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A new Arab family with CEDNIK syndrome suggests a possible founder effect for the c.223delG mutation

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Loss-of-function of SNAP29 is responsible for a pleiotropic rare autosomal recessive disorder named cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma syndrome (CEDNIK, MIM 609528). CEDNIK has been described in only 3 families and two sporadic cases (1-3) and we, therefore, report here a consanguineous Jordanian family with two affected children harboring a recurring mutation. Both had severe global developmental delay, facial dysmorphic features, and skin abnormalities. The index patient was the product of a normal pregnancy and delivery. Her birth weight was 3100gm and she was covered with a thick layer of skin (collodion phenotype) that gradually desquamated leaving a scaly rough skin all over her body. She had feeding difficulties and attacks of choking leading to aspiration pneumonia requiring several hospital admissions. She had severe global developmental delay and was unable to sit alone or respond to mother till 3 years of age. On evaluation at the age of 4 years she exhibited brachycephaly, triangular face, short and down slanting palpebral fissures, small mouth which was difficult to open, high arched palate, small ears with over folded helix, flat maxilla, wrist drop with radial deviation of the hands which appeared small with contractures of the proximal interphalangeal joints, abnormal dermatoglyphics, bilateral 2nd-3rd toe syndactyly, and prominent toe pads. The skin was dry with scales particularly over the legs consistent with ichthyosis and keratoderma over the soles of the feet. She had severe hypotonia and absent deep tendon reflexes and optic atrophy. Brain MRI showed hypoplastic corpus callosum and brain atrophy.

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Conflict of interest

No competing interests exist.

Echocardiography and transferrin isoelectric focusing were normal. The affected sister exhibited similar phenotype (Table 1).

CGH microarray analysis showed that the index case and unaffected father have an interstitial duplication at 10p11.22 spanning approximately 155 kilobases. Whole-exome sequencing identified a homozygous 1bp deletion (c.223delG) in exon 1 of *SNAP29* gene in the affected sisters. This mutation segregated well in the family and has been reported previously (1). Our patients have the typical features of this syndrome including ichthyosis, keratoderma, dysmorphic features and global developmental delay (Table 1). However, ichthyosis in the previously described cases was of late onset compared to our patients presented with a collodion phenotype at birth that evolved into generalized ichthyosis. In addition, our patients had peripheral camptodactyly that has not been previously described in CEDNIK. Furthermore, they did not have microcephaly, cortical abnormalities or sensorineural deafness described in previous cases. The clinical variability observed between the families carrying the c.223delG mutation could be due to modifier genes. All reported SNAP29 mutations causing CEDNIK were truncating mutations (1-3). The presence of c.223delG mutation in two unrelated families suggests a possible founder effect in the Arab population. However, this needs to be formally established via haplotype analysis.

In conclusion, we report a recurring mutation in *SNAP29* in a Jordanian family with two children affected by CEDNIK syndrome. The affected children exhibited some phenotypic variability including early skin manifestations and we therefore suggest including CEDNIK in the differential diagnosis of collodion phenotype in neonates.

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Table 1

Clinical features of Patients with CEDNIK syndrome

	Present Study		Sprecher et al. 2005				Fuchs-Telem et al 2011		McDonald-McGinn et al.2013	
Patients	**1**	**2**	**1**	**2**	**3**	**4**	**1**	**2**	**1**	**2**
Origin	**Jordan**		**Arab Muslims from north Israel**				**Pakistan**		**ND**	
Dysmorphic features										
• Down slanting palpebral fissures	+	+	+	+	+	+	-	-	ND	ND
• Flat nasal bridge	+	+	-	-	-	-	-	-	ND	ND
• Small mouth	+	+	-	-	-	-	-	-	ND	ND
• Abnormal Ear	+	+	-	-	-	-	-	-	ND	ND
CNS										
• Global delay	+	+	+	+	+	+	+	+	+	+
• Microcephaly	-	-	+	+	+	+	+	+	+	+
• Absent/thin corpus callosum	+	+	+	+	+	+	+	+	ND	ND
• Cortical abnormality	-	-	+	+	+	+	+	+	+	+
• Seizures	-	-	-	-	-	-	+	+	ND	ND
• Hypotonia	+	+	+	+	+	+	↑tone	+	ND	ND
• Sensorineural deafness	-	-	+	+	+	+	+	+	+	+
Skin										
• Collodion phenotype	+	+	-	-	-	-	-	-	-	-
• Generalized ichtyosis	+	+	+	+	+	+	+	+	+	+
• keratoderma	+	+	+	+	+	+	+	+	+	+
GI										
• Feeding difficulties	+	+	+	+	+	+	+	+	+	+
• Failure to thrive	+	+	+	+	+	+	+	+	+	+
Ophthalmology										
• Squint	+	+	-	-	-	-	-	-	+	+
• Hypoplastic optic disc	+	+	+	+	+	+	ND	ND	+	+

	Present Study		Sprecher et al. 2005				Fuchs-Telem et al 2011		McDonald-McGinn et al.2013	
Patients	**1**	**2**	**1**	**2**	**3**	**4**	**1**	**2**	**1**	**2**
Origin	**Jordan**		**Arab Muslims from north Israel**				**Pakistan**		**ND**	
Skeletal										
• Contracture of Joints	proximal interphallangeal Joints		-	-	-	-	Knee talipes varus	-	-	-
Mutations	c.223delG		c.223delG				c.487dupA		c.387_388dupGA	c.29_33delCGTTC
Type	Homozygous		Homozygous				Homozygous		Hemizygous	Hemizygous

+: presence; -: absence; arrow: increased; dup: duplication; del: deletion