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GH and IGFs
P2-P207

Clinical and preliminary molecular description of a cohort of patients with growth retardation due to severe primary IGF1 deficiency (GROWPATI study)

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Background

Severe primary insulin-growth factor-1 (IGF1) deficiency (SPIGF1D) is a rare cause of growth retardation. Diagnostic criteria include age- and sex-dependent low basal IGF1 levels (<2.5th percentile), height ≤-3SDS, absence of growth hormone (GH) deficiency and of any secondary causes of growth failure.

Objectives

Phenotypic description, follow-up and molecular studies in a cohort of patients diagnosed with growth failure due to SPIGF1D

Patients and Methods:

Thirty patients have been identified with SPIGF1D through selection of patients with growth failure referred to Necker Children's University Hospital, Paris between 2004 and 2009[1]. We further included 15 patients with SPIGF1D referred to the clinics, leading to a total number of **45 patients**.

At diagnosis:

- Mean age : 5.4 years, all patients were prepubertal
- Mean height SDS: -3.5 SDS (range from -9 SDS to -3 SDS)

- Patients underwent regular **clinical evaluation**
- **Molecular studies** were based on a candidate-gene approach by Sanger sequencing.

Results

45 patients with SPIGF1D (M/F : 24/21)

27 SGA patients | **18 ISS patients**

Follow-up:

- Ongoing puberty for most patients, normal onset
- Final height: 157cm (-2.8SDS) and 159cm (-2.5SDS) for 2 male patients, 152cm (-1.2SDS) for one female patient
- Constitutional bone disease diagnosed for 4 patients (2 SGA, 2 ISS)
- Treatment: Growth hormone for 27 patients, rhIGF1 for 2 patients (*patient#1 and#3, below*) without any adverse effects

Clinical and biochemical features in patients with identified mutations in known genes so far

Patient	Age (years)	Sex (M/F)	Birth Weight SDS	Birth Height SDS	Target height SDS	Actual height SDS	GH basal (mIU/L)	GH max (mIU/L)	IGF1 (ng/mL)	IGF1 SDS	Clinical features	Consanguinity and ethnicity	Gene and mutation
1	17	F	+0.2	-0.5	-1	-6	47.3	ND	<5	-24	Dwarfism, protruding forehead, acromicria, truncal obesity	+ Algerian	Hom *GHR* c.703C>T, p.R217X, **Laron syndrome**
2	9	F	+0.4	-1.2	-0.8	-1.7	10.6	28.1	33	-2.5	_	- Caucasian	Het *GHR* c.535C>T, p.Arg179Cys
3	14	M	-0.7	-1.2	-2.3	-4.1	12.6	43	65	-3.2	-	- Caucasian	Het *GHR* c.876G>T, p.Arg292Serfs*7
4	14	F	-0.6	-1.5	-1.8	-1.4	5	34	19	-2	Skeletal dysplasia	- Caucasian	Het *FGFR3* c.1657G>A, p.Val553Met, **Hypochondroplasia**
5	9	F	-0.1	-0.2	-2.8	-3.2	2.1	32.3	61	-5.2	Deafness, cardiac malformations, dropping eyelids	- Caucasian / Morocco	Het *PTPN11* c.1472C>T, p.Pro491Leu, **Noonan syndrome**
6	5	M	-2	-2	+0.8	-4	2.2	22.4	38.6	-3.7	Hypotrophia, relative macrocephaly, triangular face	- Caucasian	Maternal uniparental disomy chr.7, **Silver Russell syndrome**

ND: not done, M: male, F: female, Ho: homozygous, Het: heterozygous, GHR: GH receptor, FGFR3: fibroblast growth factor receptor 3, PTPN11: protein tyrosine phosphatase, non-receptor type11

Conclusions

- **The clinical description of this well-caracterized cohort of patients confirms the heterogeneous spectrum of the disease**
- **Long-term follow-up is necessary especially for adult height**
- **Genetic studies (candidate gene-approach or targeted next generation sequencing) expand the current knowledge and provide more insights in the understanding of SPIGF1D**

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References
1 Teissier et al, Characterization and prevalence of severe primary IGF1 deficiency in a large cohort of French children with short stature; EJE 2014