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• 专题报道 •

## 胶原 XXVII $\alpha 1$ 型基因突变所致 Steel 综合征 1 例并文献分析

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**[摘要]** **目的** 探讨胶原 XXVII  $\alpha 1$  型 (*COL27A1*) 基因突变所致 Steel 综合征的临床特征、诊断、基因检测、治疗及预后。**方法** 报告海军军医大学(第二军医大学)长海医院骨科收治的 1 例汉族 Steel 综合征合并脊柱侧凸青少年患者资料, 同时利用 PubMed 数据库以“Steel syndrome” AND “COL27A1”为主题词检索 1993 年 1 月至 2020 年 10 月相关文献, 共检索到 13 篇文献(共 54 例 Steel 综合征患者), 纳入其中全外显子测序确诊的 *COL27A1* 突变所致 Steel 综合征患者 17 例。对包括本例在内共 18 例 *COL27A1* 突变所致 Steel 综合征患者的临床特征进行分析。**结果** 本例患者除有发育迟缓、腕骨融合、脊柱侧凸、长椭圆脸、前额突出、鼻前倾等常见临床表现外, 还有蹼状颈和颈后低发际线等特殊表现。全外显子测序提示 *COL27A1* 存在 2 个复合杂合突变位点: p.Pro705Ser 和 p.Asn1723Ser, 分别来源于父亲和母亲。综合各项检查和全外显子测序结果, 确诊 Steel 综合征合并先天性脊柱侧凸。患者完善术前检查后行脊柱侧凸后路三维矫形植骨融合内固定术, 手术节段 T<sub>3</sub>~L<sub>1</sub>。术后 3 个月、1 年、2 年门诊复查全脊柱正侧位 X 线片示固定节段骨性融合良好, 无断钉、断棒、交界性后凸、远端附加现象等并发症。18 例患者中男 9 例、女 9 例, 确诊年龄为 0.17~14 岁, 3 例为 *COL27A1* 复合杂合突变(1 例 p.Pro705Ser 和 p.Asn1723Ser、1 例 c.93del 和 c.3075del、1 例 p.Cys174Serfs\*34 和 p.Arg707\*), 15 例为纯合错义突变(11 例 p.Gly697Arg、1 例 p.Gly802Glu、1 例 p.Gly904Arg、1 例 c.4261-1G>A、1 例 c.3556-2A>G)。1 例患者临床特征不详, 余 17 例主要临床表现有脊柱侧凸(17 例)、身材矮小(12 例)、长椭圆脸(9 例)、前额突出(9 例)、发育迟缓(5 例)、听力受损(5 例)等; 18 例患者的影像学特征有髋关节脱位(16 例)、桡骨头脱位(11 例)、腕骨融合(9 例)等。**结论** *COL27A1* 突变导致的 Steel 综合征是一种罕见的常染色体隐性遗传病, 患者家族史、临床特征、影像学检查等仅能为该综合征提供倾向性诊断, 最终确诊需要依据基因检测结果。对于该病的治疗应加强研究以改善预后。

**[关键词]** Steel 综合征; 胶原 XXVII 型; 脊柱侧凸; 手术治疗

**[中图分类号]** R 596.2; R 682.1

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### Steel syndrome caused by collagen type XXVII $\alpha 1$ chain mutation: a case report and literature review

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**[Abstract]** **Objective** To investigate the clinical features, diagnosis, gene detection, treatment and prognosis of Steel syndrome caused by the mutation of collagen type XXVII  $\alpha 1$  chain (*COL27A1*). **Methods** A case of Han adolescent Steel syndrome complicated with scoliosis in the Department of Orthopaedics, Changhai Hospital, Naval Medical University (Second Military Medical University) was reported. Altogether 13 related articles (54 cases of Steel syndrome) from Jan. 1993 to Oct. 2020 were retrieved by using “Steel syndrome” AND “COL27A1” as subject word in the PubMed database. Among them, 17 cases of Steel syndrome caused by *COL27A1* mutation and confirmed by whole exome sequencing were included. The clinical features of the 18 patients with Steel syndrome caused by *COL27A1* mutation were analyzed. **Results** In this case, in addition to common clinical manifestations such as developmental delay, carpal coalition, scoliosis, long oval-shaped face, prominent forehead, anteverted nares and other common clinical manifestations, the patient also had webbed neck and low hairline at the back of neck. Whole exome sequencing indicated that *COL27A1* gene

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had two compound heterozygous mutations: p.Pro705Ser and p.Asn1723Ser, which originated from father and mother, respectively. The diagnosis of Steel syndrome with congenital scoliosis was confirmed by the results of all examinations and the whole exome sequencing. After the preoperative examination, the patient was treated with posterior three-dimensional orthopaedic bone graft fusion and internal fixation (surgical segments T<sub>3</sub>-L<sub>1</sub>). The anteroposterior and lateral X-rays of the full spine of the patient were performed in the outpatient department at 3 months, 1 year and 2 years after the operation. The results showed satisfactory segmental fusion without complications such as fracture of screws and rods, junctional kyphosis and distal adding-on phenomenon. Among the 18 patients, there were nine males and nine females, with a diagnosis age of 0.17-14 years. Three were *COL27A1* complex heterozygous mutations, including p.Pro705Ser and p.Asn1723Ser (one case), c.93del and c.3075del (one case), and p.Cys174Serfs\*34 and p.Arg707\* (one case); 15 were homozygous missense mutations, including p.Gly697Arg (11 cases), p.Gly802Glu (one case), p.Gly904Arg (one case), c.4261-1G>A (one case), and c.3556-2A>G (one case). The main clinical features (unknown in one patient) included scoliosis (17 cases), short stature (12 cases), long oval-shaped face (nine cases), prominent forehead (nine cases), developmental delay (five cases), hearing loss (five cases), etc. The imaging features of the 18 patients included hip dislocation (16 cases), radial head dislocation (11 cases), carpal coalition (nine cases), etc. **Conclusion** Steel syndrome caused by *COL27A1* mutation is a rare autosomal recessive genetic disease. Its family history, clinical features and imaging examinations provide a preferential diagnosis, but the final diagnosis should be based on the result of gene sequencing. The treatment of this disease should be further researched to improve the prognosis.

**[Key words]** Steel syndrome; collagen type XXVII; scoliosis; surgical treatment

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由胶原 XXVII  $\alpha 1$  型 (collagen type XXVII  $\alpha 1$  chain, *COL27A1*) 基因突变导致的 Steel 综合征是一种累及多系统的常染色体隐性遗传病, 其临床特征主要有面部畸形、身材矮小、腕骨融合、桡骨头和髌关节脱位、脊柱侧凸、弓形足、颈椎畸形等<sup>[1-2]</sup>。该病属于新生儿时期即开始发病的罕见遗传病, 发病率非常低 (<1/100 万)<sup>[3]</sup>。本研究报告了海军军医大学 (第二军医大学) 长海医院骨科收治的 1 例汉族 Steel 综合征合并脊柱侧凸青少年患者资料, 同时回顾性分析国外文献报道的 *COL27A1* 基因突变所致 Steel 综合征病例资料, 总结 Steel 综合征新的基因突变位点及临床特征, 为 Steel 综合征的诊治提供参考。

## 1 资料和方法

1.1 病例资料 患者男, 14 岁, 汉族, 体重 45 kg, 身高 163 cm, 父母为非近亲结婚, 母亲足月妊娠经阴道分娩, 出生体重为 2.8 kg。因“发现脊柱侧凸 1 年”于 2017 年 9 月 3 日收入海军军医大学 (第二军医大学) 长海医院骨科。患者 1 年前于外院诊断为脊柱侧凸后一直采取支具穿戴等保守治疗。自患病以来无肢体麻木、精神障碍、体力减退、食欲食量改变、大小便异常等特殊临床表现。既往无慢性疾病史、传染病史、手术史、外伤史和过敏

史。入院体格检查: 长椭圆脸, 前额突出, 鼻前倾, 扁平胸, 蹼状颈、颈后发际线低, 椎体较小、胸椎左侧凸、剃刀背畸形, 肘关节外翻, 双手小指侧弯 (图 1), 桡骨头和腕关节脱位, 下蹲受限, 无异常步态, 无骨盆前倾, 无肢体缩短, 髌关节无内收外展、内旋外旋等畸形, 单足站立试验阴性。无头颅发育畸形、皮肤黏膜黄染、皮下结节包块、异常毛发、色素沉着、牛奶咖啡斑等, 无听力障碍、言语或运动发育迟缓。骨龄测试显示发育落后。查血常规示白细胞计数  $6.32 \times 10^9/L$ , 红细胞计数  $5.02 \times 10^{12}/L$ , 血红蛋白 147 g/L, 血小板计数  $221 \times 10^9/L$ ; 查肝肾功能示总胆红素  $13.4 \mu\text{mol}/L$ , 白蛋白 42 g/L, 球蛋白 29 g/L, 白球比 1.45, 丙氨酸转氨酶 12 U/L, 天冬氨酸转氨酶 15 U/L, 碱性磷酸酶 266 U/L, 乳酸脱氢酶 166 U/L, 钠 142 mmol/L, 钾 4.2 mmol/L, 葡萄糖 5.0 mmol/L, 血肌酐  $53 \mu\text{mol}/L$ ; CRP 3.29 mg/L; 红细胞沉降率 2 mm/1 h; 凝血酶原时间 16.6 s, 凝血酶原时间国际标准化比值 1.3, 活化部分凝血活酶时间 40.0 s, 凝血酶时间 23.4 s, 纤维蛋白原 2.10 g/L, D-二聚体 0.22  $\mu\text{g}/\text{mL}$ 。心电图检查示窦性心律伴不完全性右束支传导阻滞。心脏超声检查示少量心包积液, 心脏大小正常, 收缩功能正常; 阴囊、睾丸、附睾超声检查未见明显异常; 腹部超声检查示肝脏、胆囊、胰头体、脾脏、双肾未见明显异常; 胸

部 CT 检查示右锁骨下动脉异常, 扁平胸, 心脏前缘受压; 全主动脉 CT 血管造影检查未见明显异常; 全脊柱正侧位 X 线片检查示脊柱侧凸 (图 2A), 冠状面 Cobb 角  $T_5 \sim T_{12}$   $42^\circ$ 、 $T_{12} \sim L_4$   $24^\circ$ , 矢状面 Cobb 角  $T_5 \sim T_{12}$   $11^\circ$ 、 $T_{10} \sim L_2$   $4^\circ$ 、 $L_1 \sim L_5$   $30^\circ$ 。脊柱 CT 三维重建示先天性脊柱畸形合并多节段和发

育性缺陷、 $T_7 \sim T_8$  和  $T_9 \sim T_{11}$  阻滞椎 (图 2B)。全脊柱 MRI 检查示脊柱侧凸畸形,  $C_{4/5}$ 、 $C_{5/6}$  椎间盘和  $L_2 \sim S_1$  椎间盘轻度膨出。本研究通过海军军医大学 (第二军医大学) 长海医院伦理委员会审批, 患者家属同意该研究并签署研究知情同意书。

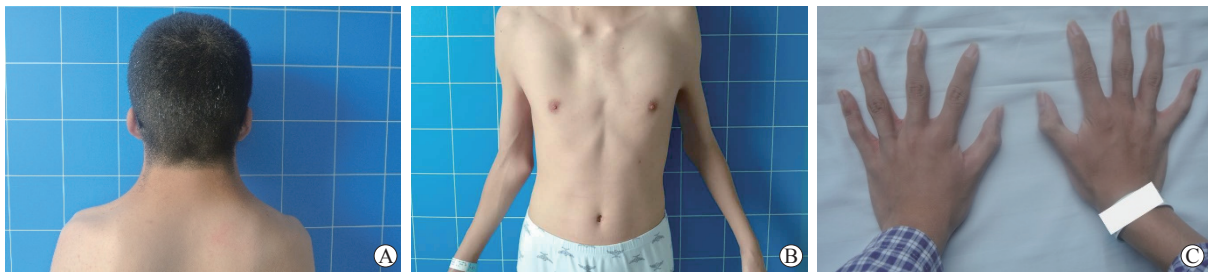


图 1 体格检查示患者蹼状颈和颈后发际线低 (A)、肘外翻 (B)、手指畸形 (C)

Fig 1 Physical examination showed webbed neck and low hairline (A), cubitus valgus (B) and finger deformity (C)

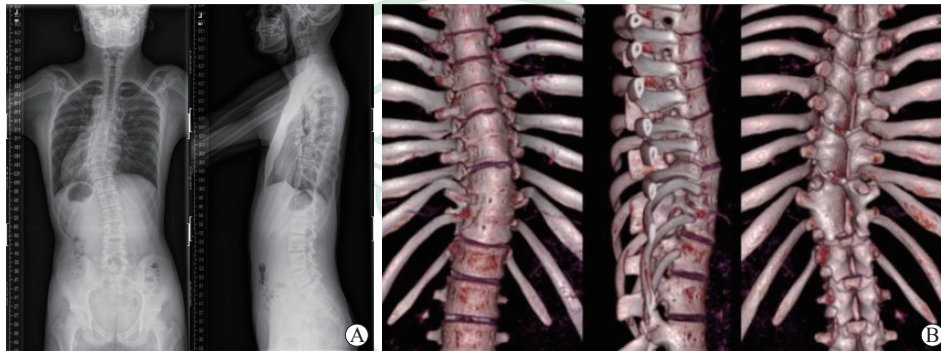


图 2 全脊柱正侧位 X 线片和脊柱计算机断层扫描三维重建图像

Fig 2 Full-spine anteroposterior and lateral X-ray radiographs and three-dimensional reconstructed images of spine by computed tomography

A: Full-spine anteroposterior and lateral radiographs showed scoliosis; B: Three-dimensional reconstructed images of the spine showed a congenital spinal deformity complicated with multiple segmentation and formation defects (block vertebrae at  $T_7 \sim T_8$  and  $T_9 \sim T_{11}$ )

1.2 文献回顾 利用 PubMed 数据库以“Steel syndrome” AND “COL27A1”为主题词检索 1993 年 1 月至 2020 年 10 月相关文献。纳入标准: (1) 基因检测结果提示有明确的 Steel 综合征相关 COL27A1 突变; (2) 有发育迟缓、长椭圆脸、前额突出、鼻前倾、双侧髋关节脱位、髋内翻或双侧髋臼浅、脊柱侧凸等 Steel 综合征临床特征至少 2 项。

## 2 结果

### 2.1 患者家谱图、基因测序结果与治疗

2.1.1 患者家谱图 患者为独生子, 先证者谱系显示其父亲、母亲、祖父、祖母均无异常表型或相关临床表现 (图 3A)。

2.1.2 全外显子测序 采集患者和一级、二级

亲属 (患者父亲、母亲、祖父、祖母、舅舅) 的外周血, 用 TIANamp 血液 DNA 分离试剂盒 (DP318, 北京天根生物科技有限公司) 提取基因组 DNA, 使用美国 IDT 公司捕获探针 (xGen<sup>®</sup> Exome Research Panel)、美国 Illumina 公司 HiSeq4000 测序平台进行全外显子测序。目标区捕获高通量测序参数: 目标基因数 19 396, 目标区域长度 39 000 000, 目标区域覆盖度 98.0%, 目标区域平均深度 141.3, 目标区域平均深度 >10 位点所占比例 96.8%。结果显示患者 9 号染色体 COL27A1 基因存在 2 个致病性复合杂合突变, 分别位于外显子 7 [c.2113C>T (p.Pro705Ser) (NM\_032888.3, 116958281), 来源于父亲] 和外显子 59 [c.5168A>G (p.Asn1723Ser) (NM\_032888.3, 117070009), 来源于母亲] (图 3B~3D)。

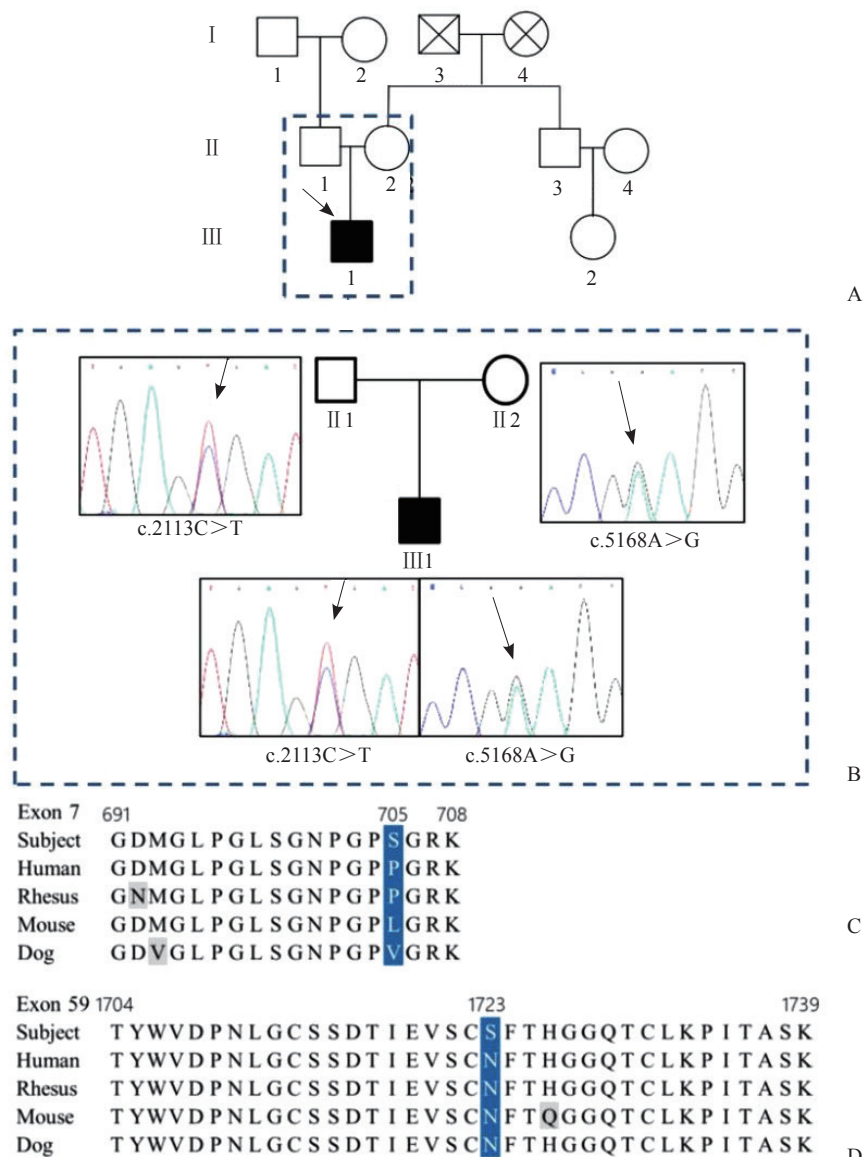


图3 患者家谱图和全外显子测序结果

Fig 3 Pedigree reconstruction of the family and exome sequencing

A: Pedigree reconstruction of the family (arrow indicates proband); B: Gene capture through high-throughput sequencing chromatograms (arrows indicate mutation sites); C: Exome sequencing showed p.Pro705Ser variant; D: Exome sequencing showed p.Asn1723Ser variant. □ represent normal male; ○ represent normal female; ■ represent the patient; ☒ represent dead male; ☒ represent dead female. Gray represents nonsense mutation; blue represents mutation site

2.1.3 诊断与治疗 综合患者临床表现和体征、既往史(无宫内窘迫、无脊髓灰质炎等)、家族史(无神经纤维瘤病等), X线片、CT三维重建(T<sub>7</sub>~T<sub>8</sub>和T<sub>9</sub>~T<sub>11</sub>阻滞椎)和MRI检查(排除椎管内占位、小脑扁桃体下疝畸形)结果,以及全外显子测序结果,确诊Steel综合征合并先天性脊柱侧凸。于2017年9月13日在全身麻醉下行脊柱侧凸后路三维矫形植骨融合内固定术,手术节段T<sub>3</sub>~L<sub>1</sub>,术中失血量约800 mL,采用自体血回输及异体血(红细胞悬液4 U,血浆400 mL)输注,手术时间

共3 h 40 min。手术过程顺利,术中神经电生理监测未见异常,生命体征平稳,麻醉清醒后四肢活动良好。患者术后第5天拔除伤口引流管并佩戴支具下地活动,术后第7天复查全脊柱正侧位X线片示内固定位置良好,于2017年9月21日出院。患者术后恢复顺利,切口愈合良好,术后3个月、1年、2年门诊复查全脊柱正侧位X线片(图4),术后2年全脊柱正侧位X线片示固定节段骨性融合良好,无断钉、断棒、交界性后凸、远端附加现象等并发症。

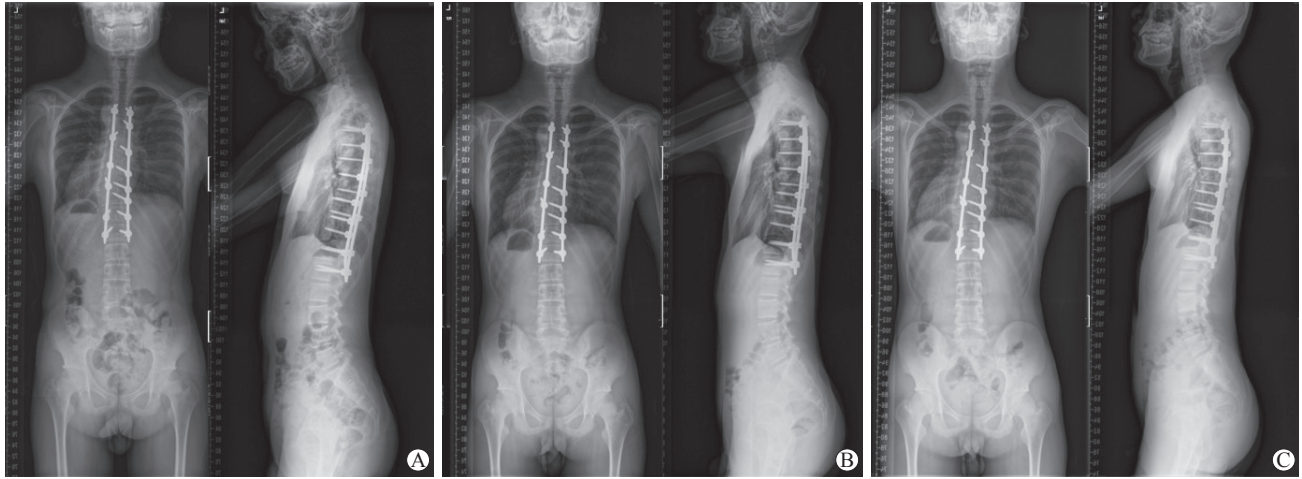


图 4 患者术后全脊柱正侧位 X 线片

Fig 4 Anteroposterior and lateral X-ray radiographs of full spine of the patient

A: Postoperation 3 months; B: Postoperation 1 year; C: Postoperation 2 years

2.2 文献回溯结果 检索到文献 13 篇共 54 例 14 岁, 11 例来自美国波多黎各, 印度、阿联酋、Steel 综合征患者, 其中波多黎各血统 44 例、非波多黎各血统 10 例。最终纳入 9 篇文献, 共有全外显子测序确诊 COL27A1 突变所致 Steel 综合征患者 17 例, 包括本例患者共纳入 18 例, 其中 3 例为复合杂合突变 (1 例 p.Pro705Ser 和 p.Asn1723Ser、1 例 c.93del 和 c.3075del、1 例 p.Cys174Serfs\*34 和 p.Arg707\*), 其余均为纯合错义突变 (11 例 p.Gly697Arg、1 例 p.Gly802Glu、1 例 p.Gly904Arg、1 例 c.4261-1G>A、1 例 c.3556-2A>G)。除 1 例患者临床特征不详外, 余 17 例患者的临床表现有脊柱侧凸 (17 例)、身材矮小 (12 例)、长椭圆脸 (9 例)、前额突出 (9 例)、发育迟缓 (5 例)、听力受损 (5 例)、胸廓畸形 (5 例)、语言迟缓 (4 例)、手指畸形 (4 例)、宽鼻梁 (3 例)、肘外翻 (3 例)、眼距增宽 (1 例) 等; 影像学特征有髋关节脱位 (16 例)、桡骨头脱位 (11 例)、腕骨融合 (9 例)、髋关节发育不全 (1 例) 等。见表 1。

表 1 COL27A1 突变所致 Steel 综合征患者的基本特点

Tab 1 Characteristics of patients with Steel syndrome caused by COL27A1 mutation

Study	Gender	Age (year)	Region	Clinical feature	Radiological feature	Mutation of COL27A1
Amlie-Wolf, 2020 <sup>[4]</sup>	Male	7	Puerto Rico, USA	Short stature, midface hypoplasia, down-slanting palpebral fissures, high arched palate, thoracic deformity, long thorax with narrow hips, finger deformity, scoliosis	Radial head dislocation, bilateral hip dislocation	c.2089G>C, p.Gly697Arg, homozygous
	Male	14	Puerto Rico, USA	Developmental delay, thoracic deformity, long oval-shaped face, prominent forehead, cubitus valgus, scoliosis	Radial head dislocation, bilateral hip dislocation	c.2089G>C, p.Gly697Arg, homozygous
	Female	0.17	Puerto Rico, USA	Thoracic deformity, hip dysplasia, mild hypotonia, developmental delay, long oval-shaped face, prominent forehead, cubitus valgus, scoliosis	Bilateral hip dislocation	c.2089G>C, p.Gly697Arg, homozygous
Kritioti, 2020 <sup>[5]</sup>	Male	3	Cyprus	Short stature, delayed speech, hearing loss, long oval-shaped face, prominent forehead, finger deformity, mild scoliosis	Shallow bilateral acetabula, poor ossification of femoral epiphyses, finger deformity	c.2405G>A, p.Gly802Glu, homozygous
Pölsler, 2019 <sup>[6]</sup>	Female	9	Syria	Short stature, developmental delay, delayed speech, hearing loss, long oval-shaped face, prominent forehead, scoliosis	Radial head dislocation, congenital hip dislocation	c.93del, p.Phe32Leufs*71; c.3075del, p.Lys1026Argfs*33

续表

Study	Gender	Age (year)	Region	Clinical feature	Radiological feature	Mutation of COL27A1
Thuresson, 2019 <sup>[7]</sup>	Female	NA	Iraq	Developmental delay, hypertelorism, widely spaced nipples, sacral dimple, scoliosis, short upper limbs coxa vara and pes cavus, hearing loss	Bilateral hip dislocation	c.2710G>A, p.Gly904Arg, homozygous
Maddirevula, 2019 <sup>[8]</sup>	Male	5	Yemen	Long oval-shaped face, thoracic deformity, frontal bossing, broad nasal bridge, low set of ears, scoliosis	Bilateral hip dislocation	c.4261-1G>A, homozygous
Belbin, 2017 <sup>[9]</sup>	Male	NA	Puerto Rico, USA	Short stature, scoliosis	Bilateral hip dislocation, carpal coalition, radial head dislocation, spine anomaly, skeletal anomaly	c.2089G>C, p.Gly697Arg, homozygous
	Male	NA	Puerto Rico, USA	Short stature, scoliosis	Bilateral hip dislocation, carpal coalition, radial head dislocation, spine anomaly, skeletal anomaly	c.2089G>C, p.Gly697Arg, homozygous
	Female	NA	Puerto Rico, USA	Short stature, scoliosis	Bilateral hip dislocation, carpal coalition, radial head dislocation, spine anomaly, skeletal anomaly	c.2089G>C, p.Gly697Arg, homozygous
	Female	NA	Puerto Rico, USA	Short stature, scoliosis	Bilateral hip dislocation, carpal coalition, radial head dislocation, spine anomaly, skeletal anomaly	c.2089G>C, p.Gly697Arg, homozygous
	Female	NA	Puerto Rico, USA	Short stature, scoliosis	Bilateral hip dislocation, carpal coalition, radial head dislocation, spine anomaly, skeletal anomaly	c.2089G>C, p.Gly697Arg, homozygous
Kotabagi, 2017 <sup>[10]</sup>	Female	5	India	Long oval-shaped face, prominent forehead, finger deformity, scoliosis, short stature, developmental delay, delayed speech, hearing loss	Bilateral hip dislocation, carpal coalition, radial head dislocation	c.521_528del, p.Cys174Serfs*34; c.2119C>T, p.Arg707*
Gariballa, 2017 <sup>[11]</sup>	Male	3	United Arab Emirates	Flat face, short stature, upturned nose, long philtrum, thin lips, delayed speech, hearing loss, scoliosis	Bilateral hip dislocation, right elbow dislocation, short upper limbs, coxa vara	c.3556-2A>G, homozygous
Gonzaga-Jauregui, 2015 <sup>[12]</sup>	Male	14	Puerto Rico, USA	Normal intelligence, long oval-shaped face, prominent forehead, broad nasal bridge, short stature, scoliosis	Bilateral hip dislocation, coxa vara, odontoid hypolaisa, carpal coalition, radial head dislocation	c.2089G>C, p.Gly697Arg, homozygous
	Female	12	Puerto Rico, USA	Normal intelligence, long oval-shaped face, prominent forehead, broad nasal bridge, short stature, scoliosis	Bilateral hip dislocation, coxa vara, odontoid hypolaisa, carpal coalition	c.2089G>C, p.Gly697Arg, homozygous
	Female	NA	Puerto Rico, USA	NA	Bilateral hip dislocation, leg length discrepancy	c.2089G>C, p.Gly697Arg, homozygous
Present case	Male	14	China	Normal intelligence, webbed neck, low hairline, developmental delay, prominent forehead, long oval-shaped face, thoracic deformity, finger deformity, cubitus valgus, scoliosis	Carpal coalition, radial head dislocation	c.2113C>T, p.Pro705Ser; c.5168A>G, p.Asn1723Ser

COL27A1: Collagen type XXVII  $\alpha$ 1 chain; NA: Not available

### 3 讨论

Steel 综合征作为一种罕见的常染色体隐性遗传病,其家族史、临床特征、影像学检查等可提供倾向性诊断。与既往报道的 17 例确诊患者<sup>[4-12]</sup>相似,本例患者也有发育迟缓、腕骨融合、脊柱侧凸、长椭圆脸、前额突出、鼻前倾等临床特征,还表现为既往尚未报道的蹼状颈和颈后低发际线,但未出现听力障碍、双侧髋关节脱位、髓内翻或双侧髓白浅等<sup>[1-2]</sup>,而既往报道的 17 例患者均存在双侧髋关节脱位<sup>[4-12]</sup>。因此,Steel 综合征患者临床特征存在异质性,最终确诊需要依据患者的基因检测结果。

目前 *COL27A1* 基因突变已被认为是 Steel 综合征的致病突变。*COL27A1* 是 Pace 等<sup>[13]</sup> 在 2003 年首次报道的新的编码胶原蛋白的基因,其位于第 9 号染色体,全长约 156 000 bp,包含 61 个外显子。*COL27A1* 基因调控着 XXVII 型胶原的生成,参与软骨和其他组织的合成。因此,*COL27A1* 在眼和耳的软骨组织中高表达,而在皮肤、胃、性腺或大脑等其他结缔组织中低表达<sup>[14]</sup>。XXVII 型胶原是脊椎动物纤维胶原家族中的一类,是构成细胞外基质的主要成分<sup>[15-16]</sup>,在软骨钙化和骨化中起着重要作用<sup>[17-18]</sup>。Plumb 等<sup>[19]</sup> 在纯合子突变 *COL27A1* 基因敲除小鼠研究中发现 *COL27A1* 蛋白 87 个氨基酸缺失可导致严重的软骨发育不良。Christiansen 等<sup>[20]</sup> 研究发现 *COL27A1* 基因敲除斑马鱼在发育早期会出现脊索弯曲畸形,到发育后期则演变成以椎体形态异常为特征的脊柱侧凸。

既往人群筛查结果提示,由于波多黎各人群的奠基者效应,*COL27A1* 基因在该人群中突变率高达 2%,而在世界其他人群中此突变极为罕见<sup>[9]</sup>。波多黎各人群中 *COL27A1* 基因 p.Gly697Arg 突变最为常见<sup>[12]</sup>,其携带率高达 1/51<sup>[9]</sup>。生物化学模型研究表明,*COL27A1* 基因 p.Gly697Arg 破坏了  $\alpha 1$  胶原蛋白头端保守的三螺旋结构域,与其他常见的胶原结缔组织疾病(如 Ehlers-Danlos 综合征和 Alport 综合征等)的发病机制类似<sup>[21]</sup>。之后多个国家的学者陆续报道了 *COL27A1* 基因其他位点突变所致 Steel 综合征的不同表型,如印度(p.Cys174Serfs\*34 和 p.Arg707\*)<sup>[10]</sup>、阿联酋(c.3556-2A>G)<sup>[11]</sup>、也门(c.4261-1G>A,剪

接位点)<sup>[8]</sup>、伊拉克(c.2710G>A)<sup>[7]</sup>和叙利亚(c.93del, c3075del)<sup>[6]</sup>。

本例患者是汉族人群中发现的第 1 例通过全外显子测序确诊并报道的 Steel 综合征患者,基因测序提示第 9 号染色体 *COL27A1* 基因存在 2 个致病性复合杂合突变,分别位于外显子 7 的 p.Pro705Ser (来源于父亲)和外显子 59 的 p.Asx1723Ser (来源于母亲)。这之前报道的突变位点并不一致,且千人基因组计划、外显子组整合数据库(Exome Aggregation Consortium, ExAC)、Exome Variant Server 和内部数据库中均未见报道。Sanger 测序结果显示 p.Pro705Ser 也存在于患者的祖母和父亲,但通过与突变数据库和 ExAC 进行比对分析认为该变异是无义替换突变。对患者母亲存在的 p.Asx1723Ser 进行进化保守性分析,结果显示其处于进化保守性最高的位置。本例患者的基因突变位点导致的具体功能改变尚待研究。

目前,对于综合征性脊柱畸形的诊断方法包括临床表型诊断、影像诊断、染色体诊断、基因诊断及肌肉活检诊断<sup>[22]</sup>。在本例患者的诊疗过程中,外院拍摄全脊柱正侧位 X 线片提示脊柱侧凸,Cobb 角为 20°~40°(具体不详),未见明显半椎体,先按照特发性脊柱侧凸采用保守支具治疗。1 年后因自觉脊柱畸形保守治疗效果不佳、进展较快,来我院复诊,建议进一步检查脊柱 CT 并行三维重建。结果提示椎体分节不全和椎体形成障碍(T<sub>7</sub>~T<sub>8</sub>和 T<sub>9</sub>~T<sub>11</sub>阻滞椎),结合患者发育迟缓、蹼状颈和颈后低发际线等外貌特征与肘外翻、手指畸形等临床特征,考虑 Steel 综合征合并先天性脊柱畸形。其临床体征鉴别诊断包括 Larsen 综合征、Ehlers-Danlos 综合征、Turner 综合征、Klippel-Feil 综合征等。Larsen 综合征为全身结缔组织发育障碍,常存在全身多部位关节先天性脱位、脊柱侧凸及前额突出、眼距较宽、颜面扁平、鼻梁塌陷等面部畸形,几乎所有患者均存在膝关节脱位<sup>[1,23-24]</sup>。Ehlers-Danlos 综合征属于遗传性结构蛋白病,可表现为皮肤弹性增大和前额、眼距、鼻梁较宽的特殊面容,累及骨关节系统可表现为关节过度活动、脊柱畸形等<sup>[25-26]</sup>。Turner 综合征是雌性个体 X 染色体完全或部分缺失所致的疾病,临床表现为身材矮小、脊柱侧凸、肘外翻、蹼状颈、颈后低发际线、听力受损等<sup>[27-29]</sup>。Klippel-Feil 综合征又称先天性

颈椎融合畸形,颈部活动受限、短颈和颈后低发际线为其三大临床特征,部分患者可有脊柱侧凸、听力障碍和其他脏器系统畸形<sup>[30-31]</sup>。根据本例患者临床表现鉴别诊断较难,建议患者取全血行外显子测序,结果提示 *COL27A1* 基因突变,确诊为 Steel 综合征。

对于 Steel 综合征的手术治疗目前存在争议,不仅限于脊柱畸形,还包括髋关节脱位等,可能与患者的特殊体质相关。对于 Steel 综合征的治疗和预后, Flynn 等<sup>[1]</sup> 研究发现,61% 合并髋关节脱位的 Steel 综合征患者接受复位治疗后疼痛主诉更多且日常活动更受限制,因此不建议 Steel 综合征合并髋关节脱位患者行关节复位治疗,而合并桡骨头脱位的 Steel 综合征患者行桡骨头切除不仅可改善外观而且对运动和功能无明显影响;97% 合并腕骨融合的患者无明显运动或功能受限,无须临床干预;53% 的 Steel 综合征患者合并脊柱侧凸,其中 1 例先天性脊柱侧凸及 31% 的非先天性脊柱侧凸患者接受了后路矫形自体骨移植融合内固定术,非先天性脊柱侧凸的融合节段选择参照特发性脊柱侧凸,术后随访效果良好,未发现近、远期并发症;10% 的 Steel 综合征患者合并颈椎畸形,但仅 1 例寰枢关节半脱位患者接受了手术固定;34% 的 Steel 综合征患者合并弓形足,长期随访未发现足踝症状相关主诉。本例患者需手术干预的骨科相关畸形主要为先天性脊柱侧凸 ( $T_7 \sim T_8$  和  $T_9 \sim T_{11}$  阻滞椎),选择行  $T_3 \sim L_1$  的后路矫形植骨融合内固定术,术中无异常出血、置钉失败、硬脊膜破裂、脊髓监测信号异常,术后恢复顺利,2 年随访未见内固定失败、畸形进展等并发症。

Steel 综合征较为罕见,随着全世界报道病例的逐渐增多,相信未来对这一疾病的认识会更加深入,加之成熟的辅助技术,患者预后将会得到明显改善。

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