Supplementary Table. Causes of tall stature and/or accelerated growth with incidence, prevalence and clinical features, based on the International Classification of Paediatric Endocrine Diagnoses

Primary growth disorders

ICPED code	Diagnosis and pathophysiology	Incidence (*I*) and prevalence (*P*)	Clinical features accompanying tall stature and/or accelerated growth
2A.1	**Syndromes with sex chromosome anomaly**		
2A.1a	**Klinefelter syndrome [1-4]** 47,XXY genotype	*I*: 1-1.5/1,000 [2, 3] *P*: 1/500	behavioural problems or autism spectrum disorder motor and/or speech development disorders late puberty cryptorchidism (prevalence: 0-37%) scoliosis and kyphosis gynaecomastia hypotonia
2A.1b	**47,XYY syndrome [4, 5]**	*I*: 1/1,000 *P*: 1-5/10,000	behavioural problems or autism spectrum disorder motor and/or speech development disorders scoliosis and kyphosis hypotonia
2A.1c	**47,XXX syndrome [5-7]**	*I*: 1/1,000 *P*: 1-5/10,000	behavioural problems or autism spectrum disorder developmental delay motor and/or speech development disorders later menarche hypotonia
2A.1d	**Triple copy *SHOX* gene syndrome [8]**	*I*: 3.7% of girls with tall stature [8]	sitting height/height ratio <-2.0 SDS
2A.1e	**Fragile X syndrome [9-11]** *FMR1* trinucleotide mutation	*I*: boys: 0.94/10,000, girls: 0.23/10,000 *P*: boys: 1/7,000, girls: 1/11,000	behavioural problems or autism spectrum disorder developmental delay family history of intellectual disability facial dysmorphic features

ICPED code	Diagnosis and pathophysiology	Incidence (*I*) and prevalence (*P*)	Clinical features accompanying tall stature and/or accelerated growth
2A.3b.1	**Marfan syndrome [12-14]** *FBN1* mutation	*I*: 23.3/100,000 *P*: 10.2/100,000	scoliosis lens dislocation, retinal detachment "wrist sign", "thumb sign" arachnodactyly pectus excavatum cardiac anomalies
	Marfan-like syndromes		Marfanoid habitus: thin, arachnodactyly, joint hypermobility
2A.3a.1	**Homocystinuria [15]** *CBS* mutation	*I*: 1/157,000	intellectual disability thrombosis subluxation lens
14B.16	**Ehlers-Danlos syndrome, kyphoscoliotic type [16]** *PLOD1* mutation	*I*: 1/100,000	hypotonia skin fragility and hyperextensibility aneurysmata pectus deformities blue sclerae
2A.3c.3	**Lujan-Fryns syndrome [17]** *MED12* mutation	unknown	behavioural problems: instability, hyperactivity and shyness psychotic disorders facial dysmorphic features developmental delay
	Congenital contractural arachnodactyly [18] *FBN2* mutation	unknown	aorta dilatation contractures
	Loeys-Dietz syndrome [17] *TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2 or TGFB3* mutation	unknown	aneurysmata facial and skeletal dysmorphic features
14D.2c	**Multiple endocrine neoplasia (MEN) type IIB [19, 20]** *RET* mutation	*P*: 1/600,000 [19] and 1/4,000,000 [20]	mucosal neuromas higher risk of medullary thyroid carcinoma and phaeochromocytoma

ICPED code	Diagnosis and pathophysiology	Incidence (*I*) and prevalence (*P*)	Clinical features accompanying tall stature and/or accelerated growth
	Syndromes with foetal overgrowth		
2A.3c.9	**Simpson-Golabi-Behmel syndrome [21]** *GPC3* mutation	unknown, ±250 cases in literature	behavioural problems cardiac anomalies facial dysmorphic features higher risk of Wilms tumour, embryonic tumours and hepatocellular carcinoma
2A.3c.11	**Sotos syndrome [22-24]** *NSD1* mutation	*I*: 1/10,000 and 1/50,000 *P*: 1-9/100,000	behavioural problems or autism spectrum disorder intellectual disability hypotonia macrocephaly advanced bone age kidney pathology aortic dilatation cardiac anomalies (prevalence: 8%) Sotos score [25]
2A.3c.13	**Weaver syndrome [26]** *EZH2* mutation	unknown, ± 50 cases in literature	developmental delay macrocephaly facial dysmorphic features advanced bone age higher risk of neuroblastoma
2A.3d.1	**Beckwith-Wiedemann syndrome [27, 28]** epigenetic changes on chromosome 11p15	*I*: 1/137,000 [27] *P*: 1/13,000 [28]	neonatal hypoglycaemia macrosomia macroglossy hemihyperplasia omphalocele renal abnormalities adrenocortical cytomegaly higher risk of Wilms tumour and embryonic tumours
14D.5	**Phosphatase and tensin homolog hamartoma tumour syndrome (PTEN syndrome) [29, 30]** *PTEN* mutation	unknown	developmental delay macrocephaly hamartomas and colon polyps benign thyroid pathology higher risk of breast and thyroid carcinoma

Secondary growth disorders

ICPED code	Diagnosis and pathophysiology	Incidence (*I*) and prevalence (*P*)	Clinical features accompanying tall stature and/or accelerated growth
2B.1	**Overgrowth associated with increased hormone secretion or action**		
2B.1a	**Growth hormone excess [31]** pituitary adenoma, GHRH overproduction, McCune-Albright syndrome, MEN1	unknown, ±100 cases in literature	symptoms of intracranial tumour: headaches, visual symptoms, elevated intracranial pressure hypertension
2B.1e	**Hyperthyroidism [32, 33]**	*I*: 0.9/100,000 <15 years *P*: 1/5,000	heat intolerance and sweating goitre weight loss palpitations
2B.1f	**Sex steroid excess**		secondary sex characteristics sooner than expected advanced skeletal age
3A	**Central precocious puberty [32, 34]** pituitary of hypothalamic activation of sex steroid production	*I*: boys: <5/10,000 girls: 20/10,000	
2B.1f.1/2	**Peripheral precocious puberty [32]** adrenal or gonadal activation of sex steroid production		
2B.1f.1	**Congenital adrenal hyperplasia [35]** defect in steroid synthesis	*I*: 1/5,000 to 1/15,000 *P*: 1/10,000	ambiguous genitalia advanced bone age premature pubarche

ICPED code	Diagnosis and pathophysiology	Incidence (*I*) and prevalence (*P*)	Clinical features accompanying tall stature and/or accelerated growth
2B.2	**Overgrowth associated with decreased hormone secretion or action**		
2B.2a	**Familial isolated glucocorticoid deficiency [36]** ACTH-receptor defect caused by a *MC2R, MRAP, NNT or TXNRD2* mutation	*P*: <1/1,000,000	hyperpigmentation of skin and gums hypoglycaemia recurrent infections failure to thrive
2B.2b	**Gonadotropin deficiency**	unknown	primary or secondary amenorrhoea stagnation of puberty micropenis cryptorchidism anosmia
2B.2c	**Oestrogen deficiency** aromatase deficiency or 17-alfa hydroxylase deficiency (46,XX)	unknown	osteoporosis eunuchoid body proportions hyperglycaemia
2B.2d	**Oestrogen receptor dysfunction [37]** *ESR1* mutation	unknown, ±5 cases in literature	osteoporosis eunuchoid body proportions
2B.3a	**Obesity [38, 39]** increased linear growth	*P*: 14% (Netherlands)	advanced bone age
Idiopathic tall stature			
2C.1	**Familial idiopathic tall stature [40]** height SDS > +2.0 and height SDS within target range [41]	80% of idiopathic tall stature	tall parents
2C.2	**Non-familial idiopathic tall stature [40]** height SDS > +2.0 and height SDS outside target range [41]	15% of idiopathic tall stature	parents with normal height
	Constitutional advancement of growth [40, 42]	5% of idiopathic tall stature	typical growth pattern: growth acceleration till 2-4 years advanced bone age relatively early pubertal development relation with obesity

Footnote

We made several adaptations to the ICPED list of diagnoses. For example, we omitted a few diagnoses that are very unlikely to be found in children referred for isolated TS/AG. We furthermore made some changes to the structure of the list of diagnoses. For instance, we grouped MFS together with Marfan-like syndromes. Patients with these conditions display a Marfan-like appearance: tall, thin, arachnodactyly and hyperlaxity. We also grouped syndromes leading to foetal overgrowth. In the ITS section we included constitutional advancement of growth (CAG), characterized by growth acceleration till 2-4 years followed by normalization of the growth rate until puberty, and an advanced bone age, as proposed by Papadimitriou et al. [42].

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