Supplementary File 1

Detailed clinical description of affected families with variants in *CEP104* and *CEP290*

A) Families with *CEP104* variants;

M8800138

The patient was the only affected child of first-cousin, healthy parents originating from the Semnan province in the northern part of Iran (Shahrood city). The patient (M) was born via cesarean section with an unremarkable pregnancy, delivery and neonatal period. Birth measurements were normal for head circumference, height and weight, although he showed delays in major motor and speech developmental milestones. His birth weight was 3550 g, height was 50 cm and OFC was 35 cm. His head control developed at the age of 7 months and he started to sit at the age of 10 months. He said his first single words at 2 years of age. He had no history of seizure. At the age of 2 years, his height was 90 cm (97th percentile) and OFC was 49 cm (0SD). His facial appearance was normal. He had no hyperactivity, aggressiveness or self-mutilation. He had normal hearing and vision. He made very little eye-to-eye contact and did not have the ability to communicate or to follow simple commands. His reexamination at 10 years showed OFC: 54cm (+1SD), height: 132cm (15th percentile) and weight: 30 kg (30th percentile). The brain MRI was normal. He showed autistic behavior, stereotypic speech and movement in the head and index finger as well as rarely self-injuring behavior showing as hand-biting. He also showed joint laxity and delayed wound healing. Developmental testing at the age of 10 years using the Wechsler Intelligence Scale for Children (HAWIK-IV) showed Intelligence Quotients (IQs) of 25, in the range of severe intellectual disability (ID).

M9100012

Three patients were from first-cousin, healthy parents originating from the Markazi province in the central part of Iran. The patients were born at term with unremarkable pregnancies and neonatal periods. They had psychomotor delay including starting to walk at the age of 3 and saying single words at the age of about 4 years. The patients had no history of seizure or aggression. Their vision and hearing were normal, they could follow simple commands, count money and had bowel and bladder control since 4 years. When they were aged 30, 28 and 20 years, their heights were 165 (5th percentile), 155 (10th percentile), and 171 cm (25th percentile), respectively and their OFCs were 56 (0SD), 54 (–0.7SD) and 56 cm (0SD). Their facial appearance was normal. They had normal gait and spoke using multi-word phrases. Cognitive status evaluated in IV:5, IV:6 and IV:4 using WAIS-IV showed IQs of 53, 50 and 55, respectively, in the range of moderate ID. At reexamination, they were 36, 34 and 26 years. They did not develop any regression in motor, cognition, behavior or neurological testing. There was no evidence of brain structural abnormality or skeletal disorders without any reported self-injury or autistic behavior.

B) Families with *CEP290* variants;

M9609908

The 24-year old male proband was born to first-cousin consanguineous parents. He was diagnosed to be affected by night blindness, a phenotype of retinitis pigmentosa. Both sides of the pedigree showed variable phenotypes including night blindness, hearing loss and diabetes. Targeted exome sequencing for 436 genes known to be associated with vision disorders was carried out for this patient.

M9708501

This consanguineous (first-cousin) family showed a history of miscarriages due to similar findings in three successive pregnancies. The third trimester screening test in the first pregnancy at the 11^{th} week was indicative of a child with meningomyelocele which resulted in therapeutic abortion at the 13^{th} week of pregnancy. The second pregnancy resulted in termination of pregnancy at the 18^{th} week due to similar findings in addition to polycystic kidney phenotype. The third fetus (proband) showed similar clinical features including meningomyelocele, brain developmental abnormality and occipital meningoencephalocele without polycystic kidneys. The screening for

trisomies of 13, 18, 21 and X chromosomes was normal. The proband was diagnosed with Meckel-Gruber syndrome type 4. Exome sequencing for 3504 genes known to be associated with mendelian disorders was carried out for this aborted fetus.

M9403135
The female proband in this family was born to first-cousin consanguineous parents and had an affected sister with a similar phenotype. The ophthalmic phenotype, Leber congenital amaurosis (LCA), is thought to be the only clinical manifestation in the patient. Targeted exome sequencing for 120 genes implicated in retinitis pigmentosa (RP) was carried out for this patient.

M9201216
The male proband in this family was born to first-cousin consanguineous parents. He showed clinical manifestations including hypotonia, ataxia, protruding tongue, intellectual disability and developmental delay. His ophthalmic examination was indicative of retinal disorder (Leber congenital amaurosis) together with nystagmus and strabismus. His prenatal screening tests were normal. MRI revealed Molar Tooth Sign and cerebellar vermis hypoplasia. He was suspected of having Joubert syndrome and targeted exome sequencing for 23 genes implicated in Joubert syndrome was carried out for this patient followed by cosegregation analysis in parents.

M9101057
This non-consanguineous family experienced two therapeutic abortions due to severe renal and cerebral disorders observed in the third trimester prenatal screening at the 18th week of pregnancy. The female proband fetus was autopsied and diagnosed to be affected with Meckel-Gruber syndrome. Major phenotypes included cystic renal dysplasia, occipital meningocele, congenital hepatic fibrosis, hypertelorism and low-set ears. Carrier detection of the parents for Meckel syndrome was carried out using targeted exome sequencing for 23 genes implicated in Joubert syndrome as most Meckel and Joubert syndrome genes overlap.

Table S1- Primers used for human *CEP104* qPCR

Primer	Primer seq (5' to 3')	Forward/ Reverse	Gene	Product size (bp)
CEP104-EX1-F	CTCTAAGCAGCCCAAACGTG	F	*CEP104*	144
CEP104-EX2-3-R	GCAAAATCTAGGTGACCGCC	R		
GAPDH-F	GGAGCGAGATCCCTCCAAAAT	F	*GAPDH*	197
GAPDH-R	GGCTGTTGTCATACTTCTCATGG	R		

Table S2- Pathogenicity predictions and allele frequency for mutations identified in this study

Gene	Family	Variant	MutationTaster	CADD Phred score	PhyloP score/ PhastCons score	ClinVar	1000 Genome	ExAC
CEP104	8800138	NM_014704:c.2356_2357insTT	Disease causing	35	(flanking) 3.036/1 (flanking)	--	--	--

		p.(Cys786Phefs*11)			2.321/1			
	9100012	NM_014704:c.1901_1902insT p.(Leu634Phefs*33)	Disease causing	34	(flanking) 1.428/0.997 (flanking) 3.178/0.99	--	--	--
CEP290	9609908	NM_025114.3:c.322C>T p.(Arg108*)	Disease causing	36	0.888/0.93	Pathogenic	--	--
	9708501	NM_025114.3:c.4393C>T p.(Arg1465*)	Disease causing	38	2.526/1	Pathogenic	Homo: 1 Hetero: 1 AF: 0.000199681	Homo: 0 Hetero: 3 AF: 0.00002705
	9403135	NM_025114.3:c.7341_7344dupACTT p.(Ser2449Thrfs*8)	Disease causing	35	(flanking) 3.057/1 (flanking) 0.803/1	--	--	Homo: 0 Hetero: 1 AF: 0.00000834
	9201216	NM_025114.3:c.5668G>T) p.(Gly1890*)	Disease causing		1.356/0.91	Pathogenic	Homo: 0 Hetero: 1	Homo: 0 Hetero: 15 AF: 0.0001432
	9101057	NM_025114.3:c.1666dupA p.(Ile556Asnfs*20)	Disease causing		(flanking) 4.449/1 (flanking) 1.242/0.983	Pathogenic	--	Homo: 0 Hetero: 196 AF: 0.007273