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## Review Article

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### HUNTINGTON'S DISEASE: AN INDIAN UPDATE ON GENETICS AND WIDESPREAD

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#### ABSTRACT

Huntington's disease (HD) is a dominantly transmitted progressive neurodegenerative disorder due to an abnormal elongation of the polyglutamine (polyQ) chain in the Huntington (Htt) protein. Children of HD gene carriers have a 50% chance of inheriting the disease. The loss of medium GABAergic spiny neurons, and specific neuronal loss in layers V and VI of the cerebral cortex lead to the decline in motor, cognitive and psychiatric functions. In HD the number of CAG repeats play a major role in the gene, hence the disease is termed as "trinucleotide repeat" disorder. The present study focussed on prevalence and expanded CAG repeats on Huntington disease in Indian population. Repeats of 26 and smaller are normal, repeats between 27 and 35 are not associated with disease expression but may expand in paternal transmission, 40 or larger are associated with disease expression, Intermediate repeats of 36–39 are associated with reduced penetrance. Age of onset (AOS) at disease diagnosis is associated with length of the expanded gene mutation, such that individuals with longer repeat lengths have a younger age at diagnosis. The identification of the genetic defect in HD permits direct genetic testing for the presence of the gene alteration responsible for the disease.

**Keywords:** HD, Htt gene, CAG repeats, Epigenetics Prevalence.

#### INTRODUCTION

Huntington disease (HD) is a rare progressive neurodegenerative disorder with a prevalence of 1/10,000-1/20,000 in the Caucasian population<sup>[1]</sup>. The neuronal loss occurs mostly in the striatum, particularly in the caudate nucleus, and in the advanced stages of the disease neuropathological changes occurs in the subcortical and cortical regions<sup>[2]</sup>. The characteristic features of HD are unintentional choreoathetoid movements, loss of intellectual abilities, dementia, behavioural changes and psychiatric disturbances. Most of the symptoms typically appear

between the age of 35 and 44 years. The duration from symptom onset until death is typically 15 to 20 years<sup>[3,4]</sup>. HD is inherited in an autosomal dominant manner, thus each child of a person with Huntington disease has a 50 percent (1 in 2) chance of inheriting the mutation and if one copy of the mutated gene is present, the symptoms will appear<sup>[5]</sup>. The other less common, early-onset form which begins before the age of 20, is called as juvenile Huntington disease, akinetic-rigid, or Westphal variant HD<sup>[6]</sup>. In 75% of the juveniles, the father is the affected parent<sup>[7]</sup>. In 1841, Charles Oscar Waters gave the first description of HD which depicts a

clear picture of one of its main clinical features, chorea, and its hereditary nature<sup>[8]</sup>. HD is named after George Huntington, who provided a classic account of HD in 1872 in "The Medical and Surgical Reporter"<sup>[9]</sup> that it became known as Huntington's chorea. He identified the condition to a family of immigrants from Bures in Suffolk, England, who came to Boston in 1630. Later, considering the non-motor symptoms and signs, the name was changed to (HD). This review projects on prevalence of HD and CAG repeats among worldwide and in Indian scenario.

### MANIFESTATION OF HD

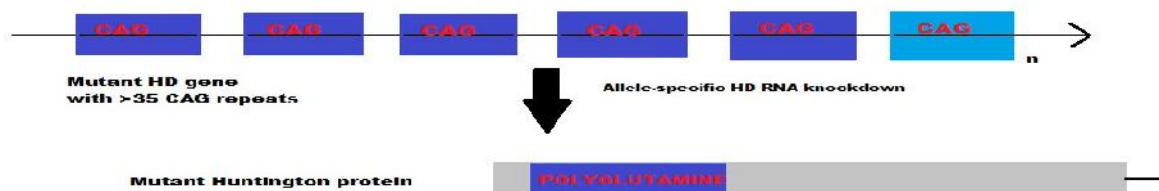
The major symptoms and signs of HD consist of motor, cognitive and psychiatric disturbances. The prominent characteristic physical symptoms are jerky, random, and uncontrollable movements called chorea which may be initially manifested as general restlessness, small, lack of coordination, or slowed saccadic eye movements. As the disorder progresses symptoms such as rigidity, writhing motions or abnormal posturing appears which leads to physical instability, abnormal facial expression, and difficulties in chewing, swallowing, and speaking leads to physical instability, abnormal facial expression<sup>[10]</sup>. Eating disorder results in weight loss and may lead to malnutrition<sup>[11]</sup> and Sleep disturbance<sup>[12]</sup>. Juvenile HD differs from these symptoms in that it generally progresses faster and chorea is exhibited briefly, if at all, with rigidity being the dominant symptom. Mutant Huntingtin is expressed throughout the body and associated with abnormalities in peripheral tissues that causes abnormalities include cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, muscle and testicular atrophy<sup>[13]</sup>.

Genetic influence (heredity) is one of the major causes in case of HD. The HD cannot be prevented by the inheritance of wild type HTT gene from a parent and it does not alter the activity of abnormal gene. Dominant inheritance in rare cases leads to 100% abnormal gene in HD<sup>[14]</sup>. Some of the symptoms like Bradykinesia, dystonia, depression, difficult learning, weight loss, motor movements and tremors have an resemblances with Wilson disease, Creutzfeldt–Jakob disease, forms of ceroid neuronal lipofuscinoses, chorea with red blood cell acanthocytosis, hereditary non-progressive chorea, paroxysmal choreoathetosis, mitochondrial disorders, corticobasal degeneration, basal ganglia calcification, forms of hereditary dystonia, Sydenham chorea, vitamin E deficiency, and cerebral vascular disease<sup>[15]</sup>.

### ORGANISATION OF Htt:

HD is a neurodegenerative disease (an autosomal – dominant) which originates from the basal ganglia of a brain. It has repeated CAG sequences (tandem repeats) in the first exon of IT15 gene in a chromosome 4p16.3. The expansion of CAG repeats leads to the formation of polyglutamine residues, codes a protein Huntingtin. It expressed in both brain and peripheral tissues<sup>[16]</sup>. Huntingtin protein has a molecular weight of 348-kDa. The huntingtin specific feature is polyQ at NH2 terminus. It has continuous sequences which associates with elongation factor 3, protein phosphatase 2A and TOR 1 repeats. It helps for protein-protein interaction. The Htt gene plays an vital role for producing huntingtin protein. The mutation of this gene leads to elongated stretch of glutamine (polyglutamine) in NH2 terminus<sup>[17]</sup>. The mutation of a huntingtin creates deleterious effect in brain cells. Meanwhile, it affects normal huntingtin

### Mutant HD gene expression



**Figure 1:** The CAG repeats more than 35 in number may lead to mutant htt due to the formation of polyglutamine residues.

for basic activities and survival. The pathology of HD is observed in brain specific with eminent cell loss and atrophy in the caudate and putamen<sup>[18]</sup>.

HD patients are homozygous for CAG expansion and seems to show progression than those of heterozygous for the mutation<sup>[19]</sup>. Lymphoblastoid cell lines studies reveal that homozygotes have a more aggressive molecular phenotype than heterozygotes<sup>[20]</sup>. Michael Hayden's team observed cell death can be modulated by normal huntingtin expression. Due to overexpression of wild-type huntingtin it suppresses the activity of a tk-RE1/NRSE-cat construct in 109/7Q knock-in cells, which indicates that wild-type protein repress the silencing activity of the RE1/NRSE and promotes BDNF gene transcription in HD<sup>[21]</sup>. Wild-type huntingtin expression in 109/109Q knock-in cells seems to be able to rescue release of BDNF, though the number of analyzed cells was in a minimizing factor<sup>[22]</sup>. Van Raamsdonk and colleagues in Hayden's lab recently done an in vivo experiment to know the overexpression of wild-type huntingtin in HD is beneficial. Crossingover was done between YAC128 mice were crossed with YAC18 mice to generate YAC18/128 mice carrying mutant huntingtin in human with 128Q of normal huntingtin which is overexpressed<sup>[23]</sup>. It was proposed that HD on treatment with wild-type huntingtin might not be sufficient to ameliorate the symptoms of the disease<sup>[24,25]</sup>.

#### **Structure of HTT:**

##### **The polyQ :**

The polyQ stretch in human huntingtin originated at the 18th amino acid<sup>[17]</sup>. In case of rodents, it shows a shorter polyQ . In higher vertebrates (particularly in mammals), the polyQ region is pursued by a polyproline (polyP) stretch . It was investigated that the polyP function may attribute in the stabilization of the polyQ tract in soluble manner<sup>[26]</sup>. The polyQ tract is an important one for huntingtin binding to its partners and that huntingtin interacts with a large number of partners<sup>[27]</sup>. The hypothesis of wild-type and binding of different set of interactors is helped with the presence of HEAT repeats. These repeats along with sequence needs protein-protein interaction<sup>[28]</sup>. HEAT repeats are found 40-amino acid-long sequences which occurs many times in a given protein and are take part in protein-protein interactions<sup>[28]</sup>. A recent study of HEAT repeats number and

distribution estimated total of 16 HEAT repeats in huntingtin, which are organized into 4 clusters<sup>[29]</sup>.

##### **Other consensus sites:**

Proteolytic enzymes are well-characterized in huntingtin and have consensus sites that cleave the protein to produce many fragments. Proteins like calpain, caspases, and aspartyl proteases are involved. And the enzymes like caspase-3, caspase-7 cleaves huntingtin at amino acids 513 and 552, and caspase -6 at amino acid cleaves at 586, and caspase-2 amino acid at 552<sup>[30,31]</sup>. Two specific calpain cleavage have been identified in the region of caspases cleavage sites of huntingtin protein in residues 469<sup>[25,32]</sup>. Caspase produce-independent cleavage from huntingtin and produce fragments which accumulate in the nucleus and cytoplasm<sup>[33,34]</sup>. Huntingtin in the field of proteolysis to cell functioning is unclear. According to the hypothesis associated with huntingtin's perinuclear and nuclear distribution and by the demonstration that the 17 amino acids following the polyQ region interact with the nuclear pore protein TPR (translocated promoter region), which exports proteins from the nucleus.

##### **GENETIC DEVELOPMENT OF HTT:**

Epigenetics refers to the changes in DNA or DNA packaging, occurs mitotically such that the regulation of gene transcription is altered without any change in the DNA sequence<sup>[35]</sup>. DNA methylation, an epigenetic mark in which methyl group is attached to the cytosine on 5' carbon at CpG dinucleotides<sup>[36]</sup>. The CpG sites are not present randomly from everywhere in human genome and they have enriched regions called CpG islands. DNA methylation is related with gene expression silencing at the promoter region of a gene<sup>[37,38]</sup>. DNA methylation is driven by variance of tissue similarity by cellular heterogeneity within a tissue<sup>[39]</sup>. In human brain samples (the striatum), confirmed DNA methylation changes the patterns in the adenosine A (2A) receptor (ADORA2A) and expression gene are low in HD patients. The DNA methylation has an relation between HD-related transcriptional dysregulation and methylation of DNA<sup>[40]</sup>. Rhes, a small G protein located in striatum, but its expression is seen in HD affected areas<sup>[41]</sup>. Rhes binds to mutant huntingtin, promotes its sumoylation, and augments its neurotoxicity in vitro in non-neuronal cells. Huntingtin-associated protein 1(HAP1) has two isoforms (HAP1-A and

HAP1-B) which are huntingtin's interactors. It expressed in brain tissues that interacts with the p150 subunit of dynactin, and also involved in intracellular transport. An another protein known as huntingtin-interacting protein 1 (HIP1), which binds to adaptin and clathrin. It mainly involved in endocytosis and cytoskeleton assembly.

#### **DNA methylation:**

Human blood samples were collected and targeted for HTT locus in which there was no association between HTT DNA methylation and age of onset<sup>[42]</sup>. DNA methylation profiles is carried out on genome level in which local DNA methylation at HTT gene locus in somatic tissues remain unknown, which may be useful in focusing HTT transcriptional regulation in HD pathology. Transcriptional regulation of the HTT locus in the field of DNA methylation had not been known.

#### **CAG REPEATS:**

In wild type alleles, CAG repeats has approximately 17-20 repeat and affected ones has more than 35 repeats.<sup>[43]</sup> Some studies shows no other symptoms for HD and it has CAG repeats from 27 – 35.<sup>[44]</sup> Due to genetic inheritance, the expandable CAG trinucleotides are not stable and it can transmit commonly by paternally. Generally, complete transmission has more than 40 and repeated sequence lengths varies from 35 to 39 in intermediate alleles.<sup>[45]</sup> At present, CAG repeated trinucleotides has been inversely proportional to the onset- age of the disease. Moreover, younger ones have longer CAG trinucleotides.<sup>[46]</sup> The percentage of onset age begins with the presence of genetic, epigenetic and environmental factors and also the CAG trinucleotides is related with the variability of age in disease<sup>[47,48,49,50,51,52,53]</sup>. On mitotic condition, the repeated sequences is mostly present in spermatogenesis which caused by replication slippage when compared with oogenesis. When paternally HD occurs to the offspring, the CAG repeats are more in number and symptoms has been develop at frequent stages<sup>[54]</sup>. The length of the CAG repeats is mostly associated with symptomatic onset<sup>[55,56]</sup>. The CAG repeats are highly common for HD but it couldn't seen as much in other neuropsychiatric disorders. Meanwhile, the CCG repeats has been analyzed which present adjacent to CAG repeats and also the haplotypes were found out. In case of Juvenile HD, the CAG repeats are higher in number and also linked with a disease. The CAG trinucleotides is

mainly due to onset-age and also environmental factors<sup>[47,54,55,57]</sup>. The normal huntingtin allele can also determine the disease severity. The wild-type huntingtin with expandable CAG repeats, results would be mutant protein fragments and leads to coaggregation<sup>[24]</sup>.

#### **GLOBAL EXTENSION OF HD:**

In Western populations, linkage disequilibrium was identified in normal and HD alleles between CCG 7 and larger CAG repeat length. Conversely, the association of CAG repeat numbers was with CCG10 in Japanese and Chinese populations<sup>[58,59]</sup>. In Caucasian population, a particular set of 22 tagging SNPs in HTT were related to the CAG instability of expansion<sup>[60]</sup>. Based on the inverse relationship between AAO and the CAG repeat number, the CAG normally exceeds 60<sup>[54]</sup>. In a study, the largest CAG repeat was reported with approximately 250 trinucleotides<sup>[61]</sup> followed by 214 and 180 copies<sup>[62]</sup>. Conversely, in JHD (Juvenile Huntington's Disease) cases the CAG repeats were about <60, or as low as 42. Between many generations, the CAG expansion is observed in sons and daughters, hence the sex of the parent is an important factor<sup>[63]</sup>. A single sperm study has demonstrated that the inheritance of HD from intermediate HD alleles and in normal families were about 10% and 6%<sup>[64]</sup>. These values are consistent with population studies in Caucasians. The high new-mutation rate may be related to the cis-element in specific predisposing haplogroups in Caucasians. The higher prevalence of HD in Caucasians is due to the high instability of the CAG repeat in haplogroups<sup>[60]</sup>. In the Japanese populations, the expanded alleles were associated with (CCG)10 with the percentage of 84.5% and in normal populations, the frequency is about 37.3%<sup>[65]</sup>. According to their study, the prevalence rate of CAG size is high on normal chromosomes of African Blacks, Japanese and Finnish populations have been found to be smaller when compared to Western populations<sup>[66]</sup>. Hence, the mean CAG repeat size varies from  $15.9 \pm 1.21$  to  $17.9 \pm 2.95$ . But the mean value is about  $16.8 \pm 2.08$  which is close to the frequency observed in African and Oriental populations<sup>[67]</sup>. In Western families, inheritance of transmission between father-child pairs is found to be higher as compared to that of mother child pairs with Huntington disease<sup>[68]</sup>. The CAG repeats were studied with the help of specific haplotypes in each population of South African.

**Table 1:** The frequency of HD and CAG repeats has been studied in top most countries and shown in the above table.

S. No	Population	CAG repeats (in numbers)	Reference
1	Scotland	35	Barron LH,1993
2	America	36	Stine OC,1993
3	Italy	37	Novelletto A, 1994
4	Canada	38	Andrew SE 1993
5	German	39	Zuhlke C,1993
6	Danish	39	Norremolle A,1993
7	Russia	41	Illarioshkin SN,1994
<b>Frequency of HD</b>			
8	United State	54	Pearson js,1995
9	Western Scotland(Uk)	52	Bolt jm, 1970
10	East Anglia (UK)	92	Caro a, 1977
11	France	70	Leger jm,, 1974
12	Germany	27	Wendt gc,, 1972
13	Victoria	46	Brothers crd, 1964
14	South Africa	22	Hayden MR, 1980

**Table 2:** Distribution of HTT: Indian study.

S. No	Year	Authors	Title	No. of samples	Polymorphism	Conclusion
1	2000	PramanikS, Basu P, Gangopadhaya PK et al.,	Analysis of CAG and CCG repeats in Huntingtin gene among HD patients and normal populations of India.	28 cases	HD: 41 to 56 CAG repeats	Prevalence of HD in Indian populations may not be as high as in Western populations
2	2016	Chandrasekhar Gopalakrishnan, Shraha Jethiet al.,	Biophysical Aspect of Huntingtin Protein During polyQ: An In Silico Insight	In silico analysis	Gene with 141–157 units gives a progressive, neurological phenotype similar to HD	Mutant Htt 36Q showed more protein–protein interaction (with PACSIN1) when compared to native Htt (with PACSIN1).

3	2003	Saleem Q, Roy S, Murgood U, Saxena R, Verma IC, Anand A,	Molecular analysis of Huntington's disease and linked polymorphisms in the Indian population	HD samples = 30 Controls =250	<b>Normal population:</b> (9 to 33 repeats). The HD mutation in families did not show any significant association with either the (CCG)7 or (CCG)10 allele while haplotype analysis suggested the over-representation of the 7-2-1 (CCG-D4s127-Delta 2642 loci) haplotype in a subset of families.	The distribution of CAG repeats in the normal population suggests a higher prevalence of HD, closer as that of Western Europe. Haplotype analysis suggests the presence of a founder mutation in a subset of families and provides evidence for multiple and geographically distinct origins for the HD mutation in India
4	2015	C. Venkatramaniah . A. Mary Antony Praba	A study on the behaviour of huntington's chorea rat models on rotarod: treated with withanolide a and the ethanolic extract of withania somnifera	6 rats	Nil	In this study they have pretreated the animals with the formulated drugs and performed lesion surgery to produce HD which is equivalent with human HD.
5	1997	WK Ng MRCP, BT The MBBS et al.,	Huntington disease in Malaysia: a clinical and genetic study	4 chinese 1 malay 2 Indian	Difference in CAG trinucleotide polymorphism at residue 2642 is related to CAG size on normal chromosome and CCG triplet sequence is 3' adjacent to the CAG repeat is polymorphic	The interim results reveal that HD exist in all major racial groups in Malaysia. All cases have in excess of 35 (CAG) trinucleotide repeats on chromosome 4p16.3

6	2015	Sheth J, Shah S et al.,	A Study on Triplet Repeat Expansion Disorders in Western Indian Population	HD patients= 172 suspected patients =50, for HD, 79 for SCA, 20 for FA and 23 for MD	For FA, Frataxin gene (FXN) gene was amplified. and for MD, DMPK1 gene was amplified and for SCA (ATXN1, ATXN2, ATXN3 and CACNA1A) were amplified	79 patients investigated for SCA and 34 patients have increased CAG repeats,9 patients of FA have GAA repeats,17 patients are diseased with CTG repeats.
7	2015	Zahara Ali a,b, Mohammad Waseema et al.,	Unveiling the interactions among BMPR-2, ALK-1 and 5-HTT genes in the pathophysiology of HAPE	200 HAPE patients (high altitude pulmonary edema)	The genetic variants of BMPR-2, ALK-1 and 5-HTT associated with HAPE risk independently and in an interactive manner. The interactions of variants contributed more to the biomarkers BMP-2 and 5-HT and hold information about the phenotype than individual SNPs, improving the predictive accuracy of the disease.	The article reveals that the genes, BMP-2, ALK-1, 5-HTT, TPH-1, under stress were differentially expressed, which may eventually lead to a susceptible condition due to change in physiological function.
8	.1990	ShiwachRS, Lindenbaum RH	Prevalence of Huntington's disease among UK immigrants from the Indian subcontinent	Not known	There are no epidemiological studies of HD from India hence a survey of immigrants from the Indian subcontinent to Britain found that 22 patients among immigrant population of 1.26 million, showed the prevalence with an estimate of 1.75 100,000.	Not known
9	2001	Uday A. Murgod a , Quasar Saleem b,c, et al.,	A clinical study of patients with genetically confirmed Huntington's disease from India	4 patients 15.4% with Juvenile HD	The mean (SD) CAG repeats on normal alleles in sample was 18.0 (2.4) while in the abnormal allele the CAG repeat length was 48.4 8.7 . The number of CAG repeats shows a significant positive correlation with the age at onset of illness	In 88.5% of patients presented with neurological symptoms, while a few are 11.5% presented with psychiatric symptoms. Among the neurological symptoms, as in other reports 10 , chorea was commonest, and was the initial symptom in majority of our patients 88.5% .

The molecular genetics history of the Caucasian and mixed subpopulations were imaginable, but the results found out that there was an similarity in Caucasian population and mixed population. The prevalence of HD modified from zero in Alaska, Idaho & North Dakota to 4.09 per million samples in South Dakota. The death rate was thought to be high (1.35 million per year ) in the North Central & West regions when compared with South (0.93 per million per year). During this time, the death rate was reduced for HD whites. All-encompassing, the rates were 1.22 million per year for whites and 0.38 million per year<sup>[68]</sup>. Kurtzke,<sup>[69]</sup> concises the death rate in United States. The rude death rate was examined in Sweden at 1969-74 which has 1.71 prevalence and Denmark has 1.76 per million population in the year of 1971-1975. The frequency of HD and disorders has been analyzed in the Brazilin families and reported that there was no family history, but the clinical aspects were same in HD and non HD Patients. There might be a negative correlation between number of CAG sequences and age of disease<sup>[70]</sup>

In China and Japan, the prevalence of HD was estimated as 0.1-0.5 per million<sup>[71,72]</sup>. In Scottish population, the normal prevalence ranges at 16 and HD ranges at 41 whereas there was no overlap of the two existence. Here, they found out normal alleles ranges from 8-33 triplets and HD alleles ranges from 35-62 triplets. In Saudi, HD was confirmed by PCR with the help of repeated gene and migration of the diseased gene to Saudi Arabia, leads to HD. The de novo mutations of prevalence in HD is significant<sup>[73]</sup>. If de novo mutations arise in the ranges of 27-35, alleles attains the CAG size would be closer to that range. In general population, 21% of Caucasian alleles have more than 20 repeats when compared with 8% black alleles. The prevalence of HD in Canada was estimated 12.6-14.8 per 100000 in general and 17.2 per 100000 in Caucasian population<sup>[74]</sup>. The prevalence of HD in Mexican population was estimated by the presence of alleles in the CAG region of chromosome 4p16.3. In Spanish families, the HD alleles were diagnosed by gathering the information from HD patients and also it resolved by genetic counseling. In Singapore, the repeated sequences were performed by using Metaphor gel sizing and GeneScan. The 63 HD patients was examined, totally 45 – 54 repeats were present in HD allele whereas normal ranges between 15 to

30 repeats<sup>[75]</sup>. In Malaysia, the prevalence of HD was investigated 5-10 persons per million. The prevalence of HD in Hong Kong is 0.4 per million. Recently studies shown that the prevalence of HD in Japan was 0.65 per million and 0.5-1.0 per million<sup>[76]</sup>.

#### **INDIAN SCENARIO:**

Indian sub-continent represents one of the most ethnically and genetically diverse regions of the world. In 2000, one study from India analyzed the distribution of CAG and adjacent CCG repeats which has also been the target of many molecular studies in the Huntingtin gene in 28 unrelated, clinically diagnosed HD patients and in normal individuals belonging to different ethnic groups. The expanded CAG repeats in patients ranged from 41 to 56, whereas in normal individuals this varied between 11 and 3. For the first time, a study has reported one four-repeat CCG allele which has not been identified in any population so far and also suggested; among the Indian population the overall prevalence of HD may not be as high as in Western population<sup>[77]</sup>. Even though variations across ethnic groups, the overall prevalence of HD in Indian populations is expected to be low, whereas one of the two Austro-Asiatic speaking tribal population had the lowest mean of CAG repeat size and does not have normal alleles greater than 18 CAG repeats. It has been explained that these Austro-Asiatic speaking groups moved from Africa and settled in India 60,000 years ago<sup>[78]</sup> and the CTG repeat variation in these populations in the DM-PK gene and CAG repeat variation in the HTT gene support this notion. The ranges of the expanded repeat in HD were similar to the other populations obtained earlier.<sup>[79,80]</sup>

#### **CONCLUSION:**

The prevalence of HD varies between different geographical regions where there is a consistent result with a lower incidence in Asian population. There are also evidences that shows higher incidence rate over the past 50 years in Australia, North America and in Western Europe. The difference in prevalence is elucidated by huntington gene haplotypes. Whereas in India, the research is less but from previous findings it is known that the overall prevalence is not as high as when compared with Western population. When compared with the studies in North and South Indian population it was noted that the prevalence of juvenile HD



was higher in South Indian cohort. From this data, we conclude that the prevalence is less in India and further studies need to be done to identify the origin of HD mutation in Indian population.

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