mikir, Naga, pawl, Synteng) and nine plain tribes (Barmans, Boro, Deori, Hojai, Sonowal, Lalung, Mech, Mishng, Rabha) and the state accounted for merely 11.0% tribal popu-

lation. The tea garden workers have groups of Santhals and Mundas as well. Tribals from other parts of India like Santhals, Oraons, Mundas and Lushais and members of scheduled castes like Namasudras, Mahisya class, Malis, Dhobis and Chamars are also present.

In West Bengal tribals are mostly Santhals, Oraons and Mundas. The number here is low being 8.28% of the population of Medinipur and 6.95% in Birbhum.

Molecular studies of alpha- and beta-thalassaemia and their interaction in the tribal population (mainly Santhal tribals) have been reported in Sian village, Birbhum, West Bengal (Gajra et al., 2003; Sen et al., 2005 a). A high incidence (11%) of abnormal haemoglobin was detected from the total 100 cases (34 showed Hb < 11 gm) of the tribal population under study by agarose gel electrophoresis. This comprised of 9% beta thalassaemia trait, 1% sickle cell (HbS) trait, and 1% Haemoglobin E (HbE) trait. Thirty cases were selected for alpha thalassaemia mutation (mainly  $-3.7\alpha$  and  $-4.2\alpha$  deletions) studied by molecular methods on the basis of low MCV (<78fl) and low MCH (<28pg). In case of five persons alpha-beta interactions were found. Presence of only alpha mutations were found in eighteen persons and in one case interaction of alpha thalassaemia with HbS was reported. Among the Santhals 80% were found to have  $\alpha$ -globin gene defects (Gajra et al., 2003; Sen et al., 2005). In West Bengal, the Santhals mix freely with local population and previous studies have shown that other genetic variants like haptoglobin, transferrin and lipoproteins were found in different subgroups and Bhumij (local populations) in Midnapore (Giri et al., 1981).

Alpha and beta thalassaemias have been reported among the tribal population of Arunachal Pradesh, Assam, and West Bengal (Sen et al., 2005 a, b).

In a total of 234 cases studied in Assam Ahom were the most common. Out of 234 cases 128 were Ahoms and 55 were Garos. Among the Ahoms, 63 persons had Hb < 11 g/dl and among the Garos, 23 persons had Hb < 11 g/dl. 80 cases were further studied for  $\alpha$ -thalassaemia using molecular methods on the basis of low MCV (<78fl) and low MCH (<28pg). Nine persons showed a mutation of which 5 had interaction with  $\beta$  mutation. Among Ahoms 11.62% (5/43) were found to have  $\alpha$ -globin gene defects. Among the Garos 36.3% (2/22) were found to have  $\alpha$ -globin gene defects. 13.31% (2/

15) showed the presence of  $\alpha$ -globin gene defects among the rest.

179 cases were studied in Itanagar, Arunachal Pradesh 32 were tested for alpha thalassaemia mutations by PCR methods on the basis of low MCV (<78fl) and low MCH (<28pg) of which 7 showed alpha mutation alone. 21.87% (7/32) were shown to have  $\alpha$ -globin gene defects.

In earlier studies in Arunachal Pradesh tribals both mutants were found but they differed in tribals of different villages suggesting absence of admixture among different tribal subgroups as most villages had persons of one or two clans.

Among the tribals of Arunachal Pradesh only 3.7 mutation was found. Most of these tribals belong to Tibeto-Burman stock who do not as a rule mix with the local population, they also have a low incidence of beta thalassaemia but HbE has been found to be present (Sengupta et al., 2002).

Prevalence and molecular heterogeneity of  $\alpha$ -thalassaemia in two tribal populations, Koya Dora and Konda Reddi of Andhra Pradesh, India by DNA restriction analysis and conventional electrophoretic methods have been studied. A remarkably high incidence of deletional and non-deletional  $\alpha^+$  thalassaemia mutations had been found characterized by different mutations in different villages (Fodde et al., 1988, 1991).

9.4% of a tribal population from East Godavari district in Andhra Pradesh were found to have the variant Hb Koya Dora, which is caused by  $\alpha$ -globin chain termination mutant (Nayudu et al., 1985)

Alpha thalassaemia carriers were found in both the caste and tribal communities, reached a frequency of >90% in the latter case (Mohanty et al., 2002). Genetic heterogeneity and population structure of a thalassaemias have been reported among the Gond related tribes in Vidarbha region in Maharashtra (Rao et al., 1992, Mohanty et al., 2002)

The presence of deletional  $\alpha^+$  thalassaemia among the Baiga tribes in Central India have been found (Das et al., 1971; Das and Flatz, 1975, Chakrabarty et al., 1996; De et al., 1997 a, b; Das and Talukder, 2000, 2001 b).

Mutation in in polyadenylation signal of alpha 2 gene (AATAAA  $\rightarrow$  AATA  $\rightarrow$ ) was reported in Asian Indians (Hall et al., 1994). Others reported alpha thalassaemias in Central India (Curuk et al., 1993). Alpha thalassaemias have been reported among the Danuwar and Tamang tribes of Nepa

(Sakai et al., 2004). Alpha thalassaemia has been found in Rajasthan, in Orissa, in the Kachari population in Assam (Hundrieser et al., 1987; Kulozik et al., 1998; Choubisa et al., 2000).

### **Incidence of $\alpha$ -Thalassaemias among Non-tribals in India**

A total of 100 cases were referred to our unit for testing of  $\alpha$ -thalassaemia 60.9% were found to be normal, 3.80% had 3.7 homozygous mutation, 13.33% were found to be -3.7 $\alpha$  carrier, 5.71% were found to be -4.2 $\alpha$  carrier. -4.2 $\alpha$  homozygous mutation were found in 0.95% cases and 2.85% were detected as -3.7 $\alpha$ /-4.2  $\alpha$  double heterozygotes. There were 16.19% cases of Hb H disease (Sen et al., 2004).

Of the total 105 cases tested for  $\alpha$  thalassaemia among those referred to our unit, most of them belonged to Kolkata and adjacent 24 parganas only 13 belonged to Bangladesh. One was Chinese and two were Oriya. Their age varied from 1 to 77 years and the majority had Hb levels below 11 gm/dl. We studied 17 cases of HbH disease where H band was detected by electrophoresis in which 5 showed the presence of alpha mutation (-3.7del, -4.2del, —SEA del). 3.7  $\alpha$  (-3.7 $\alpha$ /-3.7 $\alpha$ ) homozygous mutation was present in one person, 3.7/4.2 (-3.7 $\alpha$ /-4.2 $\alpha$ ) double heterozygous mutation was present in 3 cases and (-3.7 $\alpha$ /—SEA) mutation was present in one case.

HbH disease belonged to two families. In one family a 3 yr old boy had HbH disease with the presence of -3.7 $\alpha$ / -4.2 $\alpha$  mutation. In the other family two girls had Hb H disease but we did not get common (-3.7 $\alpha$ / -4.2 $\alpha$ ) mutation was absent (Sen et al., 2004).

282 Indians from Orissa State and found 3.7 $\alpha$  and -4.2 $\alpha$  deletions with a gene frequency of 0.29 (Kulozik et al., 1998).

The prevalence of  $\alpha$ -thalassaemia was much higher in West Central Gujarat (95%) and Nilgiri hills in South India (85.7%) suggesting that the condition is almost genetically fixed in India (Labie et al., 1989).

6 of 126 alpha globin loci triplicated, giving a frequency of 5% in some population in Punjab, though this event is rare in India (Garewal et al., 1994).

Some cases of HbH diseases have been found in newborn in West Bengal and Bombay showed that 2% and 4% of cord samples contained Hb Bart's (Chouhan, 1970; Mitra, 1983). Two cases

of HbH disease has been reported from Bengalee families in Calcutta, West Bengal (Sen et al., 2004).

South African type alpha-thalassaemia 1 mutation in combination with a novel splice donor site mutation alpha2 IVS1-1 (G→A) was identified in an Indian family (Shaji et al., 2003).

### **ALPHA-BETA/HAEMOGLOBINOPATHY INTERACTIONS IN INDIA**

Alpha-beta / Haemoglobinopathy interactions were observed among nontribal as well as tribal population in India.

Interaction of  $\alpha$ -thalassaemia has been implicated clinical severity and haematological expression of sickle cell anaemia in Western India (Mukherjee et al., 1997 a, b; Mukherjee et al., 1998). Thalassaemia intermedia-heterozygous  $\alpha$ -thalassaemia and co-inherited triplication of alpha gene are found in Uttar Pradesh, India (Agarwal et al., 2002)..We studied Alpha – beta interactions among the Santhal tribals of West Bengal. The majority of  $\beta$  mutation observed in Bolpur were IVS 1nt 5 (G→C) or codon 26 (G→A) among the  $\beta$  mutations while -3.7 $\alpha$  mutation was more common in  $\alpha$  thalassaemias cases. Presence of alpha mutation and its interaction with E mutation among the Assam tribals were studied where a total 9  $\alpha$  mutation was detected, and majority occurred with homozygous E.

Our previous studies have shown that HbE disease is milder than as reported in Southeast Asia and haplotyping have shown a a Tripuri as well as a Bengal variant which show a milder phenotype even in conjunction with  $\beta$ -thalassaemia (Das et al., 2000). Another interesting feature is the milder phenotype of  $\alpha$ -thalassaemia deletions as well mostly causing HbH disease with Hb Barts hydrops fetalis not commonly reported. This feature has also been reported in Western India (Mukherjee et al., 1998).

The interaction of  $\alpha$ -thalassaemia with  $\beta$ -thalassaemia and point mutations in  $\beta$ -globin gene like HbE and HbS produces a milder phenotype seen mostly among tribals of Bolpur. This could possibly be due to alterations of the LCR region as has been reported by us earlier in  $\beta$ -thalassaemia (Mukherjee et al., 1997a, b; Kukreti et al., 2002).

We could therefore suggest that  $\alpha$ - and  $\beta$ -globin gene interactions may be affected by alterations in other parts of the globin gene and detailed sequence analysis would reveal interesting new mutants. Globin gene mutations have occurred repeatedly over hundreds of years

**Table 1: Reports of  $\alpha$  thalassaemia: India (1970-2005)**

<i>Mutation</i>	<i>Country</i>	<i>Origin</i>	<i>Reference</i>
$\alpha$ -thalassaemia	India	Indian	Chouhan et al.(1970) <i>J. Indian Med. Assoc.</i> , <b>54(8)</b> : 364-367.
Hb Koya Dora	East Godavari district, Andhra Pradesh	Tribal	Nayudu et al. (1988) <i>Birth Defects Orig. Artic. Ser.</i> , <b>23(5B)</b> : 357-9.
$\alpha$ -thalassaemia	Assam, India	Kachari population	Hundrieser et al. (1987) <i>Hemoglobin</i> , <b>11 (5)</b> : 517-519
$\alpha$ -thalassaemia	Andhra Pradesh	Tribal	Fodde et al. (1988) <i>Hum. Genet.</i> , <b>80(2)</b> :157-60
Genetic heterogeneity and population structure	Vidarbha region, Maharashtra	Gond related tribes	Rao et al. (1992) <i>Hum. Biol.</i> , <b>64(6)</b> : 903-917.
$\alpha$ -thalassaemia determinants - 60%	Central India	Indian	Curuk et al. (1993) <i>Br. J. Haematol.</i> , <b>85 (1)</b> : 148- 152
An IVS 1-117 (G $\rightarrow$ A) acceptor site mutation in the $\alpha$ -2 globin gene. A non-deletional $\alpha$ -thal 2 determinant	Central India	Tribal population	Curuk et al. (1993) <i>Br. J. Haematol.</i> , <b>85 (1)</b> : 148- 152
Mutation in polyadenylation signal of $\alpha$ 2 gene (AATAAA - - @ AATA - -)	India	Asian	Hall et al. (1994) <i>Br. J. Haematol.</i> , <b>88 (1)</b> :225-227
Triplication of a globin gene	Punjab	Punjabi	Garewall et al. (1994) <i>Br. J. Haematol.</i> , <b>86(2)</b> : 372-6.
Deletional $\alpha$ -thalassaemia	Central India	Baiga tribe	Reddy et al. (1995) <i>Eur. J. Haematol.</i> , <b>55(2)</b> :103-109
$\alpha$ -thalassaemia with Sickle cell disease	Indian sub continent	Indian	Mukherjee et al. (1997a) <i>Blood</i> , <b>89(2)</b> : 732.
$\alpha$ -thalassaemia gene (-3.7 $\alpha$ & -4.2 $\alpha$ deletion)	Orissa, India	Orissa	Kulozik et al. (1998) <i>Blood</i> , <b>71 (2)</b> : 467-472.
A novel $\alpha$ 3.5 deletion removing the alpha 1 globin gene with some of its flanking sequences	Orissa, India	Orissa	Kulozik et al. (1998) <i>Blood</i> , <b>71 (2)</b> : 467-472.
$\alpha$ -thalassaemia -1.88%	Rajasthan, India	Rajasthani	Choubsia et al. (2000) <i>Haematologica (Budap)</i> , <b>30(3)</b> : 209-213
Thalassaemia intermedia-heterozygous $\alpha$ -thalassaemia and triplication of a gene	UP, India	Indian	Agarwal et al. (2002) <i>Hemoglobin</i> , <b>26(3)</b> :321-323)
Initiation Codon mutation	India	Indian	Gupta et al. (2002) <i>Am. J. Haematol.</i> , <b>71(2)</b> :134-136.
$\alpha$ -thalassaemia-1 deletion with (novel splice donor mutation) alpha 2 IVS 1-1 (G $\rightarrow$ A) in HbH disease.	India	India	Shaji et al. (2003) <i>Br. J. Haematol.</i> , <b>123(5)</b> : 942-947
$\beta$ -thalassaemia in association with a new delta chain Hb variant [delta 116(g18) Arg Leu]	East India	East Indian	Waye et al., (2003) <i>Am. J. Haematol</i> ; <b>74 (3)</b> : 179-181
Alpha thalassaemia	WB, India	Santhal tribe	Gajra et al. (2003) <i>Nucleus</i> , <b>46 (1&amp;2)</b> : 23-33.
Hb H disease	West Bengal, India	Bengalee	Sen et al. (2004) <i>JVIMS</i> , <b>27 (I&amp;II)</b> : 77-80.
$\alpha$ 3.7I / aa	Nepal	Danuwars-6.3%, Tamang-5%	Sakai et al. (2004) <i>J. Hum. Genet.</i> , <b>45 (3)</b> : 127-132
$\alpha$ -thalassaemia	WB, Assam, Arunachal Pradesh, India	Santhal tribe, Ahom tribe.	Sen et al. (2005a) <i>Hemoglobin</i> , <b>29 (4)</b> : 277-280.

and specific mutants are maintained at high levels due to the caste endogamy of our large heterogeneous population. The high incidence among the tribals are also due to the fact that in North East states they live in distant areas are localized to villages where usually only one tribe live. These tribals have not so far been studied earlier except for those of Assam and Tripura (Das et al., 1971; Das and Flatz, 1975, Chakrabarty et al., 1996; De et al., 1997 a, b; Das and Talukder, 2000, 2001 b).

### ACKNOWLEDGEMENTS

The study was carried out with support of a grant from the Department of Biotechnology, Ministry of Science & Technology, Government of India. The support and help provided by the Secretary Ramakrishna Mission Seva Pratishthan is gratefully acknowledged. The technical assistance of Supriyo Bose and Tanmoy Maji is also gratefully acknowledged.

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**KEYWORDS**  $\alpha$ -Thalassaemias. Haemoglobinopathies. Variation, Ethnic Groups

**ABSTRACT** Thalassaemias and haemoglobinopathies are the most common genetic disease and impose a major burden on the population of India due to its high degree of morbidity and moderate to severe anaemia among different segments of the society. Amongst the population of 1000 million at the new millennium (2000) forty-five million carriers and fifteen thousand infants with major haemoglobinopathies have been reported in India. A highly heterogenous distribution of  $\alpha$ -thalassaemia mutations have been reported in different parts of India. Migration, and gene flow of the mutant alleles of  $\alpha$ -thalassaemias by social, political and commercial reasons from different populations of the world are possibly responsible for these heterogenous nature of these mutations. Our study on  $\alpha$ -thalassaemias with an special emphasis on the detection of -3.7 and -4.2 deletions showed remarkably high incidence of this disease among the tribal population in Eastern India. We have also reported high prevalence of this disease among nontribal Bengalees in Kolkata and adjacent areas. This article provides a glimpse on the epidemiology, occurrence and different kinds of  $\alpha$ -thalassaemia mutations in different parts of India.

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