Supplementary Material

Genetic Evaluation of 114 Chinese Short Stature Children in the Next Generation Era: a Single Center Study

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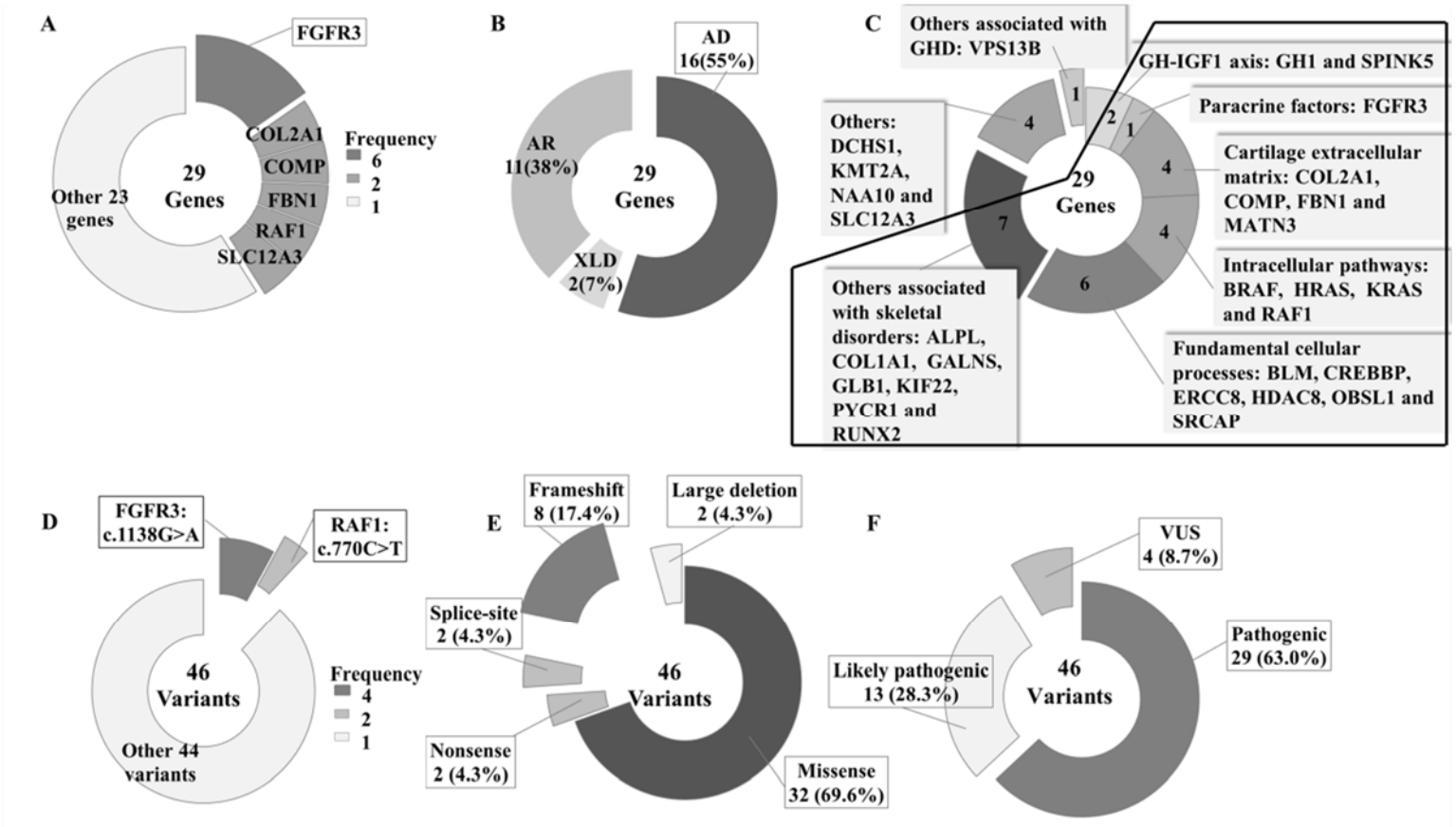
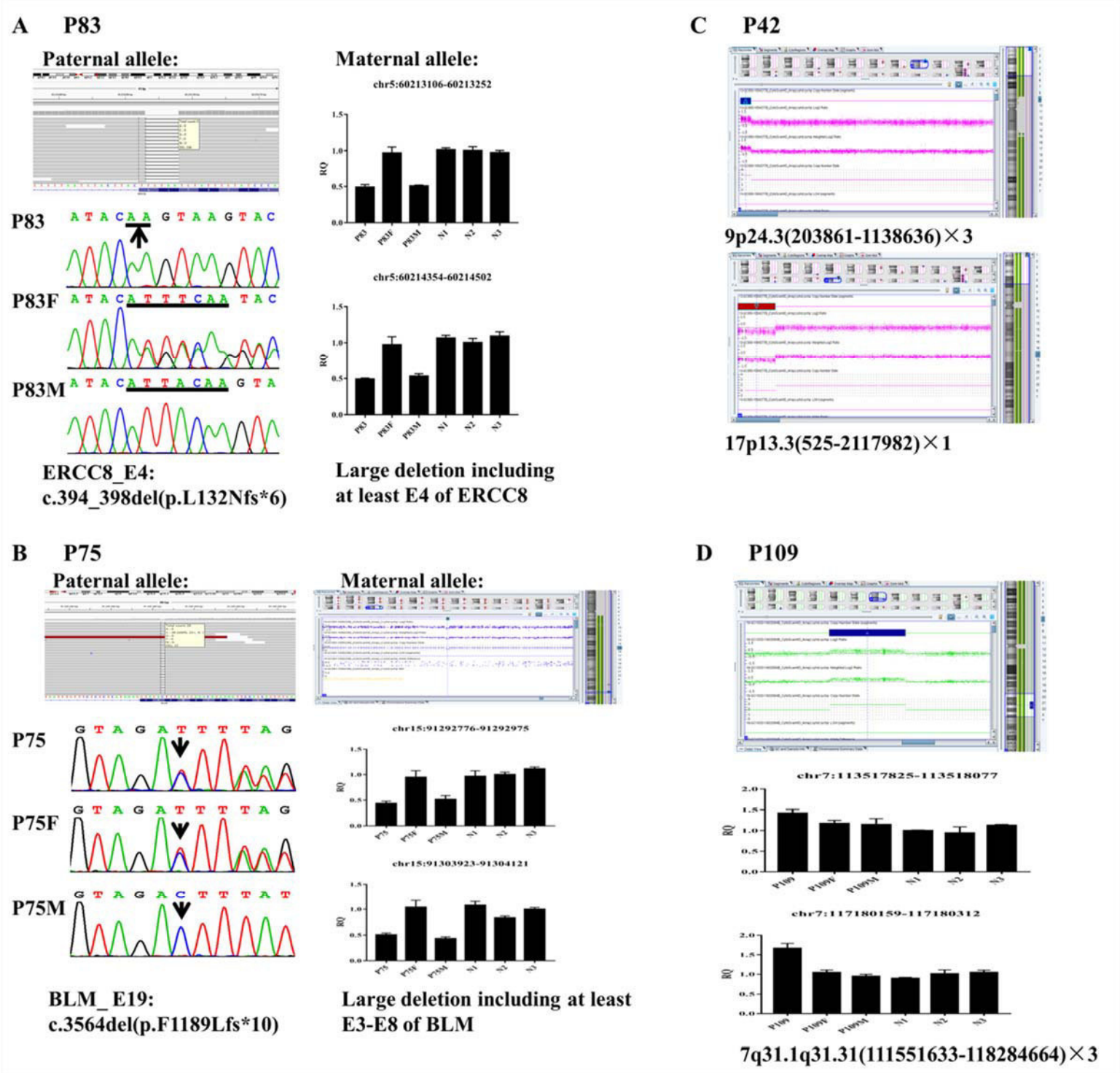


Supplementary Figure 1. Characteristics of the identified 29 genes (A-C) and 46 variants (D-F).

Note: 46 variants included two large deletions (size > 1 kb) involving only one gene.

Abbreviation: VUS, variant of uncertain significance.



Supplementary Figure 2. Visualization and validation for patient P83 (A), P75 (B), P42 (C) and P109 (D).

Note: N1 to 3 were normal controls.

Abbreviation: F, father; M, mother; RQ, relative quantification.

Supplementary Table 1. Detailed clinical and laboratory findings of the 114 enrolled patients

Patients	Gender	Age	HtSDS	WtSDS	Mid-parental height (cm)	Positive family history	Subgroups of short stature	SGA	Microcephaly	Dysmorphic facial features	Skeletal abnormalities	DD/ID	Cardiac anomaly	Other congenital anomalies	Additional clinical features	GHD	Low serum IGF1	Other laboratory finding	BA	Brain MRI	Results of the high-throughput molecular detection techniques	ISS
P1	M	5.8	-3.01	-2.34	163.5	-	Isolated	-	-	-	-	-	-	NA	NA	complete	+	NA	Delayed	N	Unsolved	-
P2	F	4.3	-3.40	NA	NA	-	With more than one additional phenotype	-	+	+ (Grimacing smile; Hypertelorism; Arched eyebrows; High-arched palate; Broad nasal bridge; Prominent nose)	+ (Broad first digits)	+	-	Cleft palate	NA	complete	+	NA	Delayed	Reduction of bilateral periventricular white matter	CREBBP variant	-
P3	M	8.3	-3.87	-1.68	133.25	+ (father and mother)	With one additional phenotype	-	-	-	+ (Genu varum; Metacarpal and carpal anomalies)	-	-	NA	NA	NA	-	NA	Delayed	NA	COMP variant	-
P4	M	1.4	-2.55	-0.51	NA	-	With more than one additional phenotype	-	-	+ (Ptosis)	+ (Polydactyly)	+	-	Cryptorchidism; Micropenis	Hydrocele	NA	NA	NA	NA	NA	Unsolved	+
P5	M	1.1	-3.65	-3.98	NA	-	With more than one additional phenotype	+	-	+ (Prominent forehead; Midface hypoplasia; Wrinkly skin; Prominent ears; Short palpebral fissures; Prominent ears; High-arched palate)	+ (Joint hyperextensibility; Scoliosis)	+	-	Abnormal hearing	NA	NA	NA	NA	NA	Agenesis of the corpus callosum	PYCR1 variants	-
P6	M	9.1	-2.63	-2.13	165	-	Isolated	-	-	-	-	-	-	NA	NA	complete	-	NA	NA	NA	Unsolved	-
P7	M	4.3	-4.49	-3.16	160.5	+ (mother and grandma)	With one additional phenotype	-	-	-	+ (Skeletal anomalies)	-	-	NA	NA	NA	-	NA	NA	NA	Unsolved	+
P8	F	0.8	-3.60	0.12	NA	-	With one additional phenotype	-	-	-	+ (Short limbs)	-	-	NA	Hypotonia	NA	NA	NA	NA	NA	FGFR3 variant	-
P9	M	2.3	-3.25	-3.82	164.5	-	With more than one additional phenotype	+	-	+ (Long face; Low-set ears)	+ (Short second phalanx of the middle and little fingers; Leg length discrepancy)	-	-	Cryptorchidism	NA	-	-	NA	N	Pituitary hypoplasia	Unsolved	-
P10	F	1.2	-3.65	-1.76	NA	-	With more than one additional phenotype	-	-	+ (Ptosis; Downslanting palpebral fissures; Hypertelorism; Depressed nasal bridge; Low-set ears)	-	-	+ (Atrial septal defects; Hypertrophic cardiomyopathy)	NA	NA	NA	NA	NA	NA	N	RAF1 variant	-
P11	F	3.6	-3.67	-2.66	170	-	With more than one additional phenotype	-	+	+ (Long eyelashes; Depressed nasal bridge; Small nasal tip; Low-set ears)	-	+	+ (Atrial septal defects)	Deformed auditory canals; Sensorineural hearing loss	NA	NA	+	NA	NA	NA	Unsolved	NA
P12	M	5.3	-2.92	-2.34	161	-	Isolated	-	-	-	-	-	-	NA	NA	-	-	NA	Delayed	Pituitary hypoplasia	Unsolved	+
P13	M	3.5	-9.74	-5.79	NA	+ (sibling)	With one additional phenotype	-	-	-	-	-	-	NA	NA	NA	NA	Hypokalemic alkalosis	NA	NA	Unsolved	NA
P14	M	4.5	-3.90	-2.49	159.5	-	With more than one additional phenotype	+	-	-	+ (Abnormal ring figures)	-	-	NA	Hypermetropia	-	-	NA	NA	NA	Unsolved	-
P15	M	5.3	-2.97	-1.68	NA	-	With more than one additional phenotype	-	-	-	+ (Leg length discrepancy; Hip dysplasia)	+	-	NA	Epilepsy	NA	NA	NA	NA	NA	Unsolved	+
P16	F	5.3	-3.61	-2.28	171.5	-	With more than one additional phenotype	-	-	+ (Prominent ear; Small teeth)	-	+	-	NA	NA	NA	-	NA	NA	N	SRCAP variant	NA
P17	F	2.8	-3.78	-3.74	NA	-	With more than one additional phenotype	+	-	+ (Synophrys)	-	-	+ (Atrial septal defect)	Cleft lip; Absence of index fingernails; Pyelic separation with	NA	NA	-	NA	NA	NA	Unsolved	-

														malrotation							
P18	F	1.6	-3.58	-3.05	169	-	With more than one additional phenotype	-	+	+ (Almond eye; Short palpebral fissures; Hypertelorism; Depressed nasal bridge; Small mouth; Auricle malformation)	-	+	+ (Atrial septal defects)	Agenesis of external auditory canal; Abnormal hearing; Congenital laryngeal stridor	NA	NA	NA	NA	N	Delayed myelination	Unsolved	NA
P19	M	5.3	-3.86	-2.51	170.5	-	Isolated	-	-	-	-	-	-	NA	NA	complete	+	NA	Delayed	Heteroplasia in saddle area	Unsolved	-
P20	M	4.6	-5.01	-4.30	167.5	-	With more than one additional phenotype	+	+	-	-	-	-	NA	NA	NA	-	NA	Delayed	NA	Unsolved	-
P21	M	8.0	-6.80	-3.25	167	-	With one additional phenotype	-	-	-	+ (Short limbs)	-	-	NA	NA	-	-	NA	Delayed	N	FBN1 variant	-
P22	F	0.8	-3.60	-2.49	167	-	With one additional phenotype	+	-	-	-	-	-	NA	NA	NA	+	NA	NA	Pituitary hypoplasia	Unsolved	-
P23	M	3.2	-2.50	-1.27	NA	-	With more than one additional phenotype	-	-	+	+ (Skeletal anomalies)	+	+ (Pulmonary valve stenosis)	NA	Hydrocele	+	+	NA	NA	N	Unsolved	+
P24	M	2.3	-2.97	-2.37	NA	-	With more than one additional phenotype	-	-	-	-	-	-	Congenital cataract; Congenital intestinal obstruction	NA	NA	NA	NA	NA	NA	Unsolved	NA
P25	M	2.0	-6.12	-2.72	170	-	With more than one additional phenotype	-	+	+ (Coarse face; Bushy eyebrows)	+ (Short limbs; Brachydactyly)	-	-	NA	Thick skin	NA	NA	NA	NA	N	FBN1 variant	-
P26	M	1.8	-3.67	-3.85	160.5	-	With one additional phenotype	-	-	-	-	+	-	NA	NA	NA	+	NA	N	N	Unsolved	NA
P27	M	0.6	-4.03	-3.69	166.5	-	With more than one additional phenotype	+	+	+ (Short palpebral fissures; Hypertelorism; Low-set ears; Microtia; High-arched palate)	+ (Inflexible thumbs)	-	+ (Atrial septal defects)	Congenital Anal atresia	NA	NA	+	NA	NA	Small ventricles	DCHS1 variants	-
P28	M	4.9	-6.49	-4.47	165	+ (sibling)	With more than one additional phenotype	-	+	-	-	-	-	Cryptorchidism	NA	complete	+	NA	Delayed	N	Unsolved	-
P29	M	8.5	-2.77	-1.74	165	-	With one additional phenotype	-	-	-	-	+	-	NA	Hyperactivity	+	+	NA	NA	Asymmetric bilateral ventricles	Unsolved	-
P30	F	3.9	-7.31	-2.92	166.5	-	With more than one additional phenotype	+	-	-	+ (Short limbs; Genu valgum; Pectus carinatum; Rib eversion; Vertebral anomalies; Epiphyseal and metaphyseal dysplasia)	-	-	NA	Hepatomegaly	-	-	NA	NA	NA	COL2A1 variant	-
P31	M	8.8	-2.51	-0.78	153	+ (mother)	With one additional phenotype	-	-	-	+ (Carpal anomalies)	-	-	NA	NA	+	-	NA	Delayed	NA	MATN3 variant	-
P32	F	4.8	-3.52	-2.70	NA	-	With one additional phenotype	-	-	-	-	-	-	NA	Episodic muscle weakness	NA	-	Hypokalemic alkalosis	N	NA	SLC12A3 variants	NA
P33	F	1.5	-4.83	-3.38	NA	-	With more than one additional phenotype	+	+	-	-	+	-	NA	NA	NA	NA	NA	NA	NA	HDAC8 variant	-
P34	F	1.2	-8.59	-6.88	NA	-	With more than one additional phenotype	-	+	-	+ (Kyphosis)	+	+	NA	Lipoatrophy	NA	+	Hypercholesteremia	NA	Delayed myelination and agenesis of the corpus callosum	BRAF variant	+
P35	M	11.3	-3.33	-2.57	159	-	With one additional phenotype	-	-	+ (Ptosis)	-	-	-	NA	Strabismus	-	-	NA	Delayed	NA	KRAS variant	+
P36	F	5.7	-4.08	-2.03	161	-	Isolated	-	-	-	-	-	-	NA	NA	+	+	NA	N	N	Unsolved	-

P37	F	1.8	-2.50	-1.74	161.5	-	With one additional phenotype	-	-	-	+ (Delayed fontanelle closure; Vertebral anomalies)	-	-	NA	NA	NA	+	NA	N	NA	RUNX2 variant	-
P38	F	14.7	-2.50	-1.35	165	-	With more than one additional phenotype	-	-	-	+ (Scoliosis)	+	-	NA	NA	NA	NA	NA	NA	NA	Unsolved	+
P39	M	14.9	-2.91	-1.57	169	-	With more than one additional phenotype	-	-	+ (Ptosis)	-	+	-	NA	Hearing abnormality	NA	NA	NA	NA	Signal abnormalities of bilateral globus pallidus	Unsolved	NA
P40	F	2.6	-3.39	1.68	174.5	-	With more than one additional phenotype	-	-	-	+ (Multiple skeletal dysplasia)	-	-	Megalencephaly	NA	NA	NA	NA	NA	NA	COL2A1 variant	-
P41	F	1.4	-2.53	-1.86	163	-	With more than one additional phenotype	-	+	-	-	+	+ (Atrial septal defect; Mitral regurgitation)	NA	NA	NA	-	NA	NA	Developmental delay of bilateral frontotemporal lobe gyrus	VPS13B variants	NA
P42	M	5.7	-4.90	-3.55	166	-	With more than one additional phenotype	+	-	-	+ (Genu varum)	-	+ (Patent ductus arteriosus)	Cryptorchidism	NA	+	+	NA	Delayed	Pituitary hypoplasia	9p24.3(203861-1138636)×3;17p13.3(525-2117982)×1	-
P43	F	3.7	-5.62	-1.88	168	-	With one additional phenotype	-	-	-	+ (Short limbs; Genu varum; Multiple skeletal dysplasia)	-	-	NA	NA	NA	NA	NA	NA	NA	Unsolved	+
P44	M	0.8	-5.03	-3.06	169.5	-	With more than one additional phenotype	+	-	+ (Prominent forehead; Micrognathia; Low-set ears)	+ (Bulging metaphysis in knee joint; Vertebral anomalies)	+	-	NA	NA	NA	+	NA	N	Delayed myelination	Unsolved	-
P45	F	1.2	-5.76	-3.01	165.5	-	With one additional phenotype	-	-	-	+ (Short limbs; Bulging metaphysis in the distal humerus and femur)	-	-	NA	NA	NA	+	NA	N	N	Unsolved	+
P46	M	6.7	-2.53	1.32	163.5	-	With one additional phenotype	-	-	-	+ (Rib eversion; Wrist joint laxity; Vertebral anomalies; Thin metacarpal cortex)	-	-	NA	Strabismus	+	+	NA	NA	N	GALNS variants	-
P47	F	7.3	-2.82	-1.13	157.5	+ (father and sibling)	Isolated	-	-	-	-	-	-	NA	NA	+	+	NA	NA	N	Unsolved	-
P48	F	3.1	-4.27	-1.40	163	-	With one additional phenotype	-	-	-	-	+	-	NA	Epilepsy	NA	NA	NA	NA	NA	FGFR3 variant	NA
P49	M	5.6	-3.65	-2.39	167.75	-	With one additional phenotype	-	-	-	-	-	-	Cleft palate	NA	+	+	NA	Delayed	N	Unsolved	-
P50	M	8.9	-2.68	-1.06	157	-	With one additional phenotype	-	-	-	-	-	-	NA	Polydipsia; Polyuria	NA	NA	Hypokalemia; Hypomagnesemia	NA	NA	SLC12A3 variants	NA
P51	M	9.2	-3.40	-4.17	157	-	Isolated	-	-	-	-	-	-	NA	NA	complete	-	NA	Delayed	Pituitary hypoplasia	Unsolved	-
P52	M	0.8	-5.44	-4.93	158	+ (mother)	With more than one additional phenotype	+	+	+ (Micrognathia)	-	-	-	NA	NA	NA	+	NA	NA	NA	Unsolved	-
P53	F	1.0	-5.56		165	-	With more than one additional phenotype	+	-	+ (Triangular face; Prominent forehead)	-	-	-	NA	NA	NA	NA	NA	NA	NA	OBSL1 variants	-
P54	M	1.3	-4.07	-2.41	166	-	With one additional phenotype	-	-	-	+ (Short limbs)	-	-	NA	NA	NA	+	NA	NA	NA	Unsolved	+
P55	M	5.3	-4.53	-2.52	159.5	-	With one additional phenotype	-	-	-	-	-	-	NA	NA	complete	+	Other pituitary hormones deficiency	Delayed	Pituitary hypoplasia	Unsolved	-
P56	M	17.3	-3.75	-0.04	165.5	-	With one additional phenotype	-	-	-	-	-	-	NA	NA	complete	+	Other pituitary hormones deficiency	Delayed	No obvious posterior pituitary signal	Unsolved	-
P57	M	9.4	-3.37	-2.22	161	+ (siblings)	With more than one additional phenotype	-	-	-	+ (Kyphosis; Vertebral anomalies)	-	-	NA	NA	-	-	Vitamin D deficiency	Delayed	N	GLB1 variants	-
P58	M	4.0	-2.82	-2.64	163	-	Isolated	-	-	-	-	-	-	NA	NA	complete	-	NA	Delayed	Pituitary	Unsolved	-

																				hypoplasia		
P59	F	0.3	-5.36	-4.72	NA	-	With more than one additional phenotype	+	-	-	-	-	+ (Patent ductus arteriosus; Patent foramen ovale)	NA	NA	NA	+	Anemia; Dysmorphic red blood cells; Leukopenia	NA	N	Unsolved	-
P60	M	0.4	-5.32	-5.42	168.5	-	With more than one additional phenotype	-	+	+ (Triangular face; Mycrotia; Thickened lobes; Posteriorly rotated ears; Broad nasal tip; Anteverted nostrils; Cutis laxa)	-	+	-	NA	Lipoatrophy	NA	+	Glycopenia; Liver dysfunction; High levels of serum adrenocorticotropic hormone, cortisol and testosterone	NA	N	HRAS variant	NA
P61	F	1.5	-3.30	-1.44	159	-	With more than one additional phenotype	-	-	+ (Prominent forehead)	+ (Short limbs)	-	-	NA	NA	complete	-	NA	NA	Pituitary hypoplasia	GH1 variant	+
P62	M	3.6	-3.20	-2.00	156	-	Isolated	-	-	-	-	-	-	NA	NA	NA	+	NA	Delayed	Pituitary hypoplasia	Unsolved	NA
P63	M	4.4	-2.50	-1.94	NA	-	With more than one additional phenotype	-	+	-	-	+	+ (Ventriculap septal defect)	Hearing loss	NA	-	-	NA	Delayed	N	Unsolved	+
P64	M	1.6	-3.05	0.00	169.5	-	With more than one additional phenotype	-	-	-	+ (Short limbs; Genu valgum; Vertebral, metaphyseal and epiphyseal anomalies)	-	-	Megalencephaly; Mongolian spot on buttocks	Strabismus	complete	+	Vitamin D deficiency	N	Asymmetric and a bit large of bilateral lateral ventricles	Unsolved	+
P65	M	2.2	-4.23	-2.17	165.5	+ (grandma)	With one additional phenotype	-	-	-	+ (Genu varum; Spondyloepiphyseal dysplasia)	-	-	NA	NA	NA	NA	NA	NA	NA	COMP variant	-
P66	F	13.0	-2.50	-2.09	NA	-	With one additional phenotype	-	-	-	+ (Genu valgum; metaphyseal and epiphyseal anomalies)	-	-	NA	Neurogenic bladder	NA	-	NA	NA	NA	Unsolved	+
P67	F	9.7	-2.90	-0.31	165	-	Isolated	-	-	-	-	-	-	NA	NA	NA	-	NA	Advanced	N	Unsolved	NA
P68	M	14.8	-3.01	-0.52	170	-	With one additional phenotype	-	-	-	-	-	-	Congenital amblyopia	NA	NA	NA	NA	Advanced	NA	Unsolved	NA
P69	M	3.7	-3.09	-1.35	157	-	Isolated	-	-	-	-	-	-	NA	NA	+	+	NA	Delayed	Pituitary hypoplasia	Unsolved	-
P70	M	5.3	-3.93	-3.19	152.5	+ (father and mother)	Isolated	-	-	-	-	-	-	NA	NA	+	-	NA	Delayed	Uneven anterior pituitary signal and a bit large bilateral ventricles	Unsolved	-
P71	F	0.5	-2.52	-2.19	163	-	With more than one additional phenotype	-	-	-	-	-	+ (Patent ductus arteriosus; Atrial septal defect)	NA	NA	+	+	Glycopenia; Other pituitary hormones deficiency	NA	Pituitary stalk interruption syndrome and hypoglycemic brain injury	Unsolved	-
P72	F	1.1	-3.31	-1.76	169.5	-	With more than one additional phenotype	-	+	-	+ (Short limbs; Vertebral anomalies)	-	-	NA	NA	NA	+	NA	NA	NA	Unsolved	+
P73	F	6.5	-4.11	-1.86	163	-	With one additional phenotype	-	-	-	-	+	-	NA	NA	NA	-	NA	Delayed	N	Unsolved	NA
P74	F	1.0	-4.26	-1.47	167.5	-	With one additional phenotype	-	-	-	+ (Short limbs; Metaphysis enlargement)	-	-	NA	NA	NA	NA	NA	NA	NA	FGFR3 variant	-
P75	F	0.8	-5.60	-5.33	165	-	With more than one additional phenotype	+	+	+ (Triangular face; Micrognathia)	-	+	+ (Mitral regurgitation)	NA	Hyperpigmented skin	-	-	NA	N	N	BLM variants	-
P76	M	0.3	-3.57	-2.04	NA	-	With more than one additional phenotype	-	-	-	+ (Bowing of the legs ; Lack of ossification in proximaltibial epiphysis)	+	-	NA	NA	NA	NA	Decreased serum parathyroid hormone and alkaline phosphatase;	NA	N	ALPL variants	-

																		Hypercalcemia; Hypercphosphate; Elevated serum calcitonin				
P77	F	5.3	-4.20	-1.36	166.5	-	With one additional phenotype	-	-	-	+ (Short limbs; Delayed fontanelle closure; Abnormal distal radius and ulna)	-	-	NA	NA	-	-	NA	Delayed	N	FGFR3 variant	+
P78	F	5.0	-3.52	-0.71	162	-	With one additional phenotype	-	-	-	+ (Short limbs)	-	-	NA	NA	-	-	NA	Delayed	N	Unsolved	+
P79	M	10.1	-2.50	1.06	158.5	+ (mother)	Isolated	-	-	-	-	-	-	NA	NA	NA	NA	NA	Advanced	N	Unsolved	NA
P80	M	1.5	-2.65	-1.10	171.5	-	With more than one additional phenotype	-	+	+ (Ptosis)	+ (Short limbs; Bulging metaphysis)	+	+ (Patent ductus arteriosus; Patent foramen ovale)	Cryptorchidism; Sacrococcygeal fistula	NA	NA	NA	NA	NA	N	KMT2A variant	+
P81	F	9.8	-3.01	-1.13	154	+ (sibling, mother and grandma)	Isolated	-	-	-	-	-	-	NA	NA	complete	+	NA	N	Pituitary hypoplasia	Unsolved	-
P82	M	3.5	-4.51	-4.37	164	-	With one additional phenotype	+	-	-	-	-	-	NA	NA	+	+	NA	Delayed	Pituitary hypoplasia	Unsolved	-
P83	M	3.9	-4.49	-3.72	157.5	-	With one additional phenotype	-	-	-	-	+	-	NA	Hydrocele	+	-	NA	N	Agenesis of the corpus callosum	ERCC8 variants	-
P84	M	1.3	-3.12	-2.46	163.5	-	With more than one additional phenotype	-	-	-	+ (Short upper limbs; Bulging metaphysis in long bones)	+	-	NA	Hypermetropia; Astigmatism	+	+	NA	Delayed	N	Unsolved	+
P85	F	3.3	-5.01	-4.03	163	-	With more than one additional phenotype	-	-	-	-	-	+ (Patent foramen ovale; Mitral and tricuspid regurgitation)	NA	NA	+	+	Glycopenia; Other pituitary hormones deficiency	Delayed	N	Unsolved	-
P86	M	2.9	-2.96	-1.98	NA	-	With more than one additional phenotype	-	-	+ (Deep-set eyes; Blue sclerae; High-arched palate)	+ (Wrist joint hyperextensibility; Strephenopodia; Rib eversion; Pectus excavatum; Genu varum; First lumbar vertebra platyspondyly)	+	-	NA	NA	NA	NA	NA	NA	Cerebral dysplasia	Unsolved	+
P87	F	9.3	-3.74	-1.81	162	-	With more than one additional phenotype	+	-	+ (Blue sclerae; Wide nasal bridge and tip)	-	-	-	NA	Myopia; Suspected glaucoma	+	-	NA	N	N	COL1A1 variant	-
P88	F	4.1	-2.60	-0.48	164	-	Isolated	-	-	-	-	-	-	NA	NA	NA	-	NA	N	NA	Unsolved	NA
P89	M	9.8	-2.66	-0.66	159	+ (mother)	With one additional phenotype	-	-	-	+ (Cleidocranial dysplasia; Thoracic deformity)	-	-	NA	NA	+	-	NA	Delayed	N	Unsolved	+
P90	M	4.7	-4.85	-4.13	161.5	-	With more than one additional phenotype	+	+	+ (Prominent forehead; Micrognathia; Low-set ears; High-arched palate; Overlapped cranial sutures)	+ (Fifth fingers clinodactyly)	-	-	NA	Articulation difficulties; High-pitched voice	-	-	NA	N	Pituitary hypoplasia	Unsolved	-
P91	M	6.9	-3.98	-2.78	156.5	+ (father)	Isolated	-	-	-	-	-	-	NA	NA	+	-	NA	Delayed	N	Unsolved	-
P92	F	1.6	-4.07	-4.05	157.5	+ (grandpa)	With more than one additional phenotype	+	+	-	-	+	-	NA	NA	NA	NA	NA	Delayed	N	Unsolved	-
P93	M	4.8	-4.02	-3.66	157	+ (grandpa)	With one additional phenotype	-	-	+ (Prominent forehead; Deep-set eyes)	-	-	-	NA	NA	-	-	NA	Delayed	N	Unsolved	+
P94	M	4.8	-2.83	-1.67	159	+ (mother)	With one additional phenotype	-	-	-	+ (Pectus excavatum; Rib eversion)	-	-	NA	NA	complete	-	NA	Delayed	N	Unsolved	+

P95	M	4.0	-4.05	-3.20	155	+ (father and siblings)	Isolated	-	-	-	-	-	-	NA	NA	-	+	NA	Delayed	NA	Unsolved	+
P96	M	3.8	-4.09	-3.96	167	-	With more than one additional phenotype	+	+	-	-	+	-	NA	NA	NA	+	NA	NA	Enlarged bilateral ventricles, widened cerebral sulci and cisterna, high signal on the T2-weighted images in bilateral frontal lobes and delayed myelination	Unsolved	-
P97	M	2.7	-2.99	-3.15	167.5	-	Isolated	-	-	-	-	-	-	NA	Strabismus	NA	+	NA	Delayed	NA	Unsolved	NA
P98	F	12.2	-5.57	-2.57	NA	-	With more than one additional phenotype	-	+	+ (Coarse face; Bushy eyebrows; Wide nasal bridge and tip)	+ (Sixth thoracic vertebral anomaly)	+	-	NA	Convulsion	NA	NA	NA	Delayed	NA	NAA10 variant	+
P99	M	4.0	-3.69	-0.93	154.5	+ (father and grandma)	With one additional phenotype	-	-	-	+ (Rib eversion)	-	-	NA	NA	+	-	NA	Delayed	Pituitary hypoplasia	Unsolved	+
P100	M	4.6	-3.73	-2.55	160	-	With one additional phenotype	-	-	-	+ (Pectus excavatum)	-	-	NA	NA	+	-	NA	Delayed	Pituitary hypoplasia	Unsolved	+
P101	M	6.3	-4.10	-2.94	165.5	+ (sibling)(parents are consanguineous)	With one additional phenotype	-	-	-	-	-	-	Ichthyosis	NA	NA	NA	NA	NA	NA	SPINK5 variants	NA
P102	M	12.5	-3.71	-1.21	169	+ (cousin)	With one additional phenotype	-	-	-	+ (Polydactyly)	-	-	NA	Myopia; Anaphylactoid purpura	-	-	NA	N	NA	Unsolved	+
P103	M	5.0	-3.33	-2.98	156.5	-	With more than one additional phenotype	-	-	-	+ (Coarse epiphysis)	-	-	Congenital corneal endothelial dystrophy	NA	-	-	Vitamin D deficiency	NA	NA	Unsolved	+
P104	M	6.8	-3.46	-2.27	164	-	With more than one additional phenotype	-	-	+ (Bushy eyebrows; Long eyelashes)	+ (Genu valgum)	-	-	NA	Hypertrichosis	NA	NA	Vitamin D deficiency; Elevated serum parathyroid hormone	NA	N	Unsolved	+
P105	M	0.3	-2.87	-1.79	160	-	With more than one additional phenotype	-	-	+ (Depressed nasal bridge and tip)	+ (Short limbs; Brachydactyly)	-	-	NA	NA	NA	+	NA	NA	NA	FGFR3 variant	-
P106	F	1.2	-3.01	-2.07	166	-	With one additional phenotype	+	-	-	-	-	-	NA	NA	NA	+	NA	NA	NA	Unsolved	-
P107	M	16.5	-5.50	-2.11	171.5	-	With one additional phenotype	-	-	-	-	-	-	NA	NA	+	+	Other pituitary hormones deficiency	Delayed	N	Unsolved	-
P108	F	1.3	-4.10	-1.41	NA	-	With one additional phenotype	-	-	-	+ (Short limbs; Brachydactyly)	-	-	NA	NA	NA	+	NA	NA	NA	FGFR3 variant	-
P109	F	5.3	-2.67	-1.82	NA	-	With more than one additional phenotype	-	+	-	-	+	-	NA	Epilepsy	+	+	Other pituitary hormones deficiency	Delayed	N	7q31.1q31.31(111551633-118284664)×3	-
P110	M	2.8	-4.81	-4.18	164	-	With more than one additional phenotype	-	-	+ (Prominent forehead)	+ (Pectus carinatum; Joint contracture in right upper limb; Knee deformity; Vertebral and costal anomalies)	-	-	NA	NA	NA	NA	NA	NA	N	KIF22 variant	+
P111	M	0.8	-3.08	-4.55	NA	-	With one additional phenotype	-	-	-	-	+	-	NA	Necrotizing enterocolitis; Hepatomegaly; Skin warts	NA	NA	NA	NA	NA	Unsolved	NA
P112	M	2.2	-4.29	-1.95	170.5	-	With one additional phenotype	-	-	-	+ (Pectus carinatum; Rib eversion; Genu valgum; Short upper limbs; Elbow joint contractures)	-	-	NA	NA	NA	NA	NA	NA	NA	Unsolved	+

P113	F	10.2	-4.20	-1.87	168	-	With more than one additional phenotype	-	-	+ (Multiple facial moles; Downslanting palpebral fissures; Hypertelorism; Low-set ears; Short neck; Webbed neck)	-	-	+ (Patent foramen ovale; Hypertrophic obstructive cardiomyopathy)	Right renal Hypoplasis	NA	NA	-	NA	Delayed	NA	RAF1 variant	-
P114	F	7.0	-3.92	-2.29	NA	+ (sibling)	With one additional phenotype	-	-	-	-	-	-	Hearing loss	Sparse scalp hair	NA	NA	NA	NA	N	Unsolved	NA

Abbreviation: F, female; M, male; NA, not available; Ht, height; Wt, weight; SGA, small for gestational age; DD/ID, developmental delay/intellectual disability; GHD, growth hormone deficiency; IGF1, insulin like growth factor 1; BA, bone age; MRI, magnetic resonance imaging; NGS, next generation sequencing; CMA, chromosome microarray analysis.

Supplementary Table 2. NGS quality control overview

Patients	Method	Aligned reads	Average depth	Targets coverage	> 10× Target bases coverage
P1	TS	95.9%	147.6	97.8%	97.0%
P2	TS	99.0%	97.2	98.9%	98.3%
P3	WES	98.8%	103.6	98.5%	97.7%
P4	TS	95.9%	116.3	97.8%	97.0%
P5	TS	98.7%	98.1	99.2%	98.5%
P6	TS	95.8%	162.8	97.8%	97.1%
P7	TS	96.5%	127.1	97.9%	97.1%
P8	TS	95.7%	183.9	97.5%	96.9%
P9	WES	97.5%	75.2	98.4%	97.2%
P10	TS	99.0%	100.1	98.9%	98.3%
P11	TS	98.7%	139.8	98.9%	98.4%
P12	TS	95.4%	180.7	97.7%	97.1%
P13	TS	95.9%	151.8	97.8%	97.0%
P14	TS	96.3%	130.2	97.8%	97.0%
P15	TS	96.0%	181.7	97.8%	97.1%
P16	TS	98.9%	98.1	98.9%	98.2%
P17	TS	99.0%	97.1	99.0%	98.3%
P18	TS	98.9%	106.2	98.9%	98.4%
P19	TS	96.1%	109.8	97.8%	97.0%
P20	TS	96.2%	137.5	97.7%	96.9%
P21	TS	95.8%	182.1	97.8%	97.1%
P22	TS	97.2%	146.5	97.6%	96.8%
P23	WES	98.7%	106.6	98.5%	97.8%
P24	WES	98.7%	106.1	98.5%	97.8%
P25	TS	95.7%	127.3	97.8%	97.0%
P26	TS	95.9%	119.4	97.8%	97.0%
P27	WES	98.3%	74.5	99.1%	97.2%
P28	TS	96.0%	117.0	97.8%	97.0%
P29	TS	95.5%	123.8	97.8%	97.0%
P30	TS	98.9%	94.9	98.9%	97.9%
P31	TS	96.1%	102.8	97.8%	96.8%
P32	TS	96.1%	124.9	97.5%	96.8%
P33	WES	98.6%	118.2	98.3%	97.8%
P34	TS	96.2%	116.0	97.5%	96.7%
P35	TS	95.1%	171.0	97.8%	97.1%
P36	TS	91.8%	143.9	97.7%	97.0%
P37	TS	98.9%	87.3	98.9%	97.7%
P38	TS	96.4%	132.2	97.6%	96.8%
P39	WES	98.5%	123.9	98.4%	97.9%
P40	TS	98.5%	83.7	98.9%	97.6%
P41	TS	95.4%	139.2	97.5%	96.6%
P42	TS	95.7%	139.9	97.7%	96.9%
P43	TS	94.9%	173.6	97.5%	96.6%
P44	TS	96.3%	133.8	97.8%	97.1%
P45	TS	95.4%	172.9	97.5%	96.6%
P45	WES	99.0%	97.8	98.4%	98.1%
P46	TS	95.6%	145.8	97.8%	96.9%
P47	TS	96.2%	116.8	97.6%	96.7%
P48	TS	95.6%	102.5	97.6%	96.5%
P49	TS	95.2%	147.3	97.7%	96.9%
P50	TS	96.0%	177.1	97.8%	97.1%
P51	TS	96.0%	171.0	97.8%	97.1%
P52	TS	95.6%	124.0	97.8%	97.0%
P53	TS	96.5%	130.6	97.4%	96.5%

P54	TS	92.6%	124.0	97.9%	97.1%
P55	TS	96.0%	193.1	97.8%	97.2%
P56	TS	96.0%	112.4	97.6%	96.7%
P57	TS	95.8%	114.2	97.7%	96.8%
P58	TS	91.1%	142.8	97.8%	97.2%
P59	TS	96.8%	141.2	97.6%	96.8%
P60	TS	98.7%	91.7	99.1%	98.2%
P61	TS	95.2%	261.3	97.7%	97.0%
P62	TS	96.2%	116.6	97.8%	97.0%
P63	TS	95.1%	161.3	97.8%	97.0%
P64	TS	95.8%	186.1	97.9%	97.3%
P65	TS	96.0%	130.4	97.8%	97.0%
P66	TS	96.4%	116.1	97.5%	96.7%
P67	TS	96.8%	131.4	97.5%	96.7%
P68	TS	95.8%	128.1	97.9%	97.1%
P69	TS	96.4%	109.4	97.8%	96.9%
P70	TS	96.1%	120.5	97.8%	96.9%
P71	TS	96.8%	126.5	97.6%	96.7%
P72	TS	95.8%	104.5	97.6%	96.6%
P73	TS	95.7%	110.4	97.5%	96.7%
P74	TS	96.4%	109.6	97.5%	96.6%
P75	TS	95.9%	106.6	97.5%	96.7%
P76	TS	96.8%	118.2	97.8%	96.8%
P77	TS	96.8%	118.2	97.5%	96.6%
P78	TS	94.5%	114.5	97.7%	96.7%
P79	TS	92.5%	136.9	97.9%	97.2%
P80	WES	99.0%	89.6	98.5%	97.3%
P81	TS	97.2%	122.9	97.6%	96.7%
P82	TS	96.6%	134.9	97.8%	96.9%
P83	TS	96.8%	139.8	97.8%	96.9%
P84	TS	95.6%	115.4	97.7%	96.8%
P85	TS	94.1%	113.9	97.6%	96.6%
P86	TS	96.0%	142.6	97.8%	97.1%
P87	TS	96.6%	121.9	97.5%	96.6%
P88	TS	96.9%	133.2	97.6%	96.8%
P89	TS	95.7%	101.3	97.8%	96.8%
P90	TS	96.6%	114.2	97.9%	96.9%
P91	TS	96.5%	119.0	97.7%	96.8%
P92	TS	96.3%	120.8	97.6%	96.7%
P93	TS	96.5%	108.4	97.8%	96.8%
P94	TS	96.2%	129.9	97.8%	96.9%
P95	WES	97.1%	71.7	98.4%	97.1%
P96	TS	96.3%	195.9	97.9%	97.3%
P97	TS	96.2%	145.1	97.9%	97.1%
P98	TS	96.1%	235.9	97.6%	97.1%
P99	TS	96.6%	133.6	97.8%	97.1%
P100	TS	96.6%	136.0	97.8%	97.1%
P101	TS	96.5%	153.8	97.8%	97.1%
P102	TS	96.3%	204.0	97.8%	97.1%
P102	WES	99.1%	111.2	98.5%	97.8%
P103	TS	95.8%	167.8	97.8%	97.2%
P104	TS	96.1%	128.7	97.8%	97.0%
P105	TS	96.5%	128.4	97.8%	97.1%
P106	TS	96.2%	135.1	97.6%	96.9%
P107	TS	95.7%	163.5	97.8%	97.2%
P108	TS	96.2%	154.1	97.6%	96.9%
P109	TS	96.0%	125.8	97.6%	96.8%

P110	TS	96.4%	130.7	97.8%	97.1%
P111	TS	96.3%	154.7	97.9%	97.2%
P112	TS	96.1%	151.2	97.9%	97.2%
P112	WES	99.3%	109.4	98.5%	98.3%
P113	TS	98.0%	99.8	97.5%	96.5%
P114	TS	96.9%	134.7	97.6%	96.9%

Note: TS, target sequencing using ClearSeq Inherited Disease capture kit; WES, whole exome sequencing using SureSelec

Supplementary Table 3. References of variants previously reported in patients

Gene [a]	Sequencing variant	PMID (first reported)
BRAF	NM_004333.4: c.1785T>G(p.F595L)	16439621
COL2A1	NM_001844.4: c.3121G>A(p.G1041S)	17347327
COMP	NM_000095.2: c.1417_1419del(p.D473del)	7670471
FBN1	NM_000138.4: c.5096A>G(p.Y1699C)	21683322
FGFR3	NM_000142.4: c.1138G>A(p.G380R)	7913883
FGFR3	NM_000142.4: c.1138G>C(p.G380R)	7913883
FGFR3	NM_000142.4: c.1620C>A(p.N540K)	7670477
GH1	NM_000515.4: c.291+1G>C	7714096
HRAS	NM_005343.2: c.34G>A(p.G12S)	16170316
KIF22	NM_007317.2: c.443C>T(p.P148L)	22152677
KMT2A	NM_001197104.1: c.8407C>T(p.Q2803*)	27759909 [b]
KRAS	NM_004985.4: c.458A>T(p.D153V)	16474405
MATN3	NM_002381.4: c.361C>T(p.R121W)	11479597
RAF1	NM_002880.3: c.770C>T(p.S257L)	17603482
RUNX2	NM_001024630.3: c.574G>A(p.G192R)	16244783
SRCAP	NM_006662.2: c.7219C>T(p.Q2407*)	23621943
NAA10	NM_003491.3: c.247C>T(p.R83C)	27094817
ALPL	NM_000478.4: c.1120G>A(p.V374M)	23509830
GLB1	NM_000404.2: c.145C>T(p.R49C)	1909089
GLB1	NM_000404.2: c.248A>G(p.Y83C)	16941474
SLC12A3	NM_000339.2: c.2877_2878del (p.R959Sfs*11)	14750096
SLC12A3	NM_000339.2: c.947G>C (p.G316A)	14750096

Note: [a] The genes were listed in sequential order of Table 1.

b The patient in this case report is patient P80 in our study.

Supplementary Table 4. Diagnostic yields and statistical analyses of different additional phenotypic subgroups

Additional phenotype	with		without		*P* value (2-sided)	as only one accompanying phenotype		as one of accompanying phenotypes		*P* value (2-sided)
	total (n)	solved%	total (n)	solved%		total (n)	solved%	total (n)	solved%	
SGA	21	38.1%	93	35.5%	0.822	3	0.0%	18	44.4%	/
Microcephaly	21	52.4%	93	32.3%	0.083	0	/	21	52.4%	/
Facial dysmorphism	30	56.7%	84	28.6%	0.006	2	50.0%	28	57.1%	1.000
Skeletal abnormalities	51	49.0%	63	25.4%	0.009	22	45.5%	29	51.7%	0.779
DD/ID	31	45.2%	83	32.5%	0.211	6	33.3%	25	48.0%	0.664
Cardiac anomaly	16	50.0%	98	33.7%	0.207	0	/	16	50.0%	/
Other congenital anomalies	21	38.1%	93	35.5%	0.822	4	25.0%	17	41.2%	1.000
Other biochemical anomali	17	41.2%	97	35.1%	0.627	6	33.3%	11	45.5%	1.000
Family history	22	22.7%	92	39.1%	0.150	/	/	/	/	/
GHD	35	22.9%	16	37.5%	0.322	/	/	/	/	/
Complete GHD	15	13.3%	38	31.6%	0.300	/	/	/	/	/
Low IGF1	37	24.3%	40	37.5%	0.212	/	/	/	/	/
Abnormal BA	41	24.4%	16	31.3%	0.739	/	/	/	/	/
Abnormal brain MRI imag	32	25.0%	32	40.6%	0.183	/	/	/	/	/

Abbreviations: SGA, small for gestational age; DD/ID, developmental delay/intellectual disability;

GHD, growth hormone deficiency; IGF1， insulin like growth factor 1;

BA, bone age; MRI, magnetic resonance imaging.