Clinical and genetic characteristics of eleven Korean patients with hypochondroplasia and outcomes of growth hormone therapy

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Introduction

Hypochondroplasia(HCH)

A genetic disorder characterized by disproportionately short-limbe dwarfism Profound shortening of the proximal limbs (rhizomelic)

Prevalence is estimated at around 1 in 33,000.
Caused by mutation in the *FGFR3*

Sporadically with no apparent family history
Familial with Autosomal dominant inheritance.

General features of HCH

Short-limb dwarfism identifiable during childhood
Average adult height :145-165 cm for males , 133-151 cm for female

Macrocephaly, Mild frontal bossing
Normal/mild midface hypoplasia

Spine : Variable lumbar lordosis, progressive narrowing of interpediculate distance in the lumbar vertebrate
Pelvis : short, squared ilia
Limbs : shortened limbs, short tubular bones with mild metaphyseal flare, limited extension at elbows, genu varum, bowleg

Method

A Retrospective chart review.
Duration : January 2010 ~ August 2018

Clinical data were obtained from the medical records of fourteen patients with HCH from ten unrelated families.
Patients with HCH confirmed by *FGFR3* mutation anlaysis.

The *FGFR3* mutational status was studied by *FGFR3* whole exome sequencing.

Results

Clinical data of HCH patients

	Proband/Sibling	Parent
Number of patients	11	3
Median Age at diagnosis	106 months	461 months
Sex	6 Males / 5 Females	3 Females
Median F/U duration	46.5 months	-
Initial Height(cm)	112.72 ± 15.39 cm	147.07± 2.66 cm
Height SDS	-2.17 ± 0.77	-2.79 ± 0.53

Family	Proband/Sibling	Parent	Total
• brachydactyly	63.6% [7/11]	66.7% [2/3]	64.3% [9/14]
• Rhizomelia	45.5% [5/11]	0	35.7% [5/14]
• genu varum	36.4% [4/11]	33.3% [1/3]	35.7% [5/14]
• lumbar lordosis	18.2% [2/11]	0	14.3% [2/14]
• limitation of elbow extension	0	0	0
• Generalized laxity	0	0	0
• Scoliosis	0	0	0
• Relative macrocephaly	36.4% [4/11]	0	28.6%[4/14]
• mental retardation	0	0	0
• Acanthosis nigricans	9.1% [1/11]	0	7.1% [1/14]
• failure of widening of anterior lumbar interpedicular distance	45.5% [5/11]	66.7% [2/3]	50% [7/14]
• shortening of long bone	9.1% [1/11]	0	7.1% [1/14]
• long bone metaphyseal flaring	0	0	0
• short, broad femoral neck	0	0	0
• squared shortened ilia	0	0	0
• elongation of distal fibula	9.1%[1/11]	33.3% [1/3]	14.3%[2/14]
• flattened acetabular roof	0	0	0

Family	★	F1		F2	F3	F4	F5			F6	F7	F8	F9	F10	
Patient		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14
Age at diagnosis (yr)		5.8	32	8.11	9.10	2.9	10.6	35.2	7.9	14.11	7.9	4.11	3	9.7	44.10
Sex		M	F	F	F	F	M	F	M	M	M	F	F	M	F
F/U duration (yr)		7.7	-	1.7	3.6	6	2.8	-	-	0.3	0.2	0.2	1.4	2.10	1.2
Initial Height(cm)		94.7	148.5	120	126.1	118.9	114.7	138.7	114.4	142.5	108.2	98.4	87	118	144
Height SDS	★	-1.91	-2.51	-2.00	-1.66	-2.69	-2.10	-2.46	-2.15	-3.89	-3.16	-1.63	-1.64	-1.56	-3.41
BMI		16.17	-	18.75	18.24	21.9	17.18	-	-	28.66	20.07	16.73	19.82	19.68	-
• brachydactyly	★	+	+	+	+	+	+	+	+	+	-	-	-	-	-
• Rhizomelia		-	-	+	+	-	-	-	-	-	+	+	+	-	-
• genu varum		-	-	-	-	-	+	+	+	-	-	+	+	-	-
• lumbar lordosis		-	-	+	+	-	-	-	-	-	-	-	-	-	-
• limitation of elbow extension		-	-	-	-	-	-	-	-	-	-	-	-	-	-
• Generalized laxity		-	-	-	-	-	-	-	-	-	-	-	-	-	-
• Scoliosis		-	-	-	-	-	-	-	-	-	-	-	-	-	-
• Relative macrocephaly		-	-	+	+	-	-	-	-	+	-	+	-	-	-
• mental retardation		-	-	-	-	-	-	-	-	-	-	-	-	-	-
• Acanthosis nigricans		-	-	-	-	-	-	-	-	-	-	-	+	-	-
• failure of widening of anterior lumbar interpedicular distance	★	-	+	+	+	+	+	+	+	-	-	-	-	-	-
• shortening of long bone		-	-	-	-	+	-	-	-	-	-	-	-	-	-
• long bone metaphyseal flaring		-	-	-	-	-	+	+	-	-	-	-	-	-	-
• short, broad femoral neck		-	-	-	-	-	-	-	-	-	-	-	-	-	-
• squared shortened ilia		-	-	-	-	-	-	-	-	-	-	-	-	-	-
• elongation of distal fibula		-	-	-	-	-	+	+	-	-	-	-	-	-	-
• flattened acetabular roof		-	-	-	-	-	-	-	-	-	-	-	-	-	-

FGFR3 mutation of patients with HCH

		Familial/Sporadic	Nucleotide change	Amino-acid substitution	Domain	* : novel variant
Family 1	P1, P2	Familial	*c.615+38G>C			
Family 2	P3	Sporadic	c.1950G>T	p.Lys650Asn	TK2	
Family 3	P4	Sporadic	c.1949A>C	p.Lys650Thr	TK2	
Family 4	P5	Sporadic	c.1620C>A	p.Asp540Lys	TK2	ND
Family 5	P6, P7, P8	Familial	*c.989C>T	p.Thr330Ile	Ig III	
Family 6	P9	Sporadic	c.1620C>G	p.Asn540Lys	TK2	
Family 7	P10	Sporadic	c.1620C>A	p.Asn540Lys	TK2	
Family 8	P11	Sporadic	c.1620C>A	p.Asn540Lys	TK2	
Family 9	P12	Sporadic	c.1620C>A	p.Asn540Lys	TK2	
Family 10	P13, P14	Familial	c.250C>T	p.Ser84Leu	Ig I	

r-hGH treatment

	P1						P3			P4				P13
GH*2 ST	+						-			-				+
└ result (hGH peak)	Glucagon) 2.73 L-dopa) 6.76													Dopamine) 5.29 Insulin) 7.45
IGF-1	basal	1y	2y	3y	4y	5y	B	1	2	B	1	2	3	Basal
	40	147.6	138.9	164.2	250.5	179.8	223	201.9	510.9		496.3	550.3	585.5	267.9
Dose (IU/kg/wk)	0.698	0.730	0.736	0.701	0.717	0.822		1.049	1.022		0.956	0.964	0.970	
Growth velocity (cm/yr)		6.86	5.5	5.3	4.5	5		5.2	5.8		6.47	6.5	3.2	8.1

Discussion

In this study, r-hGH treatment improves **growth** velocity compared to before r-hGH treatment. However, long-term data should be studied in chilid with HCH.

Improvement of body disproportion should be studied in the further study.

Conclusion

It is difficult to diagnose HCH in early childhood because of **subtle clinical & radiographic findings**. Detailed investigations of radiologic features of HCH are important because of a mild or sometimes an absent phenotype.

It is important to have **clinical suspicion**, if any changes in clinical and/or radiologic data consistent with HCH. Body disproportion and Family history could help the diagnosis.

Whole exon sequencing of *FGFR3* gene is an useful study to diagnose with HCH that might be remain undiagnosed.