



IDENTIFYING THE IMPACT OF GENETIC VARIANTS ON SYSTEMIC STEROID RESPONSE IN PRETERM INFANTS AT RISK FOR BPD

CHILDREN'S MERCY KANSAS CITY FINDS LINK BETWEEN *CRHRI* AND STEROID RESPONSE

Bronchopulmonary dysplasia (BPD) is a frequent complication of extreme prematurity. With increasing survival of the most immature infants, rates of BPD are rising. A common preventive/therapeutic medication for BPD is systemic corticosteroids, but the clinical response to the medication in preterm babies is highly variable and unpredictable.

Tamorah Lewis, MD, PhD, neonatologist at Children's Mercy Kansas City, led a study¹ to better understand genetic variants within babies' DNA that can predict which babies will respond favorably to treatment. The study, the first of its kind, was formed around this hypothesis:

Genetic variants associated with corticosteroid metabolism and response will correlate with short-term improvement in respiratory phenotype among a clinically homogenous cohort of preterm infants.

The retrospective cohort study was performed using previously collected data from a large number of infants enrolled in a multisite randomized controlled trial^{2,3}. Dr. Lewis and the team reviewed pediatric asthma and perinatal corticosteroid treatment literature and identified pharmacogenetic variants associated with steroid response in these populations. Next, they investigated the association between those pharmacogenetic variants and the clinical response to systemic corticosteroids in infants at high risk for BPD. The primary outcome for the pharmacogenetic study was a change in respiratory severity score (RSS) at day seven of corticosteroid treatment with dexamethasone or hydrocortisone.

THE IDENTIFICATION OF *CRHRI*

Through its work, the team identified a genetic variant, a SNP in a gene called *CRHRI* that was associated with systemic steroid response in preterm infants. They believe that the observed association between *CRHRI* and exogenous steroid response in preterm infants is biologically plausible for two main reasons:

1. The SNP/gene has been proven important in other patient populations with regard to steroid response.
2. The gene is a known controller of endogenous steroid homeostasis, and thus may affect response to exogenous steroids.

As such, with this phase of the study, the team concluded that genetic variability in *CRHRI* is associated with corticosteroid responsiveness in preterm infants with evolving BPD. In the future, the identification of genetic markers of corticosteroid responsiveness may make it possible to individualize therapies, with the goal of optimizing the risk-to-benefit ratio for an individual child.

Under the leadership of Dr. Lewis, this is the first-ever pharmacogenetic study in preterm infants. Although there have been studies in other patient populations, such as older children and adults, to understand the relationship between genetics and drug response, no other study has focused on this particular population.

VALIDATING THE INITIAL FINDINGS

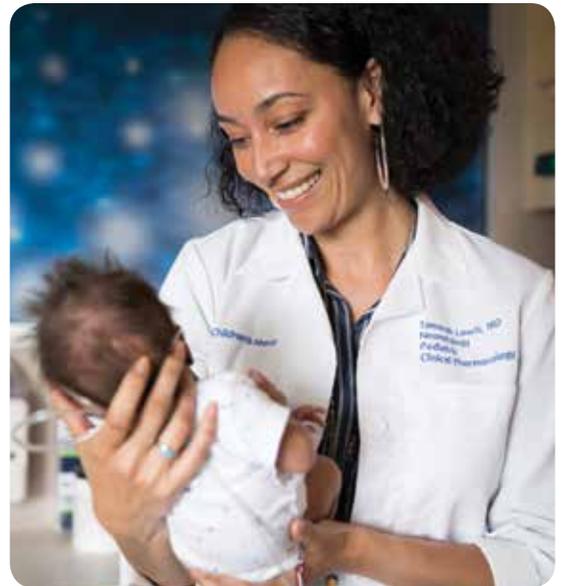
Now that the study has identified the role of *CRHR1* in variability in steroid response, the next step is to validate the findings in a larger cohort of babies. This will help the team confirm that the signal is real and eventually allow providers to use it to customize care. For example, if a baby carries no risk alleles, the neonatologist may choose to treat that baby with systemic corticosteroids due to the higher likelihood the baby will respond to the medicine. The variability in response to steroids is multifactorial, so future studies will also assess other genetic variables, metabolomic variables, and other important determinants of drug response, such as stage of development and environmental stressors.

To advance the understanding of this genetic variant, the team at Children's Mercy is organizing a prospective cohort to continue this line of study. With Internal Review Board approval, the team is actively enrolling all preterm infants who are treated with systemic steroids at Children's Mercy and The University of Kansas Hospital. The goal is to prospectively recruit a large cohort of these infants to look for confirmation of the initial findings and also attempt to identify other genetic and metabolomic changes that could predict steroid response.

While patients are being enrolled in the new cohort, the team is also in the process of applying for external funding to support expanding the study from a single-site cohort to a multisite study.

PRESENTATION OF STUDY FINDINGS

Initial findings from this study were presented in late 2018 at the annual meeting of The Children's Hospitals Neonatal Consortium. An article has been published online and a print manuscript will be published in *Pediatric Research* in April 2019, along with an Early Career Investigator highlight of Dr. Lewis and her unique training.



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SOURCES

¹ Genetic Variation in *CRHR1* is Associated with Short-Term Respiratory Response to Corticosteroids in Preterm Infants at Risk for Bronchopulmonary Dysplasia. Lewis T, Truog W, Norberg M, Ballard PL, Torgerson D. *Pediatric Research* (November 2018); <https://doi.org/10.1038/s41390-018-0235-1>.

² Randomized Trial of Late Surfactant Treatment in Ventilated Preterm Infants Receiving Inhaled Nitric Oxide. Ballard RA, Keller RL, Black DM, et al. *Journal of Pediatrics*; 168:23-29 e24 (2016).

³ The Randomized, Controlled Trial of Late Surfactant: Effects on Respiratory Outcomes at 1-Year Corrected Age. Keller RL, Eichenwald EC, Hibbs AM, et al. *Journal of Pediatrics*; 183:19-25 e12 (2017).



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