NALCN Dysfunction as a Cause of Disordered Respiratory Rhythm With Central Apnea

The sodium leak channel nonselective protein (NALCN) is a regulator of the pacemaker neurons that are responsible for rhythmic behavior (including respiration), maintaining the resting membrane potential, and are required for action potential production. NALCN-null mice show early death associated with disrupted respiratory rhythms, characterized by frequent and profound apneas. We report 3 children (2 siblings) with compound heterozygous mutations in NALCN associated with developmental impairment, hypotonia, and central sleep-disordered breathing causing apneas. Supplemental oxygen normalized the respiratory rhythm. NALCN mutations have been previously reported to cause severe hypotonia, speech impairment, and cognitive delay as well as infantile neuroaxonal dystrophy and facial dysmorphism. Nonsynonymous changes in the 2 affected extracellular loops may be responsible for the deleterious effect on the stability of the respiratory rhythm. Although oxygen is known to be a stabilizer of respiratory rhythm in central apnea in children, its role in NALCN dysfunction requires further investigation.

The sodium leak channel nonselective protein (NALCN) is a transmembrane, pore-forming protein that facilitates the intracellular movement of sodium. The NALCN gene is widely expressed in the central nervous system and is a critical component in the maintenance of resting membrane potential in excitable cells. An excellent recent review of NALCN function is provided by Cochet-Bissuel et al.1

CASE PATIENT 1 (FAMILY I.1)

The elder sister of our siblings was born by emergency cesarean delivery after a failed induction of labor (postterm) for oligohydramnios. The parents are nonconsanguineous and white. Her birth weight was 3230 g (z: −0.07) and occipitofrontal circumference was 34 cm (z: 0.1). Hypotonia with poor sucking reflex necessitated nasogastric feeding. Bottle feeding was established with specialized tests. Weight gain was slow and required calorie supplementation. At the age of 6 years, her BMI was 12.6. She showed a disturbance of her sleep-wake cycle. On occasion, she went without sleep for 48 hours. She has been diagnosed with attention-deficit/hyperactivity disorder. A diagnosis of global developmental delay was reached by 1 year and 3 months, she now attends a school for children with additional needs and has severe intellectual impairment. She has strabismus and hypermetropia requiring corrective lenses. Mild craniofacial dysmorphism is apparent with myopathic features (Fig 1A). Before this, plagiocephaly gave rise to pseudohemihypertrophy of the

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face, which has resolved. At age 7 years, she had an adenotonsillectomy after reported obstructed breathing at night. This had no effect on the underlying respiratory rhythms described below.

CASE PATIENT 2 (FAMILY I.2)
The male, younger sibling (Distributed European Community Individual Patient Healthcare Electronic Record [DECIPHER] number 257768) was born by elective cesarean at 39 weeks. His birth weight was 3232 g (z: −0.3) and occipitofrontal circumference was 36 cm (z: 1.21). Similar issues to his sibling were apparent from birth, including hypotonia and feeding difficulties, but the early use of specialized teats allowed an earlier discharge from the hospital. At age 8 years, his BMI was 13.7. Although he was sitting at 6 months old, further milestones were delayed. Speech and social skills are profoundly affected, and he has been diagnosed with autism spectrum disorder and learning disability. An MRI of the brain performed at age 3 years was normal. He attends a school for children with additional needs. He has strabismus and hypermetropia.

CASE PATIENT 3 (FAMILY II.1; DECIPHER NUMBER 263524)
Case patient 3 was born at 41 weeks’ gestation weighing 2850 g (z = −0.88). She was noted to be hypotonic and required support feeding in the neonatal period. She had marked plagiocephaly and facial asymmetry, which is still evident when she
smiles. She has a tall forehead with bitemporal narrowing and deep-set eyes. A brain MRI scan at age 3 years was reported normal. She underwent adenotonsillectomy at age 2 years and tympanostomy-tube insertion at age 5 years for glue ear.

She was delayed in her developmental milestones and sat at 1 year old. By 19 months old, she was walking with 1 hand being held but did not speak. An assessment at age 3 years highlighted difficulties with intelligibility and her expressive language, and this persisted until age 10 years. She started mainstream school with educational support but transferred to a school with additional support for learning at age 10 years. Child and Adolescent Mental Health Services offer support for behaviors and anxiety. At age 10 years, her BMI was 26.7 but this has plateaued on a weight-management program. She had normal echocardiogram, ophthalmology, and audiology assessment results. She has joint hypermobility.

A phenotypic summary of these and other published case reports is provided in Supplemental Table 1.

**BREATHING ABNORMALITIES**

The parents noticed an unusual breathing pattern from birth in case patient 1. This was characterized as a pattern of taking 3 breaths normally then “holding her breath” with no respiratory effort for the equivalent of 3 breaths. Initially this was felt to be physiologic apnea, but its persistence led to further investigations. Limited channel cardiopulmonary studies with the recording of airflow by thermistor were performed along with assessments of respiratory effort by inductance plethysmography, pulse, oxygen saturation (SpO₂) by pulse oximetry, transcutaneous carbon dioxide (TcCO₂) measurement, single lead cardiac monitoring, and video. The airflow measurement was poorly tolerated. Multiple sleep studies demonstrated frequent central apneas ameliorated with oxygen therapy (Fig 1D). A study from 2010 (aged 3 years), revealed a rhythm of 2 breaths followed by a cessation of respiratory effort, giving rise to an SpO₂ desaturation of >3% to 80% to 89%. Each event had a mean duration of 10 seconds at a frequency of 39 events per hour. The mean TcCO₂ reading was 5.6 kPa. The respiratory rate fell from 26 when awake to 14 when asleep. When supplemented with 1 L per minute of nasal cannula oxygen, there were markedly fewer respiratory pauses and no drop in SpO₂. Subsequent studies showed a notable periodicity of the events that is consistent with the effect of different stages of sleep.

Case patient 2 was not noticed to have abnormal breathing rhythm until he was 5 months old. A report from a sleep study performed at age 2 years revealed a rhythm of 1 to 2 breaths then complete cessation of effort for a mean duration of 9 seconds with a frequency of 37 per hour and an associated drop in SpO₂. TcCO₂ was stable at ∼5.5 kPa. No obstructive events were noted. With supplementation of 1 L per minute of oxygen nasal cannulae, respiratory pauses were less frequent and not associated with a drop in SpO₂. Images are unavailable because of the study quality and data storage procedures in place at his base hospital.

Case patient 3 was referred for assessment at 8 months of age and had a sleep study showing a mixture of central and obstructive episodes. An adenotonsillectomy resolved the obstructive episodes. All subsequent studies have shown the overwhelming feature to be central apnea with >100 events per hour in air and an almost complete abolition of the events with 0.5 L per minute of oxygen. The pattern consists of 3 or 4 breaths followed by a pause with a slight increase in heart rate and a drop in oxygen saturation as shown in Supplemental Fig 2. Sleep state appears to have no effect on the abnormality, and there is no evidence at 10 years of age in any change in sleep breathing abnormality.

**GENETIC ASSESSMENT**

All 3 children had negative screen results for common genetic and metabolic causes of hypotonia and congenital central hypoventilation syndrome.

On the basis of the unexplained developmental delay, case patients 2 and 3 were recruited to the Deciphering Developmental Disorders Study (www.ddduk.org). This is a United Kingdom–wide project that has recruited ~14000 probands with undiagnosed severe or extreme developmental disorders via regional clinical genetics services in the United Kingdom and Ireland with the aim of using new, genome-wide technologies to identify causative genomic variants. Trio-based, whole-exome sequencing was performed on case patient 2 and his parents as previously described. This revealed compound heterozygous mutations in 2 known developmental disorder genes: NALCN and TRAPPC9. The TRAPPC9 mutations were both missense variants; chr8 g.14145217G>A (ENST00000438773 c.853C>T; p.Arg285Trp) was paternally inherited, and chr8 g.141321437G>A (ENST00000438773 c.1532C>T; p.Thr511Met) was maternally inherited. Previous reports of biallelic TRAPPC9 mutations describe mental retardation, microcephaly, corpus callosum hypoplasia, facial asymmetry, and overweight habitus. He does not have most of these features; however, he is more severely affected than his sibling. She carries only 1 TRAPPC9 variant, and thus, he could display a composite phenotype, which has been reported in 4.9% of the rare
cases. These individuals were diagnosed with congenital contractures of the limbs and face with hypotonia and developmental delay syndrome. This appears to be a distinct condition, although phenotypic overlap does occur.

Pacemaker neurones are a class of neuron that are proposed to play a critical role in activities such as breathing, sleep-wake cycling, gut motility, and cardiac rhythmogenesis. The maintenance of resting membrane potential is facilitated by the NALCN’s passive, intracellular movement of sodium ions. One such collection of pacemaker cells resides in the pre-Bötzinger complex within the medulla, contributing to the complex network influencing our respiratory rhythm.

Apneas that occur only during sleep pose challenges to the narrative of the case, but there is precedent with conditions such as congenital central hypoventilation syndrome and Brugada syndrome, which also manifest during sleep.

The role of oxygen in alleviating this problem requires more study, although our sleep studies show similarity with those of periodic breathing of infancy. Premature infants with this condition show marked improvement of breathing regulation with supplemental oxygen therapy. The same effect has also been shown on sleep-disordered breathing in Prader-Willi syndrome. A knockout animal model observed in hypoxic and hyperoxic environments may offer insight into this relationship.

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ABBREVIATIONS

DECIPHER: Distributed European Community Individual Patient Healthcare Electronic Record
NALCN: sodium leak channel nonselective protein
SpO₂: pulse oxygen saturation
TcCO₂: transcutaneous carbon dioxide

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