Blended Phenotype of Silver-Russell Syndrome and SPG50 Caused by Maternal Isodisomy of Chromosome 7

Objective
Uniparental isodisomy can lead to blended phenotypes of imprinting disorders and autosomal recessive diseases. To determine whether a complex neurodevelopmental disorder was caused by uniparental isodisomy, a detailed clinical and molecular characterization was performed.

Methods
A combination of clinical, molecular, and imaging data and functional studies in patient-derived fibroblasts.

Results
We report a 4-year-old female with a blended, complex phenotype of Silver-Russell syndrome (SRS) and hereditary spastic paraplegia type 50 (SPG50) caused by total maternal isodisomy of chromosome 7 (UPID(7)mat) and a loss-of-function variant in AP4M1 (NM_00472.3:c.59-1G>C, IVS1-1G>C). Functional studies in patient-derived fibroblasts confirmed the loss of adaptor protein complex 4 function. Distinctive facial features, intrauterine growth restriction, short stature, feeding difficulties, and severe gastroesophageal reflux were consistent with SRS. Features associated with SPG50 included early-onset epilepsy, episodes of stereotypical laughter, and thinning of the corpus callosum and ventriculomegaly on brain MRI. Symptoms shared by both syndromes such as developmental delay, short stature, and axial and appendicular hypotonia were also present. Notably, other common manifestations of SPG50 such as microcephaly or spasticity had not developed yet.

Conclusions
This case highlights that atypical clinical features in patients with well-described imprinting disorders should lead to investigations for recessive conditions caused by variants in genes that localize to the region of homozygosity.

New Cohort of Patients With CEDNIK Syndrome Expands the Phenotypic and Genotypic Spectra

Objective
To report 6 new patients with cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma (CEDNIK) syndrome.

Methods
Clinical exome or targeted sequencing were performed to elucidate the molecular genetic cause in patients with neurocognitive abnormalities and brain imaging findings.

Results
CEDNIK syndrome is a rare genetic condition caused by biallelic pathogenic loss-of-function variants in synaptosomal-associated protein 29 (SNAP29), which encodes a vesicular membrane fusion protein. Clinical manifestations include significant developmental delay/intellectual disability (DD/ID), brain abnormalities, failure to thrive, and skin abnormalities. To date, 19 patients from 10 unrelated families with CEDNIK syndrome have been reported. We report 5 additional patients with homozygous predicted loss-of-function variants in SNAP29 and one with compound heterozygous variants: a frameshift variant and one with compound heterozygous variants: a frameshift variant and a 370 kb deletion on 22q11.2. All patients exhibit DD/ID, ichthyosis and/or palmoplantar keratoderma, and hypotonia. Four of 6 subjects had hypomyelinated white matter on MRI, 2 of 6 had early puberty, and 4 of 6 had strabismus, which were previously rarely reported. Other phenotypes were variably present, including dysmorphic features, feeding difficulties, and recurrent respiratory infections. The cohort includes 2 siblings with a c.2T>C variant who have a relatively milder phenotype, a patient with the most C-terminal variant yet described (c.622G>T), and 3 patients with previously described variants (c.354dupG, c.487dupA).

Conclusions
This cohort of 6 additional patients expands the genotypic and phenotypic spectrum of CEDNIK syndrome, highlighting previously under-recognized features such as hypomyelination, seizures, and early puberty. Owing to reduced penetrance of the skin phenotype, cerebral dysgenesis, and neuropathy, we propose renaming this syndrome SNAP29-related disorder.
What's Happening in *Neurology® Genetics*

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