USC scientist targets genetic cause of infant mortality

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A team of researchers led by Chien-Ping Ko, professor of biological sciences in USC Dornsife, has generated the first extensive study of severe denervation occurring in specific muscles affected by Spinal Muscular Atrophy, the leading genetic cause of infant mortality.

The disease is heartbreaking. It turns babies into ragdolls and extinguishes lives just as they are getting started. But one USC Dornsife scientist is working to unravel the mystery behind the leading genetic cause of infant mortality, uncovering how Spinal Muscular Atrophy (SMA) disconnects muscles from the mind.

SMA is a neurodegenerative disease caused by a recessive gene mutation that results in a deficiency of the Survival of Motor Neuron, or SMN, protein. In a phenomenon called denervation, neurons lose their physical connection to muscles, resulting in a loss of motor control and muscle

weakness.

A team of researchers led by Chien-Ping Ko, professor of biological sciences, has generated the first extensive study of severe denervation occurring in specific muscles affected by SMA. The data allows them to measure the effectiveness of drug treatments and will act as a springboard for future research that explores the cause of SMA.

One in every 40 to 50 people carries the gene for SMA. If two carriers have a child together, there is a 25 percent chance that the child will be affected. As a result, one in every 6,000 to 10,000 babies is born with SMA.

While SMA has multiple types varying in symptom severity and life expectancy, in its most severe type, SMA prevents babies from even being able to sit up. The prognosis in these cases is not good — most die before reaching the age of 2.

“That’s why you don’t often hear of this disease,” Ko said. “They die so young.”

Ko and his team are working to pull back the shroud and understand SMA better by tracing neurons down to specific muscles in mice affected by SMA to see exactly where the disease takes its toll.

“We are interested in what happens at the neuromuscular junction,” said Ko, who worked with USC graduate researchers Karen K. Y. Ling, Rebecca M. Gibbs and Zhihua Feng. Their study was published online this month by *Human Molecular Genetics* in advance of appearing in a print edition of the journal.

The results were odd, but enlightening. Muscles along the spine and hindquarters down to the legs showed varying — not uniform — degrees

of denervation. For example, several muscles controlling movement in the head and neck were severely affected, while other neighboring muscles were barely affected at all. Many of the affected muscles are involved in vital motor functions that are lost in patients, such as breathing, feeding and posture.

“So far, we don’t know the mechanism causing the loss of synapses in some muscles and not in others,” Ko said. “But this is a good preparation to study that.”

In addition, the knowledge of which muscles are affected and by how much is allowing pharmaceutical companies to quantitatively gauge the results of drug trials.

For example, although trichostatin A has been known to fight the disease in SMA animal models, Ko was able to determine exactly how much it reversed denervation in each individual muscle.

Ko is showing drug companies how to replicate his technique so that they can develop more effective drugs.

“Maybe we will have a way to mitigate or prevent the loss,” Ko said.

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