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Genetic short stature

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ABSTRACT

Adult height and growth patterns are largely genetically programmed. Studies in twins have indicated that the heritability of height is high (> 80%), suggesting that genetic variation is the main determinant of stature. Height exhibits a normal (Gaussian) distribution according to sex, age, and ancestry. Short stature is usually defined as a height which is 2 standard deviations (S.D.) less than the mean height of a specific population. This definition includes 2.3% of the population and usually includes healthy individuals. In this group of short stature non-syndromic conditions, the genetic influence occurs polygenically or oligogenically. As a rule, each common genetic variant accounts for a small effect (1 mm) on individual height variation. Recently, several studies demonstrated that some rare variants can cause greater effect on height, without causing a syndromic condition. In more extreme cases, height SDS below 2.5 or 3 (which would comprise approximately 0.6 and 0.1% of the population, respectively) is frequently associated with syndromic conditions and are usually caused by a monogenic defect. More than 1,000 inherited/genetic diseases have growth disorder as an important phenotype. These conditions are usually responsible for syndromic short stature. In the coming years, we expect to discover several genetic causes of short stature, thereby explaining the phenotype of what we currently classify as short stature of unknown cause. These discoveries will have a profound impact on the follow-up and treatment of these children.

1. Introduction

Height is a typical human trait that has a normal distribution. Therefore, short stature is defined as a height 2 standard-deviations (SD) below the mean of a specific population adjusted for age and gender; this group corresponds to approximately 2.27% of the population. Stricter classifications define short stature as heights 2.5 to 3 SD less than the given population's mean height; this group represents about 0.62 and 0.13% of the general population, respectively. Several factors can be responsible for a child's lack of longitudinal growth, thereby leading to a short adult height. Ultimately, these factors influence cell multiplication and differentiation globally and/or primarily affect the development and growth of the skeleton, which is the main determinant of height. It is widely accepted that height is strongly regulated by genetic factors which, therefore, are also key causes of short stature.

In the late the nineteenth century and early twentieth century, pioneer researchers like Francis Galton (1822–1911) and Ronald Aylmer Fisher (1890–1962) determined that inherited factors from parents can influence an individual's height. Researchers have continued to debate if height and consequently, short stature and its origins, are caused by monogenic or polygenic factors, since the XX century [1]. In this review, we highlight the main genetic influences responsible for height variability and the different forms of short stature.

2. Heritability of height

Studies in the 1970's demonstrated that the heights of adopted children correlated more closely with the heights of their biological parents than with those of their adoptive parents [2], therefore pointing to the role of genetic inheritance in determining height. In this century, large-scale studies focusing on the height variability between twins and members of large families consistently demonstrated that human height is heritable. A study analyzing the heights of 6,752 individuals from 2,508 families determined that the heritability of height varied from 0.75 to 0.98 [3]. Another study that analyzed 30,111 pairs of twins from 8 different countries estimated that between 0.87 to 0.93 of the height of adult men and 0.68 to 0.84 of adult women could be attributed to genetic heritability [4]. More recently, a large study has evaluated 45 pairs of twins from 20 different countries, including 180,520 pairs of twins from 1 to 19 years old [5]. The results of this study

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showed that height variability is more strongly determined by environmental factors in early childhood, whereas genetic factors play a bigger role in determining height in adolescence (0.83 in boys and 0.76 in girls) [5]. These studies demonstrate that genetic factors strongly influence the height variability of healthy individuals from infancy to adulthood. Although, beyond the scope of this review, it is equally accepted that epigenetic factors have an influence on height variation among individuals, generations and populations [6,7] as well as be responsible for several short stature conditions [8,9].

Investigations of the molecular basis for genetic influence on growth focused on two main types of studies [10]: 1) Genomic wide association studies (GWAS) that search for common genetic variants [Minor allele frequency (MAF) > 5%] that have a individually small but significant influence on height [11]; and 2) studies investigating monogenic diseases that cause severe short stature frequently associated with additional features, in which extremely rare genetic variants have a great influence on determining the phenotype when in homozygosis or heterozygosis [12,13]. Recently, these two approaches have been combined to help us better understand the genetic basis of short stature present in non-syndromic individuals.

3. Monogenic conditions

Genetic defects responsible for the symptoms of short stature could be present at the chromosomal level or in individual genes. After the development of the karyotype technique in 1959, the molecular basis of Down syndrome [14] and Turner syndrome [15], two syndromes whose cardinal symptom is short stature, were discovered. Down syndrome and Turner syndrome are caused by trisomy 21 and monosomy X chromosome, respectively.

With the advent of new techniques for the evaluation of chromosomal abnormalities, it became possible to identify several syndromes caused by deletions or duplications of large chromosomal regions (generally > 500,000 base pairs) that cause loss or gain of genetic material (contiguous gene syndromes), many of which are associated with growth disturbance [16]. Recent studies have demonstrated the usefulness of molecular karyotype techniques (CGH-array or SNP-array) in the identification research of children with syndromic short stature.

The analysis of submicroscopic copy number variations (CNVs) identifies the presence of pathogenic deletion or duplication in 10 to 16% of the cases of children with short stature associated with neurological and/or other malformations. [17–20]. Some of the CNVs identified are recurrent [21], as in the case of 22q11.21, which is associated with DiGeorge syndrome (OMIM 188400) [22]. The patients analyzed do not present cardinal clinical characteristics of this condition, thereby making diagnosis and molecular investigation guided by clinical suspicion difficult.

In addition to chromosomal defects, with the advent of new techniques of molecular genetics, it has become possible to identify patients with syndromic short stature associated with a single gene defect. The first disease associated with severe short stature whose genetic basis was discovered was GH deficiency caused by homozygous deletion in the *GH1* gene (OMIM 62400) [23]. In the last four decades, researchers have identified a number of genes that, when altered, are responsible for short stature associated with several other clinical manifestations [12,13,24]. From a didactic point of view, we can classify these conditions in three large groups (Tables 1 and 2): 1.) Defects that directly compromise components of the GH/IGF axis; 2.) Defects responsible for causing syndromic short stature by compromising intracellular signaling pathways or fundamental cellular processes; and, finally, 3.) Defects that cause skeletal dysplasia because they alter the function of paracrine factors, components of the extracellular matrix of cartilage or transcription factors present in the growth cartilage and essential for its correct development. Most of the disorders included in these conditions are extremely rare, with Noonan syndrome (1:1,000 a 1:2,500; OMIM 163950) [25]; Leri-Weill dyschondrosteosis (1:1,000 a 1:2,000; OMIM 127300) [26]; and Turner's syndrome (estimated prevalence of 1: 2,500) [27] being the most common short stature syndromes.

Although genetic syndromes are rare, their association with growth disorders are quite common. A search in the *Online Mendelian Inheritance in Man database* (https://www.omim.org/) shows that more than 15% of the listed conditions show growth disturbance as an important phenotype (n > 2,097). The advent of techniques that allow the simultaneous investigation of the whole genome has rapidly increased the recognition of these conditions in both research and clinical settings [28].

Table 1
Disorders of the GH/IGF-1 axis and involved genes.

Defect	Gene
GH deficiency	
• GH secretion	*GH1*, *GHRH*
• Pituitary somatotroph differentiation	*POU1F1* and *PROP1*
• Pituitary ontogenesis	*GLI2, HESX1, LHX3, LHX4, SOX2, SOX3, OTX2, others*
Biologically inactive GH	*GH1*
GH insensitivity	
• Laron syndrome (*GHR* gene)	*GHR*
• Associated to immunodisfunction	*STAT5B*, *IKBKB*
Ternary complex defect	*IGFALS, PAPPA2*
Isolated IGFs deficiency	*IGF1, IGF2*
Biologically inactive IGF	*IGF1*
IGF-1 insensitivity	*IGF1R*

GH = growth hormone; IGF-1 = insulin-like growth factor type 1; IGFBP-3 = insulin-like growth factors binding protein 3; ALS = acid-label subunit

Table 2
Important syndromic causes of short stature.

Disease	OMIM
Skeletal dysplasia	
Achondroplasia	100800
Hypochondroplasia	146000
Pseudoachondroplasia	177170
MOPD type 1 and 2	210710/210720
Acromesomelic dysplasia, maroteaux type	602875
Leri-weill dyschondrosteosis	127300
Langer mesomelic dysplasia	249700
Osteogenesis imperfect, type I and others	166200
Mucopolysaccharidosis type IV and others	253000
Syndromic short stature	
Seckel syndrome	210600
Bloom syndrome	210900
Fanconi anemia	227650
Cockayne syndrome	216400
Dubowitz syndrome	223370
Kabuki syndrome	147920
DiGeorge syndrome	188400
Velocardiofacial syndrome	192430
Williams–Beuren syndrome	194050
3M syndrome	273750
Floating Harbor syndrome	136140
Mulibrey syndrome	253250
Pseudohypoparathyroidism	103580
Prader-Willi syndrome	176270
Aarskog-scott syndrome	305400
Kearns-sayre syndrome	530000
Bartter syndrome	601678
Noonan syndrome	163950
Noonan-like syndromes	607721/613563
LEOPARD	151100
Costello syndrome	218040
Cardiofaciocutaneous syndrome	115150

MOPD-microcephalic osteodysplastic primordial dwarfism.