



## CHILDREN'S MERCY KANSAS CITY AT FOREFRONT OF NEC RESEARCH

### FINDING GENETIC LINKS TO NECROTIZING ENTEROCOLITIS IN PREMATURE INFANTS

Necrotizing enterocolitis (NEC) is a devastating inflammatory disease of the intestinal tract that affects approximately 10 percent of preterm babies born at less than 32 weeks or weighing less than 1.5 kilograms. The National Institute of Child Health and Human Development (NICHD) estimates about 10,000 babies develop NEC each year.

Although significant advancements have been made in the care of premature infants over the past decades, outcomes for NEC have remained virtually unchanged and may even be getting worse. As many as 15 to 30 percent of infants who develop NEC do not survive. Those who survive are at significant risk for serious complications, including intestinal failure and neurodevelopmental disabilities, such as cerebral palsy.

Today, the treatment for babies with NEC remains the same as two decades ago: stopping feeding, a course of antibiotics, and surgical resection for the sickest kids. A new understanding of possible genetic links to NEC could mean the opportunity to predict which infants are more likely to develop NEC and try newer patient-targeted therapies to overcome the genetic defect.

### RESEARCH YIELDS IMPORTANT RESULTS

Venkatesh Sampath, MBBS, Medical Director of Donald Thibeault Lung and Immunology Laboratories at Children's Mercy Kansas City, is leading an ongoing study of the immunogenetic basis of NEC in preterm babies. Dr. Sampath's team has published several large, multicenter studies to identify genetic risk factors for NEC, and his body of work has enhanced understanding of how

genetic variation contributes to NEC. His work is offering important new insights into the pathogenesis of NEC and creating the potential for more targeted care of infants with inherent susceptibility – including treatment to help them avoid the disease altogether.

In their work to date, Dr. Sampath and his colleagues have been able to identify two genetic links to NEC: ATG16L1 and SIGIRR.

**To date, Dr. Sampath and his team have received several intramural and extramural awards to pursue genetic studies in NEC, including a new NIH award of \$2.6 million over five years to study the role of the SIGIRR gene in NEC.**

### THE RELATIONSHIP BETWEEN SIGIRR AND NEC

SIGIRR is a gene that regulates inflammation in the gut. A preterm baby does not have a fully mature immune system in the gut, so it can react abnormally to bacteria, creating serious inflammation that may degenerate into NEC. To study the role of SIGIRR in NEC, Dr. Sampath and his team developed a mouse model that let them compare mice with normal SIGIRR gene function to mice with a loss of SIGIRR function. They discovered that the mice with loss of SIGIRR function were much more susceptible to NEC than were the control mice.

A development from this study is the ability to screen premature infants for SIGIRR function to determine susceptibility. Those babies identified as more likely to develop NEC will be offered more targeted therapy, such as probiotics and new drug therapies that may help them overcome this genetic defect and prevent the development of NEC.

## THE ATG16L1 GENE VARIANT ALTERS NEC RISK

Dr. Sampath and his colleagues developed a long-term multicenter study to investigate the relationship between sequence variants in the nucleotide oligomerization domain (NOD)-like receptor (NLR) genes and NEC in premature infants. The NLR pathway is key to regulating intestinal immune responses and altering susceptibility to inflammatory bowel disease, so Dr. Sampath hypothesized that dysregulated NLR signaling contributes to NEC in premature infants.

To test this hypothesis, the team enrolled 1,015 preterm babies from children's hospitals across the country in their study. These babies had a gestational age of 35 weeks or less. Of these, 86 infants, or 8.5 percent, were diagnosed with NEC.



*In the next five-year phase of the study, the team will perform genetic studies and animal experiments to understand how SIGIRR mutations increase risk of NEC in premature infants.*

The study looked at the group of genes within the cells that help regulate immune response to bacteria to find out whether common (minor allele frequency [MAF] >1%), function-altering NLR genetic variants affect NEC risk in premature infants. The study

determined that a loss of function of ATG16L1 variant (rs2241880, Thr300Ala) was associated with decreased NEC.

## THE FUTURE OF NEC RESEARCH

Dr. Sampath recently was awarded a \$2.6 million National Institutes of Health grant to continue his NEC research. In the next five-year phase of the study, the team will perform genetic studies and animal experiments to understand how SIGIRR mutations increase risk of NEC in premature infants. They also will test various therapies in mice with genetically mutated SIGIRR genes as an initial step toward translating newer therapies to prevent NEC in babies.

## RELEVANT PUBLICATIONS

A Functional ATG16L1 (T300A) Variant is Associated with Necrotizing Enterocolitis in Premature Infants. Sampath V, Bhandari V, Berger J, Merchant D, Zhang L, Ladd M, Menden H, Garland J, Ambalavanan N, Mulrooney N, Quasney M, Dagle J, Lavoie PM, Simpson P, Dahmer M. *Pediatric Research* (April 2017); 81(4): 582-588. doi: 10.1038/pr.2016.260. Epub 2016 Nov 28. PubMed PMID: 27893720.

Genetic predisposition to necrotizing enterocolitis in premature infants: Current knowledge, challenges, and future directions. Cuna A, George L, Sampath V. *Seminars in Fetal & Neonatal Medicine* (August 2018); pii: S1744-165X(18)30098-2. doi: 10.1016/j.siny.2018.08.006. Review. PMID: 30292709.

SIGIRR genetic variants in premature infants with necrotizing enterocolitis. Sampath V, Menden H, Helbling D, Li K, Gastonguay A, Ramchandran R, Dimmock DP. *Pediatrics* (June 2015); 135(6): e1530-4. doi: 10.1542/peds.2014-3386. Epub 2015 May 11. PMID: 25963006.



### LEARN MORE ABOUT THE STUDY OF GENETIC MUTATIONS AND NEC.

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