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Clinical reappraisal of SHORT syndrome with *PIK3R1* mutations: towards recommendation for molecular testing and management

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Key words: diabetes, insulin resistance, intrauterine growth restriction, lipoatrophy, *PIK3R1* gene, short stature, SHORT syndrome

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Abstract

SHORT syndrome has historically been defined by its acronym: short stature (S), hyperextensibility of joints and/or inguinal hernia (H), ocular depression (O), Rieger abnormality (R) and teething delay (T). More recently several research groups have identified *PIK3R1* mutations as responsible for SHORT syndrome. Knowledge of the molecular etiology of SHORT syndrome has permitted a reassessment of the clinical phenotype. The detailed phenotypes of 32 individuals with SHORT syndrome and *PIK3R1* mutation, including eight newly ascertained individuals, were studied to fully define the syndrome and the indications for *PIK3R1* testing. The major features described in the SHORT acronym were not universally seen and only half (52%) had 4 or more of the classic features. The commonly observed clinical features of SHORT syndrome seen in the cohort included IUGR $< 10^{th}$ percentile, postnatal growth restriction, lipoatrophy and the characteristic facial gestalt. Anterior chamber defects and insulin resistance or diabetes were also observed but were not as prevalent. The less specific, or minor features of SHORT syndrome include teething delay, thin wrinkled skin, speech delay, sensorineural deafness, hyperextensibility of joints and inguinal hernia. Given the high risk of diabetes mellitus, regular monitoring of glucose metabolism is warranted. An echocardiogram, ophthalmological and hearing assessments are also recommended.

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Introduction

SHORT syndrome (MIM 269880) has been clinically defined by its acronym: **S**hort stature, **H**yperextensibility of joints or inguinal **H**ernia or both, **O**cular depression, **R**ieger abnormality and **T**eething delay [1]. Additional clinical features include intrauterine growth restriction (IUGR), facial dysmorphism (triangular face, prominent forehead, deep-set eyes, hypoplastic or thin alae nasi, mild midface hypoplasia, small chin, large low-set ears, thin vermillion, border and downturned mouth) with wrinkled and thin skin that accentuates a progeroid appearance. The identification of the gene responsible for SHORT syndrome has highlighted that lipodystrophy and insulin resistance are predominant signs of the condition [2-4] Some authors have reported similar features without the label of SHORT syndrome but in retrospect these individuals had the same condition[5-6]. The differential diagnoses for SHORT syndrome include several recognizable syndromes with growth deficiency and similar facial appearance such as Russel Silver (MIM180860) or Floating Harbor syndrome (MIM136140). In addition mutations that involve *PITX2* (MIM601542), *FOXC1* (MIM601090) or *BMP4* (MIM112262) can been seen in patients with anterior chamber defects of the eye.

An autosomal dominant inheritance has been confirmed by the identification of heterozygous mutations in *PIK3R1* (MIM171833) as the cause of SHORT syndrome [2-4]. A total of seven different mutations were reported in 24 individuals with SHORT syndrome, and highlighted a recurrent substitution (p.Arg649Trp)[7-8]. *PIK3R1* codes for the regulatory subunits of the phosphatidyl inositol-3 kinase of classe IA (PI3K) and is involved in activation of the AKT/mTOR pathway to ensure proper growth and cell proliferation [9-10]. Mutations are located in a region that encodes the src-homology 2 (SH2) domains of PIK3R1 protein, domains that are present in the three known isoforms of the protein (p85α, p55α and p50α; Supplemental figure 1). The SH2 domains play a role in the regulatory activity of the PI3K and i-SH2 domain is known to perform a link with the ABD domain of the catalytic

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subunit of PI3K (p110α) allowing the formation of a dimer [9-10]. Therefore all mutations presented to date are within i-SH2 and c-SH2 domains and probably impact the regulatory activity of PIK3R1. *PIK3R1* mutations in SHORT syndrome appear to disrupt the insulin signaling pathway and thereby predispose to insulin resistance and diabetes. Downstream effects appear to be mediated by lower levels of phosphorylation of proteins in the AKT and mTOR signalling pathway [2-4].

To characterize the salient clinical features of SHORT syndrome, we present 8 unpublished patients and the previously reported patients with confirmed *PIK3R1* mutations. We highlight the clinical features that should prompt consideration of SHORT syndrome as a potential diagnosis and that can serve as indications for further molecular testing of *PIK3R1*. We also suggest recommendations for medical management

Patients and Methods

Detailed phenotypes of 8 newly ascertained individuals and the 24 previously reported SHORT syndrome patients with causal *PIK3R1* mutation [2-4;7-8] were collected, with particular emphasis on the features of the acronym, facial dysmorphism and lipodystrophy (Table 1). Clinical and biological metabolic data were also collected (Supplemental tables 1 and 2).

Results

Thirty-two SHORT individuals with *PIK3R1* mutations from 24 families were included in the evaluation (Table 1; Figure 1). There were 18 males and 14 females. Mean age at last follow-up was 21 years of age. The eight newly ascertained patients included 4 females and 4 males. Two cases presented with a family history of SHORT syndrome. Six patients of the newly identified patients had the recurrent substitution, p.Arg649Trp, and two patients (father and son) had a novel mutation that was the most distal of the *PIK3R1* mutations.

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The features of the SHORT syndrome acronym varied in their frequency: 11/21 cases (52%) presented at least 4 of 5 signs of this acronym. Short stature was described for 25/31 cases and 22/28 cases presented with height below -3SD. Deep-set eyes (ocular depression; 27/27 cases) and teething delay (20/20 cases) were constant but hyperextensibility of joints or inguinal hernia (10/29 cases) and Rieger abnormality (13/30 cases) appeared less commonly. In cases without Rieger abnormality, some patients presented with other abnormalities of the anterior chamber of eye (5/16 cases). In addition, several cases presented with hyperopia, astigmatism or myopia (12/24 cases). The facial gestalt was remarkably consistent (32/32 cases) (Figure 1; Table 1), including progeroid appearance (27/31 cases), triangular face (31/31 cases), a prominent forehead (31/32 cases), deep set eyes (27/27 cases), thin and hypoplastic alae nasi (29/30 cases), mild midface hypoplasia (25/30 cases), small chin (28/32 cases), large low-set ears (27/30 cases), thin lip and downturned mouth (29/31 cases). In 19/26 cases, thin, wrinkled skin and readily visible veins were also described. The late IUGR was also frequent (22/26 cases), leading to low birth weight that was frequently less than the third percentile (19/25 cases).

Clinical lipoatrophy, generalized or partial (8/29 cases), was present in most (26/29 cases) with body mass index (BMI) commonly less than the third centile (22/29 cases). Patients frequently presented with insulin resistance (13/17 cases), with a highly variable age at diagnosis ranging from 7 to 49 years. After 15 years of age, 9/14 cases had insulin resistant diabetes, with high insulin requirements (>1.5 U/Kg/d). In patients without diabetes, insulin resistance was frequent (4/8 cases), as assessed by increased insulinemia. Gynecological investigations revealed polycystic ovary syndrome in all tested postpubertal women (5/5 cases among the 9 postpubertal women).

Most patients had normal educational achievements (23/26 cases) but there were three cases reported as having cognitive delay: one of whom had a history of severe prematurity

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and cerebral hemorrhage (P1 [7]; P9 [2]). Other than this patient, intellectual disability was reported as mild in the two others, but this data should be interpreted with caution in the absence of detailed neurocognitive testing. Approximately half of the patients presented with a history of mild speech delay (14/27 cases).

The patients presented with other features: three patients had cardiac abnormalities (2/3 pulmonary stenosis and 1/3 ventricular septal defect) [3; 7; 8]. Five patients also presented with sensorineural deafness (new patients 1, 2 and 7; [3]) (Supplemental Table 1).

The 32 cases from 24 families presented with 9 different mutations, highlighting a mutational hotspot in 16 families and 23 cases (c.1945C>T; p.Arg649Trp). All mutations were in the two SH2 domains (Supplemental Figure 1). Otherwise, there was no obvious genotype-phenotype correlation within this group. However, it was noted that the father and son with the substitution at the most distal position of the protein p.Gly665Ser had a less striking facial appearance than others in the cohort (Figure 1K, L) and the proband was sequenced as part of a study to identify novel genes in anterior chamber defects and a diagnosis of SHORT syndrome was not initially considered.

Discussion

This study presented a meta-analysis of the available clinical data in SHORT syndrome, in the context of the *PIK3R1* causative gene discovery. The results showed that the historically defining features of the acronym were seen in less than half of patients (ie. hyperextensibilty of joints/inguinal hernia and Rieger anomaly), and that only 52% of patients presented with at least 4 of 5 signs of the SHORT acronym (Table 1). The reassessment also showed that three cardinal clinical features of the condition are absent from the acronym, including subcutaneous lipoatrophy, insulin resistance and the facial gestalt (not only ocular depression). The lipoatrophy is often generalized, with a BMI frequently less than the third

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percentile. Insulin resistance was seen in a majority of those investigated (13/17) and it showed a wide range in its age of onset with 7 years being the earliest. Facial dysmorphism appears more pronounced with age, with a progeroid aspect accentuated by a lack of facial fat and by thin and wrinkled skin (Figure 1): a triangular appearance to the face, broad forehead, deep-set eyes, and a nose with thin nasal alae, and a low-hanging columella, thin lip and down-turned mouth. The chin can be dimpled and ears are prominent and low-set.

We also particularly focused on the natural history of the syndrome to establish recommendations for medical follow-up in individuals with SHORT syndrome (Table 3). In infancy, a cardiac assessment would be warranted given the potential of heart malformation (particularly pulmonary stenosis), as well as hearing loss screening because of possible sensorineural hearing loss in first year of life. An ophthalmological assessment would also be important given the risk of Rieger abnormality and possible glaucoma. In childhood, assessment of height and developmental milestones, in particular language development should be monitored. Because of the PIK3R1 implication in insulin signaling and the frequent insulin resistance seen in individuals with SHORT syndrome, the occurrence of diabetes mellitus should be screened for by annual HbA1c, fasting glucose and an insulin level. When these investigations appear normal, an oral glucose tolerance test (OGTT) with measurement of glucose and insulin, to look for glucose intolerance and insulin resistance, should be considered in order to adapt dietary recommendations and treatment. SHORT patients present also with short stature with an adult height in males ranging between 153,7 and 167 cm and in females between 141 and 160 cm [2-4]. Indeed, it is known that PI3K/Akt pathway does not appear only the signaling pathway of insulin receptor but also of other receptors like insulin-like growth factor 1 (IGF1) receptor [14], explaining short stature, IUGR and deafness. Because GH treatment associated with a risk of decreased insulin sensitivity could aggravate the pre-

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existing insulin resistance and accelerate the onset of diabetes mellitus, its benefits/risk should be evaluated with caution.

In conclusion, the identification of mutations in *PIK3R1* as responsible for SHORT syndrome has permitted a re-evaluation of the SHORT syndrome phenotype. These results highlight the importance of the IUGR, lipoatrophy, facial gestalt and insulin resistance/diabetes as cardinal features not captured in the acronym. While we do not advocate a change in the syndrome name, in part to avoid confusion in the literature, we stress the importance of fully characterizing the clinical aspects of SHORT syndrome so that the clinician can recognize and initiate molecular testing. Given knowledge of the pathway, SHORT syndrome can be grouped with other syndromes due to aberrant insulin signaling (for example Donohue syndrome). Other mutations affecting this same pathway may lead to the delineation of additional phenotypes with overlapping clinical features to SHORT syndrome.[15]

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Legends

Figure 1



Figure 1: Pictures of new cases of SHORT syndrome (a-c: patient 1; d-e: patient 2; f: patient 3; g-h: patient 5; i-j: patient 6; k: patient 7 with relative mild facial phenotype; l: patient 8, father of patient 7 also showing mild facial phenotype), and unpublished images of a SHORT patient previously reported (m-o: P4 of Dyment *et al.* 2013) showing typical facial gestalt.

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Table 1

	N= 32*
IUGR	22/26
IUGR ≤ 3rd percentile	19/25
BMI ≤ 3rd percentile	22/29
SHORT acronym signs	
S (short stature) (< -2SD)	25/31
Height < -3SD	22/28
Hyperextensibility of joints / inguinal **H**ernia	10/29
O (ocular depression)	27/27
R (**R**ieger abnormality)	13/30
T (**T**eething delay)	20/20
Number of acronym signs ≥ 4/5	**11/21**
Facial dysmorphism	**32/32**
Triangular face	31/31
Prominent forehead	31/32
Hypoplastic or thin alea nasi	29/30
Mild midface hypoplasia	25/30
Small chin or micrognatia	28/32
Large low-set ears	27/30
Thin lip and downturned mouth	29/31
Progeroid face	27/31
Other signs	
Refractive errors	12/24
Anterior chamber of eye abnormalities (without Rieger anomaly)	5/16
Lipoatrophy	26/29
Thin, wrinkled skin and readily visible veins	19/26
Absence of hypertriglyceridemia	18/18
Insulin resistance	13/17
Diabetes (≥15 y)	9/14
Ovarian cysts	5/5
Intellectual deficiency	3/26**
Speech delay	14/27

* including 18 males and 14 females, as well as 8 new SHORT patients (4 females and 4 males) from France, Spain, China, Australia, USA and Canada and the 24 previously reported.

** one of whom had a history of severe prematurity and cerebral hemorrhage (P1 [7]; P9 [2]). The intellectual disability reported as mild in the two others should be interpreted with caution in the absence of detailed neurocognitive testing.

Table 1: Features of SHORT patients

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Table 2

Clinical indications for *PIK3R1* molecular testing
Major features 1 – IUGR < 10th per 2 – Post natal growth retardation (height < -2SD) 3 – Lipoatrophy with normal triglyceride assay 4 – Anterior chamber abnormality (including Rieger abnormality) 5 – Facial gestalt 6 – Insulin resistance or diabetes
Minor features 1 – Teething delay 2 – Thin wrinkled skin with readily visible veins 3 – Speech delay 4 – Hyperextensibility of joints 5 – Inguinal hernia 6 – Hyperopia

Table 2: Clinical indications for *PIK3R1* molecular testing: Shows the major features that are commonly seen or are specific to the syndrome as well as the minor features that are less specific and/or less frequent in SHORT syndrome

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Table 3

At diagnosis	Follow-up
- Ophthalmological examination - Screening for hearing loss - Fasting glucose and insulin +/- OGTT (according to age) - Cardiac ultrasound - Abdominal ultrasound (occasional renal anomalies) - Lipid blood test (triglyceride)	- Fasting glucose and insulin, HBA1c every year - OGTT every 5 years if no diabetes occurred - In women, gynecological ultrasound to search polycystic ovary - Screening for hearing loss - Monitor growth - Follow developmental milestones, in particular speech and langage

Table 3: Recommendations of care monitoring at diagnosis and during follow-up
Supplemental figure 1: schematic representation of the three isoforms encoded by PIK3R1, their functional domains and the mutations identified in patients.