Genotype-phenotype relationship in patients with *SHOX* region rearrangements detected by MLPA in the French population

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Background : *SHOX* and enhancer regions on PAR1 disorders have variable phenotypic consequences such as idiopathic short stature (ISS) and Leri-Weill Dyschondrosteosis (LWD).

Objective and hypotheses : The aim of this observational multicentric study was to describe phenotypes and genotypes of a large population with mutation on *SHOX* and adjacent regions and to identify a possible phenotype-genotype correlation.

Materials and methods

- **National multicentric observational study**
- **<u>Selection criterion</u> : presence of a rearrangement of *SHOX* gene and/or its regulatory region in PAR 1 (a deletion or a duplication, upstream or downstream of the gene in enhancer regions) detected with MLPA.**
- **<u>Method</u> : phenotypes and genotypes were collected between 2009 and 2013 in 7 French laboratories using MLPA (Multiplex Ligation - dependant PCR Analysis) for diagnosis (Paris-Necker, Paris-Robert Debré, Nancy, Cerba, Nantes, Saint-Etienne, Caen).**

TABLE 1. General clinical characteristics of the population (n=305)

		MD (%)
Patients characteristics		
Age (Q1; Q3)	13,3 (9.4; 3.2)	4 (1.3)
Gender (F/M) (%*)	196/109 (64.3/35.7)	0
Maternal height (DS) (Q1; Q3)	-1,6 (-2.4;-0.6)	91 (27.9)
Paternal height (DS) (Q1; Q3)	-1,1(-2.2;-0.1)	92 (30)
Target height (DS) (Q1; Q3)	-1,3 (-2.0;-0.8)	106 (34.7)
Deviation from the target height (cm) (Q1; Q3)	-3,7(-7.7;-1.0)	65 (58.5)**
Height (DS) (Q1; Q3)	-2,2 (-2.8;-1.5)	30 (9.8)
Phenotype		
No sign (%)	9 (3.7)	
ISS (%)	12 (4.9)	63 (2.,6)
LWD (%)	221 (91.3)	
Growth retardation (%)	183 (63.7)	18 (5.9)
Madelung deformity (%)	124 (48.4)	49 (16.06)
Mesomelia (%)	149 (61.6)	63 (20.6)
Radiological signs (%)	169 (84.9)	106 (34.7)

MD: missing data
* of total population with available data
** of population aged more than 18 yrs

TABLE 2. Comparison of the population according to gender (n=305)

	Girls	Boys	p
Age (yrs) [Q1;Q3]	12,7 [9.2; 30.8]	15,2 [10.6; 40.8]	**0.038**
Index cases (%)	145 (71)	61 (29)	**0.0007**
Population < 18 yrs (%)	126 (41.3 %)	64 (21 %)	
Population > 18 yrs (%)	69 (22.6 %)	42 (13.8 %)	
Height (DS) [Q1;Q3]	-2,4 [-3.0; -1.7]	-2,0 [-2.4; -1.4]	**0.007**
Target height (DS) [Q1;Q3]	-1,5 [-2.0; -0.8]	-1,2 [-1.8; 1.2]	0.158
No sign (%)	3 (1.8*)	6 (8.0**)	
ISS (%)	10 (6.0*)	2 (2.7**)	**0.044**
LWD (%)	154 (92.2*)	67 (89.3**)	
Madelung deformity (%)	97 (56.4*)	27 (32.1**)	**0.0004**
Growth retardation (%)	129 (68.6*)	54 (54.5**)	**0.018**
Mesomelia (%)	109 (67.7*)	40 (49.4**)	**0.005**
Radiological signs (%)	112 (84.2*)	57 (86.4**)	0.68

* of girls ** of boys

Results - discussion

- **205 Index Cases** (IC; 74% females) **and 100 Related Cases** (RC; 26%females) were diagnosed
- 91.3 % had phenotype of LWD
- Median age at diagnosis was 11.7 yrs in IC [Q1:9.0; Q3:15.9] and 38 yrs in RC [Q1: 14.1; Q3: 43.8].
- Median height SDS was -2.2 in IC [Q1: -2.9; Q3: -1.7] and -1.8 in RC [Q1: -2.4; Q3: -0.8].
- Girls were diagnosed earlier than boys (12.7 yrs vs 15.2 yrs, p=0.04)
- Girls were shorter (-2.4 DS vs -2.0 DS, p=0.007) and presented more frequently with Madelung deformity (78.2 % vs 21.7%, p=0.0004)
- Genetic anomalies were :
  - 40.3% *SHOX* +/- PAR 1 deletions
  - 33.7 % PAR 1 deletions
  - 5.9 % PAR 1 duplications
  - 2.0 % *SHOX* + PAR 1 duplications
  - 18 % point mutations
- **In girls, deletions were more frequently associated with Madelung deformity, short forearm and radiologic anomalies than duplications (p=0.02, p=0.006 and p=0.008 respectively).**

Conclusions

Our study is the first nationwide description of SHOX patients population diagnosed with MLPA and the first study concerning phenotype - genotype relationship of SHOX in a large national population. While most of past studies treated the prevalence of SHOX deficit, our study was set up to study only patients with anomalies in SHOX and adjacent regions, and to find a correlation between phenotype and the different genotypes in this group.
We highlighted a smaller proportion of Madelung deformity, short forearm and radiological signs, in duplications than in deletions, especially in girls. Both growth retardation and skeletal features observed tend to be more severe in girls. The severity of the phenotype in girls contributes to the highest proportion of female subjects diagnosed.