

Low oxygen levels may decrease life-saving protein in spinal muscular atrophy

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Investigators at Nationwide Children's Hospital may have discovered a biological explanation for why low levels of oxygen advance spinal muscular atrophy (SMA) symptoms and why breathing treatments help SMA patients live longer. The findings appear in *Human Molecular Genetics*.

SMA is a progressive neurodegenerative disease that causes muscle damage and weakness leading to death. Respiratory support is one of the most common treatment options for severe SMA patients since respiratory deficiencies increase as the disease progresses. Clinicians have found that successful [oxygen support](#) can allow patients with severe SMA to live longer. However, the biological relationship between SMA symptoms and low [oxygen levels](#) isn't clear.

To better understand this relationship, investigators at Nationwide Children's Hospital examined gene expression within a [mouse model](#) of severe SMA. "We questioned whether low levels of oxygen linked to biological stress is a component of SMA disease progression and whether these low oxygen levels could influence how the SMN2 gene is spliced," says Dawn Chandler, PhD, principal investigator in the Center for [Childhood Cancer](#) and [Blood Diseases](#) at The Research Institute at Nationwide Children's Hospital.

SMA is caused by mutation or deletion of the SMN1 gene that leads to reduced levels of the survival motor neuron protein. Although a duplicate SMN gene exists in humans, SMN2, it only produces low

levels of functional protein. This is caused by a splicing error in SMN2 in which exon 7 is predominantly skipped, lowering the amount of template used for protein construction.

Mouse models of severe SMA have shown changes in how genes are differentially spliced and expressed as the disease progresses, especially near end-stages. "One gene that undergoes extreme alteration is Hif3alpha," says Dr. Chandler. "This is a stress gene that responds to changes in available oxygen in the cellular environment, specifically to decreases in oxygen. This gave us a clue that low levels of oxygen might influence how the SMN2 gene is spliced."

Upon examining mouse models of severe SMA exposed to low oxygen levels, Dr. Chandler's team found that SMN2 exon 7 skipping increased within skeletal muscles. When the mice were treated with higher oxygen levels, exon 7 was included more often and the mice showed signs of improved motor function.

"These data correspond with the improvements seen in SMA patients who undergo oxygen treatment," says Dr. Chandler. "Our findings suggest that respiratory assistance is beneficial in part because it helps prevent periods of low oxygenation that would otherwise increase SMN2 exon 7 skipping and reduce SMN levels."

Dr. Chandler says daytime indicators that reveal when an SMA patient is experiencing low oxygen levels during sleep may serve as a measure to include SMA patients in earlier respiratory support and therefore improve quality of life or survival.

More information: Bebee TW, Dominguez CE, Samadzadeh-Tarighat S, Akehurst KL, Chandler DS. Hypoxia is a modifier of SMN2 splicing and disease severity in a severe SMA mouse model. *Hum Mol Genet.* 2012 Jul 20. [Epub ahead of print]

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