3-М синдром

Презентацию подготовила
С-ЛД-15-502-2 МИ СВФУ,
Эверстова Ньургуйаана Романовна

Синдром был впервые описан в 1975 г.

***Miller JD, McKusick VA, Malvaux P**, Temtamy S, Salinas C.*

The 3-M syndrome: a heritable low birthweight dwarfism. Birth Defects 1975; XI(5):39-47.

- LE MERRER SYNDROME
- DOLICHOSPONDYLIC DYSPLASIA
- GLOOMY FACE SYNDROME
- YAKUT SHORT STATURE SYNDROME

Dwarfism with gloomy face: a new syndrome with features of 3-M syndrome

M Le Merrer, R Brauner, P Maroteaux

Abstract
Nine children with primordial dwarfism are described and a new syndrome is delineated. The significant features of this syndrome include facial dysmorphism with gloomy face and very short stature, but no radiological abnormality or hormone deficiency. Mental development is normal. The mode of inheritance seems to be autosomal recessive because of consanguinity in three of the four sibships. Some overlap with the 3-M syndrome is discussed but the autonomy of the gloomy face syndrome seems to be real.

The classification of primary dwarfism is based on certain facial features and body dysmorphism. We have observed a new form of dwarfism associated with intrauterine growth retardation and particuliar dysmorphism without chondrodysplasia or hormone deficiency. Four sibships are described and in three cases the parents are cousins, so autosomal recessive inheritance is likely. We propose that this new syndrome be called dwarfism with gloomy face, because this seems to be the main feature.

ase reports (fig 1)
MILY 1 (FIG 2)
se 1 was born after an uncomplicated pregnancy. weight was 2700 g, height 42 cm, and head ference 37 cm. She was small from birth

té de Recherche INSERM sur les Handicaps es de l'Enfant, Hôpital des Enfants–Malades, de Sèvres, 75743 Paris Cedex 15, France.
Merrer
e d'Endocrinologie Pédiatrique, Hôpital des s–Malades, Paris, France.
uner
584 CNRS, Hôpital des Enfants–Malades, Paris, ce.
laroteaux
rrespondence to Dr Le Merrer.

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onwards. She was first seen when she was 5 years 9 months. Height and weight were more than 3·5 SD below the mean (height 94·5 cm, weight 13·6 kg) but the head circumference was about +1·5 SD. The face was round with full cheeks. The skull was dolichocephalic, with a high and broad forehead. The eyebrows were horizontal and the palpebral fissures were downward slanting. The nasal bridge was flat and the nose short and bulbous with anteverted nares. The philtrum was long and the mouth open with thick lips. The trunk seemed to be short, but the abdomen was large and hypotonic. There was laxity of the joints and a dimple in the clavicular region. The hands and feet were small but proportionate. *X* ray of the skeleton showed no abnormality, the vertebral bodies were normal, and bone age was concordant with chronological age. A skull *x* ray showed a normal sella turcica and dolichocephaly.

This girl had normal mental development, motor milestones were a little delayed, but language was well developed. No hypoglycaemic episode was notified. Endocrine evaluation was normal: T3 45 pg/ml, T4 10·5 pg/ml, TSH 1·3 μU/ml. Growth hormone peak after arginine-insulin stimulation was 37 mg/ml.

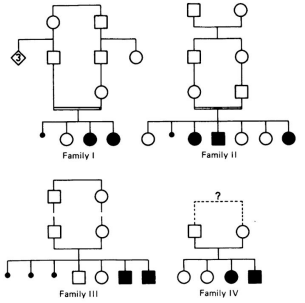


Figure 1 Family pedigrees.

3-М синдром

аутосомно-рецессивное заболевание, сопровождающееся низкорослостью, характеризующееся лицевыми дизморфиями, пре- и постнатальной гипоплазией и рентгенологическими изменениями в костях (утончение длинных трубчатых костей и укорочение в переднезаднем направлении тел позвонков).

273750: THREE M SYNDROME 1; 3M1

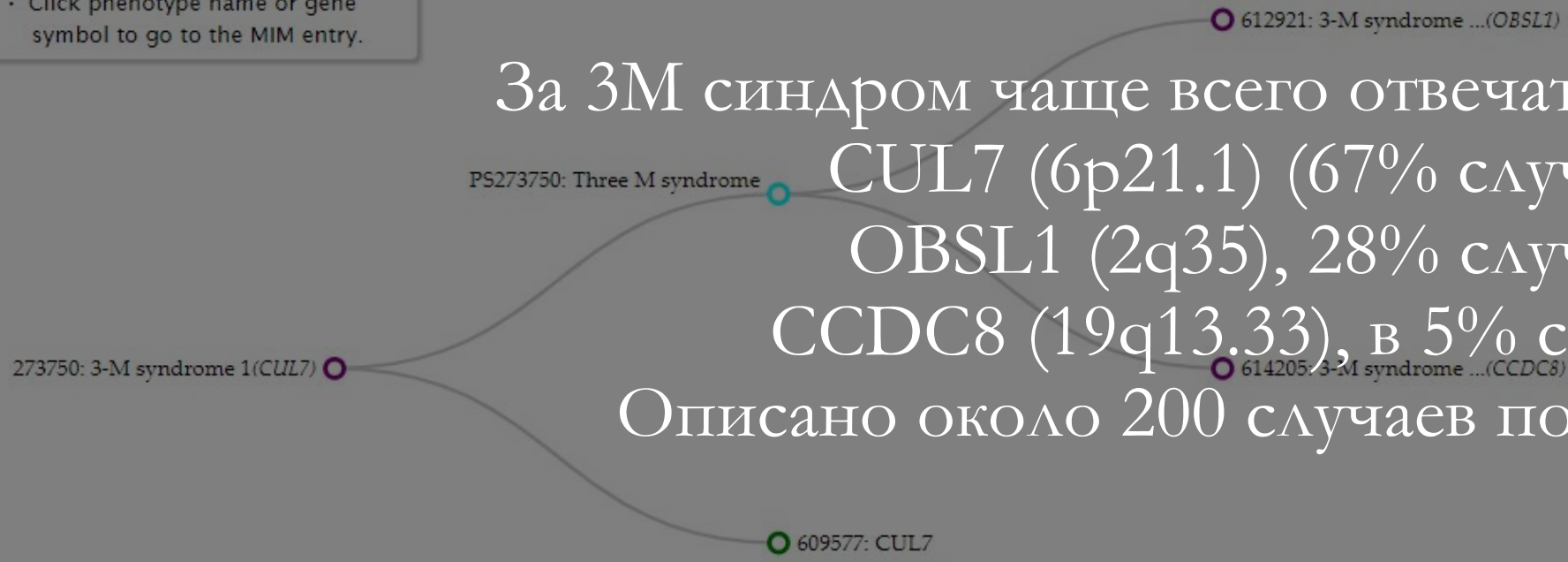
Graphical representation of phenotype/gene relationship(s) associated with this entry. Phenotypic Series (when available) are displayed with the relevant genes and subsequent phenotypes to a de
overview and guide (PDF). **No hierarchy is implied.** Feedback

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
6p21.1	3-M syndrome 1	273750	AR	3	CUL7	609577

Key:
- Phenotype
- Gene
- Phenotypic series (PS)

- Click circles to show/hide downstream relationships.
- Click MIM number or PS number to recenter map.
- Click phenotype name or gene symbol to go to the MIM entry.



За 3М синдром чаще всего отвечат мутации в гене CUL7 (6p21.1) (67% случаев).
OBSL1 (2q35), 28% случаев,
CCDC8 (19q13.33), в 5% случаев.
Описано около 200 случаев по всему миру

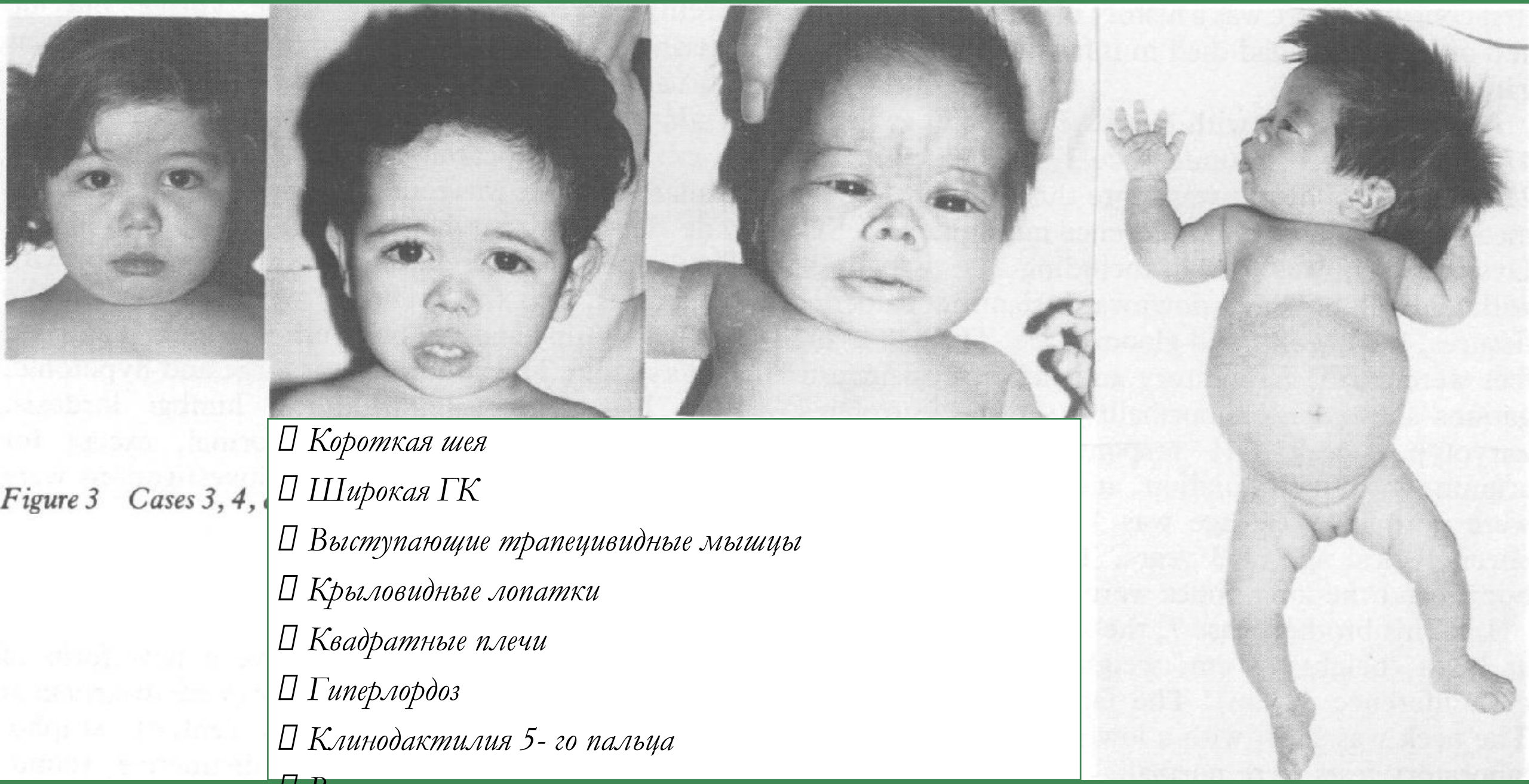


Figure 3 Cases 3, 4,

- *Короткая шея*
- *Широкая ГК*
- *Выступающие трапецивидные мышцы*
- *Крыловидные лопатки*
- *Квадратные плечи*
- *Гиперлордоз*
- *Клинодактилия 5- го пальца*
- *Выступающие мясистые пятки*

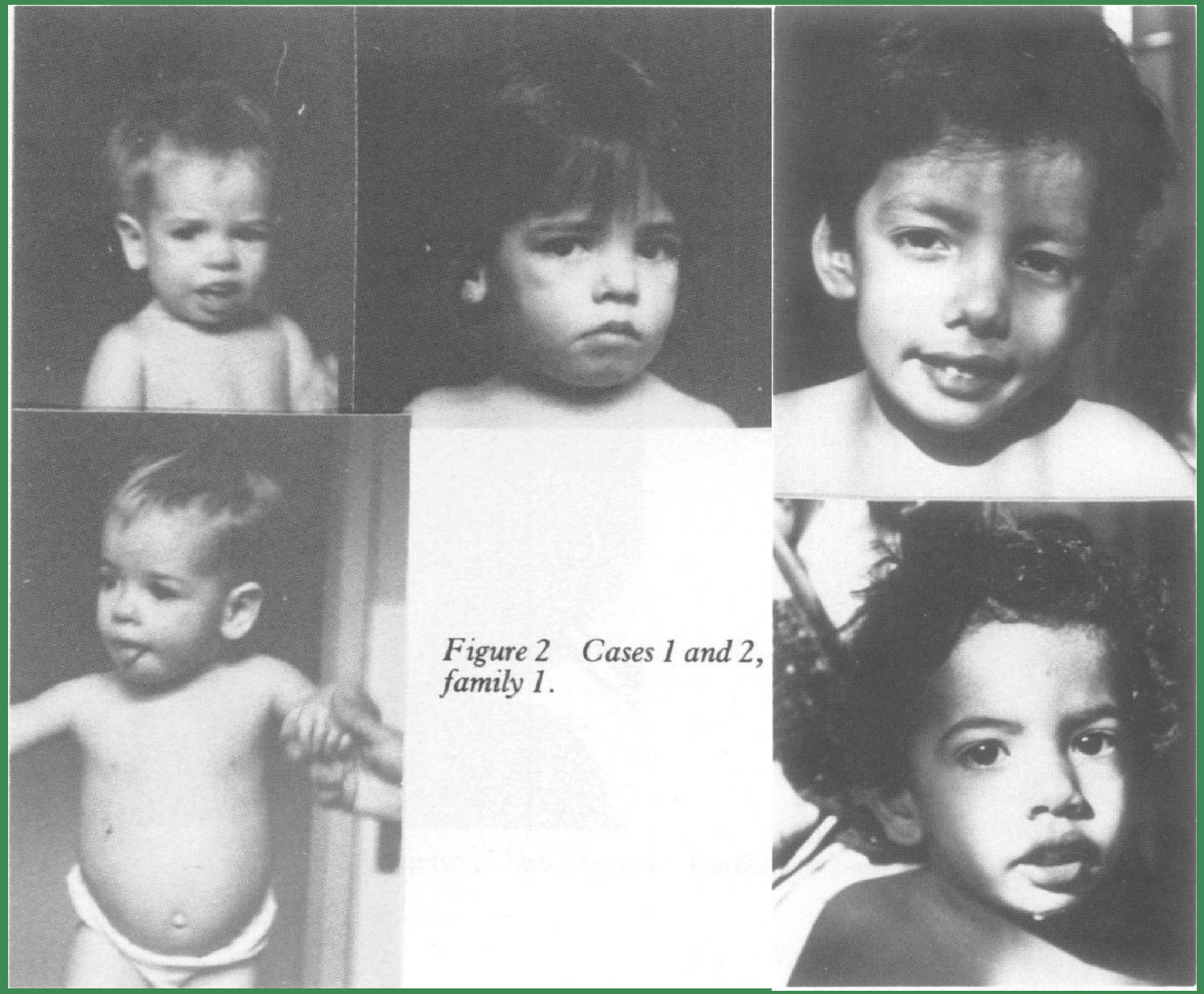
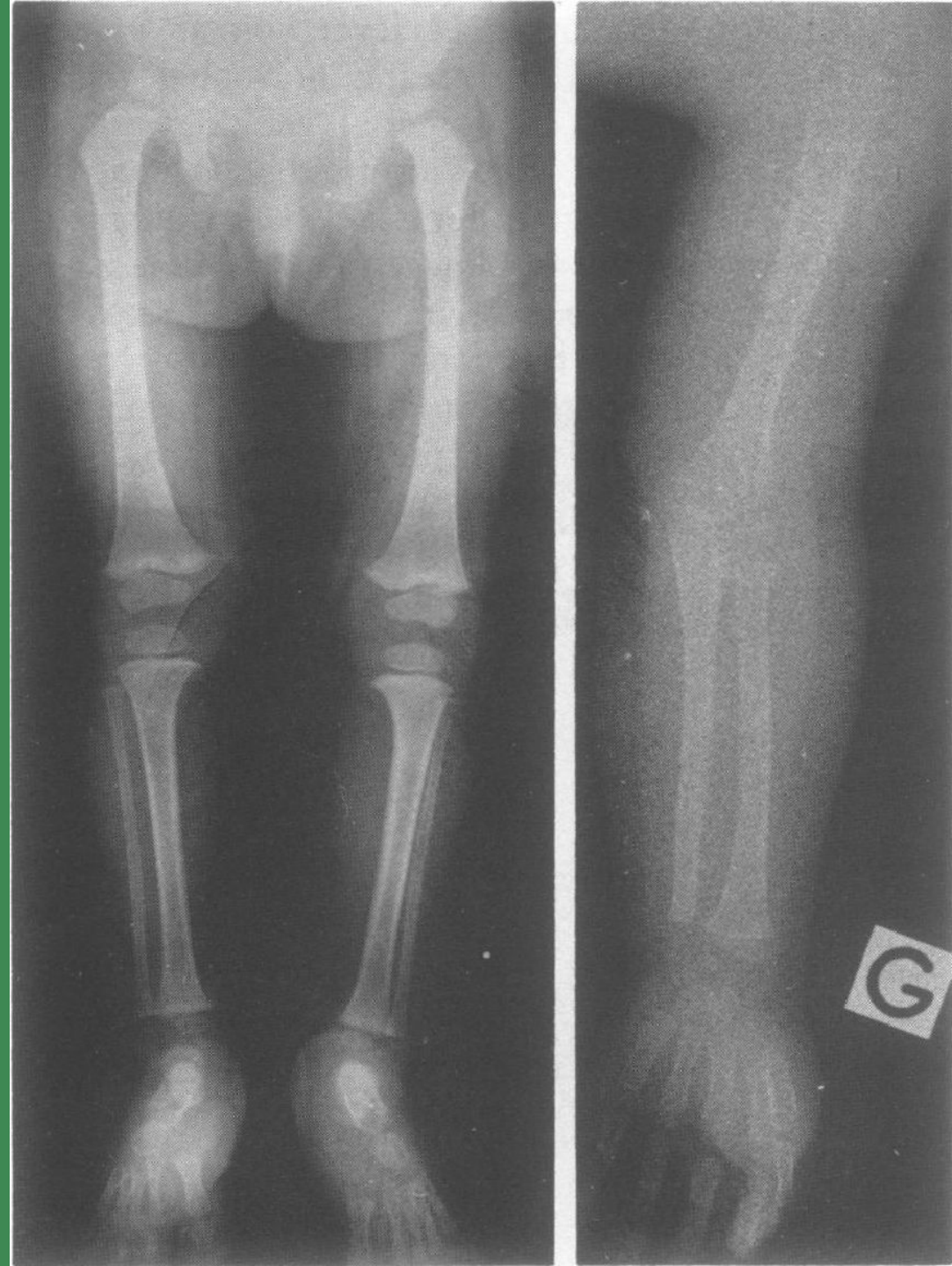


Figure 2 Cases 1 and 2, family 1.

Рентгенография:

- Тонкие / "грацильные" длинные кости
- Относительно высокие позвонки, укорочение позвонков в переднезаднем направлении
- Небольшие тазовые кости
- Широкая ГК с тонкими и горизонтальными ребрами



- Взрослые пациенты вырастают до 120-130 см (5-6 стандартных отклонений ниже среднего значения)
- У мужчин были отмечены некоторые случаи нарушения фертильности и гипоспадия. Женщины имеют нормальную функцию яичников.

TITLE	THREE M SYNDROME 2; 3M2	THREE M SYNDROME 1; 3M1	THREE M SYNDROME 3; 3M3
INHERITANCE (in 3/3)	- Autosomal recessive	- Autosomal recessive	- Autosomal recessive
GROWTH (in 3/3) ▼	*Height* - Short stature	*Height* - Short stature	*Height* - Short stature
	Weight - Low birth weight	*Weight* - Low birth weight	*Weight* - Low birth weight - Low weight
		Other - Intrauterine growth retardation - Postnatal growth retardation	*Other* - Poor growth
HEAD & NECK (in 3/3) ▼	*Head* - Relative macrocephaly - Dolichocephaly	*Head* - Frontal bossing - Increased relative head circumference	*Head* - Dolichocephaly
	Face - Triangular face - Frontal bossing - Midface hypoplasia - Long philtrum - Pointed chin	*Face* - Triangular face - Pointed, prominent chin - Hypoplastic midface - Long philtrum	*Face* - Frontal bossing - Triangular facies - Midface hypoplasia - Pointed chin
	Ears - Prominent ears		*Ears* - Prominent ears
		Eyes - Full eyebrows	
	Nose - Anteverted nares - Fleshy tip of nose - Low nasal bridge	*Nose* - Fleshy, upturned nose - Low nasal bridge - Depressed nasal root - Anteverted nares	*Nose* - Fleshy tipped nose - Anteverted nares
	Mouth - Full fleshy lips - High-arched palate - Median fissured tongue (in some patients) - Partial ankyloglossia (rare) - Bifid tip of tongue (rare)	*Mouth* - Full lips	*Mouth* - Fleshy lips
	Teeth - Delayed eruption - Enamel hypocalcification - Malocclusion		
	Neck - Short neck	*Neck* - Short neck	*Neck* - Short neck

RESPIRATORY (in 1/3) ▼		- Neonatal respiratory distress	
CHEST (in 3/3) ▼	*External Features* - Short thorax - Square shoulders - Pectus deformity - Transverse chest groove	*External Features* - Short, wide, flat thorax - Pectus excavatum	*External Features* - Short thorax - Square shoulders - Transverse chest groove
	Ribs Sternum Clavicles & Scapulae - Thin ribs - Winged scapulae	*Ribs Sternum Clavicles & Scapulae* - High, square shoulders - Rib hypoplasia - Winged scapulae	
ABDOMEN (in 1/3) ▼		*External Features* - Enlarged abdomen	
GENITOURINARY (in 1/3) ▼		*External Genitalia (Male)* - Hypospadias - Small testes	
SKELETAL (in 3/3) ▼	- Delayed bone age (rare)	- Delayed bone age - Joint hypermobility - Joint dislocation	
	Skull - Relative macrocephaly - Dolichocephaly 👤	*Skull* - Dolichocephaly 👤	
	Spine - Hyperlordosis - Tall lumbar vertebrae	*Spine* - Tall vertebral bodies - Hyperlordosis	*Spine* - Hyperlordosis - Tall vertebral bodies
	Pelvis - Small narrow pelvis	*Pelvis* - Hip dislocation - Small pelvis	*Pelvis* - Hip dysplasia
	Limbs - Slender long bones	*Limbs* - Long, slender tubular bones	*Limbs* - Slender long bones
	Hands - Short fifth fingers - Fifth-finger clinodactyly	*Hands* - Short fifth fingers - Clinodactyly 👤	
	Feet - Prominent heels	*Feet* - Prominent heels - Pes planus 👤	*Feet* - Prominent heels
SKIN, NAILS, & HAIR (in 1/3) ▼		*Hair* - Full eyebrows	
NEUROLOGIC (in 1/3) ▼		*Central Nervous System* - Normal intelligence - Spina bifida occulta	
ENDOCRINE FEATURES (in 1/3) ▼		- Decreased male fertility	
MISCELLANEOUS (in 2/3) ▼	- Facial dysmorphism becomes less prominent with age		- Five patients have been reported (as of 8/2011)
MOLECULAR BASIS (in 3/3) ▼	- Caused by mutation in the obscurin-like 1 gene (OBSL1, 610991.0001)	- Caused by mutation in the cullin 7 gene (CUL7, 609577.0001)	- Caused by mutation in the coiled-coil domain-containing protein 8 gene (CCDC8, 614145.0001)

Диагностика

- ✔ Пренатальная диагностика: УЗИ, молекулярно-генетические тесты.
- ✔ Постановка диагноза основана главным образом на клинических проявлениях: низкий вес при рождении, сильная задержка роста, выступающие мясистые пятки и т.д.
- ✔ УЗИ новорожденным (на дисплазию)
- ✔ Рентгенография
- ✔ Молекулярно-генетические тесты

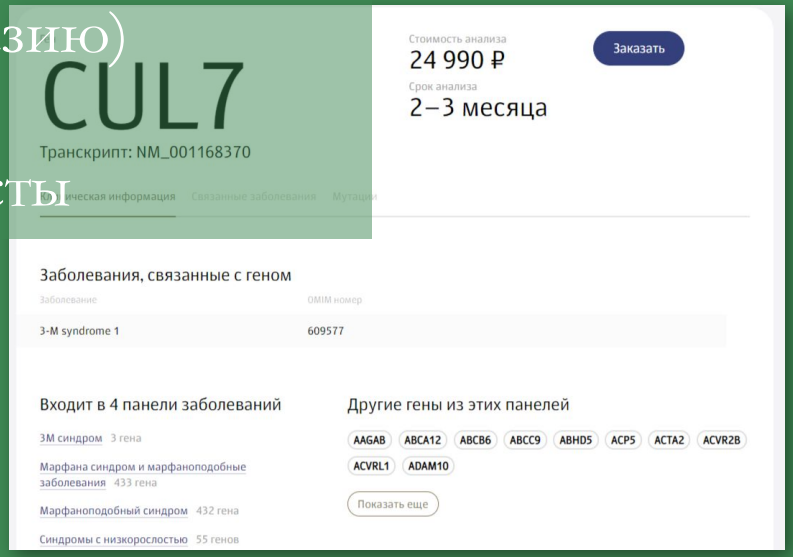


Table 2. Disorders to Consider in the Differential Diagnosis of Three M Syndrome

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/3-M syndrome	Distinguishing from 3-M syndrome
Russell-Silver syndrome (RSS)	See footnote 1	Simplex	IUGR, postnatal growth deficiency	• RSS often shows limb length asymmetry. • Characteristic radiologic features of 3-M are absent.
Dubowitz syndrome (OMIM 223370)	Unknown	AR	IUGR	• Microcephaly • Eczema • Characteristic facial features (small face w/ sloping forehead, broad nasal bridge, shallow supraorbital ridge, broad nasal tip, short palpebral fissures, telecanthus, ptosis, dysplastic ears) • Intellectual disability
Mulibrey nanism (OMIM 253250)	*TRIM37*	AR	IUGR	• IUGR often less severe than in infants w/3-M • Characteristic facial features (high forehead, pseudo-hydrocephalic skull configuration)
Fetal alcohol syndrome	NA	NA	IUGR	• Microcephaly • ↓ subcutaneous fat • Hirsutism • Nail hypoplasia • Characteristic facial features • Intellectual disability

AR = autosomal recessive; IUGR = intrauterine growth restriction; MOI = mode of inheritance

1. Hypomethylation of the paternal imprinting center 1 (IC1) of chromosome 11p15.5 is identified in 35%-50% of individuals with RSS. About 10% of individuals with RSS have maternal uniparental disomy for chromosome 7 (UPD7).

Лечение

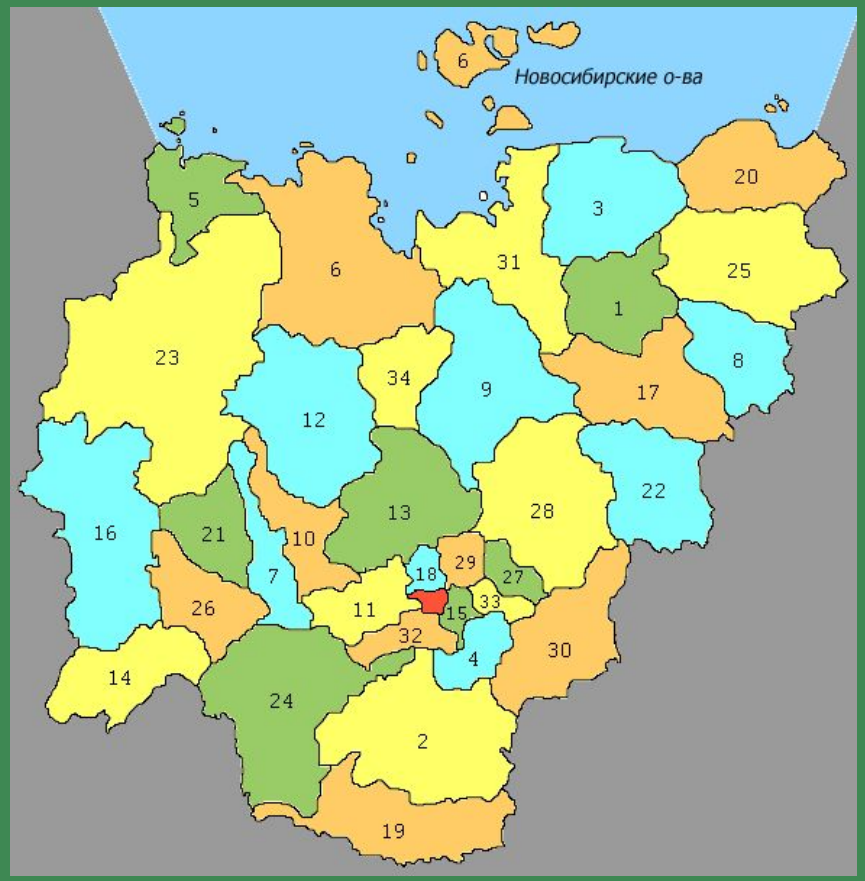
- Постановка на учет у детского эндокринолога (мониторинг роста каждые 6-12 месяцев)
- Контроль титров гормона роста
- Адаптогены, физиотерапия
- Рекомбинантный человеческий гормон роста (r-hGH). Длительность терапии – более 1 года (GH doses of 35-45 microgram/kg/day with monitoring of serum IGF-I levels)
- Higher r-hGH doses (up to 70 microgram/kg/day) have been used in individual cases.

ЯСН

Якутский синдром низкорослости

- ЯСН описан в 2007 г. д.м.н., Н.Р. Максимовой вместе с соавторами.
- Синдром был включен в каталог генов OMIM как альтернативный известному "синдрому 3-М" (OMIM 273750).

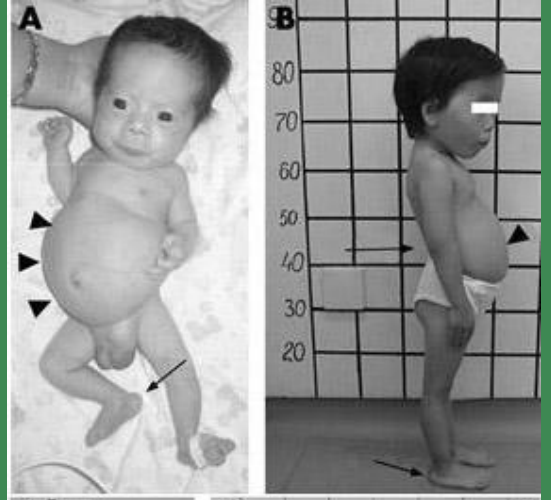
Распространенность

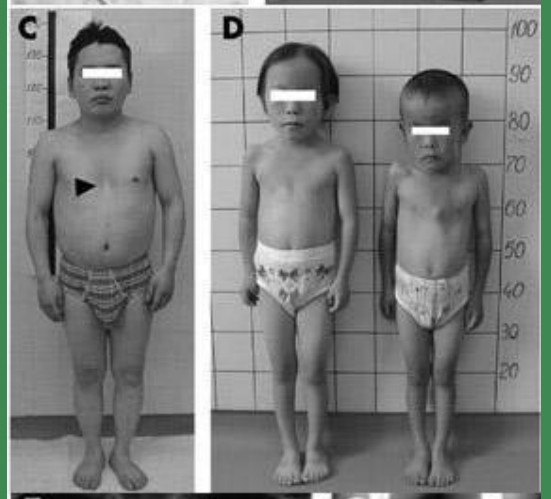


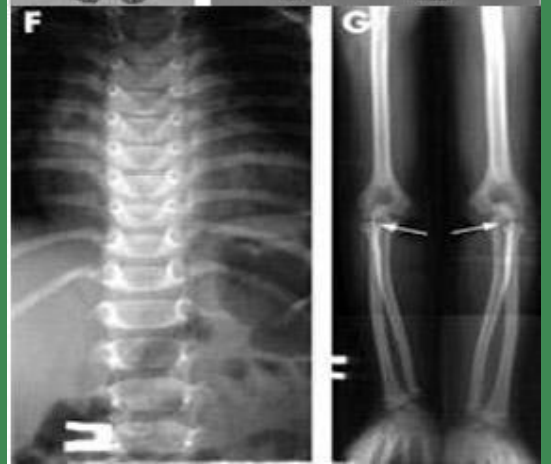
- 1:7800 или 12,72 на 100 тыс. населения, среди детей якутской национальности - 36,7 на 100 тыс. чел.
- Наибольшая частота ЯСН встречается в Ленском - 14, Оленекском - 23, Усть-Майском - 30, Амгинском - 4, Намском - 18, Сунтарском улусах - 26.

Клиническая картина

- ✔ Пренатальная и постнатальная гипоплазия
- ✔ Лицевые дизморфии, гидроцефальная голова
- ✔ Широкая грудная клетка
- ✔ Мышечная гипотония
- ✔ Гиперлордоз
- ✔ Большой живот
- ✔ Брахидактилия
- ✔ Выступающие пятки и нормальный интеллект без эндокринных нарушений
- ✔ Слабая выраженность характерных рентгенологических признаков
- ✔ Дистресс-синдром при рождении (42% - тяжелая асфиксия, 26 % -







A - маленький вес, низкий рост, лицевые дизморфии (гипоплазия средней трети лица, выступающий лоб, запавшее переносье, длинный фильтр), короткая шея, брахидактилия, большой живот, мышечная гипотония, микромелия кистей и стоп, выступающие пятки.

B - девочка 5 лет: поясничный лордоз, гидроцефальная форма головы, деформация грудины, большой живот.

C - мужчина 41 год: короткая шея, короткая и широкая грудина, короткая грудная клетка, пропорциональная низкорослость.

D- сибсы, брат и сестра, у обоих признаки заболевания.

Благодарю за внимание!