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Silver-Russell综合征的诊治与指南解读

同济医院儿科

罗小平

概述

- **Silver-Russell综合征（SRS, OMIM #180860）**

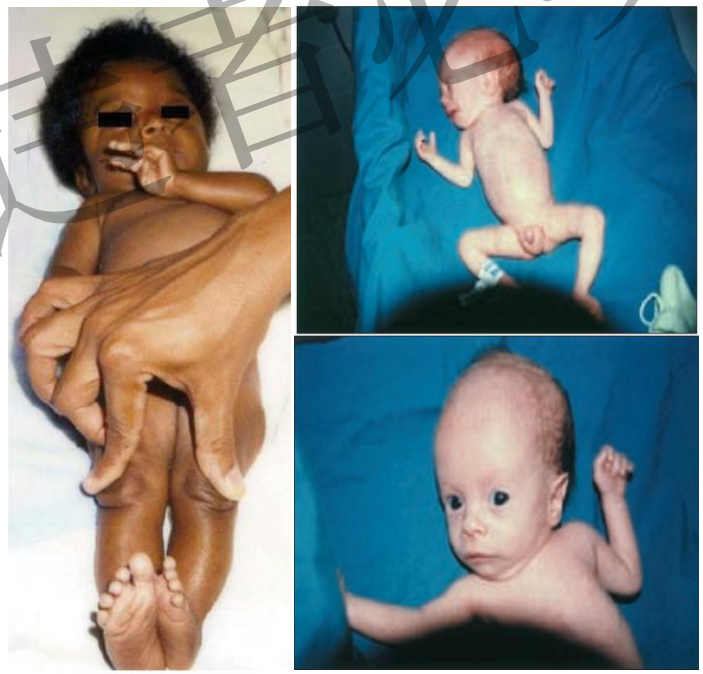
是一组临床和遗传异质性疾病

- **1953年和1954年，Silver及Russell医师首次报告**

一类具有低出生体重、生后身材矮小、特征面容和肢体不对称的疾病

- **发病率在1:30000 到1:100000，**

准确发病率不详，可能更高



Lim AL, et al. *Semin Cell Develop Biol* 2010; 21: 201-208

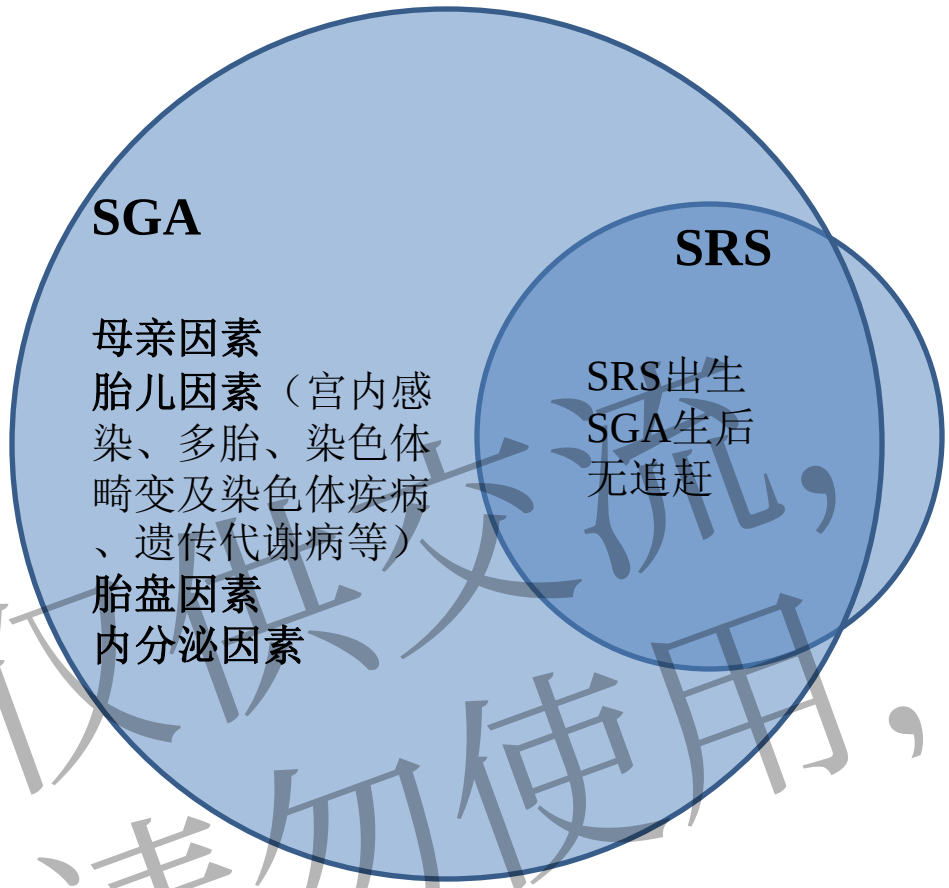
临床表现——不同年龄段各异

Neonatal Features	Infancy	Later Onset
Low birth weight and IUGR 低出生体重	Delayed closure of anterior fontanel 前囟迟闭	Delayed bone age 骨龄延迟
Neonatal hypoglycemia 新生儿低血糖	Frontal bossing 前额突出	Delayed psychomotor 精神运动发育迟缓
Feeding difficulties 喂养困难	Broad forehead tapering to a narrow chin 宽额窄下巴	Premature juvenility 发育不成熟
Narrow and high-arched palate 腭弓高狭	Downturned mouth 倒口	Scoliosis 脊柱侧凸
Protruding ears 招风耳	Lack of catch-up growth 追赶生长失败	Testicular cancer 睾丸癌
Micrognathia 小下颌	Wilms' tumor Wilms瘤	Testicular seminoma 精原细胞瘤
Genital defects, for example, ambiguous genitalia, cryptorchidism, hypospadias 生殖器异常，模糊、隐睾、尿道下裂	Craniopharyngioma 颅咽管瘤	Hepatocellular carcinoma 肝癌
Limb abnormalities, for example, limb asymmetry, clinodactyly, camptodactyly, syndactyly, clubfoot, hip dysplasia, radial hypoplasia, and absent thumbs 肢体异常，不对称、指趾弯曲、关节异常	Vitiligo 白癜风	Precocious puberty 性早熟
Inguinal hernia 腹股沟疝		
Cardiac defects, for example, ventricular and atrial septal defects, patent ductus arteriosus 心脏畸形		
Renal anomalies 肾脏畸形		
Cleft lip 腭裂		
Café au lait patches 牛奶咖啡斑		

Silver-Russell综合征临床表现各异

Spiteri, B. S., and Y. Stafrace. *Neonatal Network Nn* 36.4(2017):206.

临床表现——宫内及生后生长迟缓



- **SGA是描述性诊断，是一类受母亲、胎儿、胎盘和基因、环境影响的异质性疾病的总称，其中包括Silver-Russell综合征**
- **几乎所有SRS患儿表现为出生体重和/或身长低于同胎龄-2SDS且生后无生长追赶**
- **但并非所有SRS患儿表现为SGA，尤其是母源7号染色体单亲二倍体的患儿**

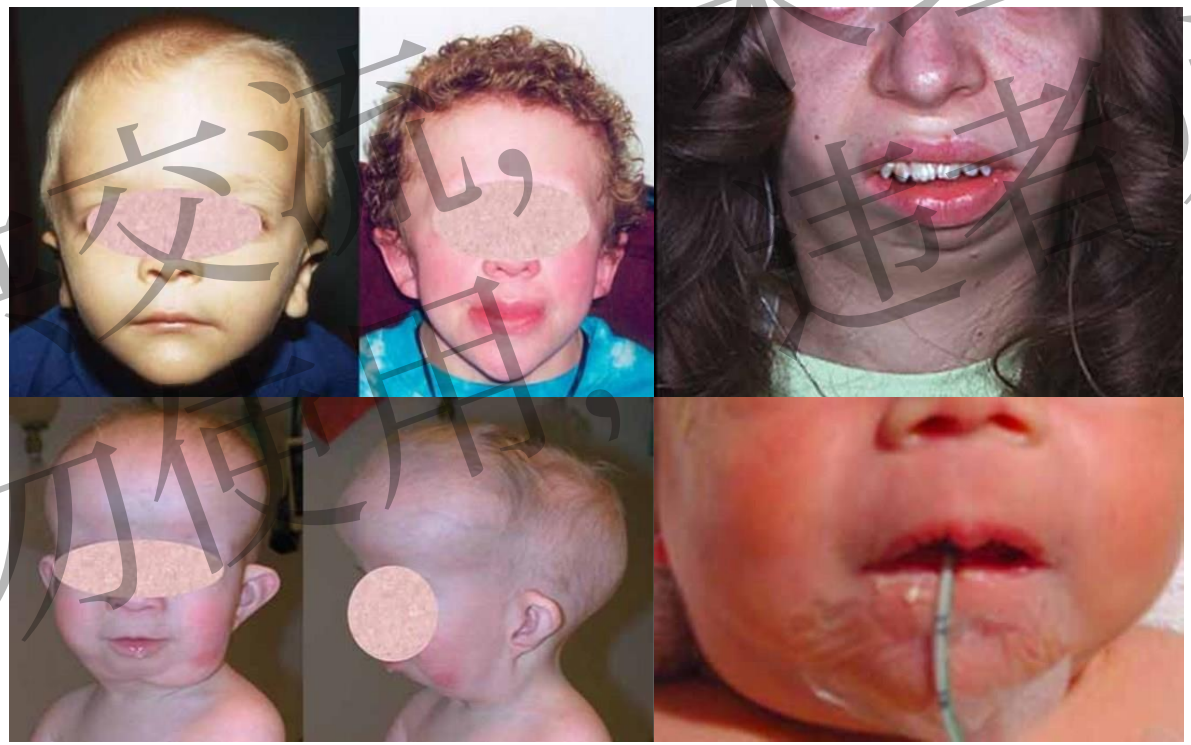
- **自然病程SRS患者成年终身高男孩151.2+7.8cm(-3.7SDS)**
  女孩139.7+7.4cm(-4.2SDS)

Wollmann, H. A. , et al. *European Journal of Pediatrics* 154.12(1995):958-968.

临床表现——特征性面容

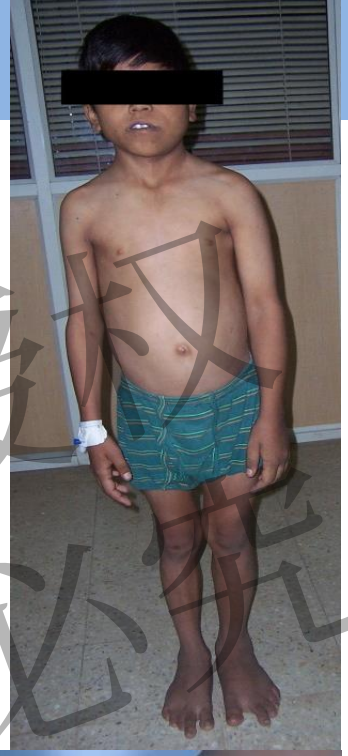
特征性面容 相对大头畸形（头围正常但体重/身长偏低）

三角脸、前额突出、小下颌、齿列不齐、口角下垂、薄嘴唇



Home page: National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD): The Library; Available from: https://ghr.nlm.nih.gov/.

临床表现



肢体异常

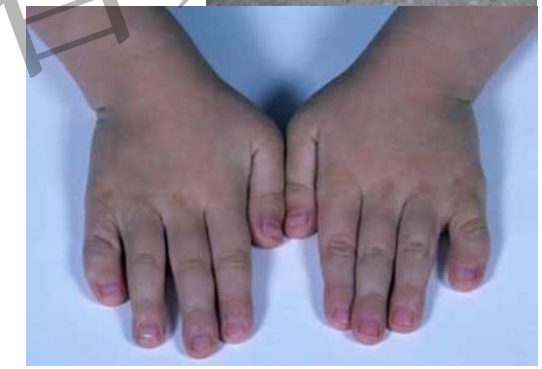
肢体不对称、脊柱侧弯、小指侧弯、多指并指

喂养困难及胃肠道异常 食欲差、胃食管反流、便秘

新生儿低血糖

心、肾、生殖系统异常 隐睾、尿道下裂、

子宫及阴 道上部发育不全



神经认知障碍

运动发育迟缓——肌肉量较少、相对大头畸形

语言发育迟缓、ASD、肌阵挛性肌张力障碍

长期代谢并发症风险增加

与非SRS的SGA类似，代谢综合征（冠心病、高血压、血脂异常、胰岛素抵抗、肥胖）风险增加，尤其是快速不成比例体重增长的患儿

Kumar, Sunil , et al. *Cases Journal* 1.1(2008):304-304.

临床表现

Characteristic	All	Boys	Girls
Age at adrenarche (y)	8.7 (7.0, 10.5)	9.2 (7.6, 10.9)	8.1 (6.6, 10.1)
Bone age at adrenarche (y)	8.0 (5.8, 10.0) (53)	8.3 (7.0, 10.0) (26)	6.8 (5.6, 9.5) (27)
Age at pubarche (y)	11.2 (10.5, 12.2) (51)	11.7 (10.7, 12.8) (27)	9.8 (8.3, 10.8) (24)
Age at gonadarche (y)	11.3 (10.0, 12.2) (51)	11.9 (11.3, 12.8) (28)	10.2 (9.7, 11.1) (23)

肾上腺功能初现 (血清DHEAS浓度＞500 ng/ml**) 轻微提前** SRS患儿肾上腺功能初现年龄，男孩9.2岁女孩8.1岁，均较正常儿童数据轻微提前1年；13% 患儿出现肾上腺机能早现，较普通人群高。不影响rhGH反应和终身高

	Total Group			SRS			
	SRS	Non-SRS	*P* Value[a]	11p15	mUPD7	Idiopathic	*P* Value[b]
At onset of puberty							
Age, y							
Total	10.8 (1.3)	11.7 (1.1)	**<.001**	10.9 (1.3)	9.8 (1.0)	11.4 (1.3)	**.02**
Boys	11.4 (1.1)	12.0 (1.1)	**.02**	11.5 (0.9)	10.3 (1.0)	12.0 (1.0)	**.04**
Girls	10.2 (1.3)	11.2 (1.0)	**.003**	10.3 (1.4)	9.2 (0.4)	10.7 (1.3)	.16

青春期启动提前 SRS患儿青春期启动年龄在正常低限，与非SRS的SGA患儿相比启动年龄提前

Binder, Gerhard , et al. *J Clin Endocrinol Metab* 102.11(2017).
Smeets, C. C., et al. *Journal of Clinical Endocrinology & Metabolism* 101.5(2016):jc20154273.

临床诊断——指南推荐NH-CSS为诊断标准

目前Silver-Russell综合征是一种临床诊断，主要基于特征性的临床表现

Netchine-Harbison CSS	Netchine *et al.* (2007) (7)	Birmingham (9)
6-factor system (4 or more positive = "likely-SRS")	**SGA mandatory + 5-factor system (3 of 5 positive = "likely-SRS")**	**4-factor system (3 or more positive = "likely-SRS")**
1) SGA birth weight and/or length ≤-2SDS	**MANDATORY**: SGA birth weight and/or length ≤-2SDS	1) SGA birth weight ≤-2SDS
2) Postnatal growth ≤-2SDS at 24 months[a] or ≤-2SDS from MPTH at 24 months[a]	1) Postnatal growth ≤-2SDS at 24 months[a]	2) Postnatal growth ≤-2SDS any time after 2 years
3) Relative macrocephaly at birth[b]	2) Relative macrocephaly at birth[b]	3) Relative macrocephaly [b']
4) Body asymmetry[c]	3) Body asymmetry	4) Body asymmetry
5) Feeding difficulties[d] and/or low BMI (BMI ≤-2SDS at 24 months)[a]	4) Feeding difficulties[c] and/or low BMI (BMI ≤-2SDS at 24 months[a]	
6) Protruding forehead as a toddler	5) Protruding forehead as a toddler	

[a] at 24 mo ± 1mo
[b] defined as head circumference SDS ≥1.5 SDS higher than birth weight or length
[b'] defined as head circumference SDS ≥1.5 SDS higher than weight or length at the time of measurement
[c] defined as LLD of ≥0.5cm OR arm asymmetry OR LLD <0.5cm with at least two other asymmetric body parts (one not relating to the face)
[d] defined as use of a feeding tube or cyproheptadine (appetite stimulation) for a child with a very low spontaneous food intake

- 一些基因型/表型相关研究表明，并非所有SRS患者出生都是SGA，所以在Netchine评分系统基础上提出NH-CSS，是指南推荐的临床诊断标准
- 相对大头畸形和前额突出，是区别SRS和非SRS的SGA患儿的最好特征；为保证诊断准确性，共识推荐在分子检测阴性时，只有满足4条标准且包括相对大头和前额突出，才临床诊断SRS
- 成人或者年长儿童诊断方法相同，需获得1-3岁照片尤其面部和出生及2岁前测量资料

Azzi, S. et al. *J. Med. Genet.* 52, 446–453 (2015) .

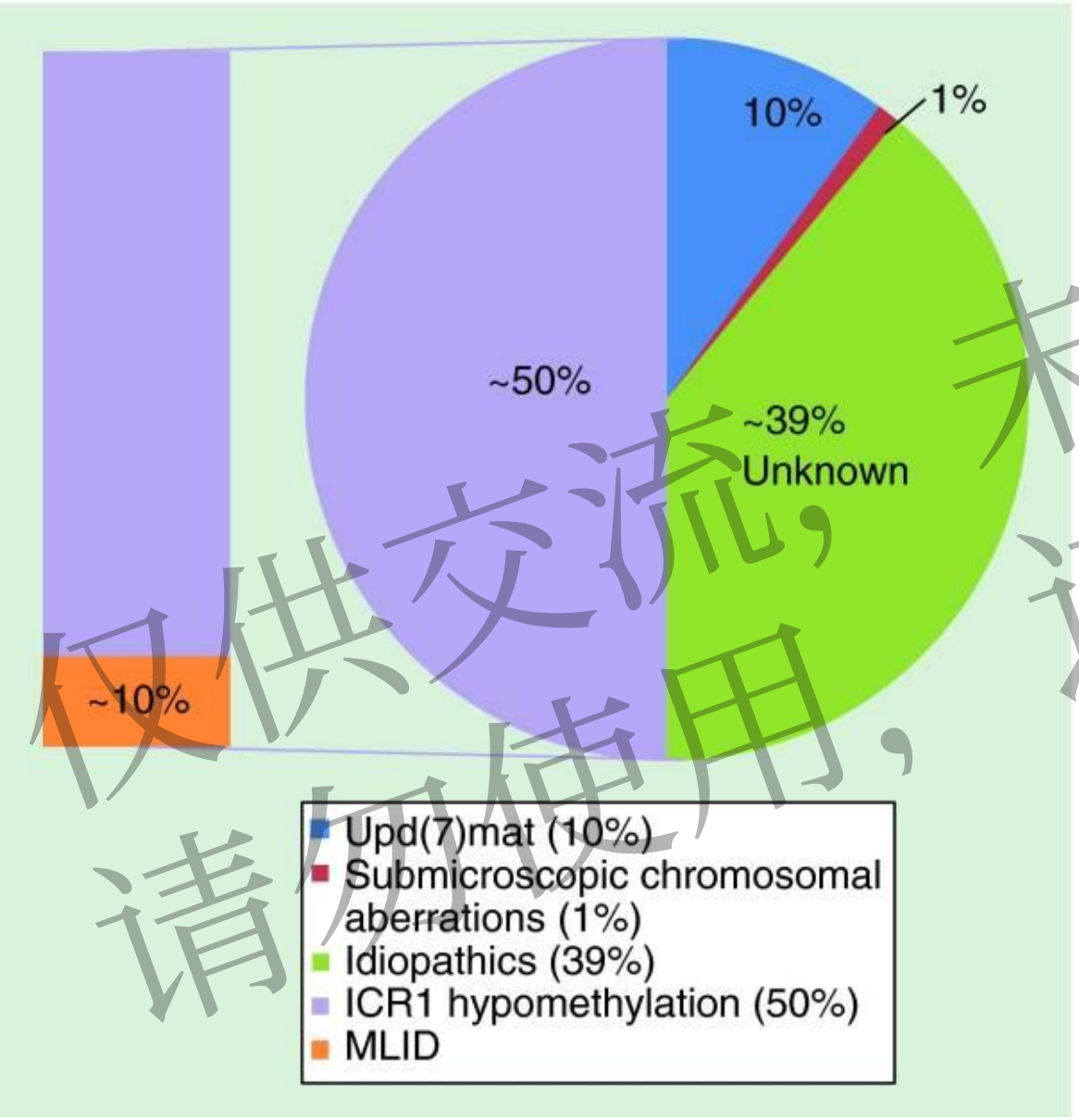
临床诊断——NH-CSS敏感性高

	NH CSS (%)	Netchine *et al*[9] (%)	Birmingham (%)
Sensitivity (Birmingham article)	N/A	70.0	82.0
Specificity (Birmingham article)	N/A	81.0	80.0
Sensitivity (Netchine-Harbison data)	97.9	91.5	83.7
Specificity (Netchine-Harbison data)	36.4	45.5	45.0
Positive predictive value	76.7	78.2	76.6
Negative predictive value	88.9	71.4	56.3

- **Netchine-Harbison临床评分系统（NH-CSS）与另两种临床评分系统相比敏感性高、特异性低、阴性预测值高**
- **NH-CSS满足少于4条标准，很大可能真正是非SRS患者**
- **即使资料不充分，NH-CSS也可灵活使用（尤其婴儿没有生后生长和BMI资料之前），临床易于使用**

Azzi, S. et al. *J. Med. Genet.* 52, 446–453 (2015) .

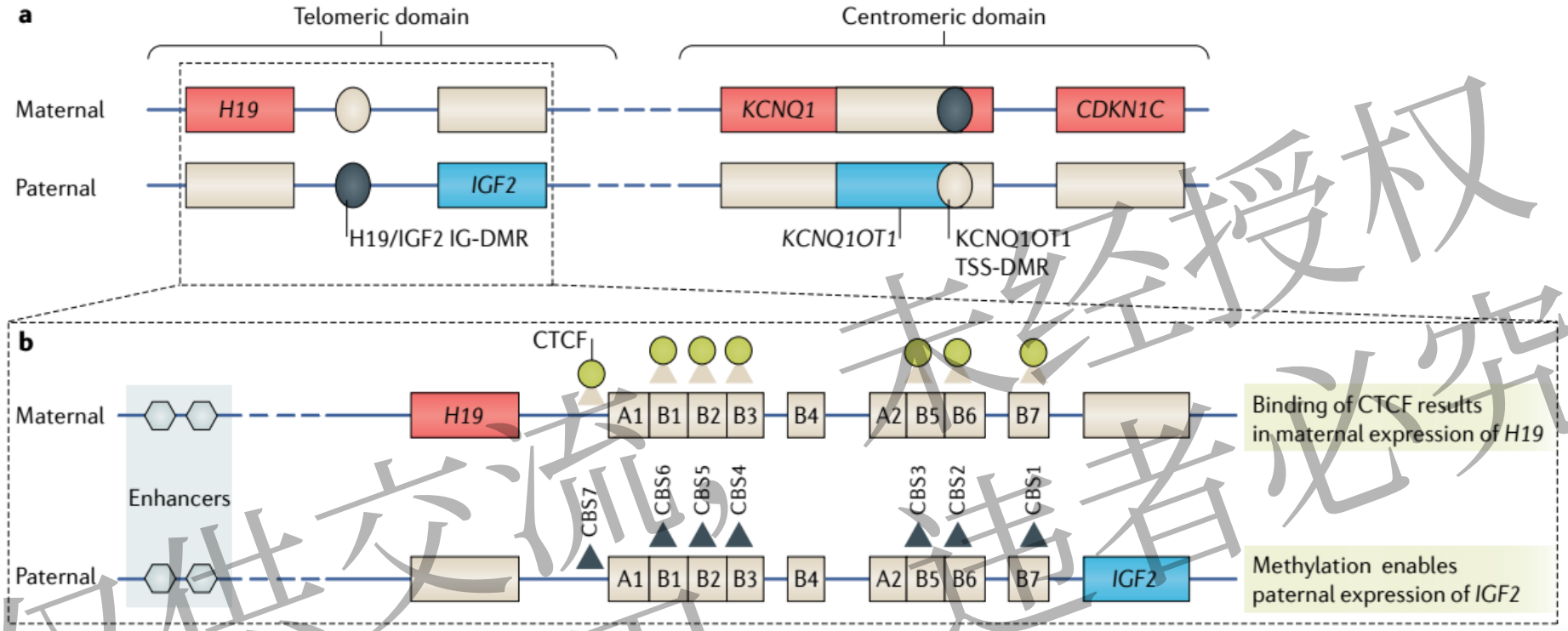
发病机制



- 大部分SRS为散发，但也存在家族聚集性
- SRS最主要的表观遗传改变定位于染色体11p15

Ishida, M. *Epigenomics* 8.4(2016):563-580.

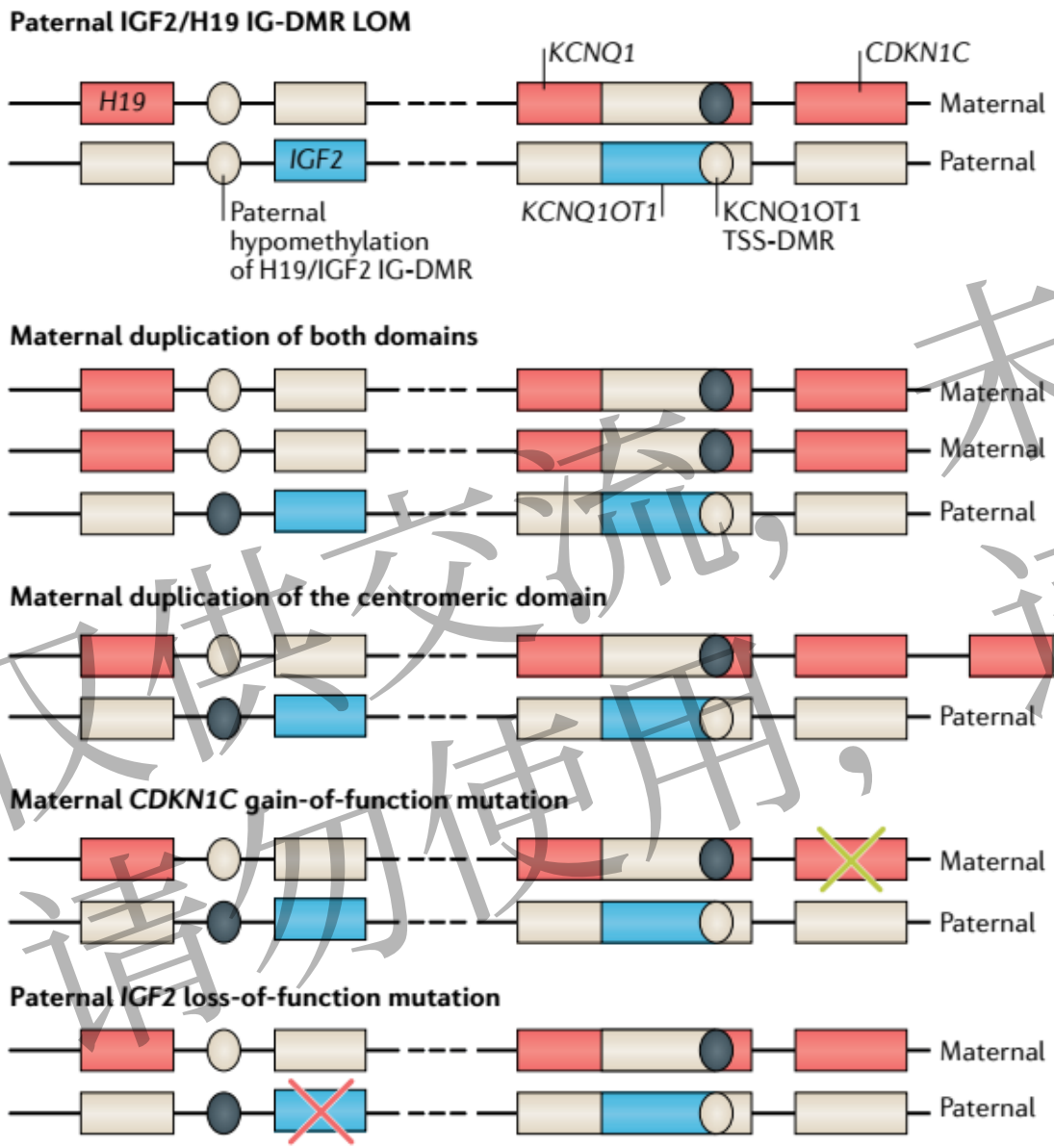
发病机制——正常染色体11p15印迹基因结构



- 父源性表达基因 (IGF1和KCNQ1OT1)和母源性表达基因 (CDKN1C和H19) 是位于染色体11p15与生长相关的印记基因
- H19和IGF2由端粒H19/IGF2 IG-DMR (基因间差异性甲基化区域，又称ICR1)调节，CDKN1C和CNQ10T1由着丝粒KCNQ1OT1 TSS-DMR（又称ICR2）调节
- 正常情况下，母源染色体ICR1处于非甲基化状态与锌指蛋白 (zinc finger protein, CTCF)结合，阻断IGF2启动子和H19下游增强子的相互作用，导致母源性IGF2沉默；父源染色体ICR1处于甲基化状态并阻止CTCF结合，使父源性IGF2表达

Wakeling, E. L., et al. *Nature Reviews Endocrinology* 13.2(2017):105-124.

发病机制——染色体11p15表突变和基因重排



主要：

父源性H19/IGF2 IG-DMR低甲基化，使父源性IGF2表达减少，母源性H19表达增加，导致生长受限

CNV：

母源性着丝粒或着丝粒和端粒两个结构域重复，CDKN1C表达增加

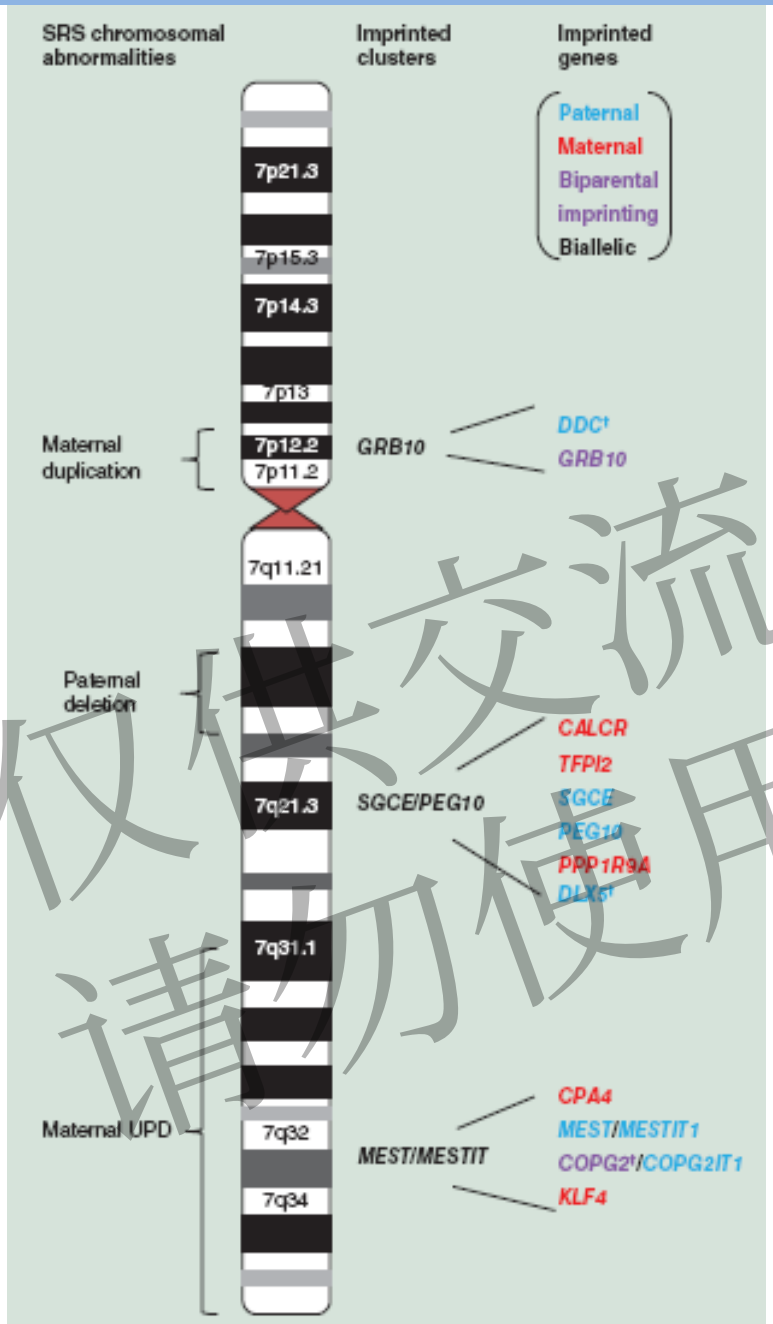
家族性：

母源性CDKN1C功能获得型突变

父源性IGF2功能丧失型突变

Wakeling, E. L., et al. *Nature Reviews Endocrinology* 13.2(2017):105-124.

发病机制——母源7号染色体单亲二倍体



- 母源7号染色体单亲二倍体出现在于近10%的患者中
- 目前认为upd(7)mat SRS的发病机制极有可能是7号染色体印迹基因表达异常所致；父源促生长基因表达减少，母源抑生长基因过表达
- 候选区域7p11.2-p13包含一个印迹基因(GRB10)和二等位基因表达的生长相关基因(IGFBP1、IGFBP3和EGFR)，7q31-qter包含4个印迹基因 (CPA4、MEST、COPG2和KLF4)和2个印迹非编码RNA(MESTIT1和COPG2IT1)

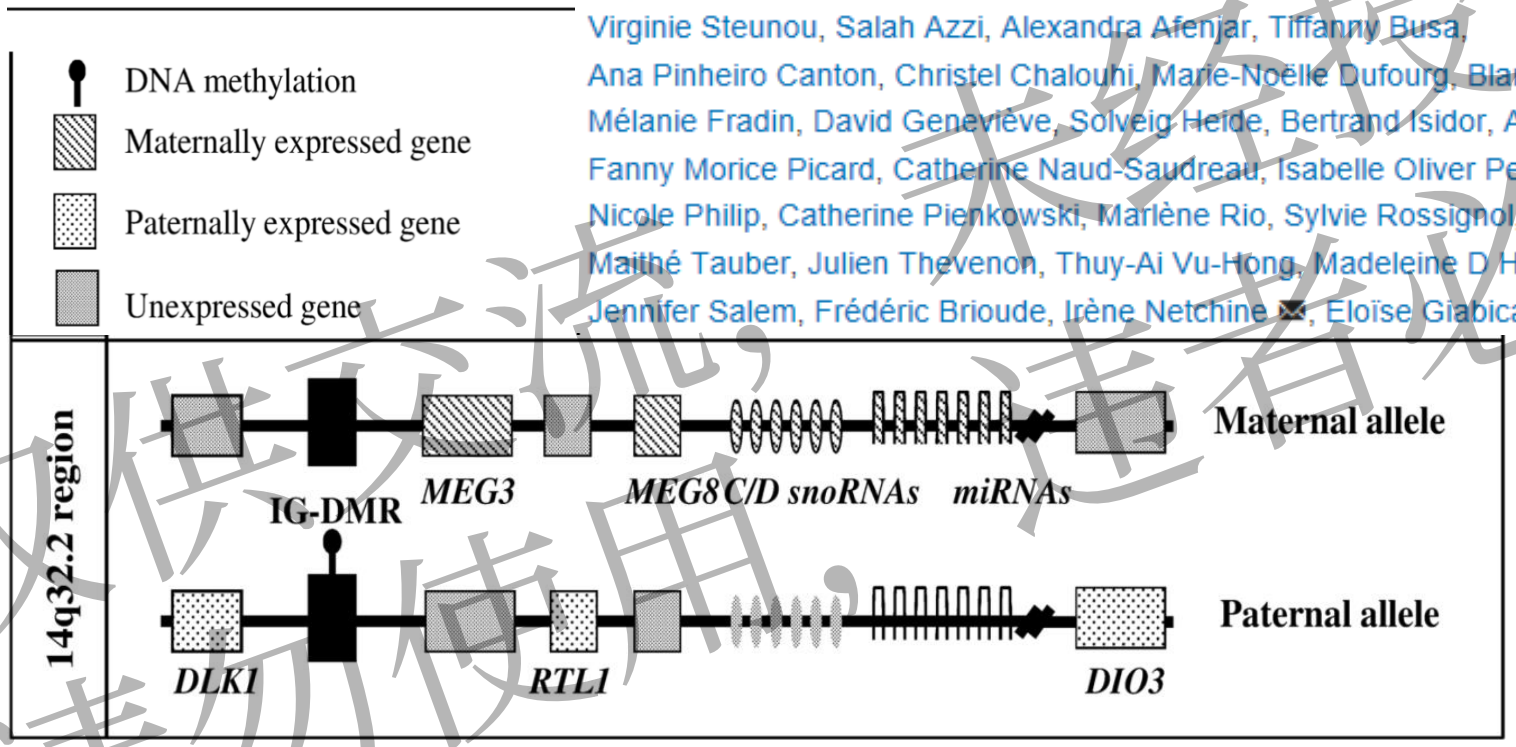
Ishida, M. *Epigenomics* 8.4(2016):563-580.

发病机制——染色体14q32.2印记区域异常

OXFORD ACADEMIC
JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Chromosome 14q32.2 Imprinted Region Disruption as an Alternative Molecular Diagnosis of Silver-Russell Syndrome

Sophie Geoffron, Walid Abi Habib, Sandra Chantot-Bastaraud, Béatrice Dubern, Virginie Steunou, Salah Azzi, Alexandra Afenjar, Tiffanny Busa, Ana Pinheiro Canton, Christel Chalouhi, Marie-Noëlle Dufourg, Blandine Esteva, Mélanie Fradin, David Geneviève, Solveig Heide, Bertrand Isidor, Agnès Linglart, Fanny Morice Picard, Catherine Naud-Saudreau, Isabelle Oliver Petit, Nicole Philip, Catherine Pienkowski, Marlène Rio, Sylvie Rossignol, Maithé Tauber, Julien Thevenon, Thuy-Ai Vu-Hong, Madeleine D Harbison, Jennifer Salem, Frédéric Brioude, Irène Netchine ✉, Eloïse Giabicani



SRS和Temple综合征(TS)是表型和基因型重叠的印迹基因疾病

28名14q32.2印记区域异常的患者中，72.7% (16/22) 患者NH-CSS评分≥4/6可临床诊断SRS；非11p15 LOM和upd(7)mat患者，14q32.2印记区域异常可作为SRS分子诊断的又一选择，包括upd(14)mat、MEG3/DLK1区域父源性缺失或者MEG3/DLK1:IG-DMR LOM

发病机制——其他

- **MLID** —— 多个印迹位点甲基化异常，可能是通过反式作用因子基因突变(如NLRP2、ZFP42)影响正常甲基化的建立和维持而引起
- **upd(20)mat和upd(16)mat**
- **CNVs** —— 已报告超过30种致病性拷贝数变异

Fontana, L. *Epigenomics* (2018):897-909.

分子检测技术——甲基化特异性检测

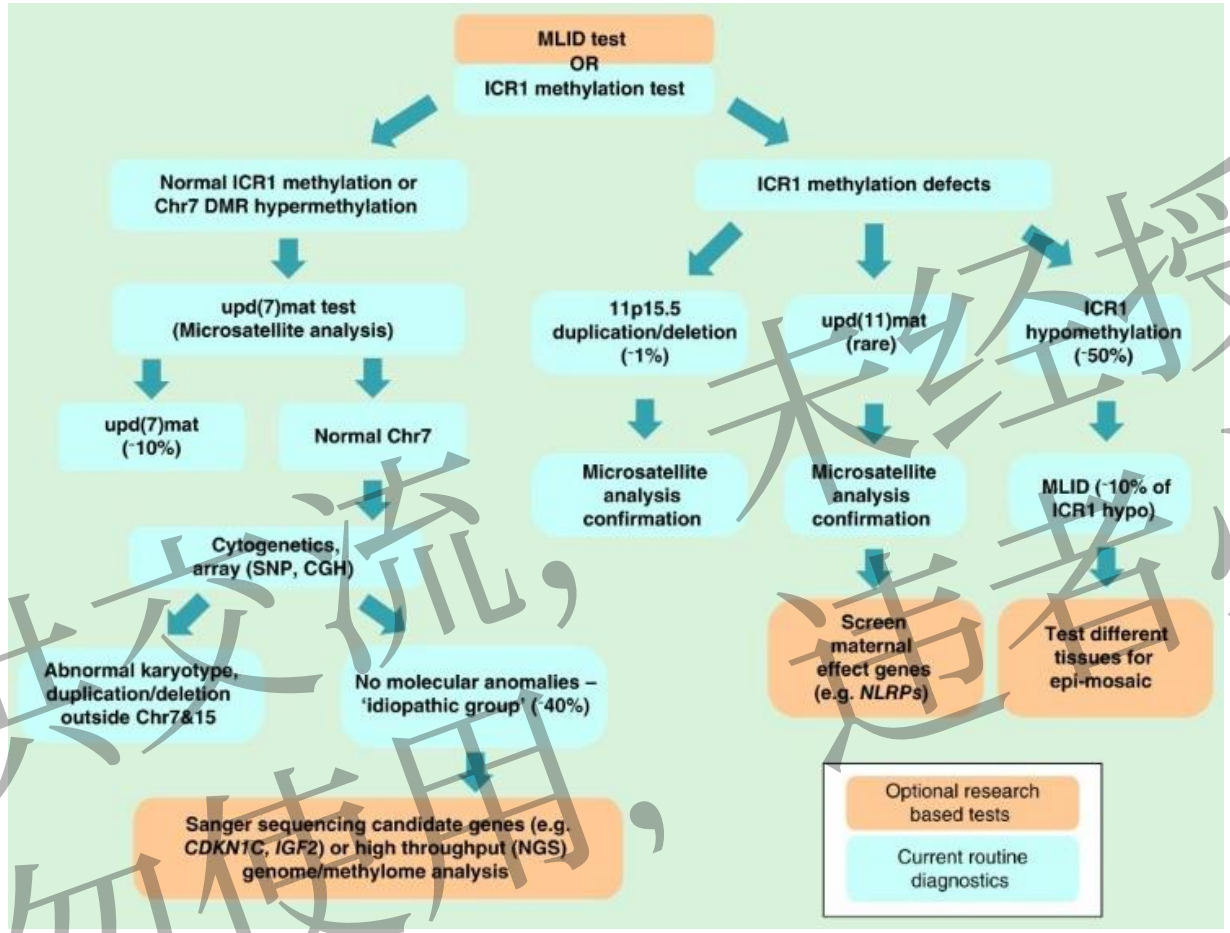
Method	Detection of UPD	CNVs	Epimutation	Number of loci in one assay	Advantage	Disadvantage
Methylation-specific tests						
MS Southern blot	Yes	Single loci	Yes	Single	Quantitative	Large amounts of DNA required; time-consuming; no differentation between different types of (epi)mutations
MS PCR	Yes	Single loci	Yes	Single	Fast and easy	No differentation between different types of (epi)mutations; only semiquantitative
MS pyrosequencing	Yes	Single loci	Yes	Single	Quantitative	No differentation between different types of (epi)mutations
QAMA real-time PCR-based methylation assay	Yes	Single loci	Yes	Single	Quantitative	No differentation between different types of (epi)mutations
Bisulfite sequencing	Yes	Single loci	Yes	Single	Quantitative	Time-consuming, cloning necessary; no differentation between different types of (epi)mutations
MS MLPA	Yes	Several loci	Yes	Up to 46 target sequences	Quantitative; differentiation between (epi) mutations; detection of MLMD	Sensitive for DNA quality
MS SNuPE	Yes	Several loci	Yes	Multilocus	Quantitative; detects MLMD	No differentation between different types of (epi)mutations

†Indeed, a huge number of techniques have been reported but we can present only those procedures widely applied by many laboratories.
CGH: Comparative genome hybridization; CNV: Copy number variation; MLMD: Multilocus methylation defect; MS: Methylation-specific; MS MLPA: Methylation-specific multiplex ligation probe-dependent amplification; MS SNuPE: Methylation-specific single nucleotide primer extension; MSA: Microsatellite analysis; QAMA: Quantitative analysis of methylated alleles; SNP: Single nucleotide polymorphism; UPD: Uniparental disomy.

目前经济有效使用最普遍的是甲基化特异性多连接依赖性探针扩增技术(**MS-MLPA**)，可**同时分析多位点拷贝数变异和甲基化**情况，但**检测位点受限制性内切酶位点识别的限制**

Eggermann, T , et al. ***Expert Review of Molecular Diagnostics*** **12.5(2012):459-71.**

分子诊断



分子检测有助于SRS**确诊和分类，阴性结果并不能排除SRS**

一线分子检测包括H19/IGF2 IG-DMR和KCNQ1OT1 TSS-DMR, GRB10 alt-TSS-DMR和MEST alt-TSS-DMR的DNA甲基化分析；如果11p15或7号染色体的检测结果呈阳性，则应区别**表观遗传学改变、CNV和upd**，以评估再发风险

对于未发现分子异常临床诊断SRS患者，可通过**高通量（NGS）基因组/甲基化测序**分析

Ishida, M. *Epigenomics* 8.4(2016):563-580.

nature REVIEWS ENDOCRINOLOGY

CONSENSUS

VOLUME 13 | FEBRUARY 2017 | 105

OPEN

EXPERT CONSENSUS DOCUMENT

Diagnosis and management of Silver–Russell syndrome: first international consensus statement

Emma L. Wakeling[1], Frédéric Brioude[2–4], Oluwakemi Lokulo-Sodipe[5,6], Susan M. O'Connell[7], Jennifer Salem[8], Jet Bliek[9], Ana P. M. Canton[10], Krystyna H. Chrzanowska[11], Justin H. Davies[12], Renuka P. Dias[13–15], Béatrice Dubern[16,17], Miriam Elbracht[18], Eloise Giabicani[2–4], Adda Grimberg[19], Karen Grønskov[20], Anita C. S. Hokken-Koelega[21], Alexander A. Jorge[10], Masayo Kagami[22], Agnes Linglart[23], Mohamad Maghnie[24], Klaus Mohnike[25], David Monk[26], Gudrun E. Moore[27], Philip G. Murray[28], Tsutomu Ogata[29], Isabelle Oliver Petit[30], Silvia Russo[31], Edith Said[32,33], Meropi Toumba[34,35], Zeynep Tümer[20], Gerhard Binder[36], Thomas Eggermann[18], Madeleine D. Harbison[37], J. Karen Temple[5,6], Deborah J. G. Mackay[5] and Irène Netchine[2–4]

Abstract | This Consensus Statement summarizes recomm
investigation and management of patients with Silver–R
disorder that causes prenatal and postnatal growth retar
between the care of individuals born small for gestationa
specific management issues exist and evidence from con
primarily a clinical diagnosis; however, molecular testing
diagnosis and defines the subtype. A 'normal' result from
diagnosis of SRS. The management of children with SRS
approach. Specific issues include growth failure, severe f
problems, hypoglycaemia, body asymmetry, scoliosis, mo
challenges. An early emphasis on adequate nutritional st
rapid postnatal weight gain might lead to subsequent inc
benefits of treating patients with SRS with growth hormo
motor development and appetite, reduced risk of hypogl
should be aware of possible premature adrenarche, fairl
insulin resistance. Treatment with gonadotropin-releasin
progression of central puberty and preserve adult height
to determine the natural history and optimal manageme

基因型与表型关联

	Total SRS % (total no. of patients)	11p15LOM % (total no. of patients)	upd(7)mat % (total no. of patients)	Clinical SRS % (total no. of patients)	non-SRS SGA[b] % (total no. of patients)
NH-CSS Factors:					
Birth weight/height ≤ -2SDS [a]	91.7 (60)	100 (35)	72.7 (11)	85.7 (12)	
Relative macrocephaly	85.7 (209)	99.1 (112)	85.2 (27)	55.4 (56)	15.8 (146)
Postnatal height ≤ -2SDS	84.2 (317)	83.8 (173)	80.9 (47)	86.8 (83)	87.7 (146)
Protruding forehead	88.1 (201)	93.7 (126)	100.0 (27)	77.6 (76)	17.1 (146)
Feeding difficulties	70.4 (307)	71.7 (173)	87.2 (47)	54.8 (73)	25.3 (146)
Asymmetry	57.3 (473)	77.4 (226)	29 (62)	39.5 (157)	6.8 (266)

11p15 LOM 患儿出生体重和身长更低，生后身高SDS改变不明显，更易表现出肢体不对称、小指侧弯和先天异常（主要消化系统异常），但并未发现临床表现严重程度和低甲基化程度相关

upd(7)mat 患儿生后身高SDS下降明显，更易出现神经运动发育迟缓

包含H19/IGF2 IG-DMR 和KCNQ1OT1 TSS-DMR的**11p15重复**患者具有SRS表型，但通常无肢体不对称，且发育迟缓可能性增加

鉴别诊断

主要鉴别于非SRS的SGA患儿，包括多种综合征和染色体重排疾病

特殊的临床表现可用于鉴别

Table 3 | Differential diagnosis of Silver–Russell syndrome in patients with relative microcephaly

Feature	Syndrome (OMIM number)					
	Bloom syndrome (#210900)	Nijmegen breakage syndrome (#251260)	MOPD II (#210720)	Meier–Gorlin syndrome (#224690, #61380, #613803, #613804, #613805)	*IGF1R* mutation or deletion (#147370, #612626)	*IGF1* mutation (#147440)
Birth weight SDS	Mean: −4.6	Mean: −1.6	Mean: −3.9	Mean: −3.8	−1.5 to −4.9	−2.5 to −4.5
Adult height range (cm)	• Male patients: 128–164 • Female patients: 115–160	• Male patients: 161–172 • Female patients: 150–165	Mean: 96	• Male patients: 136–157 • Female patients: 127–150	*IGF1R* mutation: 1 female patient (140), 2 male patients (133 and 170)	1 male patient: 117
						moderate ID
Facial features	Narrow face with underdeveloped malar area and mandible, fairly prominent nose, sun-sensitive telangiectasia in malar distribution	Receding forehead, prominent mid-face, small mandible, up-slanting palpebral fissures, long nose and philtrum, large ears	Prominent, long, broad nose with hypoplastic tip, low insertion of columella, prominent eyes in infancy, micrognathia	Microtia, narrow, beaked nose with low insertion of columella, small mouth, retrognathia	• *IGF1R* mutation: often normal; triangular face, micrognathia. • 15q26-qter deletion: micrognathia	No consistent features reported
Other features	Patchy areas of hypopigmented and hyperpigmented skin, feeding difficulties, high tumour risk (44% develop cancer by age 25 years), hypogonadism, type 2 diabetes mellitus, immunodeficiency, chromosomal instability with increased frequency of sister chromatid exchange	Severe, progressive microcephaly, immunodeficiency, cancer predisposition, chromosomal instability and rearrangements, café au lait spots, premature ovarian failure	Mean OFC at birth −4.6 SDS, progressive microcephaly, mesomelic limb shortening, progressive metaphyseal bone dysplasia, hip dysplasia, acanthosis nigricans, insulin resistance, cryptorchidism, intracranial aneurysm, dental anomalies, squeaky voice	Patellar hypoplasia, pulmonary emphysema, cryptorchidism, mammary hypoplasia (post-pubertal 100%), hypoplastic labiae	• *IGF1R* mutation: pectus excavatum, 5th finger clinodactyly, short fingers • 15q26-qter deletion: fifth finger clinodactyly, short fingers, talipes, congenital heart disease, renal anomalies	Sensorineural deafness
Inheritance and molecular abnormality	• Autosomal recessive • Mutations in *RECQL3* • High prevalence in Ashkenazi Jewish population	• Autosomal recessive • Mutations in *NBN* • High prevalence in Slavic population	• Autosomal recessive • Mutations in *PCNT*	• Autosomal recessive • Mutations in *ORC1, ORC4, ORC6, CDT1, CDC6*	*IGF1R* mutation: majority autosomal dominant; compound heterozygosity reported in two patients	• Autosomal recessive • Mutations in *IGF1*

可通过相对小头畸形鉴别

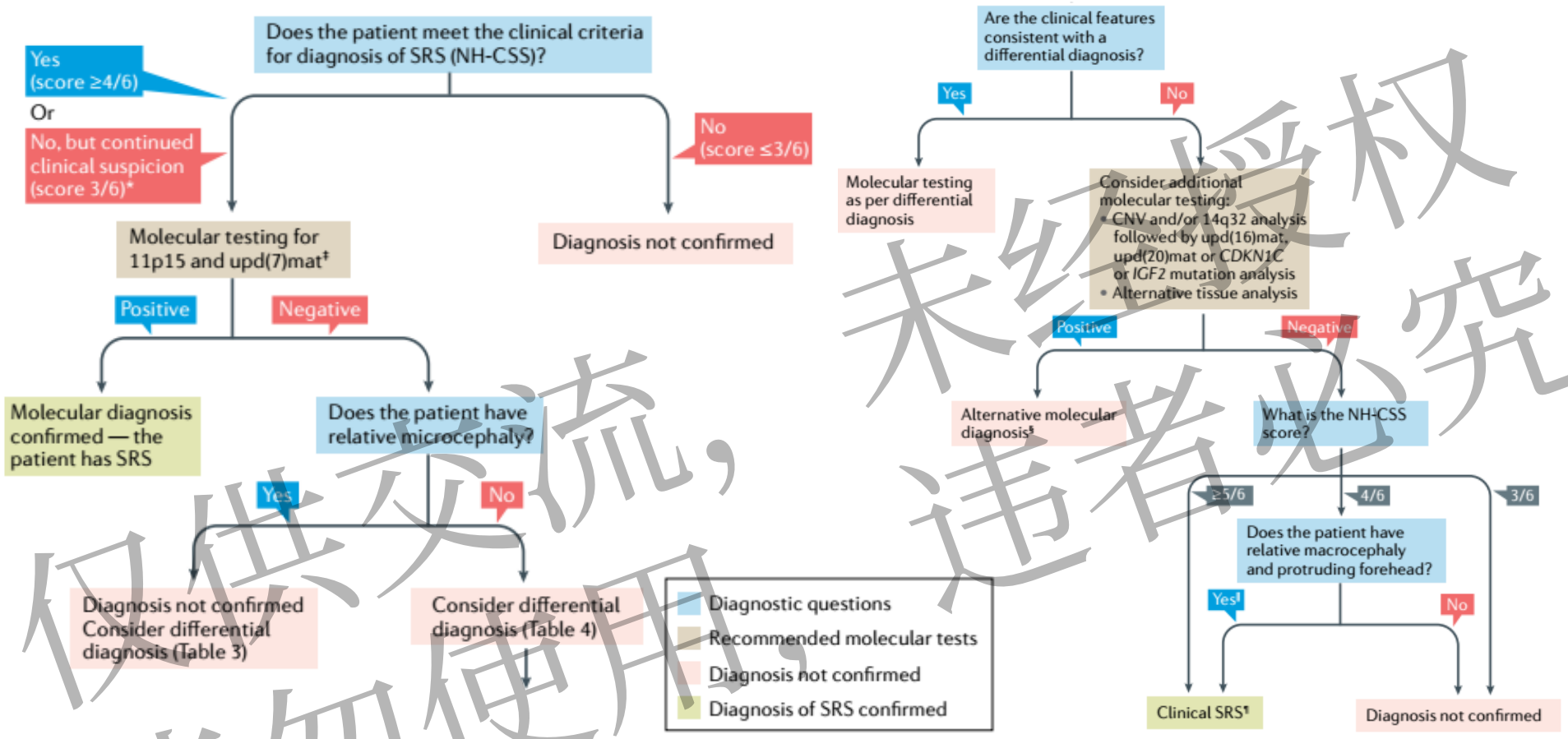
鉴别诊断

Table 4 | **Differential diagnosis of Silver–Russell syndrome in patients with relative normocephaly or macrocephaly**

Feature	Syndrome (OMIM number)				
	3-M syndrome (#273750)	Mulibrey nanism (#253250)	SHORT syndrome (#269880)	Floating harbour syndrome (#136140)	IMAGe syndrome (#614732)
Birth weight SDS	Mean: −3.1	Mean: −2.8 (range −4.0 to 0.5)	Mean: −3.3	Mean: −2.5	−2.0 to −4.0
Adult height range (cm)	115–150	136–150	Mean: 154	• Female patients: 98–156 • Male patients: 106–164	• 1 male patient: 160 • 1 female patient: 143
Cognitive function	Normal	Mild motor and speech delay only	Normal	Delayed speech, intellect variable: normal to significant ID	Normal or mild ID
Facial features	Anteverted nares, full lips, mid-face hypoplasia, long philtrum	Triangular face, frontal bossing	Micrognathia, high broad forehead, triangular-shaped face, deep-set eyes, prominent nose, low-set posteriorly rotated ears, hypoplastic nasal alae, facial lipodystrophy, thin hair	Triangular face, deep-set eyes, long eyelashes, bulbous nose, wide columella, short philtrum, thin lips	Frontal bossing, low-set ears, flat nasal bridge, short nose
Other features	Prominent heels (also in upd(7)mat), short broad neck, pectus deformity, short thorax, winged scapulae, hyperlordosis, hip dysplasia, subtle radiographic changes (slender long bones, tall vertebral bodies)	Hepatomegaly, yellow spots on retina, progressive restrictive perimyocarditis, insulin resistance, high pitched voice, slender long bones with thick cortex and narrow medullar channels, shallow sella turcica, increased tumour risk (particularly Wilms and ovarian stromal tumours)	Rieger anomaly, dental delay, partial lipodystrophy, transparent skin, dimples on elbows and buttocks, herniae, fifth finger clinodactyly, hyperextensible joints, hypogonadism, high pitched voice, type 2 diabetes mellitus, nephrocalcinosis, thin gracile bones	Delayed speech development with expressive language delay, considerably delayed bone age, broad fingertips	Congenital adrenal hypoplasia, metaphyseal and/or epiphyseal dysplasia, male genital anomalies
Inheritance and molecular abnormality	• Autosomal recessive • Mutations in *CUL7*, *OBSL1*, *CCDC8*	• Autosomal recessive • Mutations in *TRIM37* • High prevalence in Finnish population	• Autosomal dominant • Mutations in *PIK3R1*	• Autosomal dominant • Mutations in *SRCAP*	Imprinted – maternally inherited mutations in *CDKN1C*

存在生长落后家族史需考虑其他疾病可能

Silver-Russell综合征国际共识推荐诊断流程

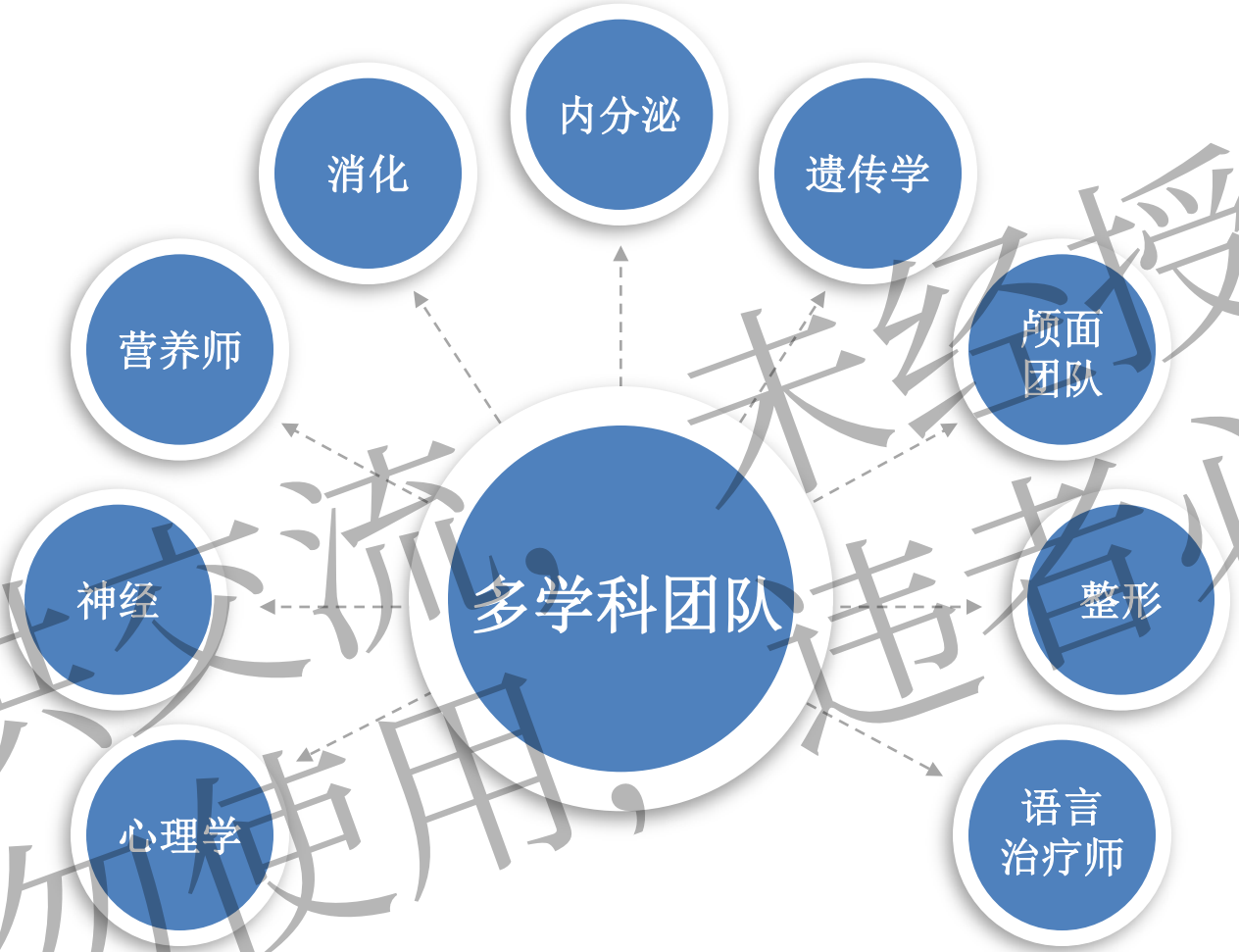


对于**符合3条**NH-CSS标准，**小于2岁**儿童、青少年和成人缺少数据或者**upd(7)mat**临床表现不典型，但临床高度怀疑SRS时，也应进行分子检测

11p15和upd(7)mat分子检测阴性，鉴别诊断排除后，需考虑**分子检测**CNV、14q32、upd(20)mat、upd(16)mat及其他未知异常，并考虑到**嵌合型**对其他组织进行检测

分子检测阴性时，**符合4条NH-CSS标准且包括相对大头和前额突出**，才临床诊断SRS

治疗



SRS导致广泛的身体结构和功能异常，该疾病患者需多学科跟踪随访和早期特异性干预

治疗——营养支持原则

早期发现消化系统异常和营养不良

喂养困难：食欲差、口腔运动障碍和能量摄入低

消化系统异常：胃食管反流、持续性呕吐、便秘

健康营养状态目标范围窄需监测

营养不良导致低血糖和生长迟缓

轻度营养过剩即可快速增加相对脂肪量以及长期代谢心血管疾病风险

营养支持目标

<2岁：补充营养预防低血糖和生长迟缓但同时注意快速生长追赶增加后期代谢风险

2-4岁：准备GH治疗，身高别体重在75-85%和/或BMI12-14kg/m^2

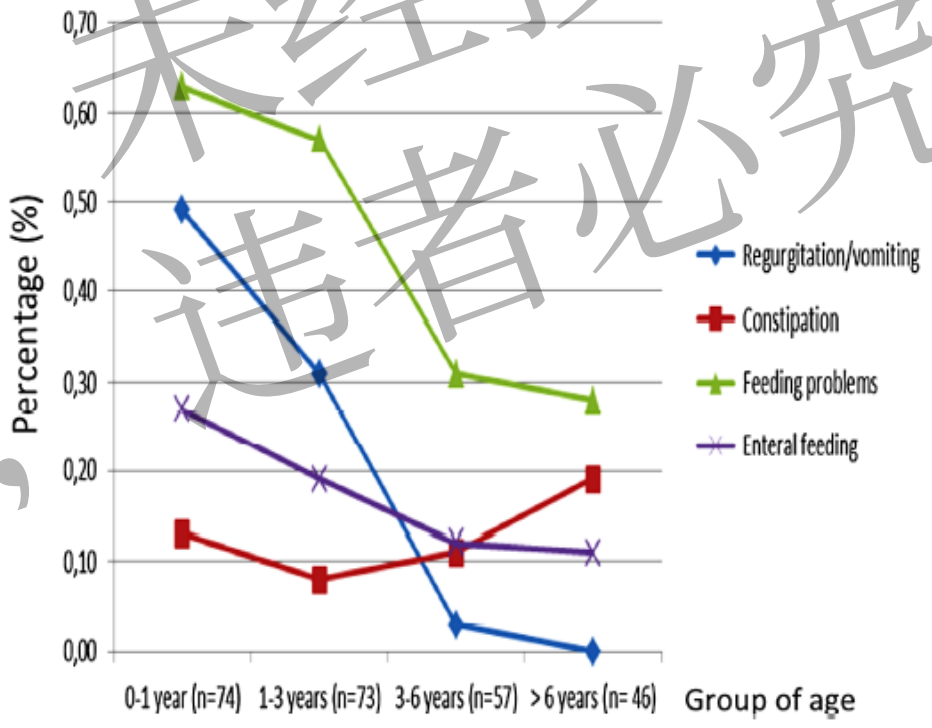
>4岁：根据肌肉量决定BMI目标；

11p15LOM肌肉量很低且肢体不对称，BMI需11-12kg/m^2；

upd(7)mat肌肉量正常，BMI在14-15kg/m^2

治疗——营养支持方法

- 喂养问题多出现于3岁前，后趋于消失；需在确诊后进行**系统的消化道检查和营养评估**，并反复评估**能量摄入**情况，尽早给予适当营养支持（包括丰富饮食、口服营养补充和肠内喂养）
- 治疗**口腔运动感觉问题**可以改善食物摄入
- **胃食管反流**可持续至儿童期需长期质子泵抑制剂治疗
- **严重喂养困难和胃食管反流、严重低血糖、完全性神经性厌食**时，考虑使用胃造口术胃导管(有或无胃底折叠术)或经胃空肠造瘘术进行肠内营养
- 6岁后**便秘**更严重通常需要长期泻药治疗



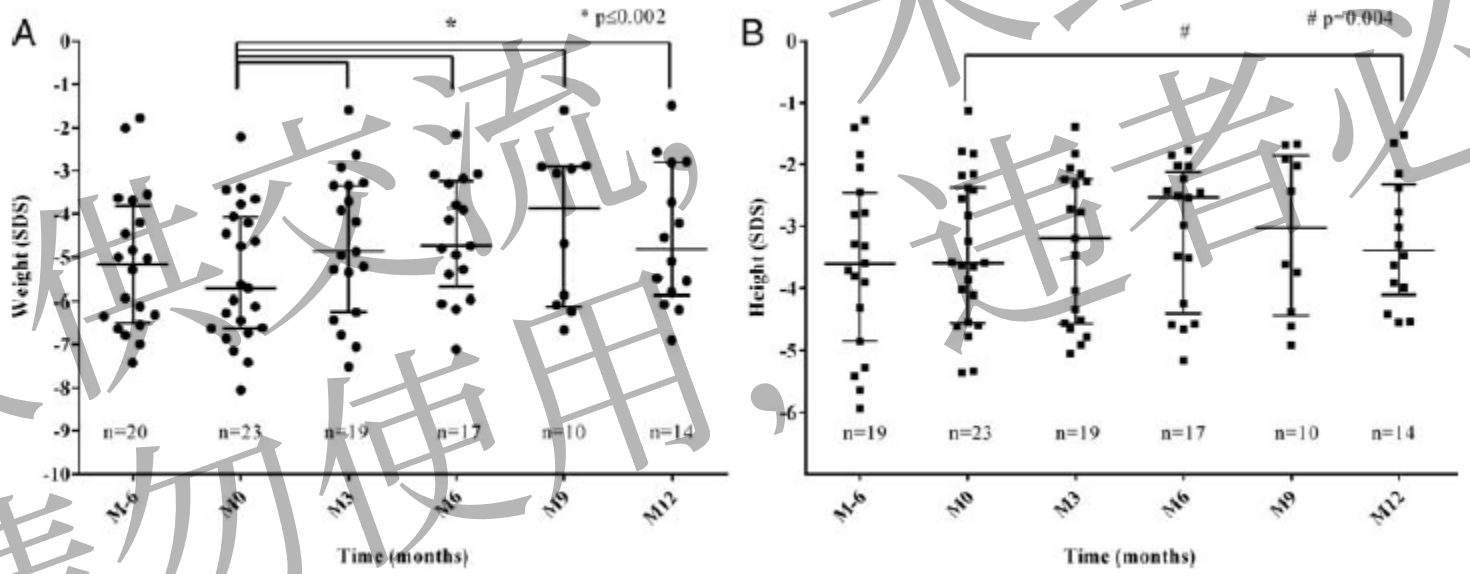
Marsaud C, et al. Arch Dis Child 2015;100:353–358.
Giabicani, E, I. Netchine, and F. Brioude. *Current Opinion in Pediatrics* 28.4(2016):1.

治疗——赛庚啶可能可用于营养支持治疗

JPGN
Journal of Pediatric Gastroenterology and Nutrition

Effect of Cyproheptadine on Weight and Growth Velocity in Children With Silver-Russell Syndrome

Lemoine, Anaïs*; Harbison, Madeleine, D.†; Salem, Jennifer‡; Tounian, Patrick*; Netchine, Irène§,||,¶; Dubern, Béatrice*



一项**回顾性**研究发现，生长激素治疗前，给予**赛庚啶**可改善SRS患儿**生长速率和营养状态**；本研究是自身对照，缺乏CYP确切剂量、能量摄入量且可能存在安慰剂效应，需要进一步**前瞻性**研究证实这一结果

Lemoine, A, et al. ***Journal of Pediatric Gastroenterology & Nutrition*** **66.2(2017):1.**

治疗——预防低血糖

- SRS患儿低血糖发生率约为27%，为自发性无症状夜间低血糖。5岁以下儿童肌肉和肝脏质量低、相对大头和进食困难，增加**空腹低血糖**和潜在的**神经认知障碍**的风险
- **监测尿酮**水平通常对预防与禁食、活动或疾病相关的低血糖有效，可用来确定儿童的“安全禁食时间”
- **预防夜间低血糖**，可以在最后一顿中添加高分子量葡萄糖聚合物(10个月以下的婴儿)或生玉米淀粉(较大婴儿童儿和高危)
- 对于**术前空腹或发热性疾病**，可能需要**静脉注射葡萄糖**(10%葡萄糖)，SRS患儿较SGA肠道休息时间更长的，建议出院前，至少无静脉葡萄糖支持的情况下，**喂养12h无酮尿**
- 若**持续低血糖**，应考虑**早期GH治疗**

治疗——生长激素已被批准用于SRS患儿治疗

	Davies 1988 [1]	Wollmann 1995 [2]	Vu-Hong 2009 [3]	Wakeling 2010 [4]	Binder 2013 [5]
No of patients: 11p15 LOM /upd(7)mat/ clinical SRS /not tested	-/-/-/18	-/-/-/40	8/-/-/-	2/1/-/-	3/1/1/8
Adult height: all	-3.6 SDS				-3.13 SDS
Adult height: males	-2.8 SDS	-3.7 SDS	-2.8 SDS	-2.10 SDS	-3.52 SDS
Adult height: females	-6.2 SDS	-4.2 SDS	-3.4 SDS	-3.25 SDS	-2.52 SDS

	FDA-approved indication (2001)	EMEA-approved indication (2003)
Age at start (yr)	2	4
Height SDS at start	Not stated	−2.5 SD
Growth velocity before treatment	No catch-up	<0 SD for age
Reference to midparental height	Not stated	Height SDS > 1 SD below midparental height SDS
Dose (μg/kg·d)	70	35

EMEA, European Agency for the Evaluation of Medicinal Products; FDA, Food and Drug Administration.

SRS患者绝大多数表现SGA且无生长追赶，**成年终身高明显偏低**

美国FDA和欧洲EMEA于2001年和2003年在SGA注册许可证下批准rhGH用于SRS治疗

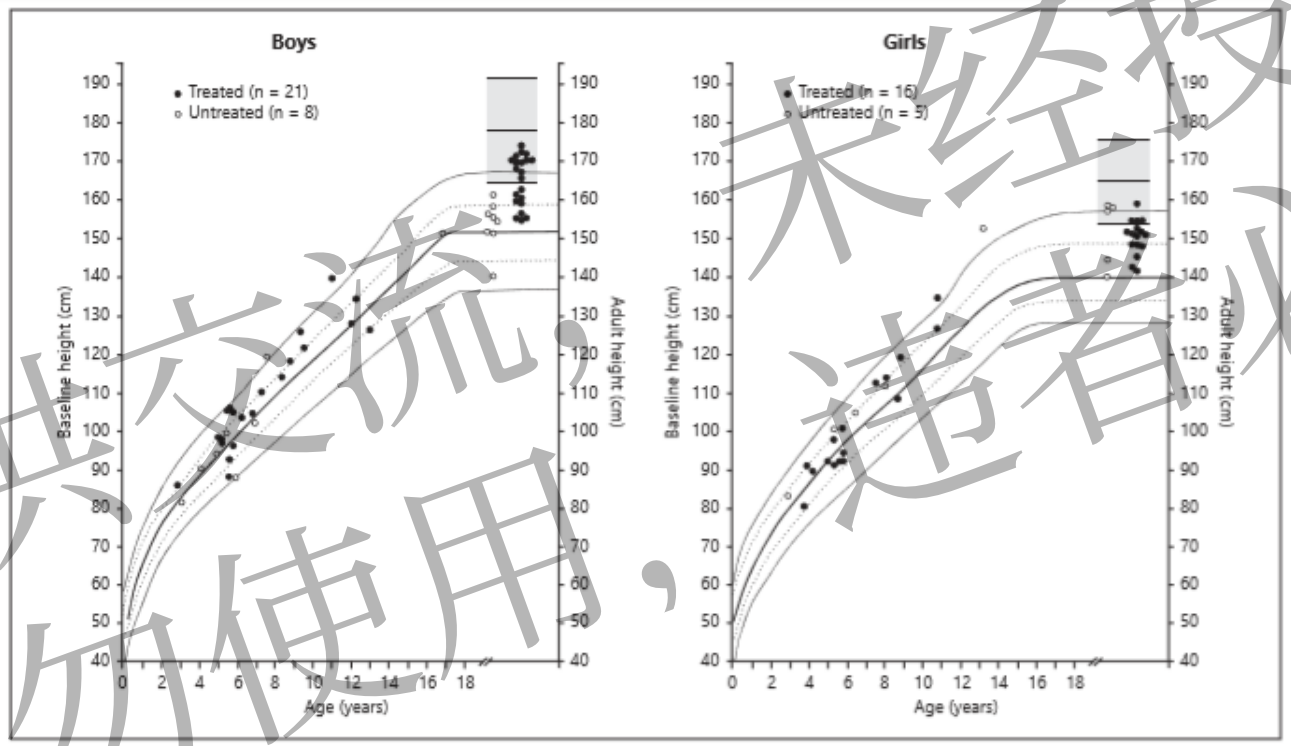
Clayton PE, et al. *Journal of Clinical Endocrinology and Metabolism* 92.3(2007):804.

治疗——单中心回顾性研究发现GH可改善SRS患者成年终身高

HORMONE RESEARCH IN PÆDIATRICS

Adult Height and Epigenotype in Children with Silver-Russell Syndrome Treated with GH

Binder G.[a] · Liebl M.[a] · Woelfle J.[c] · Eggermann T.[d] · Blumenstock G.[b] · Schweizer R.[a]



未治疗SRS患者成年终身高为–3.13±1.37 SDS，治疗后为–2.12±0.98 SDS，52%男性和25%女性SRS患者达到正常成年终身高。治疗较未治疗男性患者身高增长11.1±6.1cm (1.50±0.82 SDS)，女性患者身高增长4.0±12.7cm (0.70±2.22 SDS)

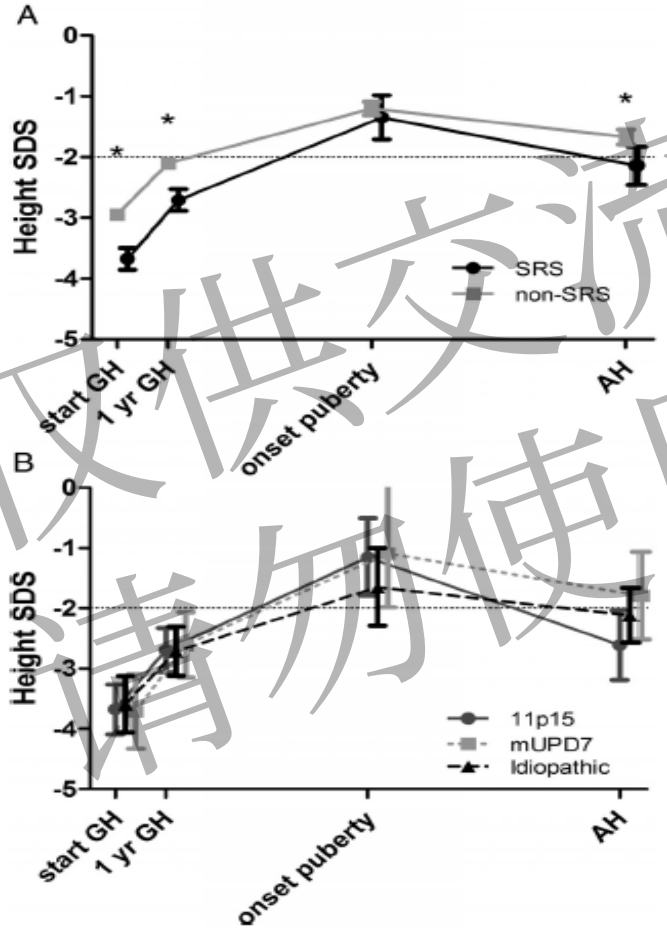
Binder, G. , et al. ***Hormone Research in Paediatrics*** **80.3(2013):193-200.**

治疗——GH治疗SRS与非SRS的SGA疗效相同

OXFORD ACADEMIC
JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Long-Term Results of GH Treatment in Silver-Russell Syndrome (SRS): Do They Benefit the Same as Non-SRS Short-SGA?

C. C. J. Smeets, G. R. J. Zandwijken, J. S. Renes, and A. C. S. Hokken-Koelega



荷兰的一项长期前瞻性研究

227名非SRS的SGA患儿，62名SRS患儿（31名11p15，11名mUPD7，20名特发性）均接受1mg/m^2/d (0.035 mg/kg/d)治疗

治疗前，SRS患儿平均身高SDS(-3.67[1.0])较非SRS(-2.92[0.6];P <.001)明显降低；SRS患儿成年终身高SDS(-2.17[0.8]) 较非SRS(-1.65[0.8];P =.002)明显低；但**总身高增长SDS未见明显差异**

所有**SRS基因亚型均受益于GH治疗，UPD7mat和特发性**身高增长的趋势更明显

Smeets, C. C., et al. *Journal of Clinical Endocrinology & Metabolism* 101.5(2016):jc20154273.

治疗——11p15 SRS患儿可能存在IGF1不敏感

OXFORD ACADEMIC
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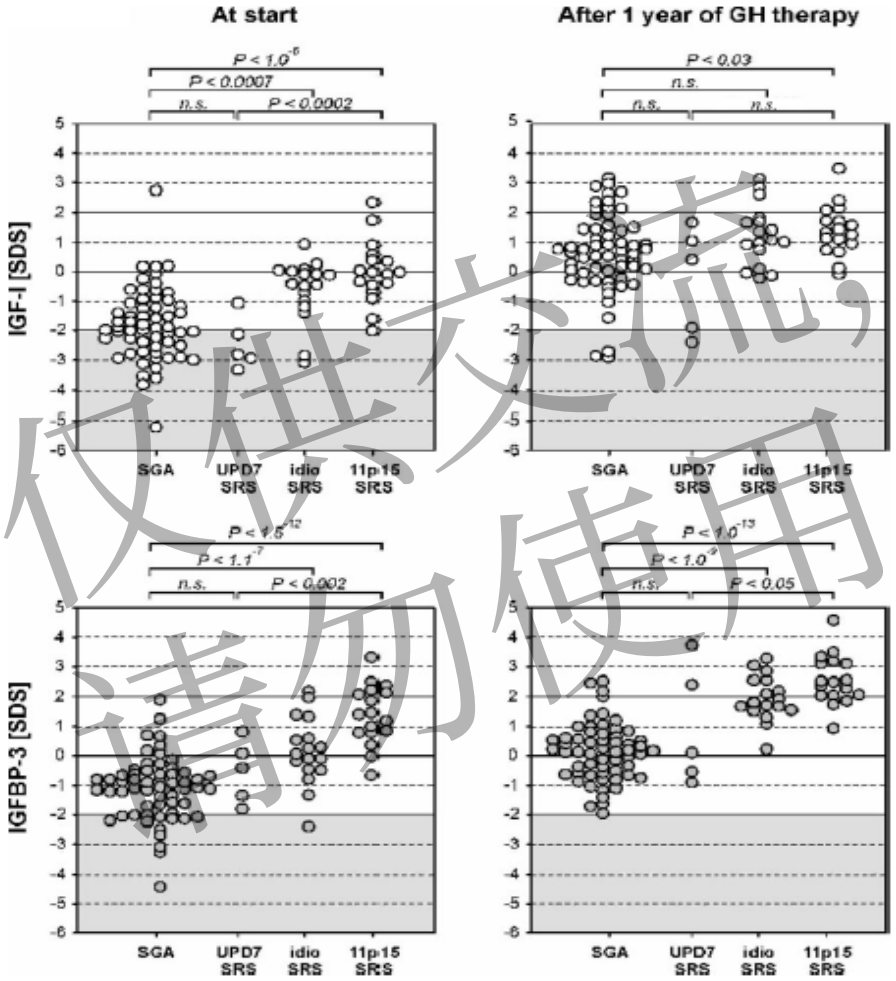
The Endocrine Phenotype in Silver-Russell Syndrome Is Defined by the Underlying Epigenetic Alteration

Gerhard Binder, Ann-Kathrin Seidel, David D. Martin, Roland Schweizer, C. Philipp Schwarze, Hartmut A. Wollmann, Thomas Eggermann, and Michael B. Ranke



11p15 SRS患儿未治疗时IGF1和IGFBP3在正常范围内较高，rhGH治疗1年后IGFBP3升高超过正常而IGF1适度增长；upd(7)mat患儿较低，但身高增长较高

11p15 SRS患儿可能存在IGF1不敏感，需要进一步研究了解如何使用IGF1和IGFBP3水平监测IGF1抵抗的SRS患儿rhGH用量

Binder, Gerhard , et al. Journal of Clinical Endocrinology & Metabolism 93.4(2008):1402-7.

治疗——生长激素可改善身体组成

OXFORD ACADEMIC
JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Muscle Function Improves during Growth Hormone Therapy in Short Children Born Small for Gestational Age: Results of a Peripheral Quantitative Computed Tomography Study on Body Composition

Roland Schweizer, David D. Martin, Eckhard Schönau, and Michael B. Ranke

	Time with GH							
	Start	6 months	To start (*P* value)	12 months	To start (*P* value)	To 6 months (*P* value)	24 months	To 12 months (*P* value)	To start (*P* value)
Age (yr)	7.31 (2.65)	7.75 (2.60)	a	8.35 (2.68)	a	a	9.45 (2.65)	a	a
Height (cm)	107.36 (13.97)	112.30 (13.54)	a	116.96 (13.39)	a	a	125.19 (12.65)	a	a
Height SDS	−3.30 (0.68)	−2.73 (0.71)	a	−2.39 (0.74)	a	a	−1.90 (0.82)	a	a
Weight (kg)	16.61 (5.44)	18.12 (5.68)	a	20.05 (6.39)	a	a	23.78 (7.25)	a	a
Weight SDS	−2.61 (0.80)	−2.34 (0.76)	a	−2.06 (0.85)	a	a	−1.63 (0.88)	a	a
BMI (kg/m^2)	14.04 (1.84)	14.02 (1.73)	ns	14.28 (2.05)	b	b	14.82 (2.34)	c	a
BMI SDS	−1.15 (0.98)	−1.16 (0.84)	ns	−1.07 (0.95)	ns	b	−0.88 (0.98)	c	a
FA (cm^2)	682.42 (288.06)	443.80 (258.22)	a	477.68 (238.09)	a	ns	507.48 (351.70)	ns	a
FA % of TCSA	35.31 (11.09)	24.30 (10.41)	a	21.10 (9.32)	a	b	21.51 (11.80)	ns	a
FA SDS_{CA}	−0.66 (1.00)	−1.44 (0.70)	a	−1.58 (0.80)	a	ns	−1.29 (0.86)	c	a
FA SDS_{Height}	−0.62 (1.85)	−1.93 (1.46)	a	−2.07 (1.55)	a	ns	−1.51 (1.54)	a	a
MA (cm^2)	1070.36 (307.27)	1300.19 (342.58)	a	1409.03 (365.57)	a	a	1565.69 (417.99)	a	a
MA % of TCSA	55.80 (9.67)	66.22 (9.34)	a	69.12 (9.56)	a	b	69.25 (11.66)	ns	a
MA SDS_{CA}	−2.87 (0.88)	−1.99 (0.93)	a	−1.72 (0.87)	a	c	−1.54 (1.05)	ns	a
MA SDS_{Height}	−1.79 (1.01)	−0.80 (1.24)	a	−0.75 (1.28)	a	ns	−0.78 (1.37)	ns	a
MIGF (N)	49.48 (34.23)	67.06 (40.82)	c	88.00 (52.37)	a	a	108.34 (51.22)	a	a
MIGF SDS_{CA}	−3.50 (2.58)	−2.42 (2.30)	b	−1.71 (1.96)	a	c	−1.23 (1.03)	ns	a
MIGF SDS_{Height}	−0.92 (2.58)	−0.20 (2.25)	ns	0.33 (1.93)	c	b	0.49 (1.15)	ns	c
MIGF/MA (N/cm^2)	4.35 (2.19)	4.87 (2.13)	ns	5.84 (2.54)	a	c	6.73 (2.14)	c	a

Values are e

[a] $P < 0.001$

[b] $P < 0.05$.

[c] $P < 0.01$.

SGA患儿（包括SRS患儿）身材矮小、肌肉质量和功能低下

生长激素治疗使身高增长的同时**增加肌肉质量和功能，降低脂肪质量**

Schweizer, Roland , et al. Journal of Clinical Endocrinology & Metabolism 93.8(2008):2978-83.

治疗——GH长期安全性良好

OXFORD ACADEMIC
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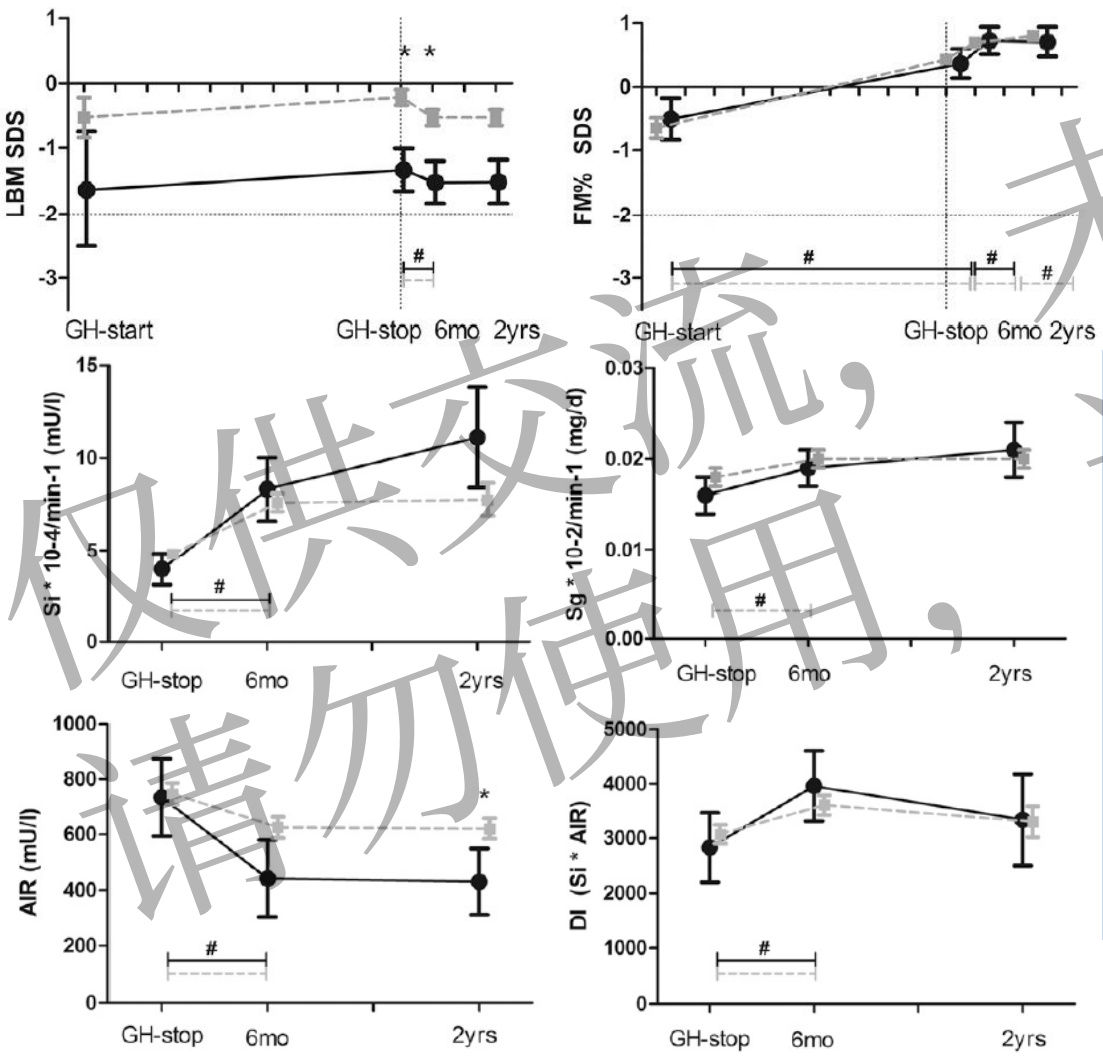
Metabolic Health and Long-Term Safety of Growth Hormone Treatment in Silver-Russell Syndrome

Carolina C. J. Smeets, Judith S. Renes, Manouk van der Steen, Anita C. S. Hokken-Koelega



GH治疗后对SRS与非SRS患儿**身体组成改善一致**，增加LBM减少FM%，但**SRS患儿LBM始终偏低**，停止治疗后两组均出现LBM减少FM%增加

GH治疗可**改善两组胰岛素敏感性和胰岛β细胞功能**

所有SRS患者均未出现代谢综合征、2型糖尿病和不良事件

Smeets, C. C., et al. Journal of Clinical Endocrinology & Metabolism 102.3(2017):jc20163388.

治疗——生长激素

- **改善能量摄入缺陷后**进行生长激素治疗
- 由于SRS患儿易出现空腹低血糖，**避免进行生长激素激发试验**
- 生长激素治疗的目标是**改善身体组成**（尤其肌肉含量）、精神运动发育和食欲，减少低血糖，**改善身高增长**
- **2-4岁开始**生长激素治疗；如果营养支持的情况下仍**严重空腹低血糖和营养不良**，甚至行胃造口术也无改善，**严重肌张力低下**，有些中心对2岁以下患儿也进行治疗
- 剂量从**35 μg/kg /d**开始
- **生长速率<2cm/y**且**男孩骨龄>17岁、女孩骨龄>14岁**，停止治疗
- 生长激素治疗期间**至少每年监测IGF1和IGFBP3**一次

治疗——GnRHa

在荷兰的长期前瞻性研究中

对于预测AH低的17名SRS患儿（12名女孩，5名11p15、5名mUPD7、7名特发性）GH治疗基础上给予GnRHa治疗2年（醋酸亮丙瑞林3.75mg/4w）

	Boy			girl		
	Without GnRHa	With GnRHa	P Value	Without GnRHa	With GnRHa	P Value
age at the start of puberty, y	11.7 [0.9]	10.7 [1.1]	.052	11.0 [1.2]	9.4 [0.9]	.004
Height at the onset of puberty, cm	145.2 [**6.2**]	142.5 [6.9]	.044	139.4 [9.9]	132.1 [8.8]	.015
Height gain, cm	22.3 [1.9]	33.1 [2.8]	.03	15.5 [5.5]	26.3 [6.1]	.004
AH, cm			.55	156.9 [4.9]	155.0 [4.6]	.41

青春期启动早身高偏矮的SRS患儿，添加GnRHa治疗可以**增加青春期身高增长量**

Smeets, C. C., et al. *Journal of Clinical Endocrinology & Metabolism* 101.5(2016):jc20154273.

治疗——芳香化酶抑制剂

芳香化酶催化雄烯二酮转化成雌二醇和雌酮，是雌激素生物合成的限速酶

第三代芳香化酶抑制剂（如阿那曲唑），可帮助肾上腺功能初现但未中枢性青春发育骨龄超前的患儿，控制骨骼成熟，但目前还没得到治疗生长障碍疾病的许可

ClinicalTrials.gov Identifier: NCT01520467

Recruitment Status : Unknown
Verified August 2016 by Assistance Publique - Hôpitaux de Paris.
Recruitment status was: Active, not recruiting
First Posted : January 30, 2012
Last Update Posted : August 24, 2016

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	27 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Efficacy and Tolerance of Treatment With an Aromatase Inhibitor (Anastrozole) to Limit the Progression of Bone Maturation Related to Pathological Adrenarche in Children With Silver-Russell or Prader-Willi Syndrome
Study Start Date :	April 2012
Actual Primary Completion Date :	July 2016
Estimated Study Completion Date :	October 2016

一项为期18个月，研究阿那曲唑治疗SRS儿童与病理性肾上腺功能初现相关的骨成熟疗效和耐受性的双盲临床试验正在进行中

https://clinicaltrials.gov/ct2/show/study/NCT01520467

治疗——其他

- **神经认知障碍**　告知家长患儿语言运动发育迟缓风险较高、尤其是UPD(7)mat患儿，需早期发现并在成长过程中监测，予以合适干预治疗
- **肢体不对称**　生长激素治疗不能改善，肢体延长手术有效。监测肢体长度，必要时手术治疗
- **脊柱侧弯**　生长激素治疗可能与侧弯加重相关，但因果关系未建立，需进一步研究；生长激素治疗前和治疗期间需与骨科合作监测
- **颅面畸形**　有经验的包括口腔科、整形外科和耳鼻喉科在内的颅面部团队进行治疗；目前正畸、上颚扩张可以帮助改善口咽功能和面部形态

遗传咨询

✓**准确的遗传咨询依赖于分子诊断**

✓**11p15 LOM —— 再发风险低**(SRS患儿的父母不太可能有另一个患病孩子)和**子代风险也很低**(SRS患者不太可能把这种疾病遗传他们的孩子)

✓**upd(7)mat —— 再发风险和子代风险均低**（如果患者**染色体核型正常**）

✓**MLID —— 可能**由于反式作用基因突变引起，**再发风险增加**较其他SRS患者高，暂无证据支持这一猜想

✓家族性SRS(**母源性11p15重复、母源性CDKN1C功能获得型突变和父源性IGF2功能丧失型突变**) —— 再发风险高达50%

✓**CNVs ——** 再发风险与CNVs**大小、位置、双亲来源**有关

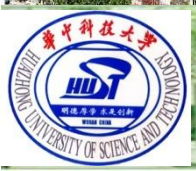
Binder, G. , et al. Hormone Research in Paediatrics 80.3(2013):193-200.

小结

- Silver-Russell综合征是一种临床和遗传异质性疾病
- 诊断主要是基于NH-CSS临床诊断
- 分子诊断有助于SRS确诊和分类，阴性结果并不能排除诊断
- 治疗采用多学科参与长期监测的综合管理模式
- 婴幼儿期以营养支持为主
- 生长激素可改善SRS患儿身高、身体组成和代谢情况，长期安全性良好
- 青春期启动早身高偏矮的SRS患儿，增加GnRHa治疗可以增加青春期身高增长量

Thank You!

xpluo@tjh.tjmu.edu.cn



華中科技大學同濟醫學院
HUAZHONG UNIVERSITY OF SCIENCE AND TECHNOLOGY