

Challenges and strategies for genetic investigation of children with syndromic prenatal onset short stature

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Introduction

- Patients born small for gestational age (SGA) with additional syndromic features to short stature are likely to present with genetic causes. Nevertheless, many cases remain without a specific diagnosis. There are almost four hundred genetic syndromes which prenatal onset growth disorder is one of the cardinal features. Each of these disorders presents distinctive clinical, laboratory and radiological characteristics, but due to their rarity, the diagnosis is difficult even in specialized groups. Additionally, some disorders overlap manifestations and/or present clinical heterogeneity and variability. The challenge increases considerably with many recently described genotype-phenotype correlations. Recently, with the advent of new technologies, a genomic approach has arisen as an important strategy for genetic investigation and also to establish the etiology of growth disorders.

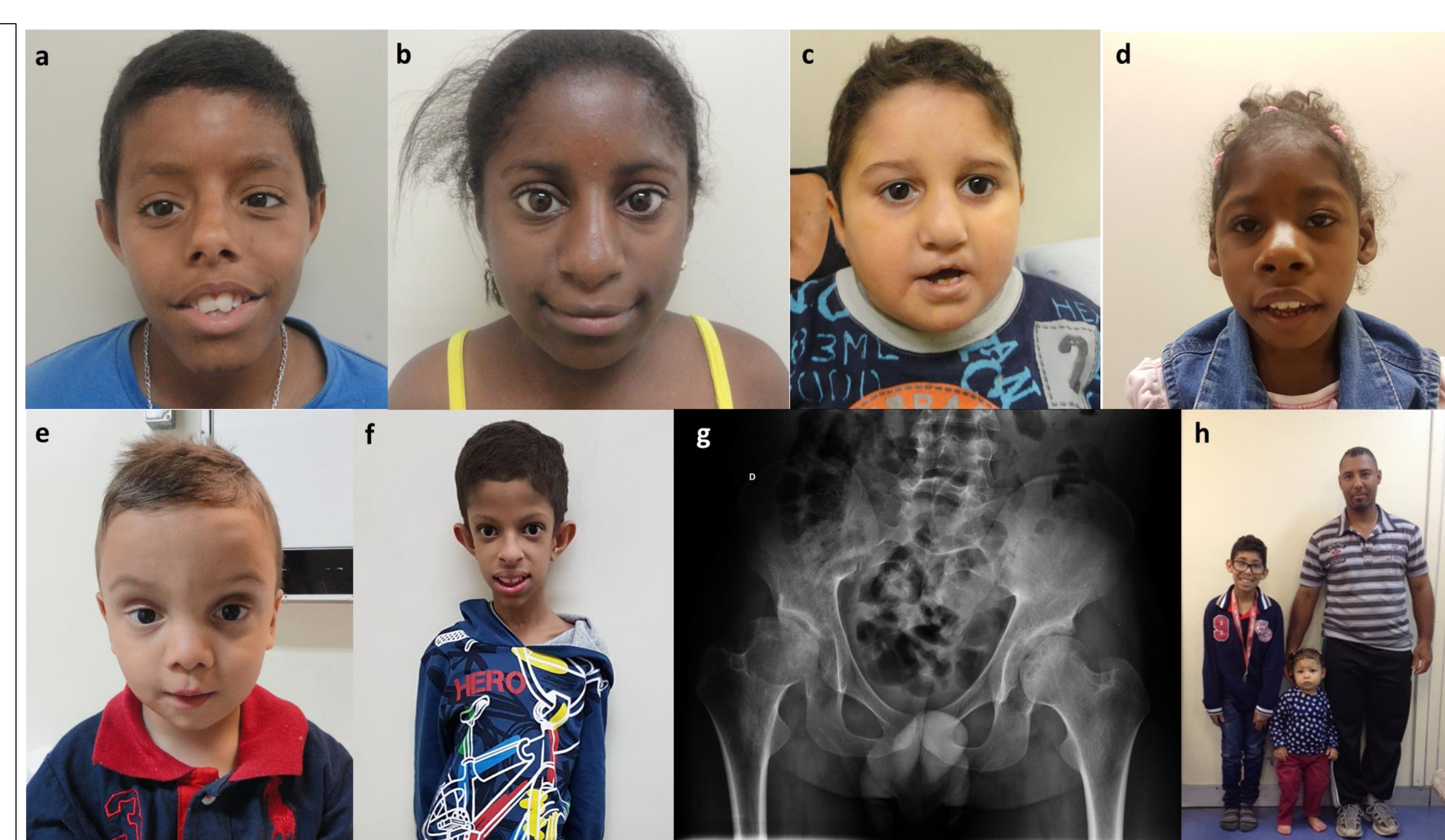
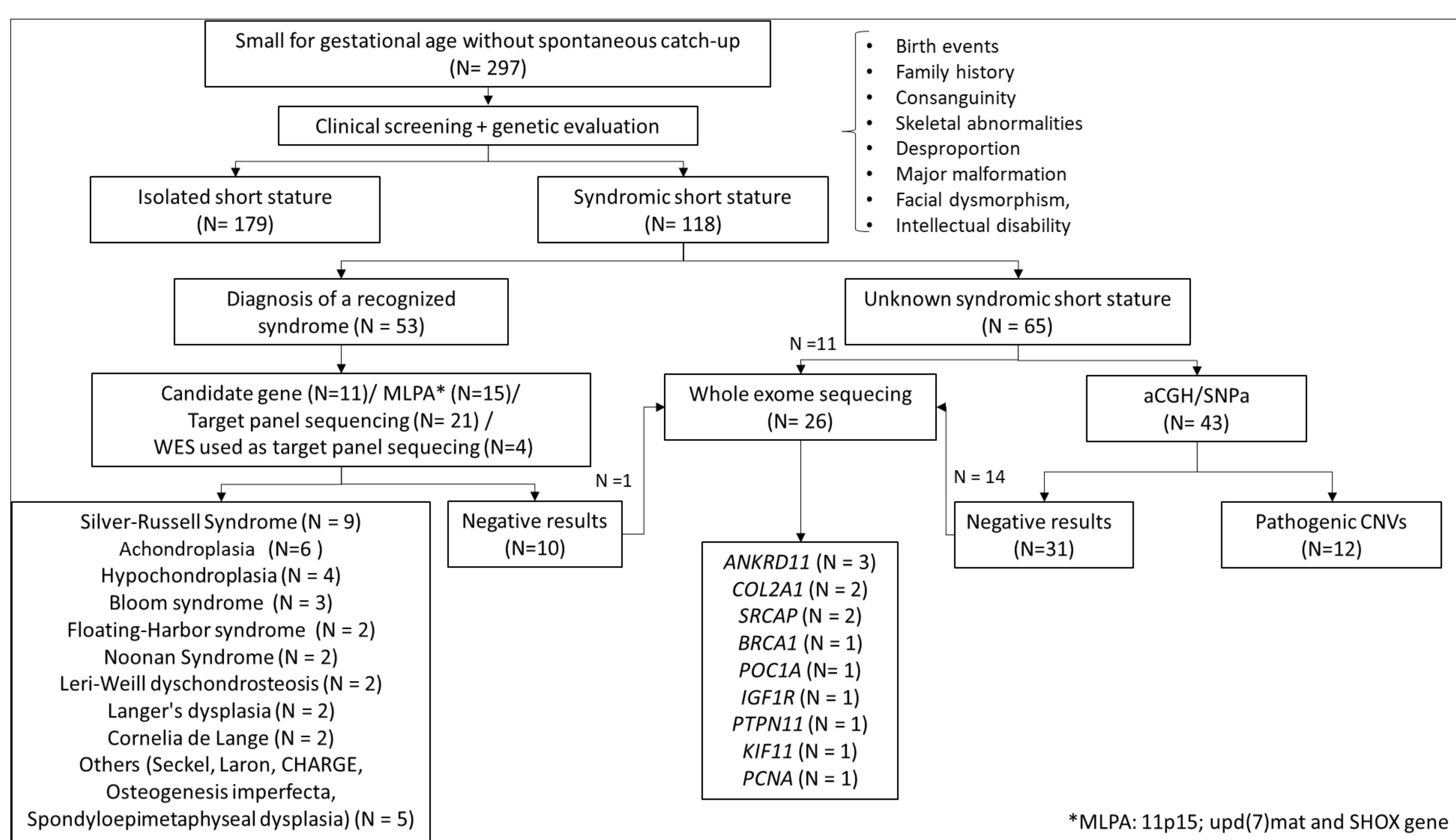
Objective

- To perform a clinical and genetic-molecular investigation of a group of syndromic SGA patients without catch-up growth.

Methods

- We selected 118 patients born SGA [birth weight and/or length standard deviation score (SDS) ≤ -2 for gestational age] without catch-up growth at the age of 2 or above [height SDS ≤ -2] and dysmorphic features, developmental delay and/or intellectual disability.
- These patients were evaluated clinically, laboratory and radiologically by professionals with expertise in dysmorphology.
- Among these syndromic patients, they were reclassified as known or unknown syndromic short stature, according to the establishment of the clinical diagnosis by routine exams and clinical evaluation.
- Molecular evaluation was performed according to the clinical diagnosis. Unknown syndromic short stature patients were submitted for molecular karyotyping (aCGH/SNPa) and/or whole exome sequencing (WES).

Results



Group of syndromic short stature diagnosed by whole exome sequencing as: a) KBG syndrome; b) Floating-Harbor; c) Floating-Harbor; d) Fanconi-Anemia like; e) Noonan syndrome; f) SOFT syndrome; g) Legg-Calve-Perthes disease; h) Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation.

Conclusions

- The rarity, variability and clinical heterogeneity of syndromic short stature makes establishing a clinical diagnosis difficult. Our genetic evaluation protocol established the definitive diagnosis in 52.5% (62/118) of a group of patients with syndromic short stature. 40.3% (25/62) of these patients had no initial clinical diagnosis. A clinical diagnostic paradigm with a systematic phenotype evaluation, targeted genetic testing and exome sequencing increases the diagnostic rate of syndromic short stature patients.

References

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