



<b>Title</b>	<b>Silver-Russell syndrome in Hong Kong</b>
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# Silver-Russell syndrome in Hong Kong

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## ABSTRACT

**Objectives:** To examine the molecular pathogenetic mechanisms, (epi)genotype-phenotype correlation, and the performance of the three clinical scoring systems—namely Netchine et al, Bartholdi et al, and Birmingham scores—for patients with Silver-Russell syndrome in Hong Kong.

**Methods:** This retrospective case series was conducted at two tertiary genetic clinics, the Clinical Genetic Service, Department of Health, and clinical genetic clinic in Queen Mary Hospital in Hong Kong. All records of patients with suspected Silver-Russell syndrome under the care of the two genetic clinics between January 2010 and September 2015 were retrieved from the computer database.

**Results:** Of the 28 live-birth patients with Silver-Russell syndrome, 35.7% had H19 loss of DNA methylation, 21.4% had maternal uniparental disomy of chromosome 7, 3.6% had mosaic maternal uniparental disomy of chromosome 11, and the remaining 39.3% were Silver-Russell syndrome of unexplained molecular origin. No significant correlation between (epi)genotype and phenotype could be identified between H19 loss of DNA methylation and maternal uniparental disomy of chromosome 7. Comparison of molecularly confirmed patients and patients with Silver-Russell syndrome of unexplained origin revealed that

postnatal microcephaly and café-au-lait spots were more common in the latter group, and body and limb asymmetry was more common in the former group. Performance analysis showed the Netchine et al and Birmingham scoring systems had similar sensitivity in identifying Hong Kong Chinese subjects with Silver-Russell syndrome.

**Conclusion:** This is the first territory-wide study of Silver-Russell syndrome in Hong Kong. The clinical features and the spectrum of underlying epigenetic defects were comparable to those reported in western populations.

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### New knowledge added by this study

- The epigenetic defects of Silver-Russell syndrome (SRS) in Hong Kong Chinese patients are comparable to those reported in western populations.
- No epigenotype-phenotype correlation was demonstrated among SRS patients in this study.

### Implications for clinical practice or policy

- All suspected SRS patients should be referred to a genetic clinic for assessment.
- A new diagnostic algorithm has been proposed for Chinese patients with SRS.

## Introduction

Silver-Russell syndrome (SRS) [OMIM 180860] is a clinically and genetically heterogeneous congenital imprinting disorder. It was first described in 1953 by Dr Henry Silver and his colleagues, who reported two children with short stature and congenital hemihypertrophy.<sup>1</sup> In the following year, Dr Alexander Russell reported five similar cases with intrauterine dwarfism and craniofacial dysostosis.<sup>2</sup> The term SRS has been used since 1970 to describe a constellation of features with intrauterine growth retardation without postnatal catch-up, distinct facial characteristics, relative macrocephaly, body

asymmetry, and/or fifth finger clinodactyly.<sup>3,4</sup> The prevalence of SRS was estimated to be 1 in 100 000,<sup>5</sup> but was probably underestimated due to the diverse and variable clinical manifestations. The majority of SRS cases are sporadic, although occasional familial cases have been reported.

Two major molecular mechanisms have been implicated in SRS—maternal uniparental disomy of chromosome 7 (mUPD7)<sup>6</sup> and loss of DNA methylation (LOM) of the imprinting control region 1 (ICR1) on the paternal allele of chromosome 11p15 region that regulates the IGF2/H19 locus.<sup>6–9</sup> According to the studies, LOM of ICR1 and

mUPD7 roughly account for 45% to 50% and 5% to 10% of SRS cases, respectively.<sup>6-9</sup> Rare cytogenetic rearrangements have also been reported in 1% to 2% of cases.<sup>4,10,11</sup> There remain 30% to 40% of SRS cases in which the molecular mechanisms remain elusive, however.

Owing to the wide spectrum of clinical presentations of SRS, there is considerable clinical overlap with other growth retardation syndromes. At present there is no consensus for the diagnostic criteria, so diagnosing SRS is challenging. Several scoring systems have been proposed to facilitate clinical diagnosis and to guide genetic testing.<sup>7,11-14</sup> Based on the prevalence of different molecular mechanisms, methylation study of the 11p15 region is the recommended first-tier investigation for patients with suspected SRS, and mUPD7 analysis is the second tier.<sup>14</sup>

The comprehensive clinical spectrum and molecular study of SRS have not been reported in the Chinese population. Therefore, a retrospective review that aimed to summarise the clinical and genetic findings of all SRS patients in Hong Kong was conducted. The sensitivity and specificity of different scoring systems<sup>7,11-14</sup> in identifying Hong Kong Chinese SRS patients have also been studied.

## Methods

### Patients

The Clinical Genetic Service (CGS), Department of Health and the clinical genetic clinic at Queen Mary Hospital (QMH), The University of Hong Kong, are the only two tertiary genetic referral centres that provide comprehensive genetic counselling, and diagnostic and laboratory service for the Hong Kong population. Patients with a clinical suspicion of growth failure due to genetic causes or possibly SRS were referred for assessment and genetic testing.

In this review, all records of patients with suspected SRS seen at the CGS or clinical genetic clinic of QMH between January 2010 and September 2015 were retrieved from the computer database system using the key words of "Silver Russell syndrome" and "failure to thrive and growth retardation". The clinical and laboratory data of these patients were retrospectively analysed. Patients with alternative diagnoses after assessment and genetic investigation were excluded. This study was done in accordance with the principles outlined in the Declaration of Helsinki.

### Clinical diagnostic criteria for Silver-Russell syndrome in this study

Currently, there is no universal consensus on the diagnostic criteria of SRS, but the Hitchins et al's criteria<sup>15</sup> are the most commonly used clinically. The diagnosis of SRS in this study was made when

## 香港的Silver-Russell綜合症

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目的：研究香港Silver-Russell綜合症（SRS）患者的分子發病機制以及表觀基因型和臨床表現型的關連性，並檢視三個臨床評分系統（Netchine等、Bartholdi等，以及Birmingham評分標準）的應用。

方法：本回顧性病例系列研究於香港瑪麗醫院和衛生署醫學遺傳服務中心的遺傳輔導診所內進行。從電腦紀錄中找出2010年1月至2015年9月期間被轉介到以上兩所遺傳輔導診所的疑似SRS患者的數據。

結果：在本研究的28名SRS患者中，分子遺傳化驗結果發現35.7%為H19甲基化損失（LOM）、21.4%為7號染色體母源單親二體症（mUPD7）、3.6%為鑲嵌11號染色體母源單親二體症（mUPD11），餘下的39.3%則屬原因不明。LOM與mUPD7在表觀基因型和臨床表現型之間無顯著相關。然而，比較分子確認患者和原因不明的患者，前者有較多頭和身體不對稱，後者的頭圍較細和咖啡牛奶斑則較為常見。三個臨床評分系統分析顯示Netchine以及Birmingham評分標準在檢測香港SRS華籍患者的敏感度相若。

結論：這是香港首項針對SRS的全港性臨床研究。結果顯示香港SRS患者的臨床特點和表觀遺傳缺陷的頻譜與西方人群相若。

a patient fulfilled three major, or two major and two minor criteria.

Major criteria included (1) intrauterine growth retardation/small for gestational age (<10th percentile); (2) postnatal growth with height/length <3rd percentile; (3) normal head circumference (3rd-97th percentile); and (4) limb, body, and/or facial asymmetry.

Minor criteria included (1) short arm span with normal upper-to-lower segment ratio; (2) fifth finger clinodactyly; (3) triangular facies; and (4) frontal bossing/prominent forehead.

### Epimutation in imprinting control region 1

Investigation of the methylation status and copy number change of the H19 differentially methylated region (H19 DMR) and KvDMR1 at chromosome 11p15 region was done with methylation specific-multiplex ligation-dependent probe amplification (MS-MLPA) method, using SALSA MLPA ME030-B1 BWS/RSS kit (MRC-Holland, Amsterdam, The Netherlands). Following the manufacturer's instructions, approximately 100 ng genomic DNA was first denatured and hybridised overnight with the probe mixture supplied with the kit. The samples were then split into two portions, treated either with ligase alone or with ligase and HhaI. Polymerase chain reactions (PCR) were then performed with the reagents and primers supplied in the kit. The PCR products were separated by capillary electrophoresis (model 3130xl; Applied Biosystems, Foster City [CA], US). The electropherograms were analysed using GeneScan software (Applied Biosystems,

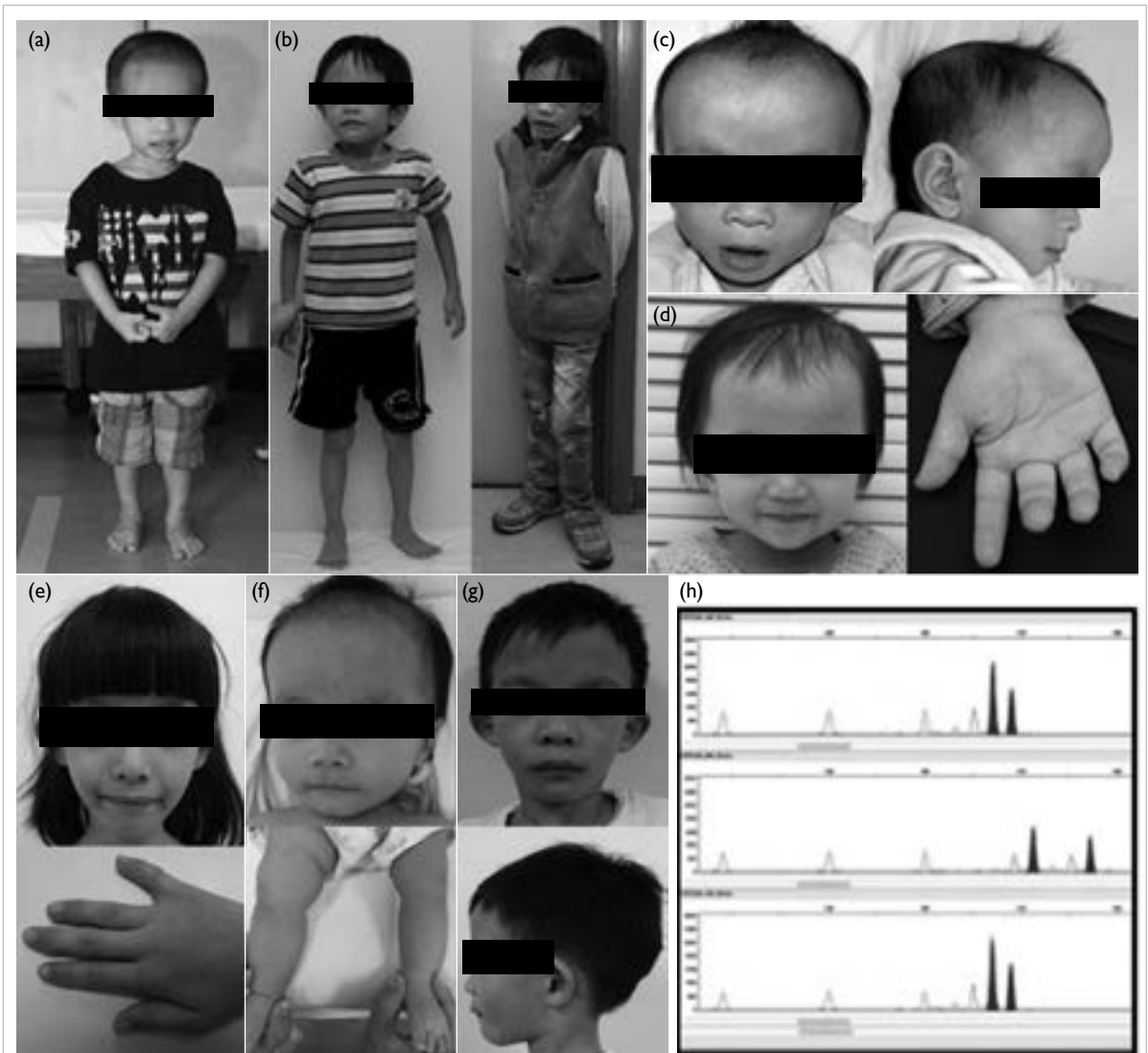
Foster City [CA], US), and the relative peak area was calculated using the Coffalyser version 9.4 software (MRC-Holland, Amsterdam, The Netherlands).

**Analysis of maternal uniparental disomy of chromosome 7**

We studied mUPD7 with eight polymorphic microsatellite markers, three on 7p and five on 7q (D7S531, D7S507, D7S2552, D7S2429, D7S2504, D7S500, D7S2442, and D7S2465), using a standard protocol. Haplotype analysis was then performed. A diagnosis of mUPD7 required evidence of exclusive maternal inheritance at two or more informative markers.

**Data analysis and (epi)genotype-phenotype correlation**

Epidemiological data, physical characteristics, growth records, and molecular findings were then collected for analysis. Clinical photographs were taken during consultation (Fig 1). In order to delineate the (epi)genotype-phenotype correlation, we divided the patients according to their (epi)genotype, namely H19 LOM, mUPD7, mosaic maternal uniparental disomy of chromosome 11 (mUPD11), or SRS of unexplained origin. The SRS of unexplained origin was defined as negative for 11p15 region epimutation and mUPD7 study. For statistical calculation, Student's *t* test was used for continuous



**FIG 1. Clinical photos for molecularly confirmed SRS in this study**

Patients with (a to d) mUPD7 and (e to g) H19 LOM. All had relative macrocephaly, frontal bossing, triangular face, and pointed chin. Patients showing (e) fifth finger clinodactyly and (f) body asymmetry. (h) Informative microsatellite markers in UPD study that shows mUPD7

Abbreviations: LOM = loss of DNA methylation; mUPD7 = maternal uniparental disomy of chromosome 7; SRS = Silver-Russell syndrome; UPD = uniparental disomy

variables and Fisher's exact test for categorical variables. Two-tailed P values were also computed. Differences were considered to be statistically significant when  $P \leq 0.05$ .

### Clinical score

Three clinical scoring systems were applied to all patients referred with suspected SRS and included Netchine et al score,<sup>7</sup> Bartholdi et al score,<sup>12</sup> and the Birmingham score.<sup>14</sup> An overview of the three SRS scoring systems is summarised in Table 1. Using the Hitchins et al's criteria<sup>15</sup> as standard in this study, the sensitivity and specificity of these three scoring systems in identifying SRS were compared.

### Results

During the study period, 83 patients with suspected SRS were referred to both genetic clinics. After clinical assessment and investigations, 54 patients had an alternative diagnosis. The remaining 29 patients were clinically diagnosed with SRS using the Hitchins et al's criteria.<sup>15</sup> All were Chinese. One was a prenatal case with maternal H19 duplication. Since termination of pregnancy was performed at 23 weeks of gestation, it was excluded for downstream analysis. For the remaining 28 SRS patients, their age at the end of the study (September 2015) ranged from 2 years to 22 years 9 months, with a median of 9 years 4 months. The male-to-female ratio was 9:5. Sequential MS-MLPA study on chromosome

11p15 region and mUPD7 study were performed on all SRS patients. Among the 28 live-birth SRS patients, 35.7% (n=10) had H19 LOM, 21.4% (n=6) had mUPD7, 3.6% (n=1) had mosaic mUPD11, and 39.3% (n=11) were of SRS of unexplained origin. The clinical features of the SRS cohort are summarised in Table 2. The clinical features of some molecularly confirmed SRS patients in this study and one illustrative microsatellite electropherogram in mUPD7 analysis are shown in Figure 1.

In order to study the (epi)genotype-phenotype correlation among the H19 LOM and mUPD7 groups, the clinical features were compared. There was no significant difference among the two groups (data not shown). When comparing the 28 molecularly confirmed SRS and 54 SRS of unexplained origin patients, postnatal microcephaly ( $P=0.01$ ) and café-au-lait spots ( $P=0.05$ ) were more common among SRS of unexplained origin, while body asymmetry ( $P<0.01$ ) and limb asymmetry ( $P<0.01$ ) were more common among the molecularly confirmed group.

The performance of the three clinical scoring systems namely Netchine et al score,<sup>7</sup> Bartholdi et al score,<sup>12</sup> and Birmingham score<sup>14</sup> in identifying SRS in our cohort was compared. The proportion of molecularly confirmed cases in those 'likely SRS' and 'unlikely SRS' based on the scoring system are summarised in Table 3. The sensitivity and specificity among different scoring systems for identifying SRS are summarised in Table 4.

TABLE 1. Comparison of three common clinical scoring systems for SRS

	Netchine et al score <sup>7</sup>	Bartholdi et al score <sup>12</sup>	Birmingham score <sup>14</sup>
Requirement for 'likely SRS'	Mandatory + 5-factor system (3 of 5 positive)	15-Factor system ( $\geq 8$ positive)	4-Factor system ( $\geq 3$ positive)
Details	Mandatory: SGA birth weight and/or length $\leq -2$ SD (1) Postnatal growth $\leq -2$ SD at 24 months (2) Relative macrocephaly at birth* (3) Body asymmetry† (4) Feeding difficulties§ and/or low BMI (BMI $\leq -2$ SD at 24 months) (5) Protruding forehead as a toddler	Growth parameters (1) Birth weight $\leq 10$ th percentile (2) Birth length $\leq 10$ th percentile (3) Relative macrocephaly at birth* (4) No catch-up growth, height $\leq 3$ rd percentile (5) OFD $\geq 3$ rd percentile and $\leq 97$ th percentile  Facial dysmorphism (6) Triangular-shaped face (7) Prominent forehead (8) Small chin or thin lips or delayed closure of fontanelle  Somatic features and intellectual function (9-11) Physical asymmetry (face/limb/body) (12) Attending regular school (13) Fifth digit clinodactyly (14) Genital abnormalities (15) Others (eg pigmentary anomalies)	(1) SGA birth weight $\leq 2$ SD (2) Postnatal growth $\leq 2$ SD any time after 2 years (3) Relative macrocephaly† (4) Body asymmetry

Abbreviations: BMI = body mass index; OFD = occipitofrontal diameter; SD = standard deviations; SGA = small for gestational age; SRS = Silver-Russell syndrome

\* Head circumference SD  $\geq 1.5$  SD higher than birth weight or length

† Head circumference SD  $\geq 1.5$  SD higher than weight or length at the time of measurement

‡ Leg length discrepancy (LLD) of  $\geq 0.5$  cm or arm asymmetry or LLD  $< 0.5$  cm with at least two other asymmetric body parts (one not relating to the face)

§ Use of a feeding tube or use of appetite stimulation for a child with a very low spontaneous food intake

TABLE 2. Summary of the clinical features in different subgroups of SRS patients

Clinical feature	H19 LOM (n=10)	mUPD7 (n=6)	Mosaic mUPD11 (n=1)	SRS of unexplained origin (n=11)
Prematurity	2	3	1	1
Small for gestational age	10	6	1	11
Relative macrocephaly	5	4	0	4
Hypoglycaemia	2	0	1	2
Catch-up growth	0	1	0	0
Postnatal microcephaly	2	0	1	8
Developmental delay	1	2	1	6
Facial asymmetry	4	2	0	1
Body asymmetry	8	3	1	0
Limb asymmetry	8	3	1	0
Triangular face	9	5	1	11
Frontal bossing	9	6	1	10
Micro/retrognathia	1	2	0	5
Downturned corners of the mouth	3	2	0	1
Fifth finger clinodactyly	7	3	1	5
Genital abnormality	0	0	1	1
Café-au-lait spot	0	1	0	4
Blue sclera	2	1	0	1
Congenital heart disease	1	0	1	1
Skeletal deformity	2	2	1	0
Growth hormone treatment	1	2	0	0

Abbreviations: LOM = loss of DNA methylation ; mUPD7 = maternal uniparental disomy of chromosome 7; SRS = Silver-Russell syndrome

## Discussion

Silver-Russell syndrome is a clinically and genetically heterogeneous disorder. This is the first comprehensive clinical and epigenetic study of SRS in Hong Kong. With sequential 11p15 epimutation analysis and mUPD7 study of SRS patients in this cohort, molecular confirmation was achieved in 60.7% of cases; H19 LOM and mUPD7 accounted for 35.7% and 21.4% of the cases, respectively. Although the proportion of H19 LOM-related SRS cases was similar to the western and Japanese populations,<sup>6-9,16</sup> the proportion of mUPD7 in our cohort was significantly higher. Nonetheless, due to the small sample size, this observation might not reflect the true ethnic-specific epigenetic alteration in the Chinese population. Further studies are necessary to confirm this difference.

In previous studies of (epi)genotype-phenotype correlation<sup>4,7,12,17-20</sup> in SRS, patients with mUPD7 had a milder phenotype but were more likely to have developmental delay. On the contrary, patients with H19 LOM appeared to have more typical SRS features such as characteristic facial profile and body asymmetry. Such a correlation could not be demonstrated in our cohort. When comparing the

molecularly confirmed and SRS of unexplained origin groups, postnatal microcephaly and café-au-lait spots were more common in the group of SRS of unexplained origin, while body/limb asymmetry was more common in the molecularly confirmed group. This observation has also been reported in Japanese SRS patients.<sup>16</sup> This might be due to the greater clinical and genetic heterogeneity in the molecularly negative SRS.

Although SRS has been extensively studied, there remains no universal consensus on the clinical diagnostic criteria. Hitchins et al's criteria<sup>15</sup> are currently the most commonly used. In order to facilitate the clinical diagnosis, several additional scoring systems have been proposed which include the Netchine et al,<sup>7</sup> Bartholdi et al,<sup>12</sup> and Birmingham scores.<sup>14</sup> Each of them has its advantages and limitations. The major caveats of those scoring systems include relative subjectivity of clinical signs, and time-dependent and evolving clinical features. The heterogeneity of clinical manifestations also limits their application. In order to validate these scoring systems, several studies have been performed to evaluate their accuracy in predicting the molecular genetic testing result.<sup>14,21</sup> We also evaluated the performance of these three scoring

TABLE 3. Proportion of different SRS subtypes with 'likely SRS' and 'unlikely SRS' score in different scoring systems in our cohort

Scoring system	Requirement for 'likely SRS'	H19 LOM (n=10)	mUPD7 (n=6)	Mosaic mUPD11 (n=1)	SRS of unexplained origin (n=11)
Netchine et al score <sup>7</sup>	≥3 Factors	100%	100%	100%	36.4%
Bartholdi et al score <sup>12</sup>	≥8 Factors	80.0%	83.3%	100%	9.1%
Birmingham score <sup>15</sup>	≥3 Factors	90.0%	100%	100%	36.4%
<b>Requirement for 'unlikely SRS'</b>					
Netchine et al score <sup>7</sup>	≤2 Factors	0	0	0	63.6%
Bartholdi et al score <sup>12</sup>	≤7 Factors	20.0%	16.7%	0	90.9%
Birmingham score <sup>15</sup>	≤2 Factors	10.0%	0	0	63.6%

Abbreviations: LOM = loss of DNA methylation ; mUPD7 = maternal uniparental disomy of chromosome 7; SRS = Silver-Russell syndrome

TABLE 4. The sensitivity and specificity of the three clinical scoring systems compared with Hitchin et al's criteria<sup>15</sup> in identifying SRS in our cohort

	Netchine et al score <sup>7</sup>		Bartholdi et al score <sup>12</sup>		Birmingham score <sup>14</sup>	
	'Likely SRS'	'Unlikely SRS'	'Likely SRS'	'Unlikely SRS'	'Likely SRS'	'Unlikely SRS'
Hitchin et al's criteria <sup>15</sup>						
Clinically SRS	21	7	15	13	20	8
Clinically not SRS	0	54	0	54	0	54
Sensitivity	75.0% (21/28)		53.6% (15/28)		71.4% (20/28)	
95% CI	74.5-75.5%		53.0-54.2%		70.9-72.0%	
Specificity	100% (54/54)		100% (54/54)		100% (54/54)	
95% CI*	NA		NA		NA	

Abbreviations: CI = confidence interval; NA = not applicable; SRS = Silver-Russell syndrome

\* All 95% CIs of specificity in these 3 scores are 1

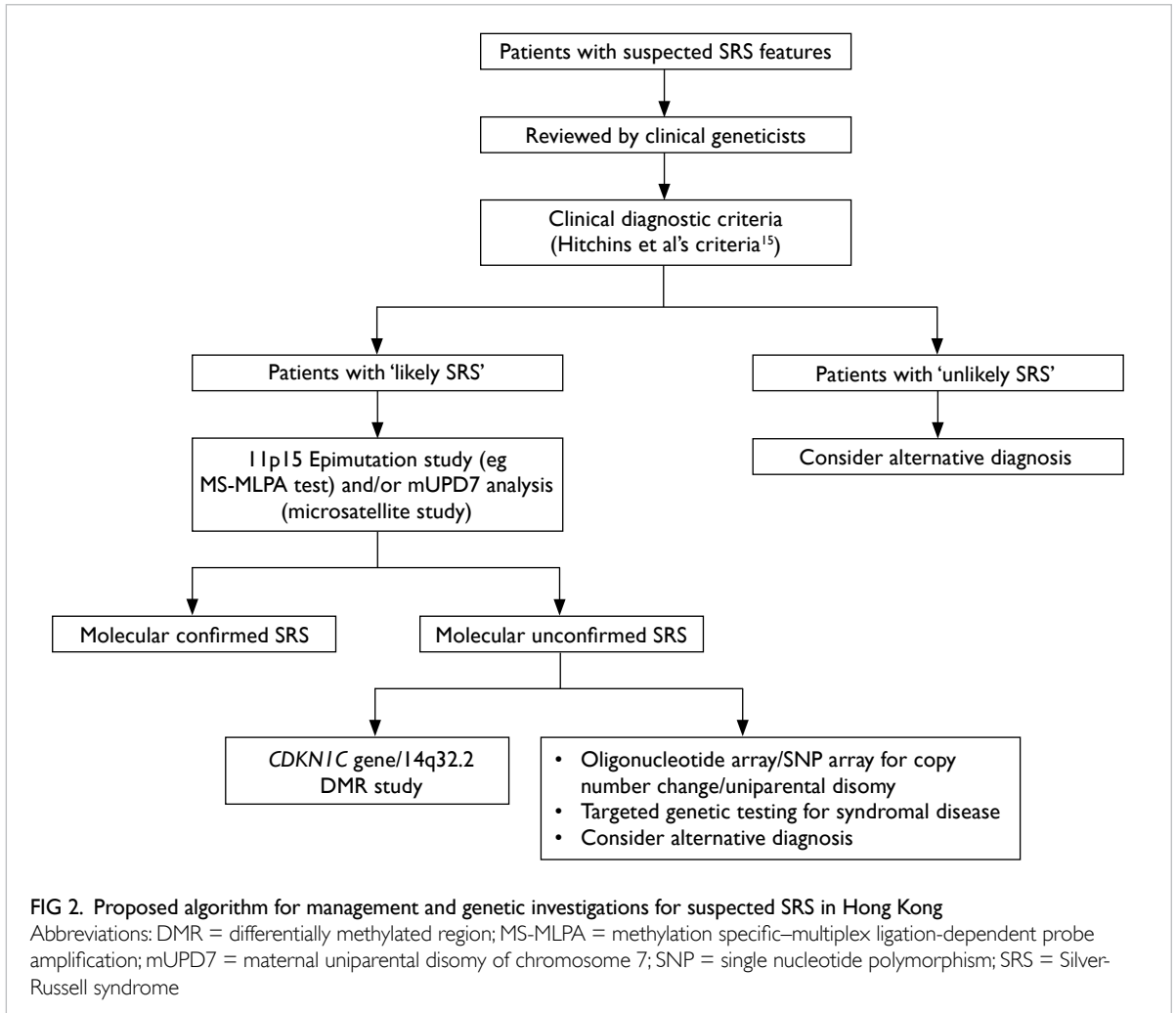
systems in this Chinese cohort. All three scoring systems are 100% specific in diagnosing SRS, but the sensitivity for Netchine et al score,<sup>7</sup> Bartholdi et al score,<sup>12</sup> and Birmingham score<sup>14</sup> is 75%, 53.6%, and 71.4%, respectively when compared with Hitchins et al's criteria.<sup>15</sup> This suggests that Hitchins et al's criteria<sup>15</sup> remain the most sensitive diagnostic criteria for SRS when used clinically.

The management of SRS is challenging and requires multidisciplinary input. Growth hormone (GH) treatment is the current recommended therapy for children with small for gestational age without spontaneous catch-up growth and those with GH deficiency. In SRS, abnormalities in spontaneous GH secretion and subnormal responses to provocative GH stimulation have been well reported.<sup>20</sup> The proposed mechanism is dysregulation of the growth factors and its major binding protein,<sup>4</sup> particularly in the H19 LOM group. Besides, SRS patients are expected to have poor catch-up growth. Nonetheless, GH therapy is not a universal standard treatment for SRS. In Hong Kong, the indications for GH therapy under Hospital Authority guidelines do not include SRS<sup>22</sup> without GH response abnormalities. In our cohort, only three patients who had a suboptimal

GH provocative stimulation test are currently receiving GH treatment. The long-term outcome is not yet known.

Although tissue-specific epigenetic manifestation has been reported in SRS,<sup>23</sup> mosaic genetic or epigenetic alteration is uncommon.<sup>24</sup> We have one patient with mUPD11 confirmed by molecular testing with peripheral blood and buccal swab samples. Mosaicism should be considered when a patient has typical SRS phenotype but negative routine testing. Testing of other tissue should be pursued so as to provide an accurate molecular diagnosis that can guide subsequent genetic counselling and clinical management.

Finally, upon review of the literature, it is well known that gain of function of the *CDKN1C* gene<sup>25</sup> and maternal UPD14 (Temple syndrome)<sup>26,27</sup> can result in a phenotype mimicking SRS. There are also other syndromic growth retardation disorders with many overlapping clinical features with those of SRS, such as mulibrey nanism and 3-M syndrome.<sup>28,29</sup> Therefore, with the latest understanding of the molecular pathogenetic mechanisms of SRS, together with evidence<sup>21,30,31</sup> and results from this study, we propose the diagnostic algorithm for



Chinese SRS patients as depicted in Figure 2. All clinically suspected SRS patients should be assessed by a clinical geneticist. Although the Netchine et al score,<sup>7</sup> Bartholdi et al score,<sup>12</sup> and Birmingham score<sup>14</sup> are highly specific, they are less sensitive than the Hitchins et al's criteria<sup>15</sup> for diagnosing SRS in our Chinese cohort. Therefore, the Hitchins et al's criteria<sup>15</sup> should be used clinically to classify those suspected SRS patients into 'likely' or 'unlikely' SRS. For those 'likely SRS' patients, sequential 11p15 region methylation study and mUPD7 analysis should be performed because 11p15 region epigenetic alteration is more prevalent than mUPD7 in SRS. For those molecularly unconfirmed SRS, further testing for other SRS-like syndromes including Temple syndrome or *CDKN1C*-related disorder should be pursued if indicated.

### Conclusion

This 5-year review is the first territory-wide study of Chinese SRS patients in Hong Kong. It showed that the clinical features and underlying epigenetic

mechanisms of Chinese SRS are similar to those of other western populations. Early diagnosis and multidisciplinary management are important for managing SRS patients. Vigilant clinical suspicion with confirmation by molecular testing is essential. Based on the current evidence and performance evaluation of different clinical scoring systems, a comprehensive diagnostic algorithm is proposed. We hope that with an increase in understanding of the underlying pathophysiology and the (epi)genotype-phenotype correlation in Chinese SRS patients, the quality of medical care will be greatly improved in the near future.

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## Declaration

All authors have disclosed no conflicts of interest.

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