Review Article

Short Stature: Understanding the Stature of Ethnicity in Height Determination

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Abstract

Height is a polygenic trait with a high degree of heritability. Most (95%) children with short stature (defined as height below the third percentile) and poor growth (growth velocity <5 cm/year) do not have an endocrine disorder. The genetic basis for stature potential has been evaluated in recent years and is increasingly being recognized as a major basis for variation in height between different ethnic populations. Numerous genome-wide association studies have identified hundreds of loci linked to human growth. Apart from the genetic factors, various environmental, nutritional, hormonal, and socioeconomic factors also influence the height, and stature of individuals varies between different geographical locations and ethnic groups. Ethnically different populations might respond differently to the same environmental factors and thus the final height in different ethnic groups is different. This review covers in detail the short stature of African Pygmies and Andamanese Islanders along with the possible causative factors responsible for the variation in height in these ethnic groups.

Keywords: Andaman, ethnicity, GH, growth, IGF1, pygmies, Sardinia, short stature

Introduction

Height is a polygenic trait with a high degree of heritability. Numerous genome-wide association studies have identified hundreds of loci linked to human growth.[1,2] Apart from genetic factors, various environmental, nutritional, hormonal, and socio-economic factors also influence the height, and stature of individuals varies between different geographical locations and ethnic groups. Ethnicity is an important factor determining the stature of an individual, and ethnically different populations might respond differently to the same environmental factors and thus final height in different ethnic groups is different. This review arose from the need to address in detail a query from the audience in one of the Endocrine Society of India meetings (Voice of Endocrinology) regarding reasons for short stature in African Pygmies. The immediate correct answer for the query that came to mind was "resistance to GH action." However, we felt the need to discuss and delve into this query in detail. Individual curiosity has always been a driving force for innovation facilitated by the Endocrine Society meetings. In this context, we try and go into details of short stature in populations and various factors for short stature in different ethnicities.

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Defining short stature

Compared with a well-nourished, genetically relevant population, short stature is defined as a standing height more than 2 standard deviations (SDs) below mean (or below the third percentile) for sex.[3] Reference data for height, weight, and head circumference have been published for many countries. These references also have data subclassified for most ethnic subpopulations (including blacks and Asians), and several common genetic disorders (achondroplasia, Turner syndrome [TS], Down syndrome, etc.). Skeletal maturation is assessed by bone age, which is compared using X-rays of the left hand and wrist to standard reference charts (Greulich Pyle, Tanner Whitehouse) or by computerized techniques such as BoneXpert (Tanner Whitehouse version 3 by Vicinia, Denmark).

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By definition, 2.5% of the population is normally short. One of the largest population-based surveys of growth in children that assessed the stature and growth velocity in nearly 115,000 American children found that most (95%) children with short stature (height below the third percentile) and poor growth (growth velocity <5 cm/year) did not have an endocrine disorder (n = 555). Interestingly, 48% of children with growth hormone deficiency (GHD) or TS were either undiagnosed or untreated.[4]

Short stature: Individual vs. ethnic

Short stature may be normal. Normal variations in stature are often related to ethnic background. For example, tall for a Chinese individual may be short for an American individual. Obtaining the family history of growth patterns and direct measurement of parents' height is crucial to determine the genetic potential for growth in a child [Table 1].

Malnutrition remains the most common cause of growth failure worldwide. Major causes of short stature such as malnutrition, chronic infections, parasites, although are not race-specific, have led to secular variations in stature over several years because of chronic endemicity in a particular geographic region, and manifest as ethnic short stature in several tribes and populations. The genetic basis for stature potential is being comprehensively evaluated in recent years and is increasingly being recognized as a major basis for variation in stature between different ethnic populations.

When we look from a clinician's perspective evaluating an individual with short stature, we need to keep in mind the familial short stature and GH resistance. Low serum IGF1 but normal-to-high GH levels are seen in congenital IGF1 deficiency syndromes. These diseases may result from (1) GH-releasing hormone receptor (GHRH-R) defects; (2) GH gene deletion (isolated GH deficiency, IGHD); (3) GH receptor (GH-R) gene deficiency (Laron syndrome); and IGF1 gene defects. Other conditions of congenital IGF1 deficiency include post-GH-R signaling anomalies (e.g., STAT5 defects), acid-labile subunit (ALS) mutations, and the mutation in PPA2 protein. The inability to identify a cause for short stature is labeled as idiopathic form. However, for this review, we looked at the role of ethnicity in short stature among different populations as a whole [Table 2].

Ethnicity and stature: India

Population stature is a function of geography, climate, and ethnicity. The effect of ethnicity on stature was studied in population groups of 601 individuals in the People of India project by the Anthropological Survey of India. In the ethnic groups from varied geographical and climatic zones, adult stature ranged from "very short" (130–149 cm) to tall (170–179.9 cm).[5] The stature varied as per the geographical location, climate, and ethnicity. It would therefore be reasonable to conclude that variations in stature in different ethnicities in the Indian subcontinent may be for various reasons including within-group endogamy, huge diversity in food habits, and social customs of various ethnic groups. Ethnicity plays a greater role in determining the mean stature in populations. In its latest report, the National Institute of Nutrition (NIN), Hyderabad, looked at nationally representative data from the National Family Health Survey-4 (NFHS-4, 2015–16), the National Nutrition Monitoring Bureau (2015–16), the World Health Organization (2006–07), and the Indian Academy of Paediatrics (IAP, 2016) to derive acceptable average height values, for which the 95th centile was taken as a representative of full growth potential.[6] The average height given for males was 177 cm and for females was 162 cm.

Ethnicity

India was divided into various ethnic groups as per caste and communities as schedule tribe (ST, original settlers of region), scheduled caste (SC, the lowest of the Hindu caste hierarchical system), general caste (Hindu caste and subcaste apart from schedule caste), and others that constituted the minority groups. The general category had the highest stature amongst all zones (except the West zone), whereas SC and ST had the lowest mean stature. In the West zone, the others group was the tallest probably because of the Parsee community who have migrated from South-West Asia. Regression analysis showed that general caste and "Others" were taller than SC and ST by approximately 4.4 cm.[5]

Geographical location and climate

Humans follow the ecological rules of Bergmann and Allen.[7] India has been populated by human groups carrying a diversity of genes and cultural traits. Ethnicity, geographical location, and climate are highly interrelated and it is difficult to correctly identify the actual effect of each separately.

The study from the People of India Project concluded that the effect of ethnicity is considered a dominant determinant of adult stature. The mean adult stature ranged from 154.57 cm in the Islands to as high as 165.05 cm in the North. The

Table 1: Short stature clinical evaluation based on comparison

Level	Evaluation method	Remarks
Individual	Peers in school–same class (crude)	Crude
Family	Parents (direct height and growth patterns)	Mid-parental height taken into consideration
	Siblings	
Population	Ethnicity	Below the third centile for population
	Well-nourished	
	Same sex	
	Genetically relevant	

population was also classified as per variations in temperature, rainfall, and humidity (seven geographical zones). Population belonging to the semi-arid steppe climate was the tallest (mean: 167.11 cm) and those of monsoon with dry winters were the shortest (Mean: 154 cm).[5] Variations in the geographical and climatic zones were less significant in "Between" ethnic groups as compared to those in "Within" ethnic groups. This effect of ethnicity on stature persisted even if conditions such as climate and geographical location remained the same.

Ethnicity and stature: World

When we take a world-view of short stature, as compared to geographical location, the tribal origin is more closely related to the stature. The stature of various ethnic groups in the African subcontinent varies more than the Europeans. Seventeen African ethnic subgroups have a lower mean stature than the shortest European population.[8] The tallest are the Dinkas of Sudan who have a characteristic low weight for height and have a linear physique with a mean height of 181.6 cm, whereas Pygmies of Congo, who have a mean height less than 150 cm, are at the other extreme. Surprisingly, countries, such as Kenya and Congo, have various tribes with varying mean stature ranging from 150 cm to 173.5 cm. Amongst the European population, Sardinians are the shortest, whereas the Pacific Islanders and Dutch are the tallest.[9] The WHO's Multicenter Growth Reference Study (MGRS) collected the data from 8,440 affluent children of varied ethnicity from six countries (India, Brazil, Ghana, Norway, Oman, and the USA). Linear growth (length and height) for age group 0 to 5 years was strikingly similar in all six sites with a difference of less than 0.2 SD and thus data were pooled and normative curves representing the single international standard from birth to 5 years of age were prepared.[10] It was concluded that all breastfed children aged 0 to 5 years, from economically advantaged countries grow in a similar fashion and thus a single set of growth charts can be used. Data from MGRS were compared to the pooled data of over 11 million children belonging to 55 countries/ethnic groups, which are not constrained by economic hardships (United Nations' Human Development Index (UN HDI) score >0.75). There was no significant variation in mean height from birth to 5 years of age and it fitted within ± 0.5 SD of MGRS means.[9] However, 20% of the total means were >0.5 SD above MGRS mean and these included participants from Pacific Islands, Netherlands, and Finland who were taller and thus constituted the + 0.5 SD outliers.[11] The majority of children from the Pacific Islands were obese (body mass index [BMI] >90th percentile) that could have accounted for increased height in childhood but not in adults.[12] However, taller height in a Dutch cohort remains unexplained as the majority had BMI <50th percentile. Infants of Iceland,[13] Denmark,[14] Netherlands[15] were longer as compared to MGRS means and constituted the outliers at 12 months of age. Data from the German cohort collected until 5 years of age showed that the mean of German boys and girls lay at 60th and 62nd centiles, respectively.[16]

These ethnic variations have to be kept in mind while using the WHO MGRS reference curve, for the taller European population might falsely underestimate short stature while using the same for shorter Asians, and the Arabian population might overestimate the numbers for short stature. Also, tribes such as Pygmies (Aka, Mbuti, and Efe), Andaman Islanders are shorter, and thus the WHO standards cannot be used for growth monitoring in them.[9]

Secular Changes: Average height increases incrementally over generations. This was exemplified by the observed increase in the mean height in schoolchildren aged 3 to 18 years from Indian data published in 2011.[17] In countries such as Denmark, Sweden, and the Netherlands, where there are no socioeconomic constraints, secular changes leading to increment in population height can still be seen. Amongst countries in the WHO MGRS study, probably only Norway has reached the peak of secular trend, whereas other countries are still on their way up.[18]

Why are the shortest ethnic groups short?: Causes Demystified

1. **Pygmies:** "Pygmoi population" has an average male adult height <150 cm with reasonably well-conserved body proportions. They reside predominantly in Africa (Aka, Baka, Bezan, Efe, and Twa Tribes) and a few clusters around the world.[19] Pygmies, commonly known as "hunter-gatherers," have reduced standing height and shorter sitting height and leg length as compared to neighboring farmers. The cause of dwarfism in Pygmies has always been enigmatic. Because most Pygmies are illiterate and to most of them their exact age is not known and due to their inherent shy, nomadic nature, longitudinal studies to determine the etiology of short stature are difficult.[20] The various postulated causes of their short stature include [Table 3]:
    a. Defect in the GH/IGF1 axis: Although their physical characteristics resemble those of GHD, they have normal GH concentration after provocation testing. They have insensitivity to somatomedin and defects in IGF1 secretion with a normal IGF2 secretion. Also, like patients of GHD, they have prolonged hypoglycemia after the insulin tolerance test and show a reduced response to arginine/glucose stimulation. Treatment with GH does not increase insulin secretion and sulfation activity in Pygmies.[21]
    b. Genetics: GH gene expression has been found to be 1.8 times lower and the GH receptor (GHR) gene expression to be 8-fold lower in adult Pygmies in comparison to sympatric adult Bantu tribes.[22] A study on Baka Pygmies showed that they have normal length at birth but for the next 2 years, they have slower growth, and thereafter their growth again follows the standard pattern and they have a growth spurt in adolescence.[23] Recently, an *HYAL-2* gene variant has been implicated in their short stature.[24] The role of genetics still cannot be overlooked as Pygmies with

genetic admixture with neighboring non-Pygmies are taller.[25]

c. Environmental factors: Other postulated theories for short stature include an adaptation to food scarcity[26] and hot and humid climates.[27] However, as per recent studies, climate and forest density also do not play a major role as was thought earlier.[25] Some theories, for example, the preference of shorter partners contributing to their shorter stature, have been refuted in further studies.[28]

2. **Sardinians:** The Mediterranean island of Sardinia has the shortest stature amongst all European tribes. The stature of Sardinians has rapidly increased after World War II. The study of this tribe has also given insights into various causes and mechanisms that have led to shorter stature in certain ethnic groups.[29] The relative importance of each of these factors is difficult to determine but rapid increase in stature after World War II highlights the impact of environmental influences and probably that these ethnic tribes never reached their genetic potential due to socioeconomic constraints and poor sanitary environment, which were partly eliminated in the 20th century. The postulated causes include [Table 3]:
   a. Genetics: Variants in the *GHR* gene and *KCNQ1* gene have been linked to short stature in the Sardinian population.[30] Also, females with genes for short stature had an increased number of children. A similar pattern of fecundity and height has been seen in western populations.[31]
   b. Epigenetics: Although DNA methylation data are not available, available epigenetic studies implicate intergenerational persistence of epigenetic markers induced by socioeconomic adversities, infectious diseases, and chronic malnutrition and these growth phenotypes require several generations to return to normal once conditions improve.[32]
   c. Nutrition: Milk-based diet, scarcity of resources, and shortage of water led to malnutrition. Poor prepubertal nutrition led to shorter legs with respect to the trunk. Shepherds who were predominantly protein consumers had higher stature as compared to peasants who predominantly consumed a carbohydrate-based diet. Short stature exemplifies the FOSTER rule or Insular dwarfism (limitation of food resources leads to a smaller size) and thus leads to the selection of stature-shortening genetic variants.[29]
   d. Infection: A high prevalence of malaria led to chronic IUGR and decreased childhood growth and mortality. Due to selective pressure of malaria, there was an increase in the frequency of β-thalassemia that further led to secondary hemosiderosis and thus delayed puberty, hypogonadism, and compromised adult stature. Prevalence of *H. pylori* was also found to be high (38–60%), especially in socially disadvantaged groups, and infected individuals were found to be shorter than the non-infected population.[33,34]
   e. Autoimmunity: Sardinia is called the island of autoimmunity and has the maximum prevalence of type 1 diabetes, celiac disease, and multiple sclerosis amongst Europeans.[35] Type 1 diabetes with uncontrolled glucose leads to hypothalamic–pituitary dysfunction and reduced levels of GH/IGF1, leading to short stature. The prevalence of celiac disease and HLA DR3DQ2 is also very high, leading to GH resistance and associated autoimmune thyroiditis, and subclinical hypothyroidism further compromises the final stature.[29]
   f. Helminthic infestations: Chronic infestation leads to decreased absorption of nutrients and systemic inflammation. In contrast, the hygiene hypothesis dictates that the decline in helminthic infestations has

Table 2: Factors affecting stature via ethnicity

Geographical location
Tribal origin
Nutrition (food scarcity)
Climate (hot-humid)
Infections (malaria)
Infestations (helminths)
Autoimmune diseases
GH/IGF1 axis defect (GH resistance)
Genetic
Epigenetic
Environmental factors (e.g., endocrine disruptors)

Table 3: Known ethnic short stature populations

Population	Region	Causes for short stature
Pygmies (Aka, Kola, Baka, Mbuti, Bezan, Efe, and Twa Tribes)	Africa (Kenya, Congo, Uganda, Cameroon, others)	Defect in the GH/IGF1 axis Genetic Environmental (food scarcity, hot humid climate)
Sardinians	Europe (Italy)	Genetic, epigenetic variation Food scarcity Infection (malaria) Infestation (Helminth) Autoimmunity
Andaman Islanders (Great Andamanese, Onge)	Islands of Nicobar and Andaman, India	Geographic location Genetic

resulted in an increase in immune-mediated diseases. Thus the effect on stature is complex.[36]

3. **Andaman Islanders:** Islanders of Andaman have the shortest stature in India. The word "Negritos" is commonly used for Andamanese and other short-statured Asians because they resemble Pygmies of Africa in having short stature with dark skin and scanty body hair. The three major tribal groups of the Andaman Islands include Great Andamanese, Onge, and Jarawa Tribes and although all three reside in the same geographical location, their heights show marked variation and significant secular trend. Various causes have been postulated to explain these variations [Table 3]. These 3 tribes established friendly relations with British and Indian governments at different times.[37] The Great Andamanese had contact with the British at the peak time of infection epidemic and mortality and thus had the lowest stature during that period. Onge tribe's stature was also documented to be the lowest during the 1920s when they had first interaction with the government and it showed marked improvement post-independence. People of the Jarawa tribe are hunter-gatherer, nomadic, ecosystem-friendly and they managed to be isolated from the colonization effect until the 1970s and thus have the highest stature with respect to others.[37] An analysis of Y chromosome satellites, mitochondrial DNA sequences, and RFLP polymorphism showed that Andamanese have closer affinity to Asian and not to African population.

Genetics of ethnic short stature

What is considered as "normal variation" in adult height is predominantly due to inherited, genetic factors. More than 80% of the variation in height is explained by genetic factors that are polygenic (example of a highly polygenic complex trait) with a relatively high degree of hereditability.[2,38-41] Environmental factors contribute to differences between populations and secular increases in the average height across generations. The characteristic difference in a polygenic trait is that slight coordinated shifts happen in frequencies of alleles (large number with small effect due to each allele) as compared to monogenic ones where change is abrupt and with visible effects such as achondroplasia.[2]

Genome-wide association studies (GWAS) have identified approximately 700 common variants that are common in the population (frequency of approximately ≥5%) and each having small recognizable effects on determining adult height.[39,42,43] There could be additional, as yet unidentified variants accounting for further height variation.[44] The source of the remaining genetic contribution to adult height may arise from unidentified variants of slightly lower frequency, from much rarer variants, or genetic interactions among variants. Known common variant contributors to height play less of a role in individuals at short tail of height distribution (below 0.5 percentile).[45] At extremes of short stature, patients often have mutations in single genes, resulting in large effects on height (example, achondroplasia). Thus, some individuals with significant short stature carry a variation in a single gene (monogenic) that plays a major role in determining their height. Copy number assessment can be an important part of the diagnostic evaluation of patients with short stature based on studies that have found pathogenic rare copy number variants (CNVs) in 4 to 10% of patients referred for short stature.[46,47] Rare recessive mutations may play a role and risk would depend on the extent of homozygosity (how much DNA has been inherited identically from both parents).[48]

In another GWAS on a population-based cohort of around 10,000 individuals from Netherlands and Germany, the variation in the C-type natriuretic peptide signaling pathway, involving the natriuretic peptide precursor type C (NPPC) and natriuretic peptide receptor 3 (NPR3) genes, was shown to play an important role in determining height.[49]

The causative mechanisms for short stature in Pygmies still remain debated. Understanding the molecular mechanisms involved is important from both a clinical and evolutionary point of view. This knowledge could provide additional information regarding potential novel causes in children with idiopathic short stature.[50] A study of different Pygmy groups has identified candidate genes contributing to their short stature phenotype.[51] *HESX1* (encodes a homeobox-containing transcriptional repressor that plays a critical role in the development of anterior pituitary), *APPL1* (involved in crosstalk between adiponectin and insulin signaling pathways), *ASB14* (encodes a SOCS box protein), and sperm-motility gene *DNAH12* are some of the identified genes.

Hyaluronoglucosaminidase-2 (*HYAL2*) gene is localized on human chromosome region 3p21.3 described to be associated with the short stature in Pygmies, containing loci associated with growth hormone (GH), insulin, and insulin-like growth factor (IGF) signaling pathways, as well as immunity and neuroendocrine signaling involved in reproduction and metabolism.[52] The positional candidate gene *DOCK3*, known to be associated with height variation in Europeans, and *CISH*, a negative regulator of cytokine signaling known to inhibit GH-stimulated STAT5 signaling is also located in this region. *HYAL2* encodes for a GPI-anchored cell surface protein that degrades hyaluronan, one of the major glycosaminoglycans of the extracellular matrix. Hyaluronan and its degradation fragments are thought to be involved in cell proliferation, migration, and differentiation.[53] In an attempt to identify genetic variants associated with short stature, a recent study on individuals from two Cameroonian populations, specifically hunter-gatherers Baka Pygmies and their neighbor Bantu non-Pygmies farmers, whole-exome sequencing (WES) analysis revealed 29 single nucleotide polymorphisms (SNPs) significantly associated with reduced height in the Baka Pygmies population.[24] The identified rs7629425 variation, located in the 5′-UTR region of the *HYAL2* gene, may have a role in determining the short height in Pygmies according to them.

Table 4: Choosing the right growth chart

Basis	Criteria	Preferred growth charts	Remarks
Age	Children <5 yr	WHO charts	
	5-18 yr	Ethnicity specific growth charts	Other charts:
		(India: Khadilkar/IAP charts 2015)	NCHS 1977, Agarwal 1989, CDC 2000
Sex	Male	Male charts	
	Female	Female charts	
Specific	Adopted child	Specific charts from the country of origin for first generation	After that charts specific to the adopting country
	Disease-specific	Turner syndrome	
		Achondroplasia	
		Down syndrome	
		Others	

A major proportion of adult height diagnostics is dependent upon GH and IGF-I axes. GH, GH-binding protein (GHBP), ALS, and IGF-I are key molecules involved in human growth.[43,54] Detecting their abnormal secretion in human growth disorders is often used for the diagnosis of endocrine short stature. There is, however, still a gap in understanding the huge phenotypic complexity of stature where components of the GH/IGF1 axes contribute only a small part of the variability of normal human growth.[55] Genetic testing plays a very small role in the current standard evaluation performed by endocrinologists. Genetic evaluation in the future may play a much larger role in the evaluation of growth disorders, and endocrinologists need to deal with modern genetic diagnostics to best determine the causes for a wide variety of short stature.

Significance of ethnicity for height evaluation

Accepting the major role of ethnicity in stature, it is accepted that national or regional growth charts should be used for defining short stature to account for height variations in various ethnicities and geographical locations. Christesen *et al*.[56] compared the WHO growth reference chart with the national growth references in 5,996 patients with short stature (GH deficiency/TS/SGA) in nine European countries and showed that a significantly lower number of patients had height below the cut-off. Thus, a higher number of patients were missed when the WHO standards were used and wherever possible, most recent national or regional growth charts and guidelines should be used.[56] In India, Khadilkar growth charts have been widely adopted for assessing growth in children.[57,58] The recommended growth charts for appropriate clinical evaluation are summarized in Table 4.

Conclusion

Stature of individuals varies between different geographical locations and ethnic groups. Ethnicity is an important factor determining the height of an individual. Ethnically different populations might respond differently to the same environmental factors and thus the final height in different ethnic groups is different. Height is a polygenic trait with a high degree of heritability. Numerous genome-wide association studies have identified multiple loci linked to human growth. Various environmental, nutritional, hormonal, and socioeconomic factors also influence height. Understanding the basis for these variations in height has led researchers to identify and better understand pathogenic disorders of growth.

This article has its origins in the discussion during one of the Endocrine Society meetings. As Albert Einstein said, "I have no special talents. I am only passionately curious." Various Endocrine Society educational fora can serve as a discussion board for widening the spectrum, bridging gaps, and enhancing knowledge into different aspects of endocrine disorders.

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Conflicts of interest

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