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中国儿童矮小症的遗传病因分析

Genetic analysis of Chinese children with short stature

武汉同济医院儿科内分泌遗传代谢疾病高峰论坛

中国·武汉

2016 12 10-11

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CLARITAS GENOMICS

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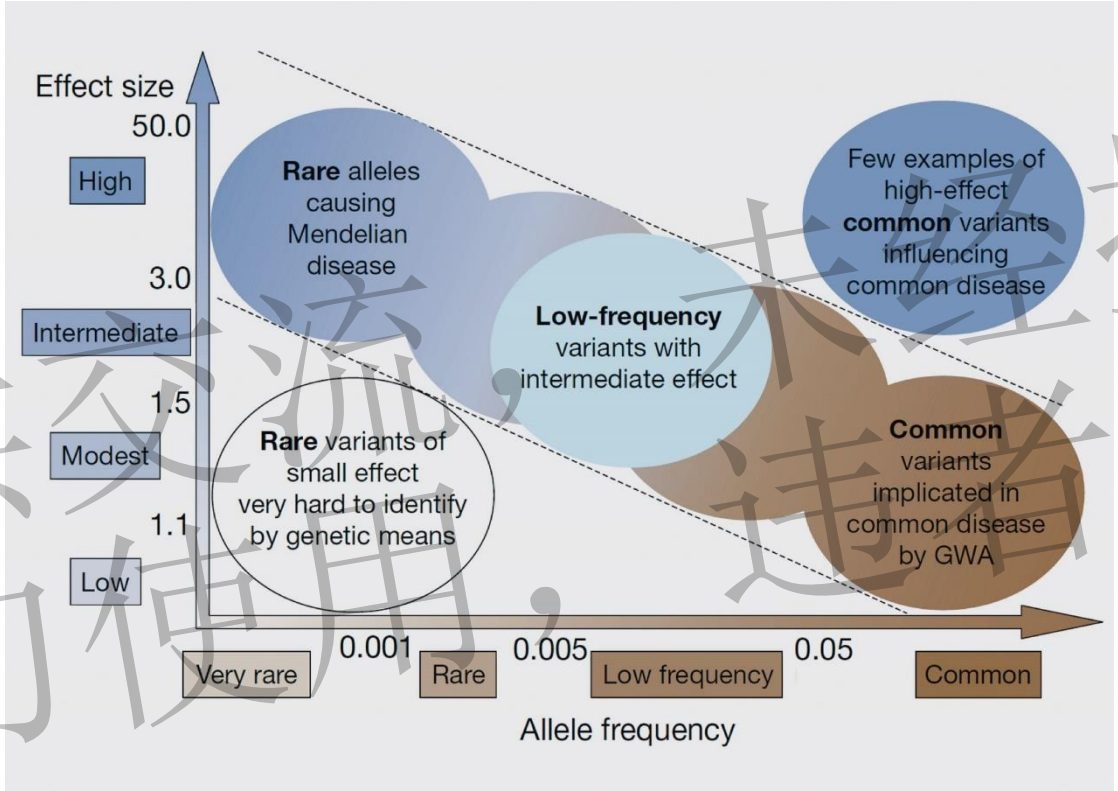
The Maternal & Child Health Hospital, The Children's Hospital, The Obstetrics & Gynecology Hospital of Guangxi Zhuang Autonomous Region

研究儿童矮小症的动机（基础研究）



身高的遗传遵循常见病的普遍规律

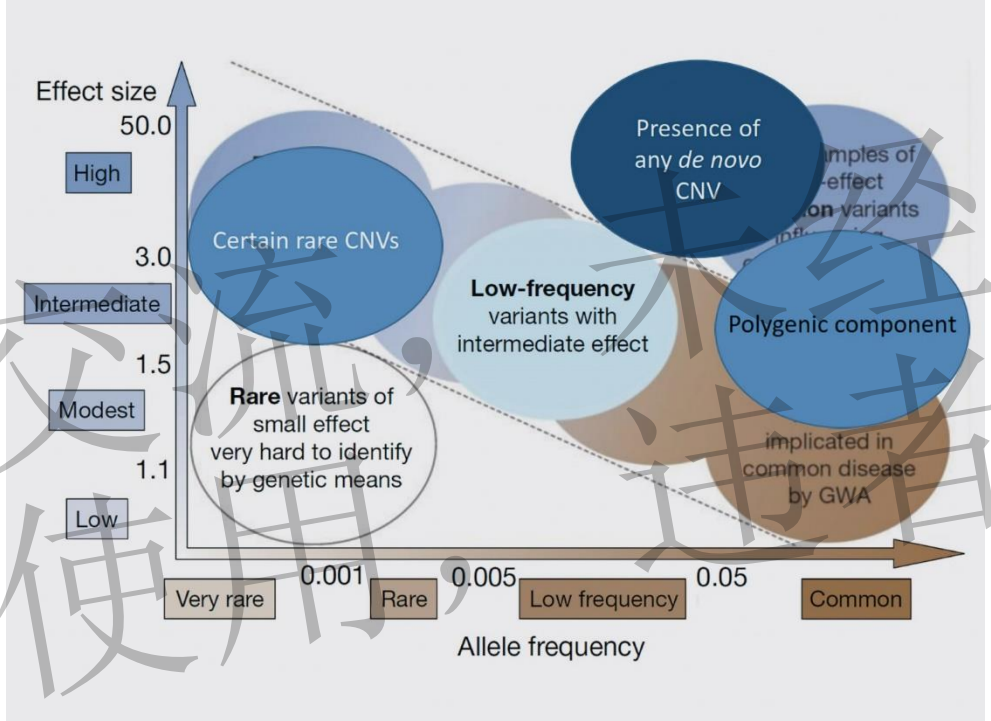
McCarthy/Manolio model: single common variants = small effects, single rare variants = large effects.

McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genetics. 2008;9:356-369

研究儿童矮小症的动机（临床研究）

- 在临床区分鉴别病理性矮小与非病理性矮小
- 诊断特定的病理性矮小，指导相应的临床干预
- 鉴别特定单基因或基因组变异引起的儿童矮小，在基因水平上确诊，了解共病，提供预后及对因治疗

与精神发育类疾病遗传基础的相似性



AJHG

Genome-wide Association of Copy-Number Variation Reveals an Association between Short Stature and the Presence of Low-Frequency Genomic Deletions

Andrew Dauber[19], Yongguo Yu[19], Michael C. Turchin, Charleston W. Chiang, Yan A. Meng, Ellen W. Demerath, Sanjay R. Patel, Stephen S. Rich, Jerome I. Rotter, Pamela J. Schreiner, James G. Wilson, Yiping Shen[19], Bai-Lin Wu[19], Joel N. Hirschhorn[19]

OPEN ACCESS Freely available online

PLOS | GENETICS

Rare Copy Number Variants Are a Common Cause of Short Stature

Diana Zahnleiter[1], Steffen Uebe[1], Arif B. Ekici[1], Juliane Hoyer[1], Antje Wiesener[1], Dagmar Wieczorek[2], Erdmute Kunstmann[3], André Reis[1], Helmuth-Guenther Doerr[4], Anita Rauch[5], Christian T. Thiel[1]*

http://www.dialogues-cns.org/publication/genetic-and-genomic-analyses-as-a-basis-for-new-diagnostic-nosologies/

矮小经常是染色体失衡的一个症状

Ha et al. Molecular Cytogenetics (2016) 9:74
DOI 10.1186/s13039-016-0286-0

CASE REPORT Open Access

The presence of two rare genomic syndromes, 1q21 deletion and Xq28 duplication, segregating independently in a family with intellectual disability

Kyungsoo Ha[1,2], Yiping Shen[3], Tyler Graves[2], Cheol-Hee Kim[4] and Hyung-Goo Kim[2,5*]

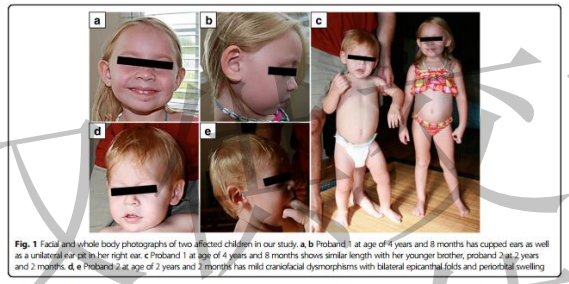


Fig. 1 Facial and whole body photographs of two affected children in our study. **a**, **b** Proband 1 at age of 4 years and 8 months has cupped ears as well as a unilateral ear pit in her right ear. **c** Proband 1 at age of 4 years and 8 months shows similar length with her younger brother, proband 2 at 2 years and 2 months. **d**, **e** Proband 2 at age of 2 years and 2 months has mild craniofacial dysmorphisms with bilateral epicanthal folds and periorbital swelling

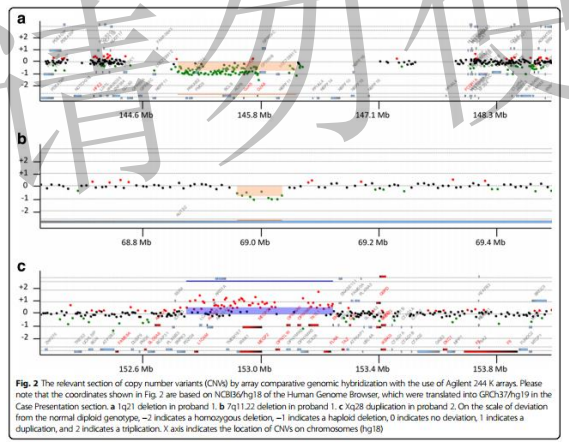


Fig. 2 The relevant section of copy number variants (CNVs) by array comparative genomic hybridization with the use of Agilent 244 K arrays. Please note that the coordinates shown in Fig. 2 are based on NCBI36/hg18 of the Human Genome Browser, which were translated into GRCh37/hg19 in the Case Presentation section. **a** 1q21 deletion in proband 1. **b** 7q11.22 deletion in proband 1. **c** Xq28 duplication in proband 2. On the scale of deviation from the normal diploid genotype, −2 indicates a homozygous deletion, −1 indicates a haploid deletion, 0 indicates no deviation, 1 indicates a duplication, and 2 indicates a triplication. X axis indicates the location of CNVs on chromosomes (hg18)

Xie et al. Molecular Cytogenetics (2016) 9:41
DOI 10.1186/s13039-016-0251-y

CASE REPORT Open Access

A novel *de novo* microdeletion at 17q11.2 adjacent to *NF1* gene associated with developmental delay, short stature, microcephaly and dysmorphic features

Bobo Xie[1], Xin Fan[1], Yaqin Lei[1], Rongyu Chen[1], Jin Wang[1], Chunyun Fu[1], Shang Yi[1], Jingsi Luo[1], Shujie Zhang[1], Qi Yang[1], Shaoke Chen[1*] and Yiping Shen[1,2*]

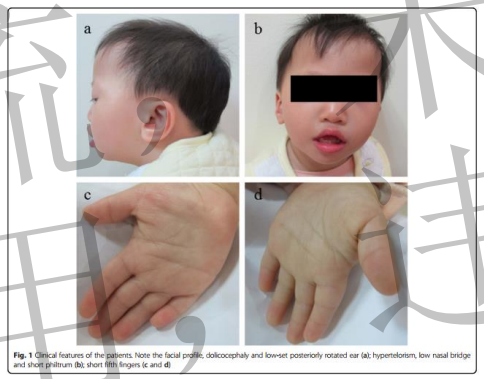


Fig. 1 Clinical features of the patients. Note the facial profile, dolicocephaly and low-set posteriorly rotated ear (**a**); hypertelorism, low nasal bridge and short philtrum (**b**); short fifth fingers (**c** and **d**)

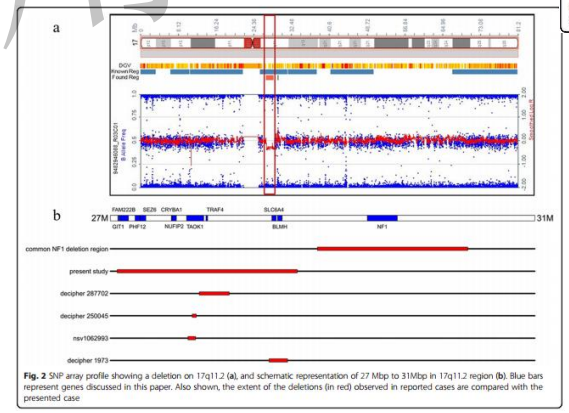


Fig. 2 SNP array profile showing a deletion on 17q11.2 (**a**), and schematic representation of 27 Mbp to 31Mbp in 17q11.2 region (**b**). Blue bars represent genes discussed in this paper. Also shown, the extent of the deletions (in red) observed in reported cases are compared with the presented case

Su et al. Molecular Cytogenetics (2016) 9:39
DOI 10.1186/s13039-016-0247-7

CASE REPORT Open Access

de novo interstitial deletions at the 11q23.3-q24.2 region

Jiasun Su[1], Rongyu Chen[1], Jingsi Luo[1], Xin Fan[1], Chunyun Fu[1], Jin Wang[1], Sheng He[1], Xuyun Hu[1], Shujie Zhang[1], Shang Yi[1], Shaoke Chen[1*] and Yiping Shen[1,2*]

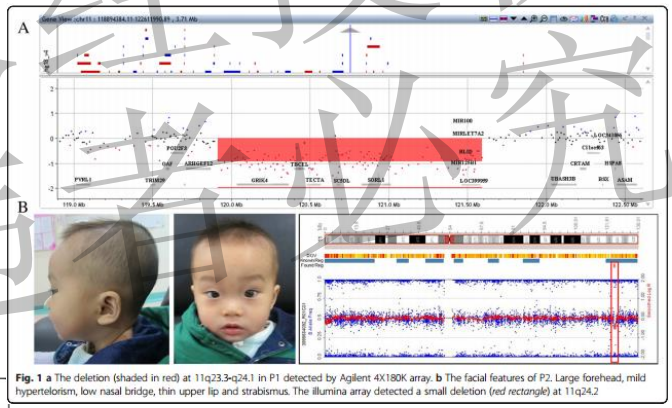


Fig. 1 **a** The deletion (shaded in red) at 11q23.3-q24.1 in P1 detected by Agilent 4X180K array. **b** The facial features of P2. Large forehead, mild hypertelorism, low nasal bridge, thin upper lip and strabismus. The Illumina array detected a small deletion (*red rectangle*) at 11q24.2

全外测序是揭示儿童矮小遗传病因的有效检测手段

Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr
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Whole Exome Sequencing to Identify Genetic Causes of Short Stature

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Jennifer E. Moon[b] Joel N. Hirschhorn[a, b, d] Andrew Dauber[b, d]

[a]Department of Genetics, Harvard Medical School, [b]Division of Endocrinology, Boston Children's Hospital, [c]Departments of Laboratory Medicine and Pathology, Boston Children's Hospital and Harvard Medical School, Boston, Mass., [d]Program in Medical and Population Genetics, Broad Institute, Cambridge, Mass., and [e]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Ind., USA; [f]Shanghai Children's Medical Center, Jiaotong University School of Medicine, Shanghai, China

Table 3. Pathogenic variants identified

Subject No.	Gene	Inheritance pattern	Position	Frequency	Functional annotation	AA change	Function	Associated diseases
P02	*B4GALT7*	compound heterozygous	Chr 5: 177035995 Chr 5: 177031251	NA 0.000077	missense missense	L41P R270C	proteoglycan synthesis	progeroid variant of Ehlers-Danlos syndrome
P07	*SRCAP*	de novo heterozygous	Chr 16: 30748691	NA	nonsense	R2444*	chromatin remodeling and transcription coactivator	Floating Harbor syndrome
P09	*OBSL1*	autosomal recessive	Chr 2: 220431551	NA	splice site donor	NA	cell scaffolding protein	3-M syndrome
P11	*CUL7*	autosomal recessive	Chr 6: 43013346	NA	frame shift	c.2837_2840dupAGAT	cell scaffolding protein	3-M syndrome
P14	*FAM111A*	de novo heterozygous	Chr 11: 58920847	NA	missense	R569H	unknown	Kenny-Caffey syndrome

5/14 (36%)

NGS based molecular diagnostics for Chinese patients with short stature

基于二代测序的中国儿童矮小症的分子诊断研究

Inclusion criteria 矮小病人入选标准（enrich for primary short stature）

- 诊断为生长激素缺乏症的儿童
- 多种垂体激素缺乏的矮小儿童。
- 身高在-2.5SD 以下，有或没有家族史的矮小儿童;
- 伴有小头畸形同时符合矮小标准的儿童。
- 伴有智力或发育落后同时符合矮小标准的儿童。
- 伴有其他先天畸形同时符合矮小标准的儿童
- 具骨骼发育异常的矮小儿童。
- 曾为 足月小样儿但没有生长追赶的矮小儿童。

Exclusion criteria矮小病人排除标准 (exclude secondary short stature)

- 明确诊断为唐氏综合征的的矮小儿童；
- 其它已经明确的染色体异常的的矮小儿童，如特纳综合征等
- 脑部明确病变者如颅内出血、脑积水的矮小儿童；
- 确诊为代谢性疾病的矮小儿童；如苯丙酮尿症等
- 严重营养不良的的矮小儿童
- 继发于肿瘤或白血病的的矮小儿童
- 精神、心理障碍性矮小 (psychosocial short stature)：常发生在有父母感情不和、离异家庭或单亲子女家庭, 患儿精神心理受挫, 影响了下丘脑-GH - IGF 轴功能, GH 分泌可正常或缺乏。典型症状是生长停滞、青春发育延迟,骨龄落后; 此外常有饮食及睡眠不佳或肠吸收不良, 消瘦, 性情孤僻, 饮食习惯及行为变异。
- 慢性系统性疾病 如消化吸收不良、肝、肾、肺功能不全、慢性感染等、地中海贫血等

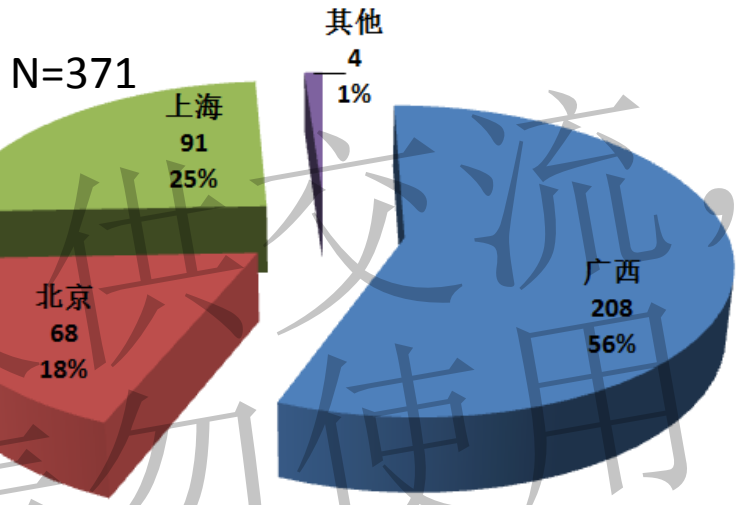
Clinical information临床信息

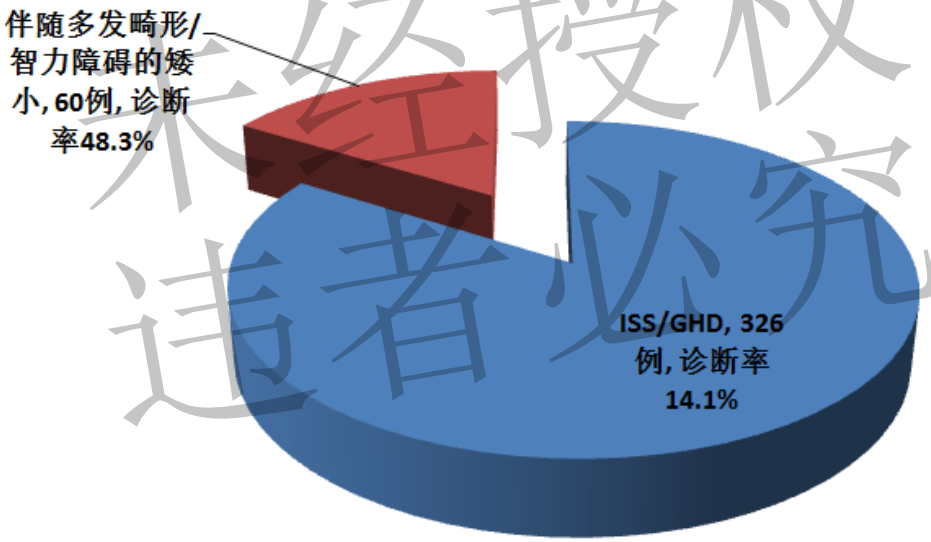
- 父母身高，
- 父母青春期发动年龄
- 患者身高、体重，以及生长曲线、生长速度（如果有），
- 矮小家族史（三代），如果有兄弟姐妹，记录兄弟姐妹的身高、体重
- 孕史（是否宫内生长迟缓），发育史，
- 骨骼系统评估结果，
- 激素水平及激发试验结果，
- 如进行垂体MRI，记录结果，
- 畸形形态学分析结果，
- 生长激素治疗一年以上，跟踪身高结果。

Study design 实验设计

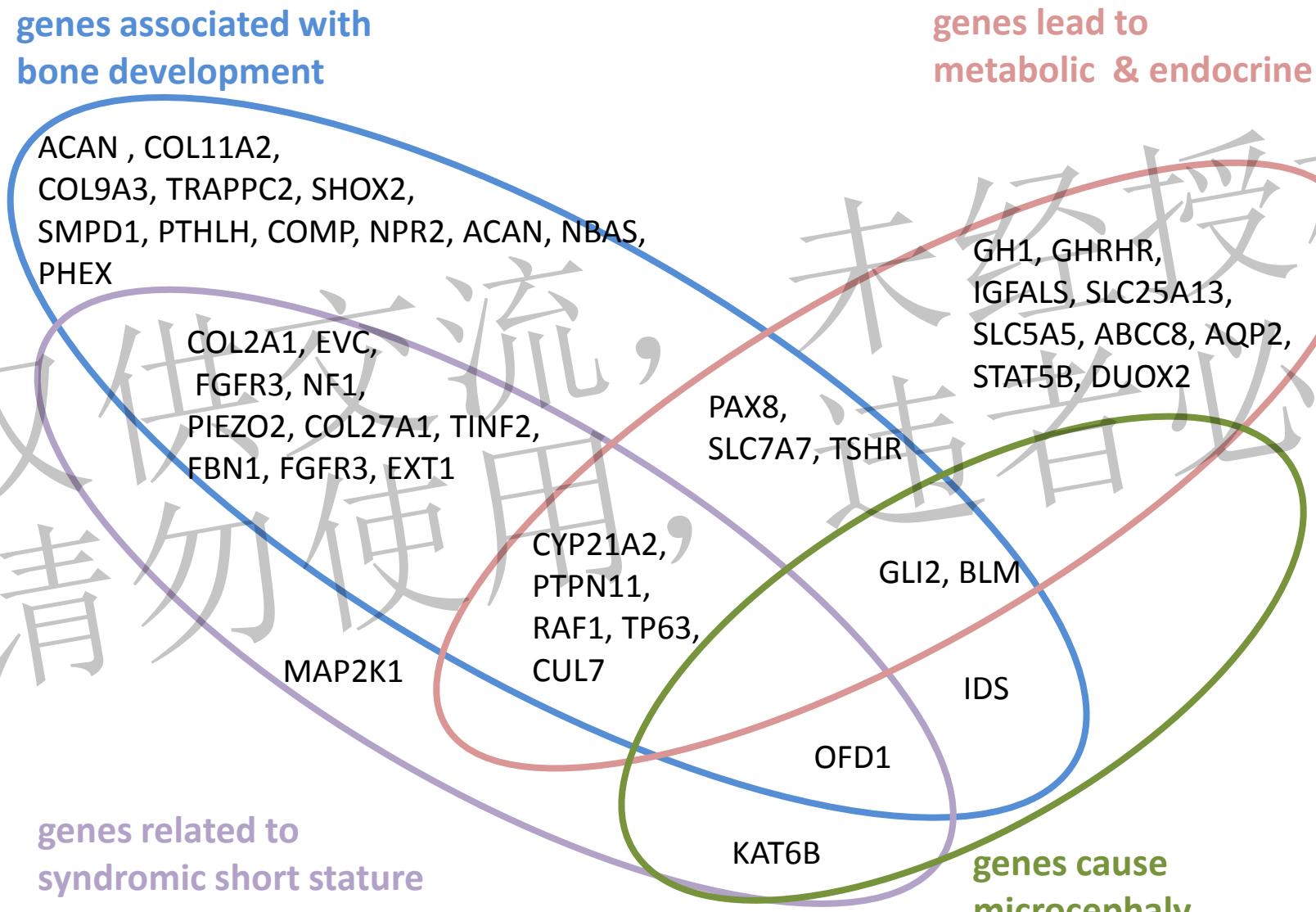
- Short stature custom panel （705 curated genes）
- Exome (trio encouraged if without family history)
- Correlate with rhGH treatment response

第一阶段结果总结





矮小致病基因的异质性

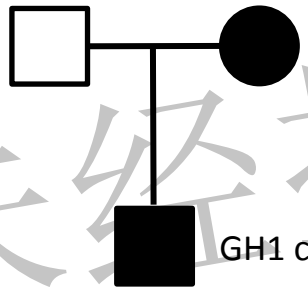


55 affected genes in total

Pathologic short stature-primary (1)

Table 1 Causes of GHD.

Disorder[a]	Gene(s)	Clinical features	Inheritance
GHD and potential for CPHD			
CPHD-1 (613038)	*POU1F1*	GH, PRL, var. TSH def.	AR, AD
CPHD-2 (262600)	*PROP1*	GH, PRL, TSH, LH, FSH, var. ACTH def. Pituitary can be enlarged.	AR
CPHD-3 (221750)	*LHX3*	GH, TSH, LH, FSH, PRL def. Sensorineural hearing loss, cervical abnormalities, short stiff neck	AR
CPHD-4 (262700)	*LHX4*	GH, TSH, ACTH def.	AD, AR
Septo-optic dysplasia (CPHD-5) (182230)	*HESX1*	Optic nerve hypoplasia, pituitary hypoplasia, midline abnormalities of brain, absent corpus callosum and septum pellucidum	AR, AD
CPHD-6 (613986)	*OTX2*	TSH, GH, LH, FSH, var. ACTH and PRL def.	AD
Axenfeld–Rieger syndrome type 1 (180500)	*PITX*	Coloboma, glaucoma, dental hypoplasia, protuberant umbilicus, brain abnormalities, var. pituitary def.	AD
Optic nerve hypoplasia and abnormalities of the central nervous system (206900)	*SOX2*	Var. GHD, hypogonadism, anophthalmia, developmental delay	AD
X-linked panhypopituitarism (312000, 300123)	*SOX3*dup[b]	GHD or CHPD, mental retardation	XLR
Dopa-responsive dystonia due to sepiapterin reductase deficiency (612716)	*SPR*	Diurnally fluctuating movement disorder, cognitive delay, neurologic dysfunction, GH and TSH def.	AR
Holoprosencephaly 9 (610829)	*GLI2*	Holoprosencephaly, craniofacial abnormalities, polydactyly, single central incisor, partial agenesis corpus callosum (or hypopituitarism only)	AD
IGSF1 deficiency syndrome (300888)	*IGSF1*	TSH, var. GH and PRL def.; macroorchidism	XLR
Netherton syndrome (256500)	*SPINK5*	Var. GH and PRL def.	AR
Pallister–Hall syndrome (146510)	*GLI3*	Hypothalamic hamartoma, central polydactyly, visceral malformations	AD
	FGF8	Holoprosencephaly, septo-optic dysplasia, Moebius syndrome	AR
	FGFR1	Hypoplasia pituitary, corpus callosum, ocular defects	AD
	PROKR2	Var. hypopituitarism	AD
	HMGA2	Severe GHD, ectopic posterior pituitary	AD
	GRP161	Pituitary stalk interruption syndrome, intellectual disability, sparse hair in frontal area, hypotelorism, broad nasal root, thick alae nasi, nail hypoplasia, short fifth finger, 2–3 toe syndactyly, hypopituitarism	AR
Isolated GHD or bioinactivity			
Isolated GHD, type IB (612781)	*GHRHR*	Low serum GH	AR
Isolated GHD, type 1A (262400)	*GH1*	No serum GH, often anti-GH ab	AR



Absent from ExAC
Dominant negative for AD Growth hormone deficiency, isolated, type II
VUS (requires extended segregation study and functional evidence)
rhGH treatment with 10.67 cm/y response

Review | J M Wit and others | Genetics of short stature | 174:4 | R145–R173

2016

MECHANISMS IN ENDOCRINOLOGY

Novel genetic causes of short stature

Jan M Wit[1], Wilma Oostdijk[1], Monique Losekoot[2], Hermine A van Duyvenvoorde[2], Claudia A L Ruivenkamp[2] and Sarina G Kant[2]

Departments of [1]Paediatrics and [2]Clinical Genetics, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

Correspondence should be addressed to J M Wit
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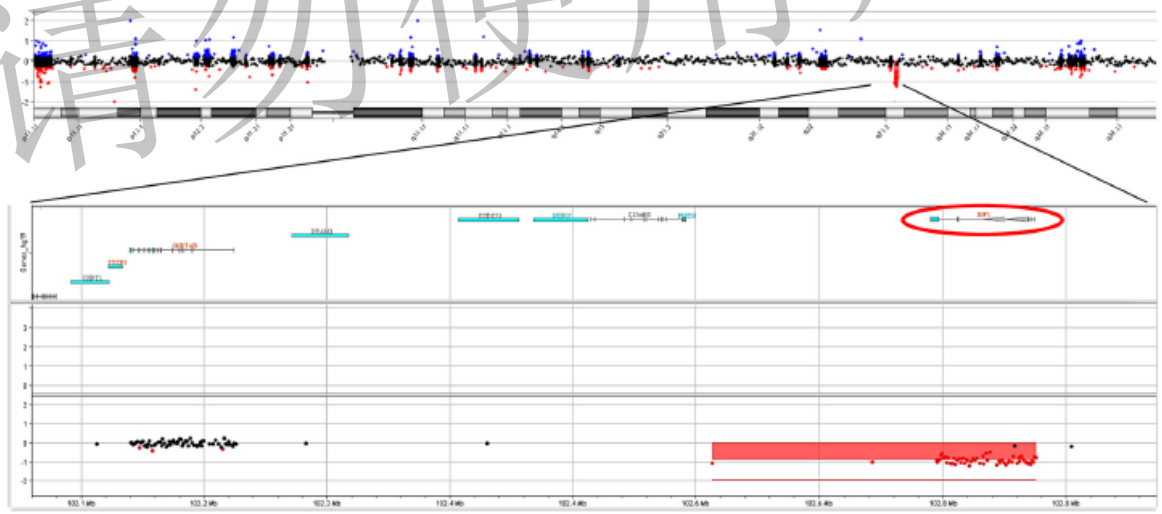
Pathologic short stature-primary (2)

Table 2 Causes of GH insensitivity or IGF insensitivity.

Disorder[a]	Gene(s)	Clinical features	Inheritance
GH insensitivity			
Laron syndrome (262500)	*GHR*	Variable height deficit and GHBP, midfacial hypoplasia; ↑GH, ↓IGF1, IGFBP-3 and ALS	AR (AD)
GH insensitivity with immuno-deficiency (245590)	*STAT5B*	Midfacial hypoplasia, immuno-deficiency; ↑GH and PRL; ↓IGF1, IGFBP-3 and ALS	AR
Multisystem, infantile-onset autoimmune disease (615952)	*STAT3* (act)	Associated with early-onset multi-organ autoimmune disease	AD
X-linked severe combined immunodeficiency (300400)	*IL2RG*	GH normal, low IGF1, non-responding to GH injections	XLR
IGF1 deficiency (608747)	*IGF1*	SGA, microcephaly, deafness; ↑GH and IGFBP-3; variable IGF1	AR
Severe growth restriction with distinctive facies (616489)	*IGF2*	↓↑/nl GH, IGFBP3; nl IGF1	Pat inheritance
ALS deficiency (615961)	*IGFALS*	Mild height deficit; GH?, ↓IGF1, IGFBP-3 and ALS	AR
	PAPP-A2	Microcephaly, skeletal abnormalities, ↑GH, IGF1, IGFBP-3, and ALS	AR
Immunodeficiency 15 (615592)	*IKBKB*	Immunodeficiency; ↓IGF1 and IGFBP-3	AR, AD
IGF insensitivity			
Resistance to insulin-like growth factor 1	*IGF1R*	SGA, microcephaly; ↑/nl GH, IGF1, and IGFBP-3	AD, AR



JCEM ONLINE

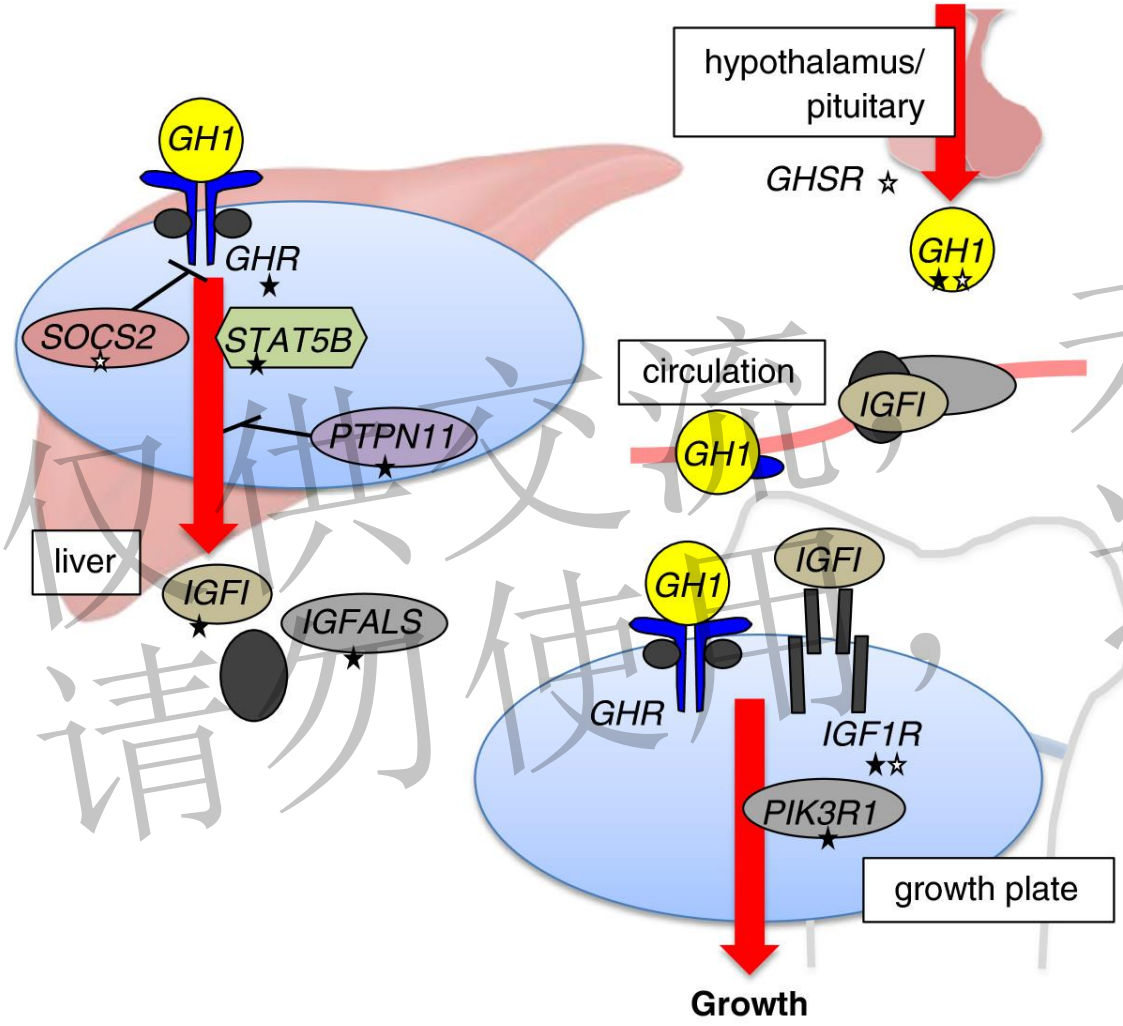
Advances in Genetics—Special Feature

A Novel Deletion of *IGF1* in a Patient With Idiopathic Short Stature Provides Insight Into *IGF1* Haploinsufficiency

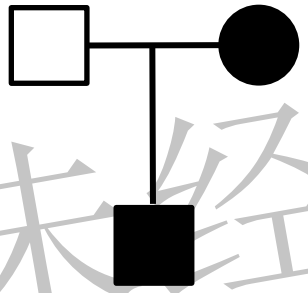
Lara Batey, Jennifer E. Moon, Yongguo Yu, Bingbing Wu, Joel N. Hirschhorn, Yiping Shen, and Andrew Dauber

Division of Endocrinology (L.B., J.E.M., J.N.H., A.D.), Boston Children's Hospital, Boston, Massachusetts 02115; Shanghai Children's Medical Center (Y.Y.), Shanghai Jiaotong University School of Medicine, Shanghai 200127, China; Pediatrics Institute (B.W.), Key Laboratory of Neonatal Diseases, Ministry of Health, Children's Hospital of Fudan University, Shanghai 201102, PR China; Program in Medical and Population Genetics (J.N.H.), Broad Institute, Cambridge, Massachusetts 02142; Department of Genetics (J.N.H.), Harvard Medical School, Boston, Massachusetts 02115; Department of Pathology (Y.S.), Harvard Medical School, and Department of Laboratory Medicine, Boston Children's Hospital, Boston, Massachusetts 02115; and Shanghai Children's Medical Center (Y.S.), Shanghai Jiaotong University School of Medicine, Shanghai 200127, China

Hormone effect targets 激素作用靶点



IGFALS c.1145C>T/p.T382M



IGFALS c.1145C>T/p.T382M

Rare in ExAC
VUS requires functional and segregation evidence
rhGH treatment is on going with 8.27cm/year growth rate

In this clinical scenario, genetic testing could be very useful to identify patients, as the one described in the present report, who are carriers of *IGFALS* mutation in the heterozygous state in which GH therapy could be indicated instead of rhIGF1 therapy. Of course, large cohorts are needed and functional characterization of mutant ALS proteins is required to confirm and clarify the role of this gene in the etiology of ISS and to guide the therapeutic choices.

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Clinical Features of a New Acid-Labile Subunit *(IGFALS)* Heterozygous Mutation: Anthropometric and Biochemical Characterization and Response to Growth Hormone Administration

Anna Grandone[a] Emanuele Miraglia del Giudice[a] Grazia Cirillo[a] Ciro Abbondanza[b] Michele Cioffi[b] Tiziana Romano[a] Flora Micillo[a] Pierluigi Marzuillo[a] Laura Perrone[a]
Departments of [a]Woman, Child and General and Specialized Surgery and [b]Biochemistry, Biophysics and General Pathology, Seconda Università degli Studi di Napoli, Naples, Italy

Pathologic short stature-primary (3)

le 3 Examples of genetic defects affecting paracrine factors in the growth plate.

rder[a]	Gene(s)	Clinical features	Inheritance
signaling			
iffer syndrome, acrocephalo-ndactyly, type V (101600)	*FGFR1, FGFR2*	Craniosynostosis with characteristic anomalies of the hands and feet (three types)	AD
anatophoric dysplasia type I 87600)	*FGFR3* (act)	Severe short-limb dwarfism syndrome usually lethal in the perinatal period	AD
hondroplasia (100800)	*FGFR3* (act)	Rhizomelic limb shortening, frontal bossing, midface hypoplasia, exaggerated lumbar lordosis, limited elbow extension, genu varum, trident hand	AD
pochondroplasia (146000)	*FGFR3* (act)	Short-limbed dwarfism, lumbar lordosis, short and broad bones, caudal narrowing of interpediculate distance of lumbar spine	AD
ort stature	*FGFR3* (act)	Relative macrocephaly for height	AD
P signaling			
achydactyly A1 (112500)	*IHH, GDF5, BMPR1B*	Middle phalanges rudimentary or fused with terminal phalanges, short proximal phalanges thumbs and big toes	AD
achydactyly A2 (112600)	*BMPR1B, BMP2, GDF5*	Malformations of middle phalanx of index finger, anomalies of second toe	AD
achydactyly C (113100)	*GDF5, CDMP1*	Deformity of middle and proximal phalanges (II, III), hypersegmentation of proximal phalanx	AD
T signaling			
binow syndrome (268310)	*ROR2, WNT5A*	Frontal bossing, hypertelorism, broad nose, short-limbed dwarfism, vertebral segmentation, genital hypoplasia	AR, AD
achydactyly, Type B1 (113000)	*ROR2*	Short middle phalanges, terminal phalanges rudimentary or absent; deformed thumbs, big toes	AD
rP-IHH pathway			
achydactyly, type E2 (613382)	*PTHLH*	Short stature and learning difficulties	AD
omstrand chondro-dysplasia 215045)	*PTHR1*	Short limbs, polyhydramnios, hydrops fetalis, facial anoma-lies, increased bone density, advanced skeletal maturation	AR
nsen type of meta-physeal hondrodys-plasia (156400)	*PTHR1* (act)	Severe short stature, short bowed limbs, clinodactyly, prominent upper face, small mandible; hypercalcemia and hypophosphatemia	AD
achydactyly type A1 (112500)	*IHH, GDF5,*	Middle phalanges rudimentary or fused with	AD

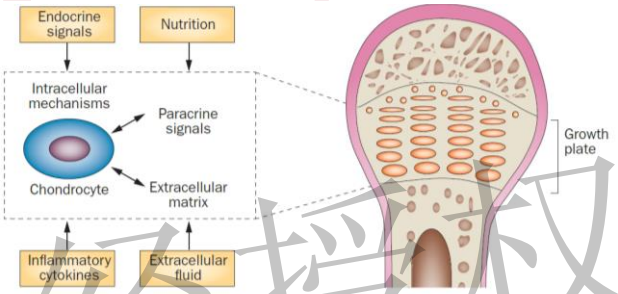


Figure 2 | Regulation of growth plate function. Chondrocyte proliferation and differentiation in the growth plate are regulated by many factors, including nutritional, endocrine, inflammatory cytokines, extracellular fluid (for example, oxygen and pH), paracrine, extracellular matrix and intracellular mechanisms. Not depicted are the interactions among many of these systems; for example, nutritional intake strongly affects endocrine regulators of the growth plate.

8 individuals with FGFR3 mutation
Including c.1618A>G/p.I538V
with hypochondroplasia
rhGH treatment with 8.52cm/yr response

Conclusions: rhGH treatment is well tolerated and effective in improving growth in HCH patients, particularly when started early. The treatment effect varies greatly and must be evaluated for each patient during treatment to determine the value of continued therapy.


Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Efficacy and Safety of Growth Hormone Treatment in Children with Hypochondroplasia: Comparison with an Historical Cohort

rhGH treatment

In conclusion, GH treatment of children with achondroplasia improves relative height during 4 y of therapy without having an adverse effect on trunk–leg disproportion. The short time response in height is in agreement with results from GH-treatment studies of Turner syndrome, Noonan syndrome and ISS. Whether a gain in height, in patients with achondroplasia, of approximately 1.5 SD is worth at least 5 y of daily injections is, however, debatable. The potential long-term effects of chronically increased serum IGF-I levels are still not known.

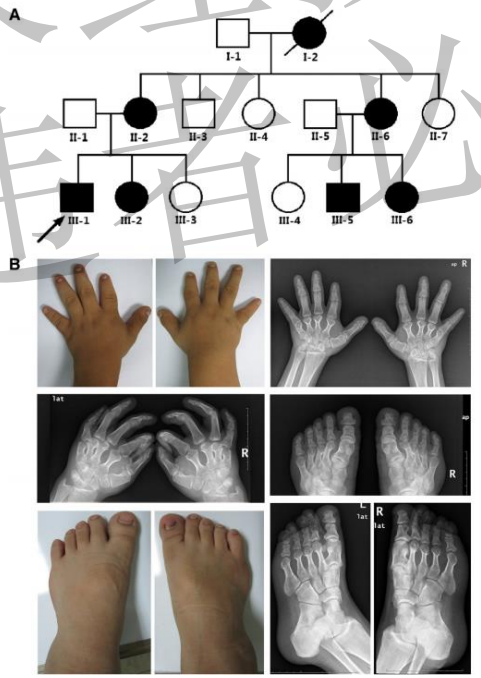
Acta Paediatrica, 2005; 94: 1402–1410

Taylor & Francis
Taylor & Francis Group

Growth hormone treatment in 35 prepubertal children with achondroplasia: A five-year dose-response trial

NIELS THOMAS HERTEL[1,3], OLE EKLÖF[2], STEN IVARSSON[4], STEFAN ARONSON[5], OTTO WESTPHAL[6], ILKKA SIPILÄ[7], ILKKA KAITILA[8], JON BLAND[9], DAG VEIMO[10], JØRN MÜLLER[3], KLAUS MOHNIKE[11], LO NEUMEYER[1], MARTIN RITZEN[1] & LARS HAGENÄS[1]

PTHLH LOF causes Brachydactyly, type E2
c.413delA/p.K138fs*11
rhGH treatment with a 12cm/y growth rate

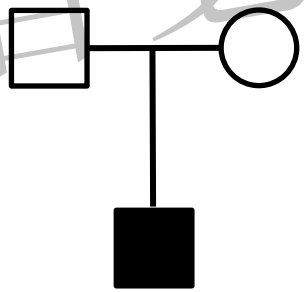


Pathologic short stature-primary (4)

Table 4 Examples of genetic defects affecting cartilage extracellular matrix.

Disorder[a]	Gene(s)	Clinical features	Inheritance
Acromicric dysplasia (102370)	*FBN1*	Severe short stature, short hands and feet, joint limitations, skin thickening	AD
Geleophysic dysplasia-2 (614185)	*FBN1*	Severe short stature, short hands and feet, joint limitations, skin thickening, heart involvement	AD
Brachyolmia type 4 with mild epiphyseal and metaphyseal changes (spondyloepimeta-physeal dysplasia, Pakistani type) (612847)	*PAPSS2*	Short trunk, normal intelligence and facies; rectangular vertebral bodies with irregular endplates and narrow intervertebral discs, precocious calcification of rib cartilages, short femoral neck, mildly shortened metacarpals, and mild epiphyseal and metaphyseal changes of the tubular bones	AR
Hurler syndrome (607014)	*IDUA*	Skeletal deformities, corneal clouding, hepatosplenomegaly, psychomotor delay	AR
Metaphyseal chondro-dysplasia, Schmid type (156500)	*COL10A1*	Short stature, widened growth plates, bowing of long bones	AD
Multiple epiphyseal dysplasia 1–6	*COMP, COL9A2, COL9A3, SLC26A2, MATN3, COL9A1*	Short-limbed dwarfism, joint pain and stiffness and early onset osteoarthritis	AD
Pseudoachondro-plasia (177170)	COMP	Disproportionate short stature, deformity of lower limbs, brachydactyly, loose joints, ligamentous laxity, vertebral anomalies, osteoarthritis	AD
Spondyloepiphyseal dysplasia congenita (183900)	*COL2A1*	Multiple presentations	AD
Spondyloepimetaphy-seal dysplasia aggrecan type (612813)	*ACAN*	Relative macrocephaly, severe midface hypoplasia, almost absent nasal cartilage, relative prognathism, slightly low-set, posteriorly rotated ears; short neck, barrel chest, mild lumbar lordosis; rhizomelia and mesomelia	AR
Spondyloepiphyseal dysplasia type Kimberley (608361)	*ACAN*	Proportionate short stature, stocky habitus, progressive osteoarthropathy	AD
Short stature with advanced bone age	*ACAN*	Advanced bone age, premature growth cessation	AD
Weill–Marchesani syndrome (613195, 608328)	*ADAMTS10, FBN1*	Spherophakia, lenticular myopia, ectopia lentis, joint stiffness, brachydactyly	AR

COL2A1 c.2059G>A/p.G687S
De novo +PM1 (Gly)+PM2
rhGH not likely to be effective
NL intelligence
Instability of cervical spine
Early onset kyphoscoliosis
Hearing loss
Myopia
Hip degeneration
Respiratory problem can be life-threatenin

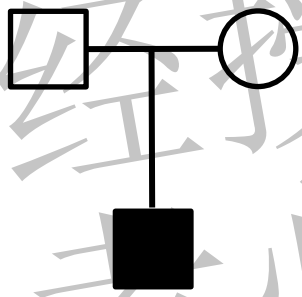


TRAPPC2 c.426+1G>T
Spondyloepiphyseal dysplasia tarda
de novo
Poor response to rhGH treatment (4.25cm

Pathologic short stature-primary (5)

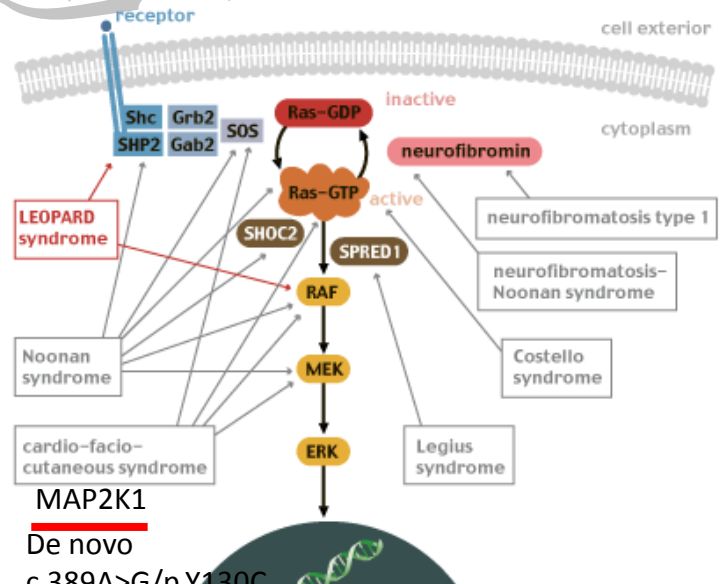
Table 5 Examples of genetic defects affecting intracellular pathways.

Disorder[a]	Gene(s)	Clinical features	Inheritance
SHOX aberrations			
Langer mesomelic dysplasia (249700)	*SHOX*	Severe limb aplasia or hypoplasia of the ulna and fibula, and a thickened and curved radius and tibia	AR
Leri–Weill dyschon-drosteosis (127300)	*SHOX*	Mesomelia, Madelung wrist deform-ity, or mild body disproportion	AD
Rasopathies			
Noonan syndrome 1–8	*PTPN11, KRAS, SOS1, RAF1, NRAS, BRAF, RIT1*	Facial dysmorphism, wide spectrum of congenital heart defects	AD
LEOPARD syndrome		Multiple lentigines, electrocardio-graphic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, sensorineural deafness	AD
1 (151100)	*PTPN11,*		
2 (611554)	*RAF1,*		
3 (613707)	*BRAF*		
Costello syndrome (218040)	*HRAS*	Coarse facies, distinctive hand posture and appearance, feeding difficulty, failure to thrive, cardiac anomalies, developmental delay	AD
Cardio-facio-cutaneous syndrome (115150)	*BRAF, KRAS*	Distinctive facial appearance, heart defects, mental retardation	AD
Neurofibromatosis-Noonan syndrome (601321)	*NF1*	Features of both conditions	AD
Neurofibromatosis type I (162200)	*NF1*	Cafe-au-lait spots, Lisch nodules in eye, fibroma-tous skin tumours; short in 13%; large head circumference in 24%	AD
Coffin–Lowry syndrome (303600)	*RPS6KA3*	Mental retardation, skeletal malformations, hearing deficit, paroxysmal movement disorders	XLR
Other syndromes			
Aarskog–Scott syndrome (faciogenital dysplasia) (305400)	*FGD1*	Hypertelorism, shawl scrotum, brachydactyly	XLR
Alström syndrome (203800)	*ALMS1*	Retinal photoreceptor degeneration, sensorineural hearing imparment, obesity, insulin resistance	AR
Campomelic dysplasia (114290)	*SOX9*	Congenital bowing and angulation of long bones, other skeletal and extraskeletal defects	AD
Congenital disorders of glycosylation	Multiple genes (>76)	Multisystem disorders caused by defects in biosynthesis of glyco-conjugates	AR
Kabuki syndrome 1 (147920) and 2	*KMT2D, KDM6A*	Long palpebral fissures, eversion of	AD



PTPN11 c.846C>G/p.I85F

rhGH treatment with 7.76cm/y response



MAP2K1

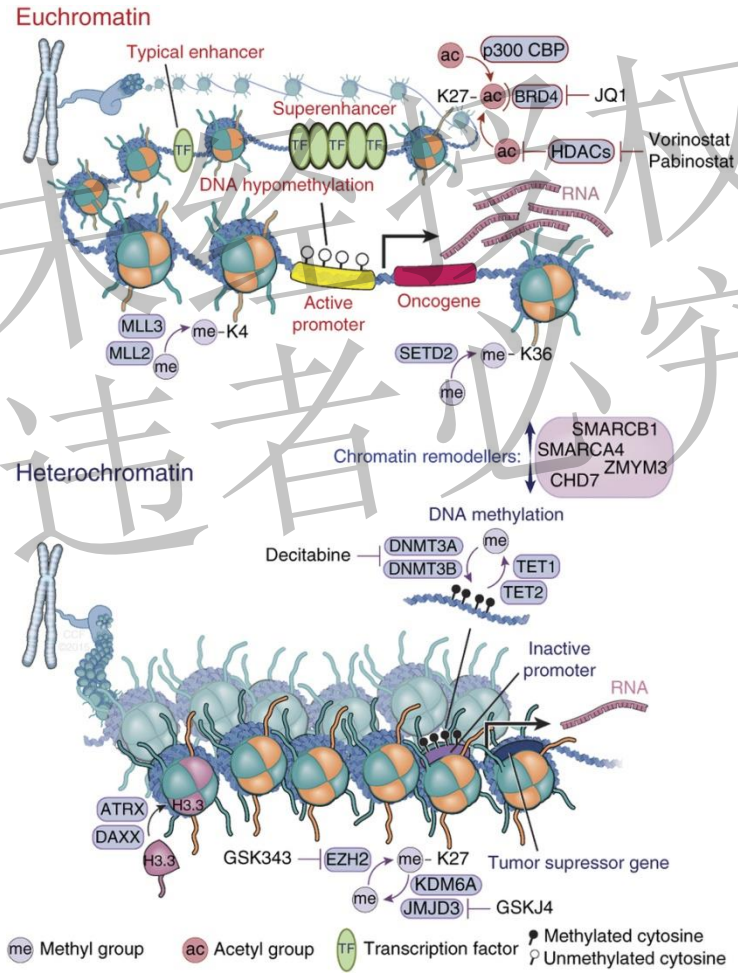
De novo

c.389A>G/p.Y130C

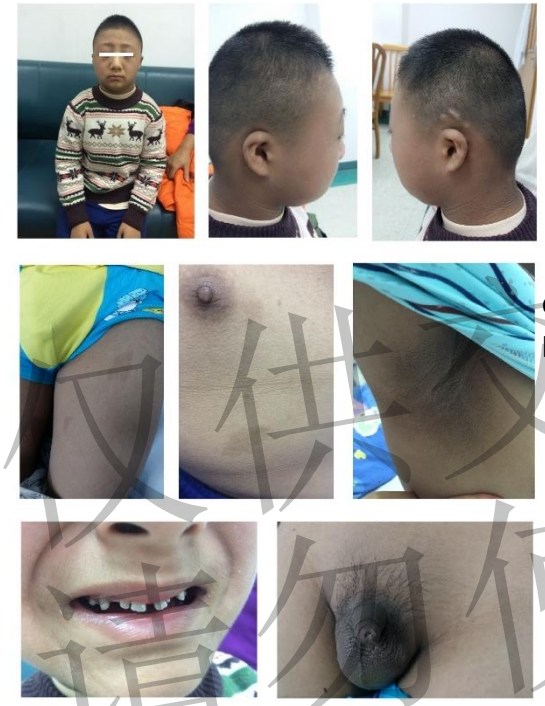
Pathologic short stature-primary (6)

Table 6 Examples of genetic defects in fundamental cellular processes.

Disorder[a]	Gene(s)	Clinical features	Inheritance
Syndromes with (usually) normal head circumference			
CHARGE syndrome (214800)	*CHD7, SEMA3E*	Choanal atresia, malformations of heart, inner ear and retina	AD
Coffin–Siris syndrome (135900)	*SMARCB1, SMARCA4, SMARCA2, ARID1A, ARID1B*	Developmental delay, speech impairment, coarse facial features, hypertrichosis, hypoplastic fifth fingernails or toenails, agenesis of the corpus callosum	AD
Floating–Harbor syndrome (136140)	*SRCAP*	Delayed bone age and speech, triangular face, deep-set eyes, long eyelashes, bulbous nose, wide columella, short philtrum, thin lips	AD
KBG syndrome (148050)	*ANKRD11*	Macrodontia of upper central incisors, distinctive craniofacial findings, skeletal anomalies, global developmental delay, seizures, intellectual disability	AD
Mulibrey nanism (253250)	*TRIM37*	Progressive cardiomyopathy, characteristic facial features, failure of sexual maturation, insulin resistance with DM2, increased risk for Wilms tumor	AR
SHORT syndrome (269880)	*PIK3R1*	hyperextensibility of joints, inguinal hernia, ocular depression, teething delay	AD
Short stature, onychodysplasia, facial dysmorphism, hypotrichosis (SOFT, 614813)	*POC1A*	Severely short long bones, peculiar facies associated with paucity of hair, triangular facies, nail anomalies, short, thickened distal phalanges. Relative macrocephaly in childhood, microcephaly in adulthood	AR
Three-M syndrome 1 (273750), 2 (612921), 3 (614205)	*CUL7, OBSL1, CCDC8*	Facial features, normal mental development, long, slender tubular bones, reduced anteroposterior diameter of vertebral bodies, delayed bone age	AR
Microcephalic primordial dwarfism			
Cornelia de Lange syndrome 1–5	*NIPBL, SMC1A, SMC3, RAD21, HDAC8*	Low anterior hairline, arched eyebrows, synophrys, ante-verted nares, maxillary prognathism, long philtrum, thin lips, 'carp' mouth, upper limb anomalies.	AD
Meier–Gorlin syndrome 1–5	*ORC1, ORC4, ORC6, CDT1, CDC6*	Bilateral microtia, and aplasia or hypoplasia of the patellae, normal intelligence	AR
MOPD I (210710)	*U4atac*	Neurologic abnormalities, including mental retardation, brain malformations, ocular/auditory sensory deficits	AR
MOPD II (210720)	*PCNT*	Radiologic abnormalities, absent or mild mental retardation in comparison to Seckel syndrome, truncal obesity, diabetes, moyamoya, small loose teeth	AR
Microcephaly and chorioretinopathy, 1 (251270), 2 (616171)	*TUBGCP6, PLK4*	Retinopathy. The gene encodes PLK4 kinase, a master regulator of centriole duplication.	AR
Rett syndrome (312750)	*MECP2*	Almost exclusively in females. Arrested development (6–18 months), loss of speech, stereotypic movements, microcephaly, seizures, mental retardation.	XLD
Rubinstein–Taybi syndrome 1 (180849), 2 (613684)	*CREBBP, EP300*	Mental retardation, broad thumbs and halluces, dysmorphic facial features	AD
Seckel syndrome 1–8	*ATR, RBBP8, CENPJ, CEP152, CEP63, NIN, DNA2, ATRIP*	Mental retardation, characteristic 'bird-headed' facial appearance	AR
Short stature with microcephaly and distinctive facies (615789)	*CRIPT*	Frontal bossing, high forehead, sparse hair and eyebrows, telecanthus, proptosis, anteverted nares, flat nasal bridge	AR



综合征病例

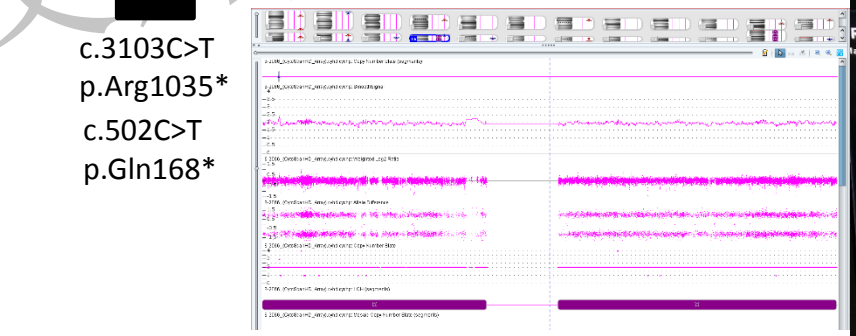


MOPD II型[小头畸形-骨发育不良（牙齿）-生后矮小症]
2型糖尿病
黑棘皮病
高血压。
牛奶咖啡斑

PCNT

c.3103C>T
p.Arg1035*

c.502C>T
p.Gln168*

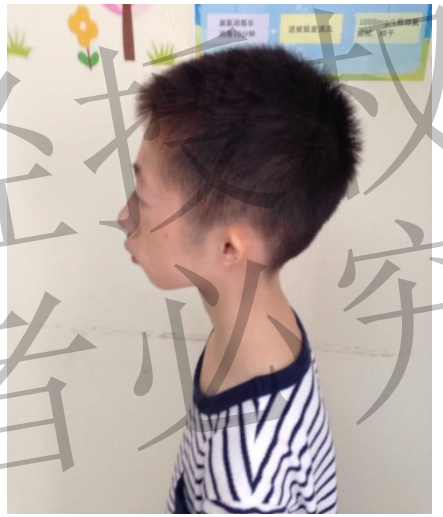


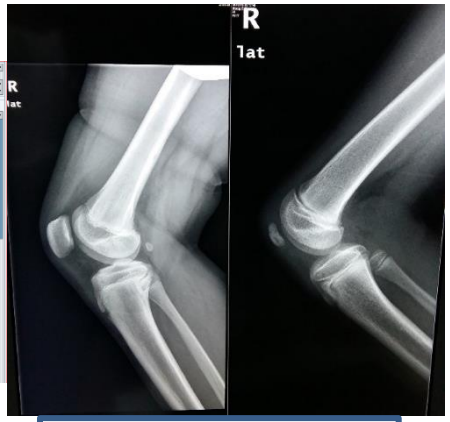
ORC6

hetero c.67A>G
Lys23Glu

homo c.67A>G/Lys23Glu

小耳畸形
髌骨发育不良或缺如
宫内发育迟缓或生后生长迟缓





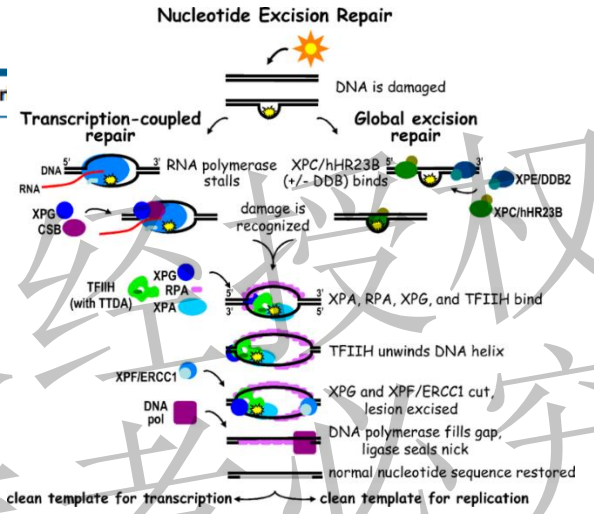
正常儿童 VS 患儿

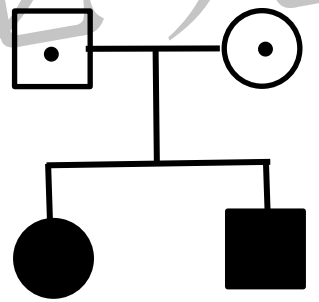
Courtesy of 王秀敏

Pathologic short stature-primary (7)

Table 7 Examples of genetic defects in fundamental cellular processes: DNA repair defects.

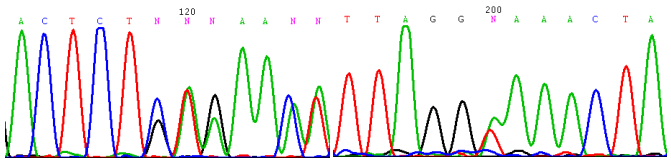
Disorder[a]	Gene(s)	Clinical features	Inher
Bloom syndrome (210900)	*RECQL3*	Sun-sensitive, telangiectatic, hypo- and hyperpigmented skin, predisposition to malignancy,chromosomal instability	AR
Cockayne syndrome A, B, XPG/CS (five types)	*ERCC8, ERCC6, ERCC5, ERCC3, ERCC4*	Cutaneous photosensitivity, thin, dry hair, progeroid appearance, pigmentary retinopathy, sensorineural hearing loss, dental caries	AR
Fanconi anemia (multiple types)	FANCA and multiple genes	Heterogeneous disorder causing genomic instability, abnormalities in major organ systems, bone marrow failure, high predisposition to cancer	AR
Hutchinson–Gilford progeria syndrome (176670)	*LMNA*	Low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, facial features that resemble aged persons	AD
Hypomorphic PCNA mutation	*PCNA*	Hearing loss, premature aging, telangiectasia, neurodegeneration, photosensitivity by nucleotide excision repair defect	AR
Immunoosseous dysplasia, Schimke type (242900)	*SMARCAL1*	Spondyloepiphyseal dysplasia, numerous lentigines, slowly progressive immune defect, immune-complex nephritis	AR
Natural killer cell and glucocorticoid deficiency with DNA repair defect (609981)	*MCM4*	Variant of familial glucocorticoid deficiency: hypocortisolemia, increased chromosomal breakage, NK cell deficiency	AR
Nijmegen breakage syndrome (251260)	*NBS1*	Microcephaly, growth retardation, immunodeficiency, predisposition to cancer	AR
Ovarian dysgenesis 4	*MCM9*	Hypergonadotropic hypogonadism, genomic instability	AR
Rothmund–Thomson syndrome	*RECQL4*	Skin atrophy, telangiectasia, hyper- and hypopigmentation, congenital skeletal abnormalities, premature aging	AR
X-linked mental retardation-hypotonic facies syndrome (309580)	*ATRX*	Mental retardation, dysmorphic facies, hypogonadism, deafness, renal anomalies, mild skeletal defects	XLR
Defective nonhomologous end-joining (NHEJ) DNA damage repair	*LIG4, NHEJ1, ARTEMIS, DNA-PKCs, XRCC4, PRKDC*	Radiosensitive, severe combined immunodeficiency	AR





c.772_773delCT
p.Leu258Glufs*7

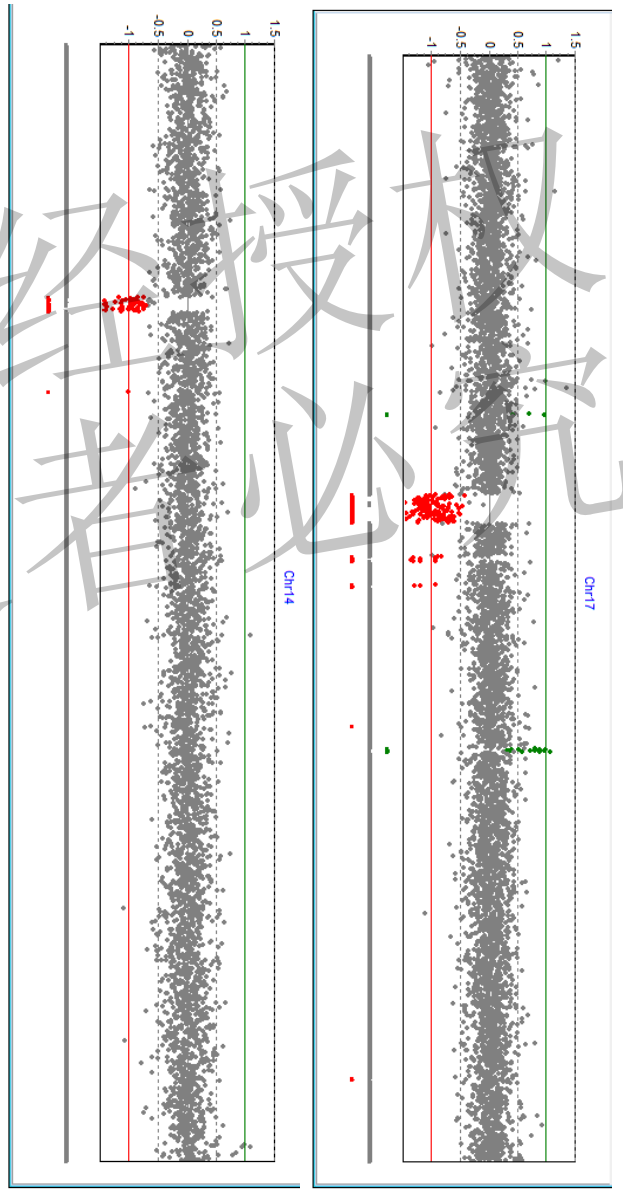
c.959+2T>A



Pathologic short stature-primary (8)

Table 8 Examples of contiguous gene deletion or duplication syndromes associated with short stature.

Disorder[a]	Location	Clinical features
Recurrent rearrangements of 1q21.1	1q21.1del	Intellectual disability, autism spectrum disorder, microcephaly, cardiac abnormalities, cataracts
2p16p22 microduplication syndrome	2p16p22dup	Delayed bone age, facial dysmorphism. Role of *EPAS* and *RHOQ*?
Wolf–Hirschhorn syndrome (194190)	4p16.3del	'Greek warrior helmet', epicanthal folds, short philtrum, downturned corners of mouth, micrognathia, seizures. Mitochondrial defect by *LETM1* haploinsufficiency
Chromosome 4q21 deletion syndrome (613509)	4q21del	Neonatal muscular hypotonia, severe psychomotor retardation, severely delayed speech, broad forehead, frontal bossing, hypertelorism, short philtrum, downturned corners of mouth
Cri-du-chat syndrome (123450)	5p15.2ter del	High-pitched catlike cry, microcephaly, round face, ocular hypertelorism, micrognathia, epicanthal folds, low-set ears, hypotonia, severe psychomotor retardation. *CTNND2*?
Short stature, microce-phaly, speech delay	5q35.2q35.3dup	Microcephaly, speech delay. Reciprocal to common Sotos syndrome deletion (increased NSD1 function?)
Williams–Beuren syndrome (194050)	7q11.23del	Supravalvular aortic stenosis, intellectual disability, distinctive facial features
Trichorhinophalangeal syndrome, type II (Langer–Giedion syndrome) (150230)	8q21.11q24.13del	Large, laterally protruding ears, bulbous nose, elongated upper lip, sparse scalp hair, winged scapulae, multiple cartilaginous exostoses, redundant skin, intellectual disability. *TRPS1*, *EXT1*?
WAGR syndrome (194072)	11p13del	Aniridia, hemihypertrophy, Wilms tumor, cryptorchidism. *PAX6*, *WT1*?
12q14 microdeletion syndrome	12q14del	Developmental delay, osteopoikilosis. *HMGA2*?
Chromosome 13q14 deletion syndrome (613884)	13q14del	Retinoblastoma, mental impairment, high forehead, prominent philtrum, anteverted earlobes
Frias syndrome (609640)	14q22.1q22.3del	Exophthalmia, palpebral ptosis, hypertelorism, short square hands, small broad great toes. *BMP4*?
Distal 14q duplication syndrome	14q32.2-qter	Mild developmental delay, high forehead, hyper-telorism, dysplastic ear helices, short philtrum, cupid bow upper lip, broad mouth, micrognathia
Smith–Magenis syndrome (182290)	17p11.2del	Brachycephaly, midface hypoplasia, prognathism, hoarse voice, speech delay, hearing loss, psycho-motor retardation, behavioral problems. *RAI1*? Can be associated with GHD
Miller–Dieker lissencephaly syndrome (247200)	17p13.3del	Lissencephaly, microcephaly, wrinkled skin over glabella and frontal suture, prominent occiput, narrow forehead, downward slanting palpebral



Pathologic short stature-primary (9)

Table 9 Examples of imprinting disorders.

Disorder[a]	Genetics	Clinical features
Silver–Russell syndrome (180860)	Hypomethylation of imprinting control region on paternal allele of 11p15.5 controling methylation of *IGF2* and *H19* Maternal UPD7 (*SRS*, 7p11.2)	Severe IUGR, triangular shaped face, broad forehead, body asymmetry, variety of minor malformations
Silver–Russell syndrome or IMAGe syndrome (614732) or IUGR + early-onset diabetes mellitus	Mutation in paternally imprinted gene *CDKN1C*	IUGR, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies; or only Silver–Russell syndrome; or IUGR and early-adulthood-onset diabetes with normal adrenal function
Prader–Willi syndrome (176270)	Loss of expression of paternal copies of imprinted genes (*SNRPN*, *NDN*), and others (15q11–q13) by deletion, maternal UPD, imprinting center defect, or Robertsonian translocation	Intellectual disability, seizures, poor gross and fine motor coordination, behavioral problems, sleep disturbances, high pain threshold
Pseudohypoparathyroidism type 1a/c (103580)	Heterozygous *GNAS1* (20q13.32) mutation inherited from mother	Resistance to parathyroid hormone and other hormones
Pseudohypoparathyroidism type 1b (603233)	Both alleles have a paternal-specific imprinting pattern on both parental alleles	Resistance to PTH is present without signs of Albright hereditary osteodystrophy
Pseudopseudohypopara – thyroidism (612463)	Heterozygous *GNAS1* mutation inherited from father	Albright hereditary osteodystrophy without multiple hormone resistance, brachydactyly
Temple syndrome (616222)	Maternal UPD14 (14q32)	Low birth weight, hypotonia, motor delay, feeding problems early in life, early puberty, reduced adult height, broad forehead, short nose with wide nasal tip, small hands and feet

Zhang et al. Molecular Cytogenetics (2016) 9:66
DOI 10.1186/s13039-016-0274-4

Molecular Cytogenetics

CASE REPORT Open Access

Maternal uniparental disomy 14 and mosaic trisomy 14 in a Chinese boy with moderate to severe intellectual disability

Shujie Zhang[1†], Haisong Qin[1†], Jin Wang[1], Luping OuYang[1], Shiyu Luo[1], Chunyun Fu[1], Xin Fan[1], Jiasun Su[1], Rongyu Chen[1], Bobo Xie[1], Xuyun Hu[1], Shaoke Chen[1*] and Yiping Shen[1,2*]

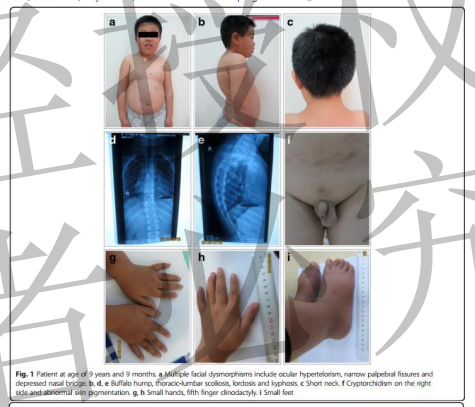


Fig. 1 Patient at age of 9 years and 9 months. a Multiple facial dysmorphisms include ocular hypertelorism, narrow palpebral fissures and depressed nasal bridge. b, d, e Buffalo hump, thoracic-lumbar scoliosis, lordosis and kyphosis. c Short neck. f Cryptorchidism on the right side and abnormal skin pigmentation. g, h Small hands, fifth finger clinodactyly. i Small feet

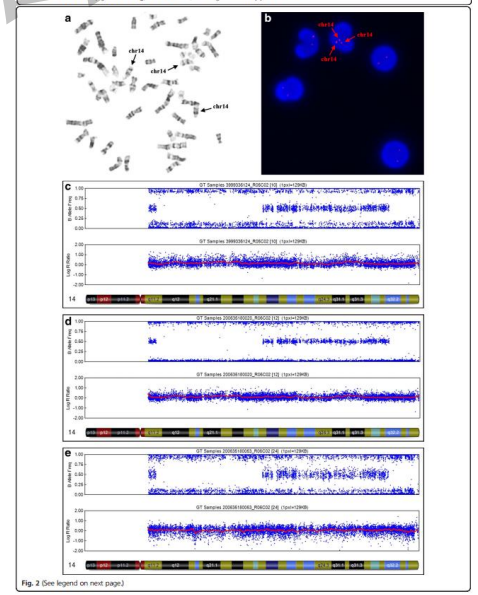
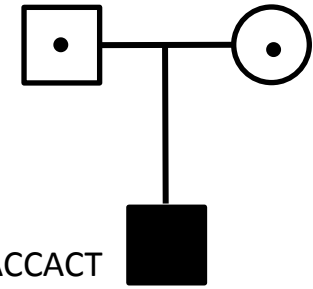


Fig. 2 (See legend on next page.)

先天性甲低



c.1604_1617delGCACGCTGACCACT
p.T536fs*45

SLC5A5

#274400

THYROID DYSHORMONOGENESIS 1; TDH1

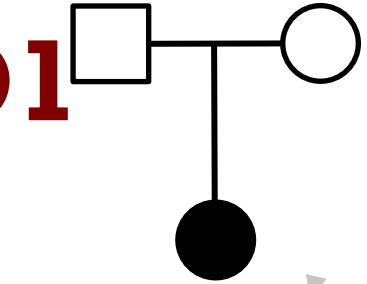
CATEGORY	SUBCATEGORY	FEATURES
Inheritance	-	Autosomal recessive
Growth	Other	Growth retardation
Head and Neck	Mouth	Macroglossia (not always present) [EoM image]
	Neck	Goiter (not always present)
		Thyroid nodules, hyperplastic and adenomatous
Abdomen	External Features	Umbilical hernia (in some patients)
	Gastrointestinal	Constipation
Skin, Nails, Hair	Skin	Dry skin
Neurologic	Central Nervous System	Mental retardation (if untreated in infancy)
	Behavioral Psychiatric Manifestations	Lethargy (when taken off of medication)
Endocrine Features	-	Thyroid iodine accumulation defect
		Hypothyroidism
Laboratory Abnormalities	-	Low T4
		Low RAI (radioactive iodine) uptake
Miscellaneous	-	Hypothyroidism is less severe in individuals with high dietary iodine intake
		Preferably treated with iodine supplementation rather than thyroid hormone replacement
Molecular Basis	-	Caused by mutation in the solute carrier family 5 (sodium iodide symporter), member 5 gene (SLC5A5, 601843.0001)

The patient is being treated with rhGH with a 8.6cm/y growth rate

Pax8 c.1087+1 (a novel variant with PVS1+PM2=likely pathogenic) rhGH treatment with 7.6 cm/y

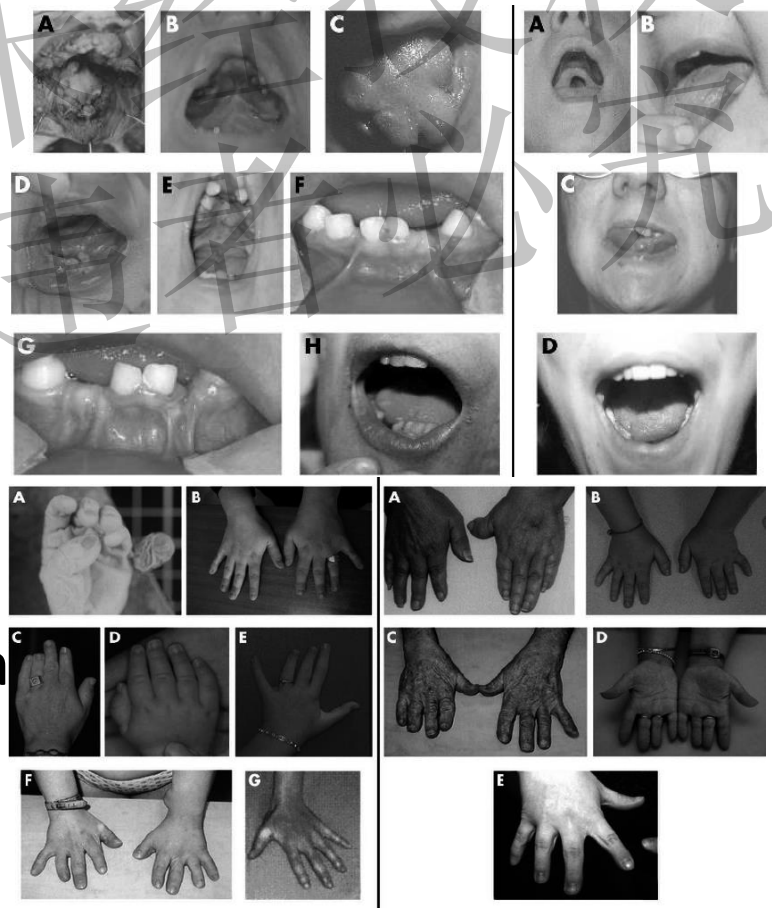
“Treatment with levothyroxine corrected the symptoms and was associated with catch-up growth”
(PMID: 23647375)

口面指综合征OFD1



c.2289dupC/p.S764fs*5

- Orofaciodigital syndrome I
- XLD male lethal
- De novo
- A ciliopathy
  - Short stature
  - Microcephaly
  - Oral phenotype
  - Digits phenotype
  - Skin phenotype
  - Cystic kidney
  - ID/major depression
- rhGH treated with 7.52cm/y growth



LETTER TO JMG

Clinical, molecular, and genotype–phenotype correlation studies from 25 cases of oral–facial–digital syndrome type 1: a French and Belgian collaborative study

C Thauvin-Robinet, M Cossée, V Cormier-Daire, L Van Maldergem, A Toutain, Y Alembik, E Bieth, V Layet, P Parent, A David, A Goldenberg, G Mortier, D Héron, P Sagot, A M Bouvier, F Huet, V Cusin, A Donzel, D Devys, J R Teyssier, L Faivre

J Med Genet 2006;43:54–61. doi: 10.1136/jmg.2004.027672

先天性肾上腺增生与矮小

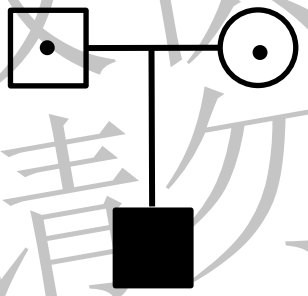
- In both sexes, linear growth in childhood is accelerated, but the epiphyses fuse early, leading to short stature.

DE GRUYTER J Pediatr Endocrinol Metab 2016; 29(7): 841–848

Lin Juan, Ma Huamei*, Su Zhe, Li Yanhong, Chen Hongshan, Chen Qiuli, Zhang Jun, Guo Song and Du Minlian

Near-final height in 82 Chinese patients with congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency: a single-center study from China

Near final height (153.35±8.31) cm, (–1.9±1.1) SD was significantly lower than the normal population ($p<0.001$).



CYP21A2
c.66G>A/ p.W22*/
c.143A>G /p.Y48C

rhGH treatment with
11.4 cm/y response

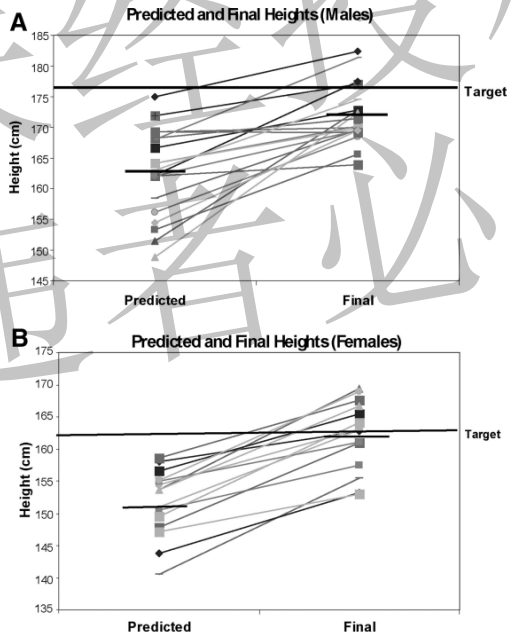


FIG. 1. A, Male final heights exceed baseline predicted heights ($P <$ 0.00001); B, female final heights exceed baseline predicted heights ($P < 0.0000001$).

ORIGINAL ARTICLE
Endocrine Care
J Clin Endocrinol Metab, June 2011, 96(6):1710–1717

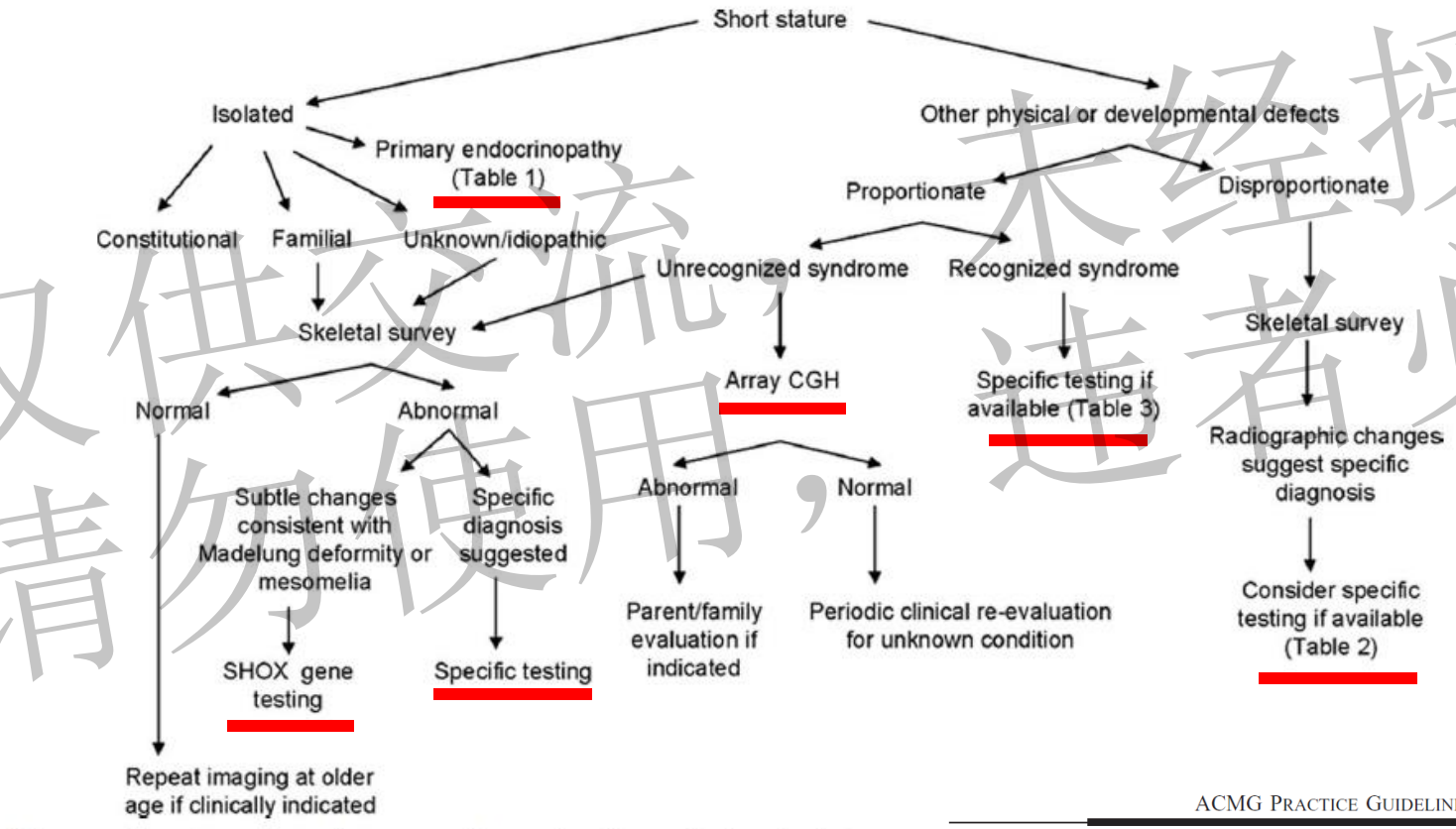
Final Adult Height in Children with Congenital Adrenal Hyperplasia Treated with Growth Hormone

Karen Lin-Su, Madeleine D. Harbison, Oksana Lekarev, Maria G. Vogiatzi, and Maria I. New

重组生长激素治疗反应总结

	ISS (n=13)	GHD (n=15)	total (n=28)
good responder (yearly growth rate>10cm)	4	4	8
intermediate responder (6cm<yearly growth rate<10cm)	8	11	19
non-responder (yearly growth rate<6cm)	1	0	1
mean yearly growth rate	8.98cm	9.13cm	9.06cm
Mean annual growth rate in controls (patients without known causal mutation)	8.75cm	9.03cm	8.89cm

矮小儿童遗传诊断ACMG 指南（2009）



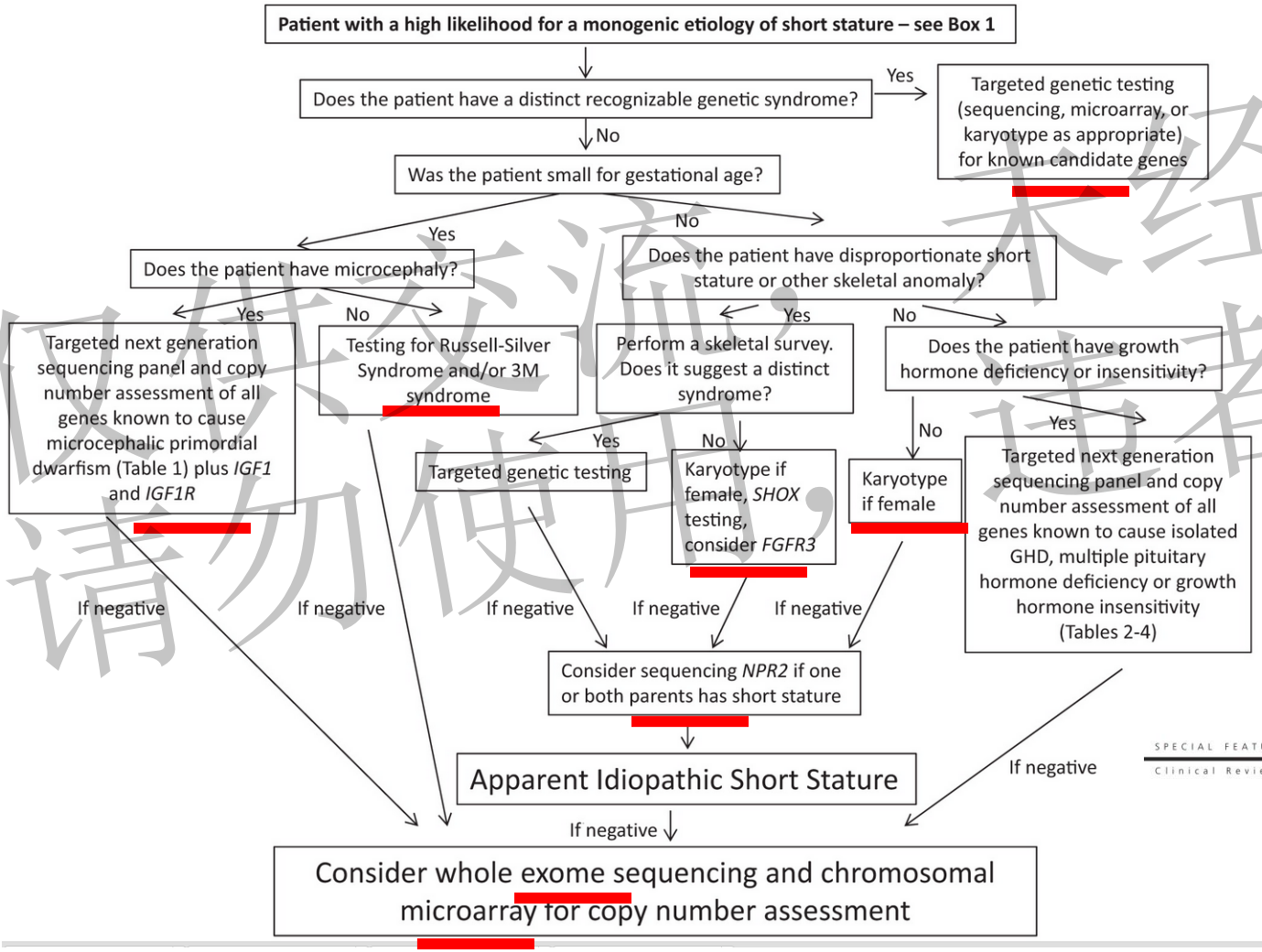
Diagnostic algorithm for genetic evaluation of short stature.

ACMG Practice Guidelines

ACMG practice guideline: Genetic evaluation of short stature

Laurie H. Seaver, MD[1,2], and Mira Irons, MD[3], on behalf of the American College of Medical Genetics (ACMG) Professional Practice and Guidelines Committee

矮小遗传评估更新版（2014）



SPECIAL FEATURE
Clinical Review

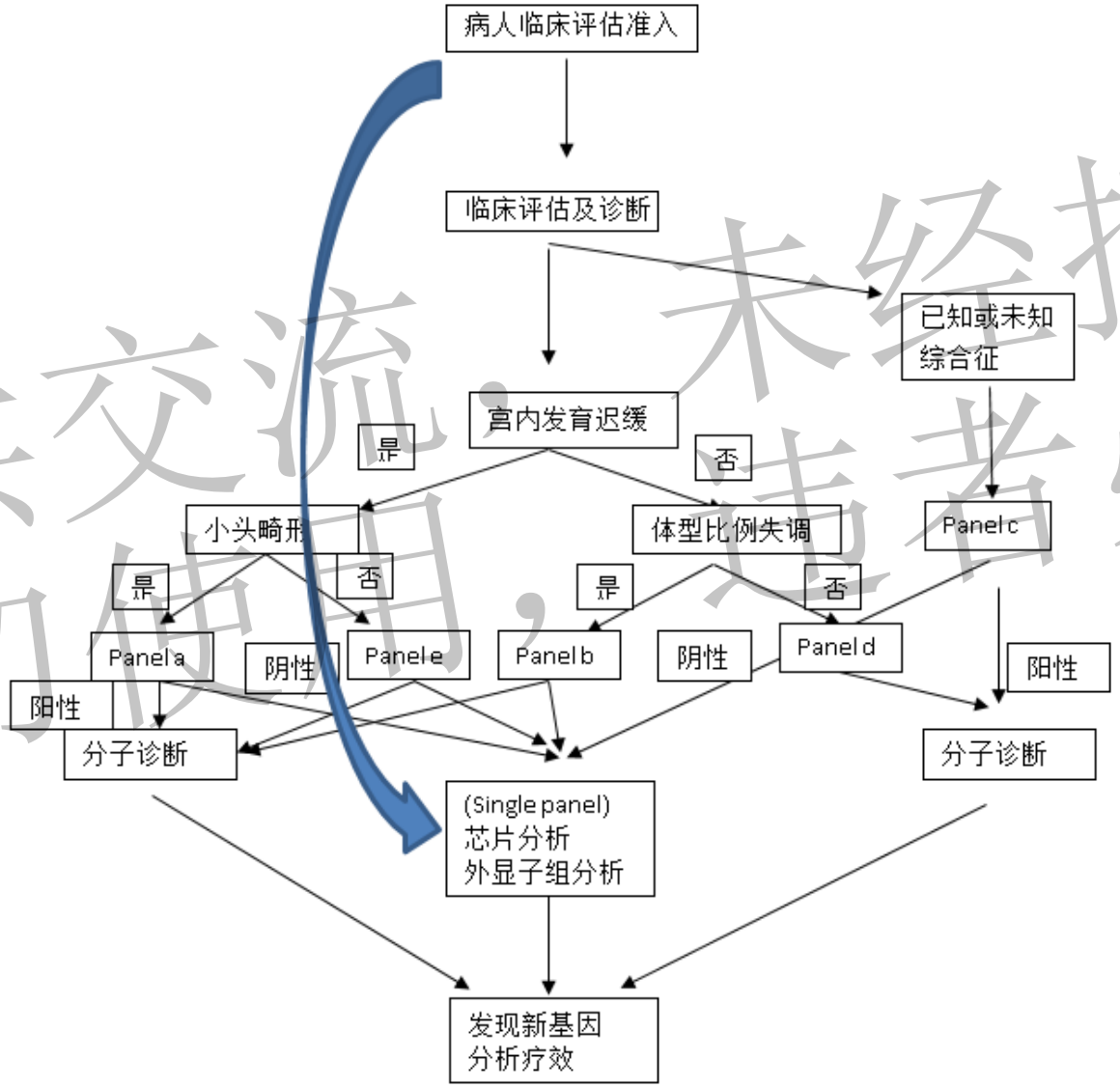
Genetic Evaluation of Short Stature

Andrew Dauber, Ron G. Rosenfeld, and Joel N. Hirschhorn

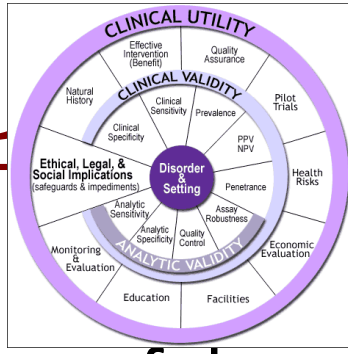
Division of Endocrinology (A.D., J.N.H.), Boston Children's Hospital, Boston, Massachusetts 02115; Broad Institute (A.D., J.N.H.), Cambridge, Massachusetts 02142; Department of Pediatrics (R.G.R.), Oregon Health & Science University, Portland, Oregon 97239; Division of Genetics (J.N.H.), Boston Children's Hospital, Boston, Massachusetts 02115; and Departments of Genetics and Pediatrics (J.N.H.), Harvard Medical School, Boston, Massachusetts 02115

J Clin Endocrinol Metab.
2014 Sep;99(9):3080-92.

新的分子诊断策略



儿童矮小症临床遗传诊断



- New molecular diagnostic tools are very powerful 新的分子诊断技术很给力
  - Analytical validity 检测的技术有效性
- Clinical validity of the test 检测的临床有效性
  - Clinical sensitivity 在多大程度上解决诊断问题
  - Clinical specificity 在多大程度上诊断是特异的
- Clinical utility of the test检测的临床功效性
  - Change in clinical practice 在多大程度上改变临床干预治疗方案
  - Change in outcomes 在多大程度上能够改善临床症状
  - Avoiding harm 在多大程度上减轻心理，经济及无效干预的压力，避免有害干预或过度治疗

Clinical significance

结合矮小遗传诊断的转化研究课题

- 遗传诊断流程在中国儿科临床的综合有效性
  - 中国的指南
- 基于特定临床表征开发的新检测项目验证及应用及临床有效性（Validity），临床功效性（Utility)
- 基因变异与疗效的相关性
- 新矮小基因的发现与突变研究

Acknowledgements 致谢

- Referring Health Care Providers and Their Patients
- Genetic Diagnostic Laboratories in BCH, SCMC and GXFY
  - R&D Teams
  - Medical Director Teams
  - Jian Wang, Xiuming Wang, Xuyun Hu, Baohen Gui, Chen Shaoke, Yongguo Yu et al.
- 中国儿童矮小基因分析合作者
- 金赛药业