SUPPLEMENTARY DATA

Supplementary Table 1. Genotypes and epigenotypes of the 14 *ZFP57*$^{mut/mut}$ and 25 *ZFP57*$^{+/mut}$ individuals

Family		Genotype	Exon	Predicted effect on protein	TNDM1	*GRB10*	*PEG3*	*PEG1*	*KCNQ1OT1*	*NESPAS*
Family 1 723C>A= C241X	I-1	+/mut			N	N	N	N	N	N
	I-2	+/mut			N	N	N	N	N	N
	II-1	mut/mut	6	Premature stop codon, result: Truncated protein	T	T	P	P	P	P
	II-2	mut/mut	6	Premature stop codon, result: Truncated protein	T	T	P	P	P	N
	II-3	+/mut			N	N	N	N	N	N
Family 2 257_258delAG= E86VfsX28	I-1	+/mut			N	N	N	N	N	N
	I-2	mut/mut	5	Frameshift introducing premature stop codon, result: Truncated protein	T	P	P	N	N	N
	II-1	mut/mut	5	Frameshift introducing premature stop codon, result: Truncated protein	T	P	P	N	N	N
	II-2	+/mut			N	N	N	N	N	N
	II-3	mut/mut	5	Frameshift introducing premature stop codon, result: Truncated protein	T	T	P	N	N	N
Family 3 1323delC= G441GfsX17	I-1	+/mut			N	N	N	N	N	N
	I-2	+/mut			NK*	NK*	NK*	N	N	N
	II-1	mut/mut	6	Frameshift introducing premature stop codon, result: Truncated protein	T	P	P	N	N	N
	II-2	+/mut			N	N	N	N	N	N
Family 4 1312C>G=	I-1	+/mut			N	N	N	N	N	N
	I-2	+/mut			N	N	N	N	N	N

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H438D	II-1	mut/mut	6	Conserved residue involving metal ion-binding amino acid histidine. Probably damaging	T	P	P	N	N	N
Family 5 683G>A= R228H	I-1	+/mut			NK†	NK†	NK†	NK†	NK†	NK†
	I-2	+/mut			N	N	N	N	N	N
	II-1	mut/mut	6	Conserved residue involving metal ion-binding amino acid histidine. Probably damaging	T	P	P	N	N	N
Family 6 769C>A= H257N	I-1	+/mut			N	N	N	N	N	N
	I-2	+/mut			N	N	N	N	N	P
	II-1	mut/mut	6	Conserved residue involving metal ion-binding amino acid histidine. Probably damaging	T	T	P	N	P	N
	II-2	+/mut			N	N	N	N	N	N
	III-1	-			-	-	-	-	-	-
	III-2	mut/mut	6	Conserved residue involving metal ion-binding amino acid histidine. Probably damaging	T	P	P	N	N	N
Family 7 683G>A= R228H + 837_844del CACCCAGG =279fsX1	I-1	+/mut 837_844del CACCCAGG			N	N	N	N	N	N
	I-2	+/mut 683G>A			N	N	N	N	N	N

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	II-1	+/mut 837_844del CACCCAG G			N	T	N	N	N	P
	II-2	+/mut 683G>A			P	P	N	N	N	P
	II-3	mut/mut	6	Frameshift introducing premature stop codon and missense mutation affects conserved residue involving metal ion-binding amino acid histidine. Probably damaging	T	T	P	P	N	P
Family 8 398delT= L133HfsX49	I-1	+/mut			N	N	N	N	N	N
	I-2	+/mut			N	N	N	N	N	N
	II-1	mut/mut	6	Frameshift introducing premature stop codon	T	P	P	N	N	N
Family 9 398delT= L133HfsX49 + 760C>T = L254F	I-1	+/mut 398delT			N	N	N	N	N	N
	I-2	+/mut 760C>T			N	N	N	N	N	N
	II-2	mut/mut	6	Frameshift introducing premature stop codon and missense mutation affects non-conserved residue but is probably damaging	T	P	P	N	N	N

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Family 10 682C>T= R228C	I-1	+/mut			N	N	N	N	N	N
	I-2	+/mut			N	N	N	N	N	N
	II-1	mut/mut	6	Affects conserved residue. Probably damaging	T	P	P	N	N	N

I-III generation number followed by individual number of each individual; mut/mut, *ZFP57* homozygous or compound heterozygous individuals (highlighted in black boxes); +/mut, *ZFP57* heterozygous individuals; TNDM1, DMR TNDM1; *GRB10*, DMR *GRB10*; *PEG3*, DMR *PEG3*; *PEG1*, DMR *PEG1*; *KCNQ1OT1*, DMR *KCNQ1OT1*; *NESPAS*, DMR *NESPAS*; N in white, normal methylation; T in dark gray, total loss of methylation; P in light gray, partial hypomethylation (> 3SD from the normal control range); NK, not known; *, MS-PCR failed; †, no results due to poor quality DNA.

Numbering of sequence variations according to den Dunnen and Antonarakis (21). Of notice: the 8 bp deletion in family 7 has changed base pair numbers to the more correct base pair numbers in this paper compared to our previous publication (5). The predicted effect on protein is obtained by entering the *ZFP57* alterations in the SIFT database, a sequence homology-based tool that **s**orts **i**ntolerant **f**rom **t**olerant amino acid substitutions (http://sift.jcvi.org/) and the PolyPhen-2 database, Polymorphism Phenotyping (http://genetics.bwh.harvard.edu/pph2/).

SUPPLEMENTARY DATA

Supplementary Table 2. Detailed clinical phenotypes of the 14 *ZFP57* homozygous and compound heterozygous individuals, 12 affected individuals and 2 non-affected individuals.

	Family 1		**Family 2**			**Family 3**	**Family 4**	**Family 5**	**Family 6**		**Family 7**	**Family 8**	**Family 9**	**Family 10**
	II-1 affected individual	**II-2 affected individual**	**I-2 non-affected individual**	**II-1 non-affected individual**	**II-3 affected individual**	**II-1 affected individual**	**II-1* affected individual**	**II-1* affected individual**	**II-1 affected individual**	**III-2 affected individual**	**II-3 affected individual**	**II-1 affected individual**	**II-1 affected individual**	**II-2 affected individual**
Coefficient of consanguinity (F)	1/8	1/8	1/16	5/32	5/32	1/32	5/64	1/16	nk	nk	n/a	n/a	n/a	n/a
Neonatal diabetes history	Glucosuria, no ketoacidosis, nonfasting C-peptide < 160pmol/l, no diabetes-associated antibodies. TND on insulin for 7m	Glucosuria, no ketonuria. NDM on insulin for 11m	No	No	TND on insulin for 3.5m	TND on insulin for 4m	TND on insulin for 1m	TND on insulin for 4m	TND on insulin for 4m	TND on insulin for 5m	TND on insulin for 1½m	TND on insulin for 18m	NDM on insulin for 14½m	TND on insulin for 1m
Sex	F	F	M	F	F	M	M	M	F	F	M	M	F	F
Birth weight (percentile)	2430g at term (0.4^{th} - 2^{nd})	2000g at term (< 0.4^{th})	nk	2400g at term (0.4^{th}-2^{nd})	2523g at term (2^{nd})	1920g at term (< 0.4^{th})	1745g at 33w (2^{nd})	2500g at term (0.4^{th} - 2^{nd})	2000g at term (<0.4^{th})	2660g at term (9^{th}-25^{th})	2350g at term (0.4^{th})	1900g at 38w (0.4^{th})	2000g at 34w (25^{th})	2200g at term (0.4^{th})
Birth length (percentile)	49cm (25^{th})	45cm (0.4^{th})	nk	nk	nk	nk	nk	50cm (25^{th} - 50^{th})	45cm (0.4^{th})	46cm (2^{nd}-9^{th})	nk	48cm (25^{th})	nk	42cm (<<0.4^{th})

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OFC at birth (percentile)	30cm (< 0.4th)	32cm (2nd)	nk	nk	33.5cm (25th)	nk	nk	34cm (9th-25th)	31.5cm (0.4th-2nd)	nk	3rd percentile	nk	nk	nk
Weight catch-up	Yes 3m (91st)	No	nk	Yes 7m (99th)	Yes 5m (25-50th)	Yes 7m (25-50th)	Yes 1m 9th	nk	Yes 9m 50th	nk	Yes 10m 90th	nk	nk	nk
Umbilical abnormality	Hernia of the cord (persistent omphalo-enteric duct; 5x3 cm)	Umbilical hernia	No	No	No	No	No	No	No	No	Yes	No	nk	No
Macroglossia	Yes	Yes	nk	nk	Yes	Yes	Yes	No	Yes	Yes	Yes	No	nk	No
Congenital heart disease	Patent ductus arteriosus	Atrial septal defect	No	No	No	No	Fallot tetralogy	No	No	A "hole in the heart", healed spontaneously	No	No	nk	No
Evidence of asymmetry	No	No	No	No	No	No	No	No	nk	No	Hemihypertro phy of left arm, left leg	No	nk	Hemihypertrophy of leg

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Other congenital abnormalities	Bilateral postaxial polydactyl yof the hands	Tracheo-malacia	No	No	No	Clinodactyl y. Bilateral failure of flexion at interphalan geal joints, 5th digit	No	Hydrocele	No	A minor oesop hageal hernia	Pectus carinatum. 5th finger clinodactyly .	No	nk	Pectus carinatum.
Other dysmorphic features	No	Bilateral ear lobe creases	No	No	Bilatera l ear lobe creases	Hypertelori sm. Micrognath ia despite macroglossi a. Deficient ear lobes with deep unusual anterior creases	No	No	No	No	Prognathis m	No	nk	No
Epilepsy	No	Severe epilepsy. EEG highly abnormal . Status epileptic us	No	No	No	Central apnoea. Possible epilepsy	nk	One epileptic seizure in neonatal period	No	No	No	No	nk	One episode of seizure at 4y (possible due to hypoglyca emia)

SUPPLEMENTARY DATA

Visual abnormalities	Bilateral hypermetropia	Cerebral blindness suspected	Episodic diplopia	No	No	Roving eye movments. ERG evidence of cone rod dystrophy. Hypermetropic	nk	No	No	No	No	No	nk	No
Hearing loss	No	Profound hearing loss suspected	No	No	No	No	nk	No	No	No	No	No	nk	No
Psychomotor development	Mild delay- attends a special class at a normal school	Severe delay	Normal	Normal	Normal	Severe delay	Mild delay. Walked at 15m	Mild delay at 1y. Functioning at normal school.	At 22m assessed at 18-20m. Developme ntally normal in adulthood	Normal	Walked at 2y. Mild delay – requires special education within a normal school. Oromotor dyspraxia, difficulties with expressive language, slow at writing, problems with tripod grip.	Normal	nk	Mild delayed motor development at 7y - now no motor impair-ment. Otherwise normal.

SUPPLEMENTARY DATA

Subsequent relevant medical history	No	Severe failure to thrive. Recurrent infections. Developed hypertrophic cardiomyopathy. Died 11m.	No	No	No	Apnoea following an inguinal hernia operation. Hypotonia. Recurrent chest infections.	Asthma	Healthy. No subsequentdiabetes	nk	No	Mild progressive contractures at wrist, elbow, fingers, knees, ankles and toes, affecting gait. Achilles tendon lengthening. Tone and reflexes normal; mild proximal muscle weakness in legs. Poor balance.	No	nk	Hypothyroidism at 11½y. Eltroxin treatment.
Brain imaging performed	No	MRI (6m): severe hypoplasia of corpus callosum, abscence of occipital horn of left ventricle	No	No	No	MRI (7m): Partial agenesis of corpus callosum. Dilatation of horns. Hypoplasia of cerebral vermis.	No	No imaging	CT (19y): normal	No	No	No	nk	No
Last recorded weight percentile	75th at 8½y	<<0.4th at 11m	75th-90th	99th at 7m	50th at 13m	75th at 1y 8m	75th at 18m	75th at 11y 3m	25-50th at 24y	nk	91st-98th at 15y	2nd at 23m	50th-75th at 14½m	75th-91st at 17y

SUPPLEMENTARY DATA

Last recorded length percentile	25th at 8½y	<<0.4th at 11m	75th-91st	91st-98th at 7y	91st-98th at 18m	2nd at 1y 8m	75th at 18m	98th at 11y 3m	9-25th at 14 y	nk	75th at 15y	2nd at 23m	25th at 14½m	91st at 17y
Last recorded OFC percentile	nk	<<0.4th at 11m	nk	50th at 7m	25th at 18m	<<0.4th at 1y 8m	nk	98th at 11y 3m	nk	nk	50th-75th at 15y	nk	nk	75th-90th at 18y
Relapse of diabetes and treatment	Relapse of diabetes at 2y 8m. Insulin 2y 8m-4½y. Sulphonyl urea 4½y-5y7m. Tolbuta-mide 5y 7m-8y. Due to adverse effects changed to Insulin and Daonil 8y-now.	n/a	n/a	n/a	No	No	nk	nk	Relapse of diabetes at 9½y. Restarted insulin at 12½ y. Puberty at 12-14y. Mainly treated on insulin but at times does not require it and is treated with diet alone	No	No	n/a	n/a	Relapse of diabetes at 11y. Mainly treated on insulin till now.

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Any other relevant diabetes investigations	5y 7m mixed meal tolerance test (90 min Boost test): fasting C-peptide 550 pmol/l; stimulated C-peptide 930 pmol/l; after 3 days of sulphonyl urea omission: fasting C-peptide 270 pmol/l; stimulated C-peptide 490 pmol/l. Used to be good control but since age 8y bad control. HbA1c 9.0% by 8½y	During infections fluctuating blood glucose levels but no ketoacidosis. HbA1c 6.2% by 8m	Repeated normal fasting blood glucose	Normal fasting blood glucose at 9y	Normal fasting blood glucose	One episode of recorded hypoglycaemia (3.4 mmol/l). Two episodes of hyperglycemia during infection with no associated ketonuria and required insulin on one episode	nk	HbA1C normal at 2.5y	No	No	No	HbA1C 10.5% (normal: 4.1-6.5) at 2y 3m	HbA1C 6.8% (normal 6.5-7%) at 1m	HbA1C 6.2% at 18y

SUPPLEMENTARY DATA

Other features	No	No	nk	nk	nk	Delayed closure of the anterior fontanelle	Rapid growth in childhood reported by clinician	nk	nk	nk	5th right digit more contracted than left.	nk	nk	No
Calcium metabolism	Normal calcium, phosphate and PTH	Normal calcium	n/a	n/a	nk	nk	nk	nk	Normal calcium, phosphate,TFT and PTH	nk	PTH raised (one occasion), subsequently normal; Calcium, phosphate, Vit D normal. EMG neurogenic change; muscle biopsy - variation in fibre size. CPK normal.	nk	nk	n/a