Supplementary data

Title: What every internist-endocrinologist should know about rare genetic syndromes in order to prevent needless diagnostics, missed diagnoses and medical complications: Five years of 'Internal Medicine for Rare Genetic Syndromes'

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Table S1. Clinical manifestations of complex rare genetic disorders seen in our center since 2015

	Endocrine manifestations	**Internal medicine – Other**	**Other disciplines**
Albright hereditary osteodystrophy	• Obesity (42) • Parathyroid hormone resistance (42) • Hypercalcitoninemia (42) • Thyroid-stimulating hormone resistance, unexplained congenital hypothyroidism (42) • Gonadotropin resistance (hypogonadism) (42) • Growth hormone deficiency (42) • Advanced skeletal maturation (42) • Short stature (42)	• Asthma (42) • Sleep apnea (42)	• Carpal tunnel syndrome (43) • Neurological problems, including impaired cognition and intellectual disability (42) • Acrodysostosis (42) • Ectopic ossifications (42) • Cataract (42) • Ear infections (42) • Oral complications (42) • Cryptorchidism (42)
Allan-Herndon-Dudley syndrome	• Dysthyroidism (high free T3, normal to low-normal serum T4, upper-normal TSH) (44) • Short stature (44)	• Pneumopathies (45)	• Hypotonia (44) • Spasticity (45) • Dystonia (45) • Hypomyelination (45) • Brain atrophy (45) • Muscular hypoplasia (44) • Intellectual disability (44) • Seizures (44) • Scoliosis (44) • Ocular abnormalities (44)
Alström syndrome	• Obesity (46) • Diabetes mellitus type II (46) • Growth hormone deficiency(47) • Hypogonadism (46) • Hypothyroidism (46) • Hyperthyroidism (46) • Advanced skeletal maturation (46)	• Hepatic disease (46) • Renal dysfunction (46) • Cardiomyopathy (46) • Hypertriglyceridemia (46) • Pulmonary failure (47)	• Visual problems (46) • Hearing impairment (46) • Mild ataxia (46) • Hypotonia (46) • Poor balance (46) • Seizures (46) • Acanthosis nigricans (47) • Intellectual disability/developmental delay (47) • Scoliosis (47)

			• Alopecia (46)
Angelman syndrome	• Obesity (48) • Osteopenia/osteoporosis (48)	• Gastroesophageal reflux (49) • Constipation (48) • Pneumonia (48)	• Intellectual disability (48) • Epilepsy (48) • Sleep disturbances (48) • Behavioral problems (48) • Visual problems (48) • Scoliosis (48) • Seizures (48)
Axenfeld-Rieger syndrome		• Kidney abnormalities (50) • Heart defects (50)	• Dental abnormalities (51) • Ocular abnormalities, including glaucoma (50) • Abnormal brain development (50) • Hearing loss (50)
Bardet-Biedl syndrome	• Non insulin-dependent diabetes mellitus (52) • Nephrogenic diabetes mellitus (53) • Metabolic syndrome (53) • Hypogonadism (52) • Growth hormone deficiency (54) • Hyperprolactinemia (54) • Structural pituitary abnormalities (54) • Obesity (52) • Subclinical hypothyroidism (53) • Short stature (52)	• Hepatic fibrosis (52) • Hypertension (53) • Hypertriglyceridemia (53) • Hypercholesterolemia (52) • Renal dysfunction (52)	• Intellectual disability (52) • Ocular abnormalities (52) • Ataxia (55) • Spasticity (55) • Congenital heart defects (53,56) • Polydactyly and dystrophic extremities (52)
Bloom syndrome	• Abnormal carbohydrate metabolism (57) • Dyslipidemia (57) • Hypothyroidism (57)	• Malignancies (57) • Diarrhea (57) • Gastroesophageal reflux (57)	• Skin abnormalities (57) • Early motor and speech delays (57)

	• Diabetes mellitus type II (57) • Infertility/subfertility (57) • Short stature (57)	• Vomiting (57) • Immune abnormalities (57)	
Börjeson-Forssman-Lehmann syndrome	• Obesity (58) • Hypopituitarism (58) • Gynaecomastia (58) • Hypogonadism (59) • Short stature (58)		• Intellectual disability (58) • Feeding difficulties (58) • Hypotonia (58) • Polyneuropathy (59) • Epilepsy (58) • Perthes disease (58) • Hearing problems (58) • Scoliosis (58)
CAMK2A variants	• Overgrowth (60) • Growth delay (61)	• Cardiac abnormalities (60) • Gastrointestinal problems (60)	• Intellectual disability (60) • Behavioral problems (60) • Hypotonia (61) • Seizures/convulsions (61) • Visual problems (61) • Cryptorchidism (60)
CHARGE syndrome	• Growth hormone deficiency (62) • Hypogonadotropic hypogonadism (62,63) • Thyroid-stimulating hormone deficiency (62) • ACTH deficiency (62) • Structural pituitary abnormalities (62) • Osteoporosis (64)	• Gastrointestinal problems, including constipation, vomiting, difficulty swallowing and gastroesophageal reflux (65,66) • Cardiovascular malformations (67,68) • Obstructive sleep apnea (69) • Renal abnormalities (68)	• Intellectual disability (67) • Cranial nerve abnormalities (70) • Brain abnormalities (68) • Seizures (71) • Autism spectrum disorder (68) • Ocular abnormalities (71) • Ear abnormalities, including hearing loss (68,72) • Cleft palate (68) • Genital/urinary tract abnormalities (68,73) • Feeding difficulties (65) • Skeletal abnormalities (68)
CHD8 syndrome	• Overgrowth (74)	• Constipation (75)	• Intellectual disability (74) • Autism spectrum disorder/autism traits (74) • Hypotonia (74,76) • Seizures (74) • Scoliosis (74)

			• Clinodactyly (74) • Umbilical hernia (74) • Glabellar hemangioma (74) • Motor delay (76) • Macrocephaly (75) • Sleep disorder (76)
Chromosome 1q21 deletion syndrome	• Hypothyroidism (77) • Short stature (77)	• Gastric ulcers (77) • Cardiac abnormalities (77,78)	• Intellectual disability (77,78) • Impaired motor function (77) • ADHD (77) • Cataracts (78) • Joint laxity (78) • Hypotonia (78) • Epilepsy/seizures (78) • Scoliosis (77) • Autism spectrum disorder (77) • Microcephaly (77) • Tremor (77) • Sensorineural deafness (79) • Genitourinary abnormalities (79) • Brain malformations (79)
Chromosome 1q25-32 deletion	• Hypothyroidism (80) • Growth hormone deficiency (80) • Short stature (80)		• Intellectual disability (80,81) • Microcephaly (80) • Genital abnormalities (80)
Chromosome 16p11.2 deletion syndrome	• Obesity (82,83) • Hyperinsulinemic hypoglycaemia (82)	• Possibly increased risk of severe combined immunodeficiency (84)	• Intellectual disability (83) • Motor/developmental delay (83) • Language disorder (82) • Autism spectrum disorder (82,83) • Psychological problems (83) • Epilepsy/seizures (82,83) • Structural abnormalities of the central nervous system (82) • ADHD (83)
Chromosome 16p13.11 deletion syndrome		• Constipation (85)	• Developmental delay (86) • Motor delay (86) • Abnormal behavior (86) • Hypotonia (86)

			• Hearing loss (86) • Microcephaly (86) • Epilepsy (87) • Schizophrenia (85)
Cockayne syndrome	• Hypogonadism (88) • Abnormal glucose metabolism (89) • Growth failure (89) • Hypothyroidism (89)	• Hypertension (89) • Dilated cardiomyopathy (90) • Aortic dilatation (91) • Gastroesophageal reflux (89) • Hepatic dysfunction (89) • Splenomegaly (92) • Renal problems (89) • Respiratory infections (89) • Restrictive lung disease (89) • Asthma (89)	• Intellectual disability (92) • Motor problems (88) • Microcephaly (89) • Ataxia (88) • Intracranial calcification (88) • Dermatologic abnormalities (89) • Sensorineural deafness (89) • Seizures (89) • Tremor (89) • Feeding difficulties (89) • Poor peripheral circulation (89) • Visual problems (90) • Scoliosis (92) • Muscle atrophy (92) • Decreased production of sweat (88)
Congenital adrenal hyperplasia	• Inadequate aldosterone production (93) • Impaired cortisol synthesis (93) • Insulin resistance (94) • Diabetes mellitus type II (94) • Decreased fertility (93)	• Salt wasting (93) • Failure to thrive (93) • Hypovolemia/shock (93) • Hypertension (94) • Increased carotid intima thickness (94) • Hyperlipidemia (94)	• Abnormal development of external genitalia (93) • Psychosocial problems (93)
Cornelia de Lange syndrome	• Hypogonadism (95) • Growth failure (95) • Obesity (96)	• Gastroesophageal reflux (96) • Constipation (96) • Renal dysfunction (95) • Aspiration (95) • Congenital heart defects (95) • Antibody deficiency (95)	• Intellectual disability (95) • Epilepsy / seizures (95,96) • Temperature intolerance (95) • Decreased pain sensation (95) • Behavioral problems (self-destructive) (95) • Autistic-like behavior (95) • Sleep disturbances (97) • Hearing problems (98) • Cleft palate (95)

			• Urinary tract abnormalities (96) • Dental problems (95) • Hypertrichosis (95) • Limb abnormalities (95) • Visual problems (95) • Abnormalities of the external genitalia (95) • Feeding problems (99)
Costello (like) syndrome	• Growth hormone deficiency (100) • Hypothyroidism (100) • Delayed or dysregulated puberty (100) • Hyperprolactinemia (101) • Parathyroid adenoma (101) • Hyperinsulinemic hypoglycemia (100)	• Increased risk of malignancy (100) • Cardiac problems (100) • Obstructive sleep apnea • Respiratory problems (100) • Pyloric stenosis (100) • Gastroesophageal reflux (100)	• Intellectual disability (100) • Hypotonia (100) • Neurologic abnormalities (100) • Failure to thrive (100) • Epilepsy (102) • Behavioral/social problems (100) • Dermatologic abnormalities (100) • Musculoskeletal abnormalities (100) • Dental abnormalities (100) • Visual problems (100)
Cri-du-Chat syndrome		• Cardiac abnormalities (103) • Renal abnormalities (103)	• Severe psychomotor retardation, including intellectual disability (104) • Microcephaly (104) • Renal abnormalities (103) • Behavioral problems (self-injurious behavior) (105) • Autism spectrum disorder (106) • Scoliosis (105) • Hypotonia (103) • Myopia and cataract (103) • Cryptorchidism (103) • Hypospadias (103)
CTNNB1 syndrome (NEDSDV syndrome)		• Vomiting and constipation (107) • Respiratory infections (107)	• Intellectual disability (108) • Behavioral problems (aggression, automutilation, fecal smearing) (108) • Autistic-like behavior (109) • Microcephaly (109) • Motor delay (109)

			• Visual problems (109) • Distal spasticity/hypertonia (107) • Truncal hypotonia (107) • ADHD (107) • Scoliosis (107) • Hip dysplasia (107)
Dandy-Walker syndrome	• Growth retardation (110) • Fetal growth restriction (111)	• Congenital heart disease (111) • Polycystic kidneys (111)	• Congenital intracranial malformation compromising a spectrum of brain abnormalities (110) • Psychomotor retardation, including intellectual disability (110) • Hypotonia (110) • Scoliosis (110) • Visual problems (110) • Facial clefts (111) • Limb and abdominal wall abnormalities (111) • Diaphragmatic hernia (111) • Ambiguous genitalia (111)
DiGeorge syndrome (22q11.2 deletion)	• Hypocalcemia (112,113) • Hypoparathyroidism (114) • Hypothyroidism (115) • Hyperthyroidism (115) • Growth hormone deficiency (116) • Obesity (115)	• Gastroesophageal reflux (117) • Constipation (117) • Vomiting (117) • Thrombocytopenia (115) • Thymic hypoplasia (115) • Recurrent infections (e.g. pneumonia, otitis media) (115) • Rhabdoid tumor (118) • Cardiac abnormalities (115)	• Intellectual disability (119) • Hemiparesis (115) • Hypotonia (120) • Camptodactyly (121) • Seizures (122) • ADHD (123) • Autistic spectrum disorder (124) • Neuropsychiatric manifestations (124,125) • Sleep disturbances (126) • Visual problems (115) • Hearing problems (115) • Scoliosis (115) • Cleft palate (127) • Urogenital problems (115)
Disorders of Sex Development[a]	• Subfertility/infertility (128) • Cortisol deficiency (128)	• Electrolyte disorders (128) • Hypotension (128)	• Ambiguous genitalia (128)

	• Disturbed androgen synthesis (128) • Failure to thrive (128)	• Renal, adrenal, and lung dysgenesis (only for loss-of-function mutations in WNT4) (129) • Congenital heart disease (especially for loss-of-function mutations in GATA4) (128)	• Campomelic dysplasia (only for loss-of-function mutations in SOX9) (128) • Psychosocial problems (130)
Down syndrome (trisomy 21)	• Hypogonadism (131) • (Subclinical) hypothyroidism (132) • Increased risk of type I diabetes (132) • Osteopenia (133) • Osteoporosis (133) • Overweight/obesity (133) • Short stature (132)	• Overall risk for autoimmune diseases (132) • Sleep apnea (133) • Congenital heart disease (134) • Gastrointestinal problems (133)	• Intellectual disability (135) • Hearing impairment (133) • Attentional impairment (136) • Early onset of Alzheimer disease (135) • Visual problems (133) • Behavioral and psychological problems (133) • Seizures (133)
Hypogonadotropic hypogonadism with anosmia (Kallmann syndrome)	• Hypogonadotropic hypogonadism (137) • Advanced skeletal maturation (137) • Obesity (138) • Short stature (137)	• Renal agenesis (137)	• Hyposmia/anosmia (139) • Cleft palate (137) • Hearing impairment (137) • Visual problems (138) • Psychological problems (137) • Low muscle mass (137) • Agenesis of corpus callosum (138)
Hypogonadotropic hypogonadism without anosmia (Kiss1R mutation)	• Hypogonadotropic hypogonadism (140) • Growth hormone deficiency (141) • Impaired cortisol secretion (141)		
Jacobsen syndrome (11q terminal deletion syndrome)	• Growth hormone deficiency (142) • Hypothyroidism (142) • Growth retardation (143)	• Constipation (143) • Abnormal platelet function, thrombocytopenia or pancytopenia (143) • Deficit of cellular or humoral immunity with low IgM and IgA (144,145) • Increased risk of malignancy (143)	• Intellectual disability (143) • Behavioral problems (143) • Genital, central nervous system and skeletal malformations (143)

		• Cardiovascular, renal, and gastrointestinal tract malformations (143)	
Joubert syndrome	• Central diabetes insipidus (146) • Diabetes mellitus type 1 (146) • Pubertas praecox (146) • Hypothyroidism (146) • Growth hormone deficiency (146) • Panhypopituitarism (146)	• Hypertension (147) • Kidney disease (147) • Alternating tachypnea and/or apnea (148) • Elevated transaminases and gamma-glutamyl transferase (146) • Gastrointestinal complications (146) • Congenital heart disease (146)	• Intellectual disability (148) • Hypotonia (148) • Brain abnormalities (146) • Ataxia (146) • Visual problems (146) • Scoliosis (146)
JS-X syndrome			• Conductive and sensorineural hearing loss (149) • Underdeveloped shoulder musculature (149) • Outer and middle ear deformity (149) • Laryngeal obstruction (149)
Kabuki syndrome	• Growth hormone deficiency (150) • Obesity (151) • Hypothyroidism (151) • Hypoglycemia (150) • Delayed sexual development (150) • Pubertas praecox (150) • Diabetes insipidus (150)	• Gastroesophageal reflux (152) • Immune dysfunction (150) • Congenital heart defects (150) • Gastrointestinal malformations (150) • Renal abnormalities (150) • Malignancies (150)	• Intellectual disability (150) • Autism-spectrum disorder (150) • Ocular abnormalities (152) • Hearing deficit (150) • Joint hypermobility (153) • Hypotonia (150) • Seizures (150) • Scoliosis (154) • Genitourinary abnormalities (150) • Feeding problems (150) • Microcephaly (150)

KAT6A syndrome		• Cardiac abnormalities (155) • Gastrointestinal complications, including reflux and constipation (155) • Infections (155)	• Intellectual disability (155) • Developmental delay (155) • Microcephaly (155) • Visual problems (155) • Behavioral problems (155) • Sleep problems (155) • Hypotonia (156) • Cryptorchidism (156) • Syndactyly (156)
Klinefelter syndrome	• Diabetes mellitus type II (157) • Obesity (158) • Hypogonadism (159) • Osteoporosis (159) • Gynaecomastia (160) • Insulin resistance (157) • Metabolic syndrome (157) • Dyslipidemia (161) • Short stature (160)	• Liver adenoma (162) • Increased risk of male breast cancer (163) • Cardiovascular problems (161)	• Genital abnormalities (160) • Neurocognitive disorders (160) • Psychosocial problems (160)
L1CAM mutation	• Growth hormone deficiency (164)	• Hirschsprung disease (165) • Dysphagia (164) • Constipation (164) • Cardiac malformations (164,166)	• Hydrocephalus (165) • Intellectuality disability (165) • Motor delay (166) • Spasticity of the legs (165) • Corpus callosum hypogenesis/agenesis (165) • Arthrogryposis (164) • Scoliosis (164)
Myhre syndrome	• Abnormal onset of puberty (167) • Advanced skeletal maturation (167) • Short stature (168)	• Hypertension (167)	• Intellectual disability (168) • Behavioral problems (169) • Deafness (169) • Restrictive joint movement (168) • Thick calvarium (168)

Neurofibromatosis type 1	• Increased risk of pheochromocytoma (170) • Growth hormone deficiency (170) • Osteopenia/osteoporosis (170) • Central precocious puberty[b] (171) • Obesity[b] (171) • Impaired glucose intolerance[b] (171) • Growth hormone excess[b] (171) • ACTH deficiency[b] (171) • Hypogonadotropic hypogonadism[b] (171) • Thyrotropin deficiency[b] (171) • Hyperparathyroidism (172)	• Hypertension (173) • Hypovitaminosis D (174) • Increased risk of malignancy (170) • Vasculopathy (170)	• Visual problems (175) • ADHD (176) • Autistic-like behavior (170) • Behavioral and learning problems (170) • Psychosocial problems (170,177) • Depression (177) • Plexiform neurofibromas (170) • Sleep disturbances (178) • Increased risk of stroke (179) • Scoliosis (170) • Dermatologic problems (170) • Brain tumors (170)
Noonan syndrome	• Male gonadal dysfunction (180) • Hypothyroidism (180) • Short stature (180)	• Thrombocytopenia (181) • Leukemia (182) • Congenital heart defects (180) • Renal abnormalities (180)	• Intellectual disability (180) • ADHD (181) • Ocular abnormalities (181) • Hearing loss (181) • Pectus excavatum or carinatum (181) • Scoliosis (181) • Feeding difficulties (181) • Urinary tract abnormalities (182) • Lymphedema (181) • Dental problems (181) • Genital abnormalities (181)
PNPLA6 gene mutation	• Anterior hypopituitarism (growth hormone, thyroid hormone, or gonadotropin deficiencies) (183) • Short stature (183)		• Cerebellar ataxia (183) • Spasticity (183) • Visual problems (183) • Peripheral neuropathy (183) • Hair abnormalities (183) • Impaired cognitive functioning (183)
PTEN hamartoma tumor syndrome	• Goiter of thyroid (184) • Obesity (185) • Increased insulin sensitivity (185)	• Hamartomatous tumors (184) • Increased risk of malignancies (184) • Vascular malformations (186)	• Macrocephaly (184) • Developmental delay, including intellectual disability (184) • Myopathy (184) • Joint hyperextensibility (184) • Pectus excavatum (184)

			• Scoliosis (184) • Autism spectrum disorder (184) • Genitourinary malformations (186) • Dermatologic problems (186)
Prader-Willi (like) syndrome	• Obesity (187) • Growth hormone deficiency (187) • Hypogonadism (18,187) • Hypothyroidism (18,188) • Diabetes mellitus type II (18,187) • Central adrenal insufficiency (22) • Hypothalamic dysfunction (187) • Osteoporosis (187) • Short stature (187)	• Hypercholesterolemia (18,189) • Hypertension (18) • Hypovitaminosis D (18,190) • Peripheral edema (191) • Constipation (192) • Sleep apnea (18)	• Intellectual disability (187) • Sleep disturbances (187) • Behavioral problems and self-injurious behavior (193) • High pain threshold (187) • Inability to vomit (187) • Ocular abnormalities (187) • Dental problems (194) • Scoliosis (18,187) • Heart failure (195) • Genital abnormalities (187) • Psychiatric problems, such as psychotic illness (196) • Autistic features (187) • Hypotonia (187)
Rett syndrome	• Osteopenia (197)	• Gastroesophageal reflux (197) • Constipation (198) • Gallbladder disease (199) • Hyperventilation (200) • Cardiovascular autonomic dysregulation (200)	• Intellectual disability (197) • Disturbed motor control (197) • Seizures (199) • Parkinsonian features (199) • Dystonia (197) • Hypotonia (198) • Sleep disturbances (198) • Behavioral problems (199) • Autistic features (198) • Psychosocial problems (199) • Scoliosis (201) • Difficulty to swallow (199)
Ring chromosome 21	• Short stature (202)	• Thrombocytopenia (203) • Association with myelodysplasia, leukemia and lymphomas (203) • Immunodeficiency (203)	• Intellectual disability (203) • Motor delay (203) • Hypertonia (203) • Seizures (203) • Microcephaly (203)

		• Cardiomyopathy (202)	
Saethre-Chotzen syndrome	• Short stature (204)	• Renal abnormalities (205) • Congenital heart defects (204) • Obstructive sleep apnea (204)	• Intellectual disability (205) • Hearing loss (206) • Intracranial hypertension (206) • Various skeletal findings (204) • Cleft palate (204) • Strabismus (205)
Say-Barber-Biesecker-Young-Simpson syndrome (KAT6B mutation)	• Thyroid abnormalities/thyroid dysfunction (207,208)	• Congenital heart disease (209)	• Intellectual disability (209) • Hypoplastic teeth (209) • Hearing impairment (209) • Cleft palate (209) • Genital and patellar abnormalities (207) • Feeding difficulties (207) • Dental abnormalities (207) • Visual problems (208)
Sifrim-Hitz-Weiss syndrome	• Hypogonadism (210) • Growth hormone deficiency (211)	• Chronic renal insufficiency (210) • Heart defects (210)	• Developmental delay (210) • Intellectual disability (210) • Macrocephaly (210) • Hypotonia (211) • Brain abnormalities (210) • Hearing loss (210) • Ocular abnormalities (210) • Skeletal and limb abnormalities (210)
Silver-Russell syndrome	• Growth hormone deficiency (104) • Hypoglycemia (104) • Delayed bone age (212) • Short stature (212)	• Gastroesophageal reflux (212) • Constipation (213) • Vomiting (213) • Cardiac defects (104) • Wilms' and other tumors (104)	• Hypotonia (214) • Joint problems (215) • Scoliosis (214) • Urogenital abnormalities (216) • Inguinal hernia (217) • Excess sweating (212) • Developmental delay (212)

Smith-Lemli-Opitz syndrome	• Adrenal insufficiency (218) • Hypo-aldosteronism (219) • Hypothyroidism (218)	• Gastroesophageal reflux (220) • Constipation (218) • Gastro-intestinal motility problems (218) • Hypocholesterolemia (221) • Immune deficiency (218) • Electrolyte abnormalities (218) • Congenital heart defects (218)	• Intellectual disability (218) • Psychiatric problems (222) • Sleep disturbance (222) • Ocular abnormalities (218) • Hearing loss (220) • Congenital dislocation of the hip (223) • Short limbs (218) • Genital abnormalities (218) • Cleft palate (218) • Skeletal problems (218)
Smith-Magenis syndrome	• Obesity (224) • Short stature (104)	• Renal abnormalities (224) • Congenital cardiac defects (104)	• Intellectual disability (224) • Developmental delay (224) • Seizures (224) • Hearing loss (224) • Ocular abnormalities (224) • Cleft palate (224) • Sleep disturbances (224) • Challenging behavior and self-injurious behaviors (224) • Skeletal abnormalities (104) • Decreased pain sensitivity (104)
Sotos-like syndrome	• Overgrowth (225) • Advanced bone age (226)	• Gastroesophageal reflux (226) • Cardiac abnormalities (226) • Increased risk of tumors (226) • Renal abnormalities (227)	• Intellectual disability (225) • Delayed motor development (226) • Hypotonia (228) • Feeding difficulties (226) • Macrocephaly (226) • Scoliosis (226) • Genitourinary abnormalities (226) • Seizures (226)
Tatton-Brown-Rahman syndrome	• Overgrowth (229) • Obesity (230)	• Autonomic dysfunction, including central sleep apnea and orthostatic hypotension (229) • Cardiac defects (229)	• Intellectual disability (229) • Hypotonia (229) • Brain abnormalities (229) • Skeletal abnormalities (229) • Joint hypermobility (229)

		• Gastrointestinal problems (229) • Possibly increased risk of tumors (229)	• Behavioral/psychiatric problems, including autistic spectrum disorder and ADHD (229,230) • Seizures (230)
TBL1X mutation	• Central hypothyroidism (231) • Obesity (231)	• Constipation (232)	• Autistic spectrum disorder (233) • Hearing loss (231) • ADHD (232) • Chiari malformation type I (232)
Tetra X syndrome (48,XXXX)	• Premature ovarian failure (234) • Pituitary hormone deficiencies due to a Rathke's cleft cyst (235) • Osteoporosis (234)	• Hemolytic anemia (236) • Thrombocytopenia (236) • Systemic lupus erythematosus (236,237)	• Intellectual disability (234,238) • Sleep disturbances (hypersomnia) (239) • Alopecia (236) • Skeletal abnormalities (238)
Triple X syndrome (47,XXX)	• Premature ovarian failure (240) • Tall stature (240)	• Abdominal pain (241) • Renal abnormalities (240)	• Hypotonia (240) • Seizures (240) • Genitourinary abnormalities (240) • Cognitive defects and learning disabilities (240) • Various psychological problems (attention deficit; mood disorders) (240)
TRPV4 mutation	• Osteoporosis (242) • Short stature (242)	• Respiratory dysfunction (242)	• Neuromuscular problems (242) • Skeletal dysplasias (242) • Sensorineural hearing loss (242)
Tuberous sclerosis complex	• Increased risk of neuroendocrine tumors (rare) (243)	• Renal abnormalities (243) • Pulmonary problems (243) • Increased risk of tumors (243) • Cardiac lipoma (244) • Gastrointestinal problems (243)	• Epilepsy/seizures (243) • Intellectual disability (243) • TAND (243) • Retinal hamartomas (243) • Dermatological problems (243)

Turner syndrome	• Hypothyroidism (245) • Hyperthyroidism (245) • Hypogonadism (245) • Obesity (245) • Osteopenia or osteoporosis (245) • Glucose intolerance (245) • Diabetes mellitus type II (245) • Infertility/subfertility (245) • Delayed bone age (245) • Short stature (245)	• Hypercholesterolemia (245) • Hypertension (246) • Celiac disease (245) • Elevated hepatic enzymes (245) • Increased risk of auto-immune disease (245) • Inflammatory bowel disease (245) • (Congenital) heart defects (245) • Renal abnormalities (245)	• Psychological problems (anxiety, depression)(245) • Visual problems(245) • Hearing problems(245) • Developmental problems (motoric, cognitive and psychosocial) (245) • Dermatological problems (245) • Dental problems (245) • Lymphedema of hands and feet (245) • Scoliosis (245)
Williams-Beuren syndrome	• Osteopenia/osteoporosis (247) • Hypercalcemia (247) • Hypothyroidism (247) • Obesity (248) • Growth hormone deficiency (249) • Diabetes mellitus (247) • Early onset of puberty (247) • Short stature (247)	• Hypertension (247) • Gastroesophageal reflux (247) • Constipation (247) • Celiac disease (247) • Recurrent otitis media (247) • Cardiovascular disease (247) • Abdominal pain (247) • Diverticular disease (247)	• Intellectual disability (247) • Epilepsy (250) • Sleep dysregulation (247) • ADHD (247) • Ocular abnormalities (247) • Hearing loss (247) • Hypotonia (247) • Scoliosis or lordosis (247) • Joint laxity (247) • Genitourinary problems (247) • Hyperacusis (247) • Increased risk of stroke (247) • Dental problems (247) • Neurological problems (247)
45,X/46,XY mixed gonadal dysgenesis	• Autoimmune thyroid disease (251) • Delayed puberty (251) • Short stature (251)	• Renal malformations (251)	• Atypical genitalia (251) • Intellectual disability (252)
48,XXXY syndrome	• Hypogonadism (253) • Hypothyroidism (253) • Diabetes mellitus type II (253) • Osteoporosis (253) • Tall stature (253)	• Asthma (253) • Allergies (253) • Cardiac abnormalities (253) • Deep vein thrombosis (253) • Constipation (253) • Obstructive sleep apnea (253)	• Intellectual disability (253) • Speech and motor delays (253) • Small testicular size (253) • Tremor (253) • Scoliosis (253) • Seizures (253)

48,XXYY syndrome	• Hypogonadism (254) • Diabetes mellitus type II (255) • Hypothyroidism (255) • Osteoporosis (253) • Tall stature (255)	• Allergies (255) • Asthma (255) • Constipation (255) • Gastroesophageal reflux (255) • Cardiac abnormalities (255) • Deep vein thrombosis (255) • Renal dysplasia (253) • Obstructive sleep apnea (253)	• Intellectual disability (253) • Speech and motor delays (253) • Autism spectrum disorder or deficits in social communication or interaction skills (256) • Psychological problems (255) • Scoliosis (255) • Seizures (255) • Tremors (254) • Cryptorchidism (255) • Brain abnormalities (255) • Tremor (253)

Abbreviations: ACTH, adrenocorticotropic hormone; ADHD, attention deficit hyperactivity disorder; TAND, TSC-associated neuropsychiatric disorders, e.g. autism, anxiety, depression, aggressive behavior, sleep disorders

In reality, some manifestations might have a similar prevalence as in the general population, because of publication bias. Although the literature was thoroughly searched, the overview might be incomplete.

[a] There are many different types of Disorders of Sex Development. Therefore, we advise to check the specific type of disorder in the literature for the specific clinical manifestations. [b] These manifestations are mostly associated with optic pathway gliomas in patients with Neurofibromatosis type 1.