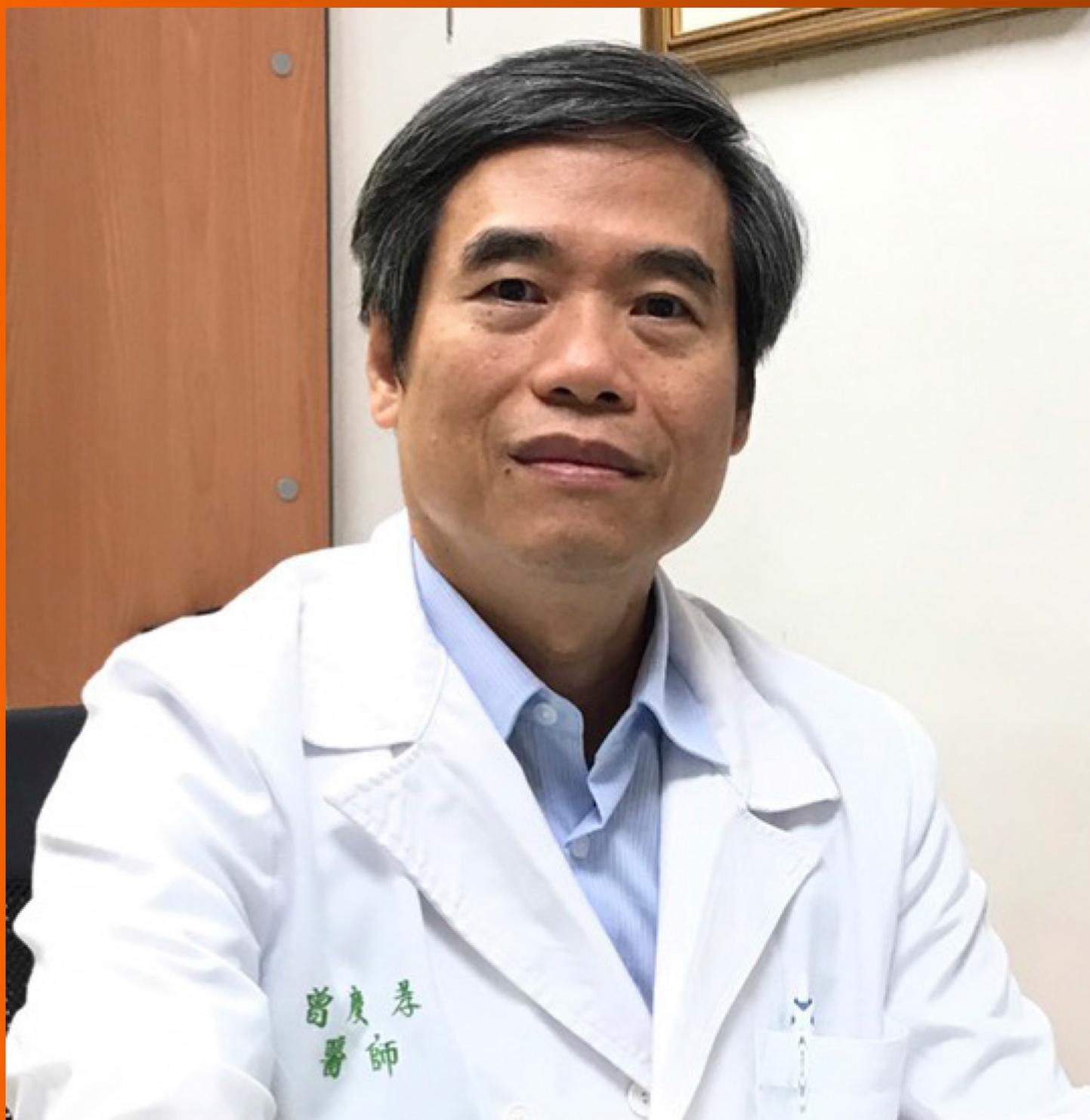


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Retrospective Study

Study on pathogenic genes of dwarfism disease by next-generation sequencing

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Abstract

BACKGROUND

There are many factors that lead to dwarfism, and the mechanism has not yet been elucidated. Next-generation sequencing may identify candidate-related gene mutations, which may clarify the molecular cause.

AIM

To analyze genetic variation by using a constructed panel related to dwarfism by utilizing next-generation sequencing platform sequencing analysis to screen candidate-related gene mutations.

METHODS

Physical and laboratory characteristics, including clinical examination, growth hormone drug challenge test, serum insulin-like growth factor-1 (IGF-1), IGF binding protein 3, other related tests, imaging examination, and chromosome karyotyping, were analyzed. Next-generation sequencing was performed to analyze pathogenicity variability.

RESULTS

In the 39 dwarfism patients, 10 had pathogenicity variability. Gene variation was found in the *OBSL1*, *SLC26A2*, *PTPN11*, *COL27AI*, *HDAC6*, *CUL7*, *FGFR3*, *DYNC2H1*, *GH1*, and *ATP7B* genes. Of the 10 patients with pathogenicity variability, the related physical characteristics included double breast development and growth hormone deficiency, enuresis and indirect inguinal hernia on the left, two finger distance of 70.2 cm, head circumference of 49.2 cm, ischium/lower body length of 1.8 cm, weak limb muscles, and partial growth hormone deficiency. After 6 mo of growth hormone therapy, the concentrations of IGF-1 and IGF binding protein 3 increased from 215.2 ± 170.3 to 285.0 ± 166.0 and 3.9 ± 1.4 to 4.2 ± 1.1 , respectively.

CONCLUSION

Data sharing statement: No additional data are available.

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OBSL1, *SLC26A2*, *PTPN11*, *COL27A1*, *HDAC6*, *CUL7*, *FGFR3*, *DYNC2H1*, *GHI*, and *ATP7B* genes may be related to the incidence of dwarfism, and more research needs to be performed to elucidate the mechanism.

Key Words: Dwarfism; Next-generation sequencing; Pathogenicity variability; Growth hormone; Therapy; Mechanism

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Core Tip: Genetic variation may relate to the incidence of dwarfism. After Solexa sequencing, the *OBSL1*, *SLC26A2*, *PTPN11*, *COL27A1*, *HDAC6*, *CUL7*, *FGFR3*, *DYNC2H1*, *GHI*, and *ATP7B* genes may be related to dwarfism and clarify the molecular cause.

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INTRODUCTION

Dwarfism is one of the most common diseases in the endocrine system of children. Dwarfism is defined as a height lower than the average height of the average population by two standard deviations (-2 SD) or lower than the third percentile (-1.88 SD) in children of the same race, sex, and age^[1]. Human height is related to a combination of genetics, hormones, nutrition, environment, and other factors. It is a complex process involving multiple genes and multiple factors. Genetic factors are the main factors affecting individual height differences, and the heritability of human height accounts for approximately 80%^[2]. There are many factors that lead to dwarfism. Genetic, nutritional, environmental, mental and mental diseases, intrauterine growth retardation, hypothalamic-pituitary-insulin-like growth factor growth axis dysfunction, chromosomal aberrations, systemic chronic diseases, genetic metabolic diseases and endocrine hormones, and other factors are related to the incidence of dwarfism^[3]. The mechanism has not yet been clarified.

With the rapid development of genetic technology, the causes of dwarfism include endocrine factors and nonendocrine factors. Endocrine factors include growth hormone deficiency, primary hypothyroidism, adrenal hyperplasia congenital adrenal hyperplasia, pseudoparathyroidism, Williams syndrome, and other diseases. Nonendocrine factors include idiopathic short stature, familial shortness, constitutional puberty, delay of puberty, intrauterine growth retardation, congenital ovarian hypoplasia syndrome, and other diseases^[4].

Due to the diverse clinical manifestations of dwarfism, the existence of phenotypic overlap between diseases and high genetic heterogeneity, the etiology cannot be clarified simply by asking about medical history, clinical manifestations, and laboratory tests^[5]. The rapid development of emerging technologies has resulted in increased knowledge on the related molecular etiological mechanisms. Some of the unexplained cases of short stature can be clarified by studying their genetic background by using related genetic testing methods^[6]. Molecular diagnosis methods have the characteristics of high sensitivity and good specificity. They can not only provide clear diagnostic evidence for the clinic to reduce the misdiagnosis and missed diagnosis of the disease but also guide genetic counseling to provide a reliable basis for prenatal diagnosis^[7]. Efficient and highly sensitive diagnosis methods have become the focus of dwarfism research in recent years.

In our study, we aimed to analyze the genetic variation by using a constructed panel related to dwarfism through next-generation sequencing platform sequencing analysis and screened candidate-related gene mutations that may clarify the molecular cause and provide a scientific basis for clinical treatment.

MATERIALS AND METHODS

Patients

The samples of patients with dwarfism disease in this study came from the Quanzhou First Hospital, and a total of 39 dwarf patients were enrolled. This study was reviewed and approved by the Quanzhou First Hospital Review Board. Informed consent was obtained from the parents or guardians of the children prior to examinations. The inclusion criteria of primary growth hormone deficiency included the following: (1) The height lags behind the average height of normal healthy children of the same area, age, and sex -2.5 SD; (2) Short shape; (3) No history of birth injury/birth suffocation, head trauma/tumor, *etc.*; (4) The peak growth hormone (GH) of two GH drug challenge tests was < 10 $\mu\text{g/L}$; and (5) Simple growth hormone deficiency and multiple pituitary hormones or total pituitary hormone deficiency. The inclusion criteria of idiopathic short stature included the following: (1) The height lags behind the average height of normal healthy children of the same area, age, and sex -2.5 SD; (2) GH drug challenge test GH peak value ≥ 10 $\mu\text{g/L}$; and (3) No chronic systemic diseases (digestion, kidney, heart, blood system diseases, *etc.*), nutritional diseases, genetic diseases, other endocrine diseases, chromosome abnormalities, bone diseases with definite genetic diagnosis (such as cartilage dysplasia, hypophosphatemia rickets, *etc.*), and other causes of short stature; and (4) No familial short stature. The exclusion criteria were as follows: (1) Chronic systemic diseases, such as congenital heart disease, chronic kidney disease, blood system diseases, disease, malnutrition, and long-term treatment of children with glucocorticoids; (2) Hereditary-familial shortness; (3) Constitutive growth delay; (4) Acquired hypothyroidism; (5) Cushing's syndrome; and (6) Dwarfism caused by tumors, trauma, surgery, radiotherapy, and chemotherapy.

Clinical examination

Clinical examination included posture, body shape, facial features, gait, skin color, nutritional status (abdominal subcutaneous fat), bone development (limbs, spine, *etc.*), thoracic frame, head and neck, cardiopulmonary and abdominal examinations, and evaluation of gonads and secondary sexual characteristics. Growth hormone drug challenge tests included clonin challenge tests and arginine challenge tests. The concentrations of serum insulin-like growth factor-1 (IGF-1) and IGF binding protein 3 (IGFBP3) were detected by an enzyme-linked immunoassay test kit. Other related tests included routine hematuria and biochemical tests, such as liver function, kidney function, electrolytes, blood glucose, and insulin determination. Imaging examinations included detecting left-hand orthotopic X-ray bone age and using the Greulich-Pyle atlas method (referred to as the G-P method for short) to judge the maturity of bone age; magnetic resonance imaging of the cranial saddle area; X-rays of the spine, pelvis, and extremities if necessary; and B-mode ultrasound. Chromosome karyotypes were analyzed by the G-banding method.

Solexa sequencing

After informed consent was obtained from the family members of the children, 2 mL of venous blood from the children and their parents was collected in ethylenediaminetetraacetic acid tubes, and the basic information of the child (name, case number, sex, age, diagnosis, *etc.*) was marked on the ethylenediaminetetraacetic acid tubes. Deoxyribonucleic acid (DNA) was extracted according to the instructions of the blood/cell/tissue gene extraction DNA kit. For ribonucleic acid probe preparation, refer to UC Santa Cruz. Polymerase chain reaction was performed to prepare a whole-genome sample library. A second-generation sequencing library construction kit was used to construct the sample DNA library, which was then captured by xGen Exome research panel v1.0 (IDT) and sequenced. The final product was analyzed on the HiSeq 4000 platform (Illumina, San Diego, CA, United States). The steps to filter the target area screening items were the 1000 Genomes Project (≤ 0.01), ExAC (≤ 0.01), Exome Variant Server (≤ 0.01), and an in-house database (≤ 0.05).

Data analysis

Statistical analyses were performed with Statistical Analysis System software SPSS 16.0 (Chicago, IL, United States), and data are presented as the mean \pm SD. $P < 0.05$ was considered as significantly difference.

RESULTS

Clinical characteristics of the patients

The clinical characteristics are shown in [Table 1](#). A total of 39 dwarf patients were enrolled in our study. The 39 dwarfism patients included 27 male and 12 female patients. The age ranged from 2 to 14 years. The mean height was 107.3 ± 16.4 cm. The mean weight was 17.7 ± 5.8 kg. The mean height stand error was 30.8. The mean arginine peak was 3.9 ± 4.0 , and the mean L-dopa peak was 5.6 ± 6.1 . As shown in [Figure 1](#), the concentrations of IGF-1 and IGFBP3 were 151.4 ± 125.5 and 3.5 ± 1.2 , respectively.

Pathogenicity variability of dwarfism disease by next-generation sequencing

All 39 patients were analyzed by Solexa sequencing. Of the 39 patients, 10 had pathogenicity variability, and the other 29 patients did not have pathogenicity variability. As shown in [Table 2](#), patient 20 had the c.252delA genetic variation of NM-015093.5 in the *TAB2* gene, which caused the Ser84fs amino acid variation. In addition, patient 20 also had the c.254insCCATGGAAGAGAAG genetic variation of NM-015093.5 in the *TAB2* gene, which caused the Gln85fs amino acid variation. Patient 29 had the c.3337C > T genetic variation of NM-015311.2 in the *OBSL1* gene, which caused the Arg1113Cys amino acid variation. In addition, patient 29 also had the c.82G > A genetic variation of NM-001173408.1 in the *OBSL1* gene, which caused the Glu28Lys amino acid variation. Patient 31 had the c.1365-1387dup genetic variation of NM-015311.2 in the *OBSL1* gene, which caused the Arg463fs amino acid variation. In addition, patient 31 also had the c.458dupG genetic variation of NM-015311.2 in the *OBSL1* gene, which caused the Leu154fs amino acid variation. Patient 32 had the c.485-486delTG genetic variation of NM-000112.3 in the *SLC26A2* gene, which caused the amino acid variation Val162fs. In addition, patient 32 also had the c.484G > T genetic variation of NM-000112.3 in the *SLC26A2* gene, which caused the amino acid variation Val162Leu. Patient 34 had the C.844A > G genetic variation of NM-002834.3 in the *PTPN11* gene, which caused the amino acid variation Ile282Val. The other patient numbers, genes, gene locations, gene variations, and amino acid variations were 35, COL27A1, NM-032888.3, c.2113C > T, and Pro705Ser, respectively, and COL27A1, NM-032888.3, c.4066C > C, Asp1356His; 36, COL27A1, NM-032888.3, c.1163C > T, Thr388Ile. COL27A1, NM-032888.3, c.2113C > T, Pro705Ser. HDAC6, NM-006044.2, c.3049G>A, Glu1017Lys; 37, CUL7, NM-014780.4, c.4898C > T, Thr1633Me. CUL7, NM-014780.4, c.4261A > G, Thr1421Ala. FGFR3, NM-000142.4, c.1738G > A, Asp580Asn. DYNC2H1, NM-001377.2, c.12316T > G, Leu4106Va; 38, GH1, NM-000515.4, c.291+28G>A; 39. ATP7B, NM-000053.3, c.3889G>A, V1297I. ATP7B, NM-000053.3, c.2785A > G, I929V.

Physical characteristics of dwarfism disease with pathogenicity variability

Of the 10 dwarfism disease patients with pathogenicity variability, patients 20, 33, and 39 had no related physical characteristic variation. Patient 29 had double breast development and growth hormone deficiency. Patient 30 had enuresis and indirect inguinal hernia on the left. Patient 31 had serrated teeth. Patient 32 showed symptoms in which the distance between the two fingers was 70.2 cm, the head circumference was 49.2 cm, the ischium/lower body length was 1.8 cm, and the limb muscles were weak. Patients 34, 35, and 36 had partial growth hormone deficiency; in addition, patient 36 had pituitary dysplasia symptoms. Patients 37 and 38 had symptoms of growth hormone deficiency.

Concentration of IGF-1 and IGFBP3 by growth hormone therapy after 6 mo

Of the 39 patients enrolled in our study, 14 patients had IGF-1 and IGFBP3 data before therapy and 6 mo after completing growth hormone therapy, and the other 25 patients lacked partial data, so the 14 patients with complete data were chosen for further analysis. As shown in [Table 3](#), of the 14 patients, 11 did not have pathogenicity variation, and the other three patients had pathogenicity variation. The concentrations of IGF-1 before therapy and 6 mo after completing growth hormone therapy in the 14 patients were 215.2 ± 170.3 and 285.0 ± 166.0 , respectively. After therapy, IGF-1 increased 1.9 ± 1.5 -fold. The concentrations of IGFBP3 before therapy and 6 mo after completing growth hormone therapy were 3.9 ± 1.4 and 4.2 ± 1.1 , respectively. After therapy, IGFBP3 increased 1.2 ± 0.5 -fold. Among the 14 patients, the concentrations of IGF-1 before therapy and 6 mo after completing growth hormone therapy in the 11 patients who did not have pathogenicity variation were 217.9 ± 173.3 and 281.4 ± 177.3 , respectively. After therapy, IGF-1 increased 1.5 ± 0.5 -fold. The concentrations of

Table 1 Clinical characteristics of 39 dwarf disease patients

Number	Gender	Age	Height	Weight	Height SD	AP	LDP
1	Male	11	132	27.7	-2.55	6.81	4.96
2	Male	11	124.7	28	-3.12	5.32	2.99
3	Female	4	94.3	14	-2.26	1.65	3.74
4	Male	4	91	12	-3.96	0.83	4.26
5	Male	8	118	19.5	-2.94	3.7	4.9
6	Male	5	101.5	14	-3.13	5.55	6.04
7	Male	14	124.8	12	-3.39	0.89	0.56
8	Male	4	90.5	11	-3.9	1.77	1.12
9	Male	10	125.8	21.6	-2.55	2.05	5.52
10	Male	10	122.2	24	-2.9	0.96	9.95
11	Female	5	95	13.5	-3.62	9.54	0.69
12	Male	7	114	19.5	-2.75	3.62	4.18
13	Male	14	145	34.6	-2.9	15.18	27.24
14	Female	6	103	17.1	-3.11	2.08	9.71
15	Male	4	93	11.5	-3.74	0.63	3.35
16	Female	10	121.4	23.9	-3.1	9.97	12.07
17	Male	14	138	29.5	-3.12	1.63	1.99
18	Male	6	107	19	-2.45	0.45	1.18
19	Female	5	101	17	-2.51	6.62	6.17
20	Male	4	90.1	12	-3.59	6.47	1.99
21	Male	13	135.5	25	-3.2	2.42	0.65
22	Male	5	97.4	15.8	-4	5.31	3.08
23	Male	5	101	17	-3.04	1.84	3.57
24	Male	6	103	18	-3.48	5.16	4.75
25	Male	7	109	18	-2.49	2.4	12.6
26	Male	3	90.7	13.5	-2.84	3.98	7.52
27	Male	5	100	15.5	-2.63	0.83	8.49
28	Female	8	114.3	17	-2.56	3.59	3.75
29	Female	5	98	15	-3.43	1.37	1.42
30	Male	7	95	15	-6	0.44	0.48
31	Female	4	85	11.5	-5.8	1.18	3.55
32	Female	2	81.6	11	-2.98	3.42	12.95
33	Male	13	135.5	25	3.2	2.42	0.69
34	Female	9	120	22	-3	5	6
35	Male	4	95	14	-2.98	19.27	26.3
36	Male	5	91	10	-3.5	6.55	6.55
37	Female	5	99	15	-2.67	1.14	1.57
38	Female	7	101	15	-4.08	1.14	0.19
39	Male	4	101	16	-3.13	0.38	1.52

AP: Arginine peak; LDP: L-dopa peak; SD: Standard deviation.

Table 2 Pathogenicity variability of dwarf disease by next-generation sequencing

Number	Gene	Location	Base change	Amino acid change	Type
20	TAB2	NM-015093.5	c.252delA	Ser84fs	Heterozygote
		NM-015093.5	c.254insCCATGGAAGAGAAG	Gln85fs	Heterozygote
29	OBSL1	NM-015311.2	c.3337C > T	Arg1113Cys	Heterozygote
		NM-001173408.1	c.82G > A	Glu28Lys	Heterozygote
31	OBSL1	NM-015311.2	c.1365-1387dup	Arg463fs	Heterozygote
		NM-015311.2	c.458dupG	Leu154fs	Heterozygote
32	SLC26A2	NM-000112.3	c.485-486delTG	Val162fs	Heterozygote
		NM-000112.3	c.484G > T	Val162Leu	Heterozygote
34	PTPN11	NM-002834.3	C.844A > G	Ile282Val	Heterozygote
35	COL27A1	NM-032888.3	c.2113C > T	Pro705Ser	Heterozygote
		NM-032888.3	c.4066C > C	Asp1356His	Heterozygote
36	COL27A1	NM-032888.3	c.1163C > T	Thr388Ile	Heterozygote
		NM-032888.3	c.2113C > T	Pro705Ser	Heterozygote
		NM-006044.2	c.3049G > A	Glu1017Lys	Heterozygote
37	CUL7	NM-014780.4	c.4898C > T	Thr1633Me	Heterozygote
		NM-014780.4	c.4261A > G	Thr1421Ala	Heterozygote
	FGFR3	NM-000142.4	c.1738G > A	Asp580Asn	Heterozygote
	DYNC2H1	NM-001377.2	c.12316T > G	Leu4106Va	Heterozygote
38	GH1	NM-000515.4	c.291 + 28G > A		z heterozygote
39	ATP7B	NM-000053.3	c.3889G > A	V1297I	Heterozygote
		NM-000053.3	c.2785A > G	I929V	Heterozygote

IGFBP3 before therapy and 6 mo after completing growth hormone therapy were 4.0 ± 1.4 and 4.3 ± 1.2 , respectively. After therapy, IGFBP3 increased 1.2 ± 0.4 -fold. The concentrations of IGF-1 before therapy and 6 mo after completing growth hormone therapy in the three patients who were diagnosed with pathogenicity variation were 205.5 ± 195.1 and 298.0 ± 147.1 , respectively. After therapy, IGF-1 increased 3.1 ± 3.2 -fold. The concentrations of IGFBP3 before therapy and 6 mo after completing growth hormone therapy were 3.7 ± 1.5 and 4.0 ± 0.8 , respectively. After therapy, IGFBP3 increased 1.4 ± 0.9 -fold.

DISCUSSION

With the rapid development of gene detection, next-generation sequencing can provide more information on gene variation. In our study, we aimed to explore the pathogenicity variability related to the incidence of dwarfism. Obscurin-like 1 (OBSL1) is a new member of the UNC-89/obscurin gene family. It contains 22 exons and is located on the nuclear membrane. OBSL1 is located in the intercalated disc of the myocardium, the nucleus of myocardial cells, and the Z line, but it is expressed at low levels in the M zone. OBSL1 functions as a cytoplasmic support network as a cytoskeletal adaptor protein connecting membrane-bound nucleoproteins^[8]. OBSL1 is expressed in many different cell types, and OBSL1 acts as a scaffolding protein. The fibronectin domain of OBSL1 is closely related to the amino-terminal fibronectin domain of obscurin^[9]. Studies have found that a mutation in the OBSL1 gene is the cause of 3M syndrome, which plays a greater role in the CUL7 ubiquitination pathway. Three M syndrome is a rare autosomal stealth genetic disease characterized by low birth weight and postpartum developmental delays associated with a series of minor developmental abnormalities^[10].

A study found that solute carrier 26 (SLC26) members had a total of 11 subtypes.

Table 3 Concentration of insulin-like growth factor-1 and insulin-like growth binding protein 3 by growth hormone therapy after 6 mo

Number	IGF-1	After therapy	Fold change	IGFBP3	After therapy	Fold change
3	283	453	1.60	4.4	6.3	1.43
5	101	266	2.63	3.4	4.8	1.41
6	98.7	149	1.51	2.9	3	1.03
7	461	527	1.14	5.2	5.3	1.02
8	31.2	63.5	2.04	1.1	2.3	2.09
11	238	220	0.92	4.5	4.1	0.91
17	572	603	1.05	6.4	5.6	0.88
18	306	340	1.11	5.3	4.8	0.91
22	101	118	1.17	3.6	3.2	0.89
24	86	160	1.86	3.5	3.7	1.06
27	119	196	1.65	3.2	4.7	1.47
29	414	464	1.12	4.8	3.2	0.67
31	175	246	1.41	4.2	4.1	0.98
38	27.4	184	6.72	2	4.8	2.40

IGF-1: Insulin-like growth factor-1; IGFBP3: Insulin-like growth binding protein 3.

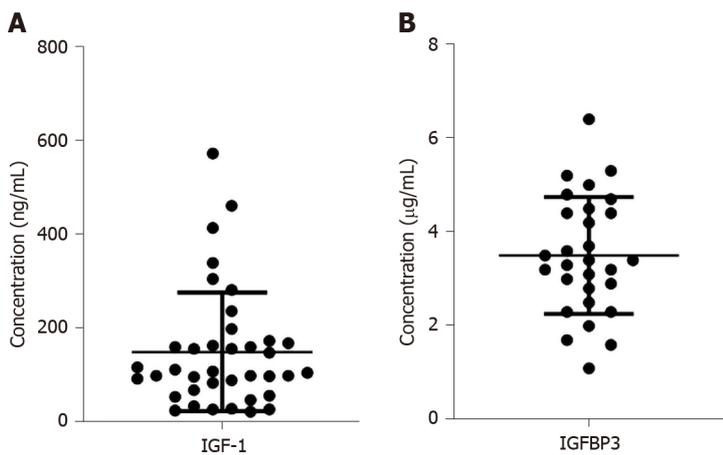


Figure 1 Concentration of insulin-like growth factor-1 and insulin-like growth binding protein 3 before therapy. IGF-1: Insulin-like growth factor-1; IGFBP3: Insulin-like growth binding protein 3.

The four most common SLC26A2 pathogenic variants account for approximately 70% of all SLC26A2-related dysplasia alleles^[11]. P.Arg279Trp is the most common pathogenic variant of SLC26A2 (accounting for 45% of alleles), except in Finland. It is a mild pathogenic variant that results in the mild recessive multiple epiphyseal dysplasia phenotype when homozygous and is mainly malformed in the complex dysplasia phenotype. P.Arg178Ter is the second most common pathogenic variant (accounting for 9% of alleles) and is associated with a more severe diastrophic dysplasia phenotype or even the perinatal lethal dysplasia type 2 phenotype. P.Cys653Ser and c.-26+2T > C are the third most common pathogenic variants (each accounts for 8% of alleles)^[12,13].

The *PTPN11* gene encodes the protein tyrosine phosphatase src homology phosphatase 2 and is located on chromosome 12 q24.13 and contains 16 exosomes^[14]. Approximately 50% of Noonan syndrome cases are caused by missense mutations in the *PTPN11* gene. Noonan syndrome is a relatively common autosomal dominant inheritance disease, and the main clinical manifestations include congenital heart disease, special face, short stature, chest deformity, and mental retardation^[15].

Collagen type XXVII alpha 1 chain plays a role during the calcification of cartilage and the transition of cartilage to bone. It is closely related to Steel Syndrome, which is characterized by dislocated hips and radial heads, fusion of carpal bones, short stature, scoliosis, and cervical spine anomalies^[16]. Facial features include prominent forehead, long oval-shaped face, hypertelorism, and a broad nasal bridge.

Histone deacetylase 6 is a cytoplasmic enzyme containing two N-terminal deacetylase domains and a C-terminal ubiquitin-binding domain. It has a relative molecular weight of 131 kDa and contains 1215 amino acid residues. It is involved in the occurrence and development of diseases such as tumors, neurodegenerative diseases, and cardiovascular diseases^[17]. Histone deacetylase 6 is also considered a potential therapeutic target for related diseases. However, to date, there has been no evidence demonstrating that it is related to the incidence of dwarfism.

The *CUL7* gene is located in the 6p21.1 region and contains 26 exons. It is a member of the Cullin family. It forms ubiquitin ligase E3 with SKP1-FBX29 and RoC1. Nonsense or missense mutations in the *CUL7* gene prevent the cullin-7 protein from recruiting RoC1, thereby preventing the substrate from ubiquitination and degradation, resulting in accumulation in the body^[18]. *CUL7* gene knockout mouse embryos showed accumulation of insulin receptor substrate 1, which caused the activation of the downstream substrates Akt and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase to increase, resulting in growth retardation^[19].

FGFR3 is a physiologically negative regulator of bone growth. As a member of the tyrosine kinase receptor family, mutations cause fibroblast growth factor receptor 3 to be rapidly ubiquitinated and the subsequent degradation of the protease body. Signal transmission is terminated immediately, which can be inhibited by varying degrees to chondrocyte proliferation^[20]. Studies found that the gene mutation was closely related to achondroplasia^[21].

The *DYNC2H1* gene encodes dynein, cytoplasmic 2, and heavy chain 1 protein. It functions as a motor for retrograde intraflagellar transport, a process required for the assembly and maintenance of cilia^[22]. Mutations in this gene cause a heterogeneous spectrum of conditions related to altered primary cilium function and often involve polydactyly, abnormal skeletogenesis, and polycystic kidneys^[23]. Alternative splicing results in multiple transcript variants encoding distinct proteins.

The *GH1* gene provides instructions for making the growth hormone protein. Growth hormone is produced in the growth-stimulating somatotrophic cells of the pituitary gland^[24]. Growth hormone is necessary for the normal growth of the body's bones and tissues. The production of growth hormone is triggered when two other hormones are turned on. The release of growth hormone into the body peaks during puberty and reaches a low point at approximately age 55.

The *ATP7B* gene provides instructions for making a protein called copper-transporting ATPase 2, which is part of the P-type ATPase family. Copper plays important roles in certain enzymes that maintain normal cell functions. Copper-transporting ATPase 2 is also important for the removal of excess copper from the body^[25]. With a shortage of ATPase 2, the removal of copper is impaired. When it accumulates to toxic levels, it can damage tissues and organs, particularly the liver and brain^[26].

However, there are still some limitations in our study. First, the sample size of our study was relatively small and cannot effectively reflect the pathogenicity variability related to dwarfism. Second, after next-generation sequencing, Sanger sequencing was not performed to validate the results, which may cause some bias in the results. Third, although some pathogenicity variability sites were screened, the mechanism of the relationship between genes and dwarfism was not explored.

CONCLUSION

Pathogenicity variability in the *OBSL1*, *SLC26A2*, *PTPN11*, *COL27A1*, *HDAC6*, *CUL7*, *FGFR3*, *DYNC2H1*, *GH1*, and *ATP7B* genes was screened, and it may be related to dwarfism incidence, which may clarify the molecular cause and provide the basis for personal therapy in the future.

ARTICLE HIGHLIGHTS

Research background

Dwarfism is one of the most common diseases in the endocrine system of children. It is a complex process involving multiple genes and multiple factors. Genetic factors are the main factors affecting individual height differences, and the heritability of human height accounts for approximately 80%. The mechanism has not yet been clarified.

Research motivation

The rapid development of emerging technologies has resulted in increased understanding of on the related molecular etiological mechanisms. Some unexplained cases of short stature can be clarified by studying their genetic background by using related genetic testing methods. Efficient and highly sensitive diagnosis methods have become the focus of dwarfism research.

Research objectives

To analyze retrospectively the genetic variation by using a constructed panel related to dwarfism through next-generation sequencing platform sequencing analysis in order to screen candidate-related gene mutations that may clarify the molecular cause and provide a scientific basis for clinical treatment.

Research methods

Data from 39 dwarf patients in Quanzhou First Hospital were collected according to the inclusion and exclusion criteria, then the clinical examination, growth hormone drug challenge test, serum insulin-like growth factor-1 (IGF-1) and IGF binding protein 3 (IGFBP3) levels, other related tests, imaging examination, and chromosome karyotyping were analyzed. Next-generation sequencing was also performed to analyze the pathogenicity variability.

Research results

Of the 39 dwarfism patients, 10 had pathogenicity variability. Gene variation was found in the *OBSL1*, *SLC26A2*, *PTPN11*, *COL27A1*, *HDAC6*, *CUL7*, *FGFR3*, *DYNC2H1*, *GH1*, and *ATP7B* genes. Of the 10 patients with pathogenicity variability, the related physical characteristics included double breast development and growth hormone deficiency, enuresis and indirect inguinal hernia on the left, two finger distance of 70.2 cm, head circumference of 49.2 cm, ischium/lower body length of 1.8 cm, weak limb muscles, and partial growth hormone deficiency. After 6 mo of growth hormone therapy, the concentrations of IGF-1 and IGF binding protein 3 increased from 215.2 ± 170.3 to 285.0 ± 166.0 and 3.9 ± 1.4 to 4.2 ± 1.1 , respectively.

Research conclusions

Pathogenicity variability in the *OBSL1*, *SLC26A2*, *PTPN11*, *COL27A1*, *HDAC6*, *CUL7*, *FGFR3*, *DYNC2H1*, *GH1*, and *ATP7B* genes was screened, and it may be related to dwarfism incidence.

Research perspectives

This study adds to the evidence-base and will clarify the molecular cause of dwarf diseases; however, larger sample size and multi-center studies are still needed in the future.

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