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遗传性疾病专题

假性软骨发育不全一家系临床特征和 COMP 基因突变分析

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[摘要] 假性软骨发育不全(pseudoachondroplasia, PSACH)是较罕见的常染色体显性遗传性脊柱骨骺发育不良疾病。该文分析总结一个5岁2月龄PSACH患儿及其父母的临床资料,对COMP基因的所有19个外显子及其侧翼序列进行PCR扩增和直接测序,并对外显子10进行分子克隆明确突变性质。患儿有手指粗短、弓形腿、短肢侏儒、长骨干骺端增宽和脊柱椎体前突等临床及影像学表现,其COMP基因外显子10检出突变c.1048_1116del(p.Asn350_Asp372del)。患儿父亲外显子10携带同样突变,但缺乏临床表现。结合临床和影像学特征,通过COMP突变分析明确了PSACH诊断。该文报道的COMP基因突变在PSACH中的不穿透现象属于首次报道。
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[关键词] 假性软骨发育不全; COMP基因; 突变; 分子克隆; 儿童

Clinical features and COMP gene mutation in a family with a pseudoachondroplasia child

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Abstract: This study aimed to report the clinical characteristics and COMP gene mutation of a family with pseudoachondroplasia (PSACH), a relatively rare spinal and epiphyseal dysplasia that is inherited as an autosomal dominant trait. Clinical information on a 5-year-2-month-old PSACH child and his parents was collected and analyzed. Diagnosis was confirmed by PCR amplification and direct sequencing of all the 19 exons and their flanking sequences of COMP gene, and the mutation was further ascertained by cloning analysis of exon 10. The child presented with short and stubby fingers, bow leg, short limb dwarfism and metaphyseal broadening in long bone as well as lumbar lordosis. A mutation c.1048_1116del (p.Asn350_Asp372del) in exon 10, inherited from his father who did not demonstrate any phenotypic feature of PSACH, was detected in the child. PSACH was diagnosed definitively by means of COMP mutation analysis, on the basis of the child's clinical and imaging features. The non-penetrance phenomenon of COMP mutation was described for the first time in PSACH.
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Key words: Pseudoachondroplasia; COMP gene; Mutation; Molecular cloning; Child

假性软骨发育不全(pseudoachondroplasia, PSACH)是一种较罕见的脊柱骨骺发育不良性疾病,属常染色体显性遗传^[1-2],其临床表现为出生时身长正常,2岁左右开始出现生长落后,成年时身高通常在82~130 cm,为典型的短肢侏儒^[1,3]。患者开始行走时即出现鸭步,童年期出现关节疼痛,尤以下肢大关节为重,脊柱侧弯及腰椎前凸

亦同期出现^[4]。青春期开始出现骨关节炎,主要累及双下肢及脊柱^[5]。病情呈进行性发展,约50%的患者最终需要接受髋关节置换手术^[6]。此外,患者常出现韧带松弛及关节伸展过度。值得注意的是,患者的头围、颅面部外貌及智力水平发育正常^[3-6]。

PSACH是软骨寡聚物基质蛋白(cartilage

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oligomeric matrix protein, COMP) 基因突变所致^[1,7-8]。该基因定位于19p13.1, 全长约26 kb, 含19个外显子^[9-10]。COMP由1个螺旋区, 4个II型类表皮生长因子重复区(EGF-like repeats)、8个类钙调蛋白重复区(calmodulin-like repeats, CLRs)及1个羧基末端球状区域(C-terminal globular domain, CTD)构成^[10-11], 主要在软骨细胞外基质、肌腱及韧带中表达^[10]。COMP不但对维持软骨细胞的正常功能及其增殖调控起重要作用^[12-13], 而且还能促使抑制凋亡蛋白因子的表达上调, 从而具有抗凋亡的作用^[14]。COMP基因突变可导致COMP蛋白无法正常转运至软骨细胞外参与细胞外基质的构成, 而在细胞内质网中大量堆积, 破坏软骨细胞的正常功能, 导致细胞死亡^[15], 从而延缓骨骼的线性生长^[16]。

目前已发现90种COMP基因突变与PSACH的发病有关^[17], 大多数集中在CLRs和CTD区域^[18-19]。CLRs区域由COMP基因外显子8~14编码, 有研究表明, 85%~90.7%的PSACH患者可检测到该区域的突变, 8%~15%的患者突变发生在CTD区域^[17,20-21], 仅极少数(1.2%)患者可在EGF-like区域检测到突变^[17]。在国外特定人群中, PSACH的患病率约为二万分之一^[3,22]。我国人群本病的具体流行病学特征尚不清楚, 国内文献中PSACH的研究报道数量相当有限^[23-26], 关于COMP基因分析的正式文献更为罕见, 仅见一篇发生在外显子8中的突变c.815T>C导致PSACH的研究报道^[27]。本文报道一个PSACH家系的临床特点和COMP基因突变特征, 希望能够为临床医师对本病的诊治提供参考。

1 资料与方法

1.1 研究对象

研究对象为一个PSACH家系, 含一个男性患儿及其父母。患儿于2012年12月因步态异常4年余在我院诊治, 其临床和影像学特点提示PSACH, 并经COMP基因突变分析证实该诊断。本研究COMP基因突变分析获得患儿父母书面知情同意。

1.2 DNA提取、PCR扩增及凝胶电泳

分别采集研究对象抗凝静脉血, 然后使用DNA提取试剂盒(Bio Teke, Hangzhou, China)提取DNA。以gDNA为模板行COMP基因1~19外显子PCR扩增。50 μL的反应体系包括5 μL 10× Buffer (Mg²⁺ plus) (Takara), 4 μL dNTP (10 mM,

Takara), 正向及反向引物各1 μL (20 μM, Takara), 1 μL DNA模板, 0.125 μL Taq DNA聚合酶(2.5 U/μL, Takara), 37.875 μL灭菌双蒸水。COMP基因外显子1~7引物及PCR反应条件参考文献^[28], 外显子8~19引物及PCR反应条件参考文献^[20]。PCR反应在PTC-200 PCR仪(Eastwin Life Science Inc)上进行电泳。PCR产物在PAC300型水平型电泳仪(Bio-Rad)上进行, 所用琼脂糖凝胶浓度为2%。电泳结果在ZF-80紫外透射仪下观察及摄像。

1.3 测序反应

基于Sanger的双脱氧终止法原理, 以PCR引物作为测序引物, 采用ABI3730测序仪及BigDye Terminator试剂盒对COMP基因19个外显子及其侧翼序列行直接测序, 测序结果使用Chromas软件判读。测序反应在英潍捷基(上海)贸易有限公司广州分部完成。

1.4 分子克隆及序列分析

PCR产物在2%琼脂糖凝胶上电泳分离, ZF-80紫外透射仪(上海顾村电光仪器厂)下切除目的条段, 经凝胶回收试剂盒(Omega)纯化。纯化后的片段利用DNA Kination Kit (TaKaRa, D402)连接到pSIMPLE-18 EcoR V/BAP Vector (Takara), 用热休克方法转化到DH5α大肠杆菌感受态细胞, 通过氨苄青霉素及蓝白斑试验筛选阳性克隆, 对克隆产物进行测序。测序结果用Chromas及DNAMAN软件进行分析。

2 结果

2.1 病例报告

患儿, 男, 5岁2个月, 因步态异常4年余就诊。患儿1岁前未发现异常。1岁后开始出现行走时步态不稳, 呈鸭步, 伴轻微躯体前倾。随后父母发现其生长发育较同龄儿落后, 四肢粗短, 无肢体疼痛。患儿颅面部外观及智力发育正常。4岁时曾在外院行X线检查发现长骨骨骺及干骺端发育异常, 椎体扁平。实验室检查: 尿粘多糖定性阴性, 白细胞粘多糖病酶学检查未见异常, 血清钙、磷、碱性磷酸酶水平正常, 外院诊治不详。为明确病因于5岁2月龄时到我院就诊。

患儿系第1胎第1产, 孕34周时因胎膜早破行剖宫产, 出生体重2.31 kg, 身长50 cm, 头围33 cm, 出生时无窒息史。父母非近亲结婚, 无遗传病家族史, 母孕期无特殊。患儿父母均体健, 无四肢粗短、行走受限、关节疼痛、弓形腿等骨

发育不良的表现。父亲身高 178 cm，母亲身高 168 cm。

体格检查：神智清楚，头颅五官无畸形。身高 89 cm (-4.7 SD)，体重 14.5 kg (-1 SD)，头围 48 cm (-2 SD)。双肺呼吸音清，心音有力。腹不胀，肝脾肋下未触及。四肢短，躯干相对较长，呈短肢侏儒；手指粗短，肘部弯曲，膝内翻，弓形腿，不能久立。双侧膝腱反射存，克、布、巴氏征均阴性。血气分析、血钙及血磷正常，碱性磷酸酶、生长激素、甲状腺激素正常。影像学检查符合 PSACH 典型的 X 线特征（图 1）。

诊断明确后患儿自动出院。半年后门诊随访时身高增长 2 cm，体重增加 0.5 kg。但步态异常无改善。

2.2 COMP 基因 PCR 产物电泳及直接测序结果

先证者 COMP 基因 19 个外显子 PCR 产物电泳结果显示，外显子 10 存在突变。其父 COMP 基因外显子 10 携带同样突变，而其母 COMP 基因外显子 10 未见异常。患儿及其父亲 PCR 产物凝胶电泳后均可见两条清晰条带（图 2），但分别切胶纯化测序均出现后重峰（图 3A, B），提示 PCR 产物内部存在短片段缺失或重复。遂进一步行分子克隆以明确突变的性质及长度。

2.3 分子克隆测序结果

与正常的外显子 10 克隆测序（图 4A）相比，患儿及其父外显子 10 均存在缺失突变 c.1048_1116del (p.Asn350_Asp372del)，缺失 69 个碱基（图 4B）。该突变国外文献已有报道^[28]，但在国内 PSACH 患者中属于首次发现。



图 1 PSACH 患儿骨骼畸形临床及影像学表现

A: 手指粗短；B: 掌指骨粗短，干骺端增宽，边缘尖角状突出，骺板狭窄，骺核细小，且仅两枚腕骨出现骨化中心，骨龄明显落后；C: 肱骨及尺桡骨短缩，干骺端增宽，骨骺出现延迟；D: 肱骨、胫腓骨短缩，干骺端扩张，边缘尖角状突出，表面呈现“山”型；E: 脊柱侧位片示椎体前缘舌状突出，呈阶梯状改变，腰椎间隙增宽。

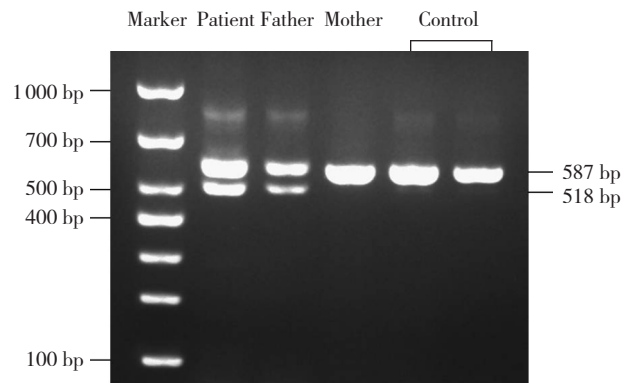


图 2 PSACH 家系 COMP 基因 Exon10 PCR 产物凝胶电泳图 患儿及其父亲 PCR 产物凝胶电泳后可见两条清晰条带，提示 Exon10 存在突变；其母亲与正常对照组均只出现一条 587 bp 的正常条带。

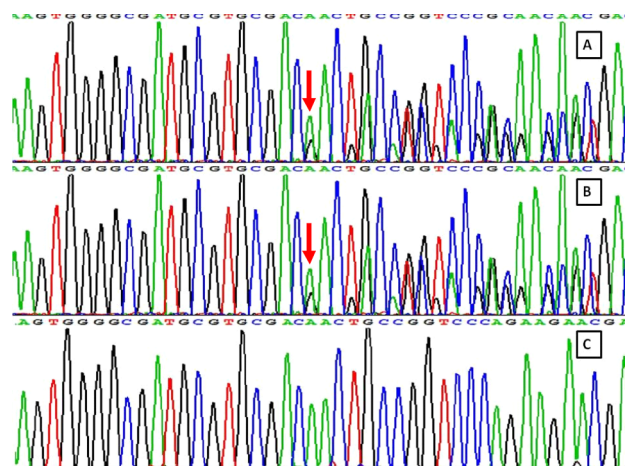


图 3 PSACH 家系 COMP 基因 Exon10 DNA 直接测序结果 A、B、C 分别为患儿、患儿父亲以及患儿母亲的测序结果；患儿突变来自父亲，其母亲测序结果无异常。箭头标示处为突变起始位置。

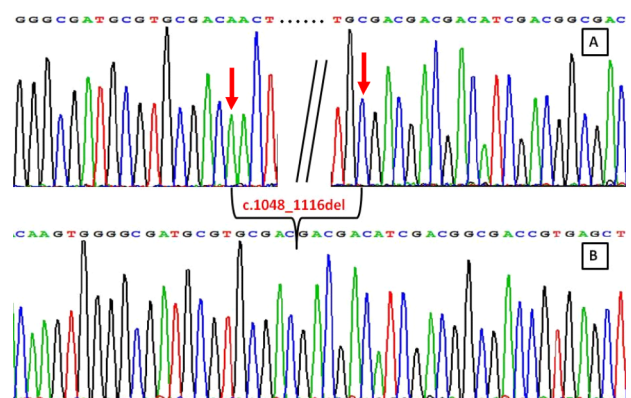


图 4 PSACH 患儿及父亲分子克隆测序结果 A: 正常 Exon10 分子克隆测序，图标注明缺失片段部位，箭头标示突变起始及终止位置；B: Exon10 缺失条带克隆测序，箭头标示处为突变缺失起始处。

3 讨论

本例 PSACH 患儿临床特征缺乏特异性,需与软骨发育不全 (achondroplasia, ACH) 和多发性骨骺发育不良 (multiple epiphyseal dysplasia, MED) 相鉴别^[29]。ACH 的致病基因是成纤维生长因子受体-3 (FGFR3)^[30]。ACH 患者有巨头、前额突出等颅面部畸形外观,且短肢畸形在宫内或出生时即存在^[31]。影像学表现为骨骺小而不规则,干骺端呈蘑菇样改变;髌臼缘不规则,髌臼平浅,可有髌内翻畸形;脊柱侧位片示椎骨扁平,前缘舌状突出,并存在椎管狭窄^[31-32]。MED 也是一种遗传性骨骼发育不良性疾病,遗传方式以常染色体显性遗传为主,但少数患者为常染色体隐性遗传。除 COMP 基因突变外,Matrilin-3 (MATN3), COL9A1, DTDST COL9A2 以及 COL9A3 等基因突变也可致 MED^[1,33]。MED 临床症状多样,主要表现为关节疼痛和身材矮小,但其矮小程度无 PSACH 严重,尤其是缺乏脊柱受累^[29]。根据其临床和影像学特征,本例患者可排除 MED 的诊断。

COMP 是一种钙结合蛋白,其钙结合能力取决于其五聚体结构^[34]。COMP 基因外显子 8~14 编码 COMP 蛋白的 CLRs 区域^[1,10,19]。突变发生在 CLRs 区域的 PSACH 临床表现较突变发生在其他区域的患者严重,且发生缺失突变的患者相比发生碱基置换突变的患者有更显著的身材矮小^[35]。当 CLRs 区域发生错义突变或缺失突变时,可影响 COMP 与钙结合的能力^[3,35-36]。本例 PSACH 患儿 COMP 基因外显子 10 发生缺失突变,影响了 CLRs 功能区,破坏了 COMP 的正常构象,致 COMP 与钙结合能力下降^[37]。患儿有较重的身材矮小表现 (-4.7 SD),说明 CLRs 区域对维持 COMP 蛋白的正常功能有重要影响。患儿父亲 COMP 基因外显子 10 携带有同样突变,但缺乏 PSACH 骨发育不良的临床表现,属突变不穿透现象 (non-penetrance)。不穿透是指虽然携带常染色体显性遗传病致病基因的突变,但是突变个体不表现相应临床特征的遗传学现象^[38]。表型多样是染色体显性遗传疾病的特征^[39];遗传与环境因素在决定疾病进展及突变基因外显率上同样重要^[40]。常染色体显性遗传病患者表现遗传不穿透,可能与单基因突变有关^[41];亦有报道认为这种现象可能是由于生殖腺嵌合所致^[39,42]。不穿透在常染色体显性遗传疾病中并不罕见,具备这种特征的遗传病还有结节性硬化症^[39,42],手裂、脚裂畸形^[43],耳硬化症^[44]等等。其中,耳硬化症的突变不穿透比例可达 60%^[45]。本研究描述

了一个典型 PSACH 患儿的临床特点和 COMP 基因突变特征,目前尚未见该基因突变在 PSACH 中不穿透的文献报道。

在治疗方面,PSACH 患者主要为对症处理。当出现颈髓受压可予 C1-C2 后融合术^[26],严重骨关节炎病例可考虑行关节置换^[4]。有报道证实,生长激素对于治疗 PSACH 的身材矮小无效^[46]。本例患儿目前无关节疼痛,未出现椎体压缩,故目前治疗上暂时不考虑手术和药物干预,予随访观察为主。

[参考文献]

- [1] Briggs MD, Chapman KL. Pseudoachondroplasia and multiple epiphyseal dysplasia: mutation review, molecular interactions, and genotype to phenotype correlations [J]. Hum Mutat, 2002, 19(5): 465-478.
- [2] Andrea SF, Sheila U. Nosology and classification of genetic skeletal disorders: 2006 revision [J]. Am J Med Genet A, 2007, 143A(1): 1-18.
- [3] Posey KL, Hecht JL. The role of cartilage oligomeric matrix protein (COMP) in skeletal disease [J]. Curr Drug Targets, 2008, 9(10): 869-877.
- [4] Mckeand I, Rotta J, Hecha JL. Natural history study of pseudoachondroplasia [J]. Am J Med Genet, 1996, 63(2): 406-410.
- [5] Rimo DL, Rasmussen IM, Briggs MD, Biggs MD, Roughley PJ, Gruber HE, et al. A large family with features of pseudoachondroplasia and multiple epiphyseal dysplasia: exclusion of seven candidate gene loci that encode proteins of the cartilage extracellular matrix [J]. Hum Genet, 1994, 93(3): 236-242.
- [6] Wynne-Davies R, Hall CM, Young ID. Pseudoachondroplasia: clinical diagnosis at different ages and comparison of autosomal dominant and recessive types. A review of 32 patients (26 kindreds) [J]. J Med Genet, 1986, 23(5): 425-434.
- [7] Briggs MD, Hoffman SM, King LM, Olsen AS, Mohrenweiser H, Leroy JC, et al. Pseudoachondroplasia and multiple epiphyseal dysplasia due to mutations in the cartilage oligomeric matrix protein gene [J]. Nat Genet, 1995, 10(3): 330-336.
- [8] Hecht JT, Nelson LD, Crowder E, Wang Y, Elder FFB, Harrison WR, et al. Mutations in exon 17B of cartilage oligomeric matrix protein (COMP) cause pseudoachondroplasia [J]. Nat Genet, 1995, 10(3): 325-329.
- [9] Briggs MD, Rasmussen IM, Weber JL, Yuen J, Reinker K, Garber AP, et al. Genetic linkage of mild pseudoachondroplasia (PSACH) to markers in the pericentromeric region of chromosome 19 [J]. Genomics, 1993, 18(3): 656-660.
- [10] Newton G, Weremowicz S, Morton CC, Copeland NG, Gilbert DJ, Jenkins NA, et al. Characterization of human and mouse cartilage oligomeric matrix protein [J]. Genomics, 1994, 24(3): 435-439.
- [11] Oldberg A, Antonsson P, Lindblom K, Heinegard D. COMP (cartilage oligomeric matrix protein) is structurally related to the thrombospondins [J]. J Biol Chem, 1992, 267(31): 22346-22350.
- [12] Halasz K, Kassner A, Morgelin M, Heinegard D. COMP acts as a catalyst in collagen fibrillogenesis [J]. J Biol Chem, 2007, 282(43): 31166-31173.

- [13] Xu K, Zhang Y, Ilalov K, Carlson CS, Feng JQ, Di Cesare PE, et al. Cartilage oligomeric matrix protein associates with granulin-epithelin precursor (GEP) and potentiates GEP-stimulated chondrocyte proliferation [J]. *J Biol Chem*, 2007, 282(15): 11347-11355.
- [14] Gagarina V, Carlberg AL, Pereira-Mouries L, Hall DJ. Cartilage oligomeric matrix protein protects cells against death by elevating members of the IAP family of survival proteins [J]. *J Biol Chem*, 2008, 283(1): 648-659.
- [15] Duke J, Montufar-Solis D, Underwood ZL, Hecht JT. Apoptosis staining in cultured pseudoachondroplasia chondrocytes [J]. *Apoptosis*, 2003, 8(2): 191-197.
- [16] Chen TL, Stevens JW, Cole WQ, Hecht JT, Vertel BM. Cell-type specific trafficking of expressed mutant COMP in a cell culture model for PSACH [J]. *Matrix Biol*, 2004, 23(7): 433-444.
- [17] Xie XM, Liao LH, Gao JZ, Luo XP. A novel COMP mutation in a Chinese patient with pseudoachondroplasia [J]. *Gene*, 2013, 521(1): 102-106.
- [18] Wang CH, Lin WD, Tsai A, Tsai FJ. Novel human pathological mutations. Gene symbol: COMP Disease: pseudoachondroplasia [J]. *Hum Genet*, 2009, 125(3): 350.
- [19] Stenson PD, Mort M, Ball EV, Howells K, Phillips AD, Thomas NST, et al. The Human Gene Mutation Database: 2008 update [J]. *Genome Med*, 2009, 1(1): 131-136.
- [20] Kennedy J, Jackson G, Ramsden S, Taylor J, Newman W, Wright MJ, et al. COMP mutation screening as an aid for the clinical diagnosis and counselling of patients with a suspected diagnosis of pseudoachondroplasia or multiple epiphyseal dysplasia [J]. *Eur J Hum Genet*, 2005, 13(5): 547-555.
- [21] Deere M, Sanford T, Ferguson HL, Daniels K, Hecht JT. Identification of twelve mutations in cartilage oligomeric matrix protein (COMP) in patients with pseudoachondroplasia [J]. *Am J Med Genet*, 1998, 80(5): 510-513.
- [22] Tufan AC, Satitoglu-Tufan NL, Jackson GC, Semerci CN, Solak S, Yagci B. Serum or plasma cartilage oligomeric matrix protein concentration as a diagnostic marker in pseudoachondroplasia: differential diagnosis of a family [J]. *Eur J Hum Genet*, 2007, 15(10): 1023-1028.
- [23] 顾海滨,唐文伟.假性软骨发育不全的临床影像学分析[J].南京医科大学学报(自然科学版),2010,30(9):1372-1374.
- [24] 李惠民,王明奎,董立新,曹桂民.假性软骨发育不全的临床及X线诊断(附6例报告及文献复习)[J].中华骨科杂志,1995,15(2):114-115.
- [25] 麻宏伟,潘诗农,王阳,宓真,姜梅,武盈玉,等.假性软骨发育不全一家系两例[J].中华医学遗传学杂志,1999,16(4):223.
- [26] 许瑞江,吴战坡,卢强,郝荣国,曾平.假性软骨发育不全的诊治[J].临床小儿外科杂志,2003,2(6):419-421.
- [27] 张续德,孟岩,彭园园,施惠平,赵时敏,黄尚志.假性软骨发育不全一家系 COMP 基因突变分析[J].中国实用儿科杂志,2010,25(4):289-291.
- [28] Jackson GC, Mittaz-Crettol L, Taylor JA, Mortier GR, Spranger J, Zabel B, et al. Pseudoachondroplasia and multiple epiphyseal dysplasia: a 7-year comprehensive analysis of the known disease genes identify novel and recurrent mutations and provides an accurate assessment of their relative contribution [J]. *Hum Mutat*, 2012, 33(1): 144-157.
- [29] Mabuchi A, Manabe N, Haga N, Kitoh H, Lkeda T, Kawaji H, et al. Novel types of COMP mutations and genotype-phenotype association in pseudoachondroplasia and multiple epiphyseal dysplasia [J]. *Hum Genet*, 2003, 112(1): 84-90.
- [30] 刘宁,史惠蓉,吴庆华,江森,孔祥东.软骨发育不全家系基因突变分析及孕早期产前诊断[J].中国优生与遗传杂志,2013,21(3):12-13.
- [31] 郭奕斌,王晶晶,杜传书.遗传性侏儒及其鉴别诊断[J].中国优生优育杂志,2007,15(11):117.
- [32] 赵宏,赵润博.小儿软骨发育不全的X线分析[J].中国医学影像技术,2007,23(10):1581-1582.
- [33] Ballhausen D, Bonafe L, Terhal P, Unger SL, Bellus G, Classen M, et al. Recessive multiple epiphyseal dysplasia (rMED): phenotype delineation in eighteen homozygotes for DTDST mutation R279W [J]. *J Med Genet*, 2003, 40(1): 65-71.
- [34] Hou J, Putkey JA, Hecht JT. Delta 469 mutation in the type 3 repeat calcium binding domain of cartilage oligomeric matrix protein (COMP) disrupts calcium binding [J]. *Cell Calcium*, 2000, 27(6): 309-314.
- [35] Kvansakul M, Adams JC, Hohenester E. Structure of a thrombospondin C-terminal fragment reveals a novel calcium core in the type 3 repeats [J]. *Embo J*, 2004, 23(6): 1223-1233.
- [36] Kleerekoper Q, Hecht JT, Putkey JA. Disease-causing mutations in cartilage oligomeric matrix protein cause an unstructured Ca^{2+} binding domain [J]. *J Biol Chem*, 2002, 277(12): 10581-10589.
- [37] Carlson CB, Bernstein DA, Annis DS, Misenheimer TM, Hannah BL, Mosher DF, et al. Structure of the calcium-rich signature domain of human thrombospondin-2 [J]. *Nat Struct Mol Biol*, 2005, 12(10): 910-914.
- [38] Dudek RW. Genetics Metabolism [M]. // Dudek RW. Genetics. 1th ed. Baltimore, United States: Lippincott Williams & Wilkins, 2009: 224.
- [39] Northrup H, Wheless JW, Bertin TK, Lewis RA. Variability of expression in tuberous sclerosis [J]. *J Med Genet*, 1993, 30(1): 41-43.
- [40] Moore AT, Fitzke F, Arden GB, Inglehearn CF, Keen TJ, Bhattacharya SS, et al. Autosomal dominant retinitis pigmentosa with apparent incomplete penetrance: a clinical, electrophysiological, psychophysical, and molecular genetic study [J]. *Br J Ophthalmol*, 1993, 77(8): 473-479.
- [41] Barber JCK. Directly transmitted unbalanced chromosome abnormalities and euchromatic variants [J]. *J Med Genet*, 2005, 42(8): 609-629.
- [42] Sampson JR, Scathill SJ, Stephenson JB, Mann L, Connor JM. Genetic aspects of tuberous sclerosis in the west of Scotland [J]. *J Med Genet*, 1989, 26(1): 28-31.
- [43] Spranger M, Schapera J. Anomalous inheritance in a kindred with split hand, split foot malformation [J]. *Eur J Pediatr*, 1988, 147(2): 202-205.
- [44] Morrison AW, Bunday SE. The inheritance of osteosclerosis [J]. *J Laryngol Otol*, 1970, 84(9): 921-932.
- [45] Causse JR, Causse JB. Otopospongiosis as a genetic disease: early detection, medical management, and prevention [J]. *Am J Otol*, 1984, 5(3): 211-223.
- [46] Kanazawa H, Tanaka H, Inoue M, Ymanaka Y, Namba N, Seino Y. Efficacy of growth hormone therapy for patients with skeletal dysplasia [J]. *J Bone Miner Metab*, 2003, 21(5): 307-310.

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