In Pursuit of the Causes of Premature Birth: The Links Between Genetics And Preterm Birth.

Preterm birth is still the world's gravest health problem for women and babies, affecting 15 million children every year—one million of them die. One of the reasons preterm birth is such a difficult health problem to solve — perhaps the most difficult of all human health problems — is that in over 50 percent of preterm births, we don't know what caused them. And if you don't know the cause of a health problem, you're not going to be very effective developing interventions to stop it.

But there’s also a lot we do know. For instance, we know that the single most important predictor of preterm birth is a previous preterm birth, whether the woman has already had one herself, or she comes from a family that has a strong history of preterm birth. That means there are important genetic indicators—ones we haven’t recognized yet—that have a big impact on this problem. In the past, pointing that chain of causality, however strongly, at the genome effectively only narrows down our search to something akin to looking for a handful of needles in a haystack the size of Kansas.

• One in ten babies in the United States is born prematurely each year
• Premature birth is the leading cause of death in children under 5
• Approximately 380,000 babies are affected in the U.S. annually
• Premature birth costs society more than $26 billion a year according to the Institute of Medicine
• 15 million children are born prematurely every year worldwide
• Premature birth often leads to a lifetime of significant health challenges, including hearing/vision loss, intellectual disabilities, and cerebral palsy

The consequences of preterm birth—including health care costs and impaired quality of life—extend to the entire family. The March of Dimes Prematurity Research Center Ohio Collaborative is a robust, integrated cross-institutional facility. Its goal is to develop fundamental new insights into the biology of human pregnancy and the disease mechanisms of premature birth in order to decrease the rate of prematurity and its associated complications.
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So while we’ve long suspected that genes play a significant role in determining gestational length, so far we’ve not been able to conclusively prove which ones, and why. Our search has yielded some clues, however. In prior studies, certain genes have been singled out as possible culprits that contribute to conditions that either accompany preterm birth, like low birth weight, or conditions that sometimes precede it, like preeclampsia.

While the technology to identify these genes has been available for the last 15 years or so, the stumbling block has been that we have never had a large enough data set to study. Previous studies have looked at the records of a thousand or so women, but what has been needed is a dataset as much as 50 times larger. From that, we could build a genome-wide study that looks at the gestational length of tens of thousands of births, whose results would allow us to identify the genes, whose expression causes, or triggers other processes to cause preterm birth.

Now, for the first time in the history of human pregnancy, that’s what we have.

The Largest Genome-wide Study of Preterm Birth Ever Conducted.

Thanks to an unprecedented level of transdisciplinary and even transcontinental collaboration, Dr. Louis Muglia and Dr. Ge Zhang of the March of Dimes Prematurity Research Center--Ohio Collaborative spearheaded, in partnership with Dr. Bo Jacobsson of Sahlgrenska Academy, University of Gothenburg, Sweden and Norwegian Institute of Public Health, Oslo Norway, and an international team, in what will certainly be hailed as an extraordinary breakthrough in the study of preterm birth: the largest genome-wide study of preterm birth ever fielded, including more than 50,000 pregnancies, resulting in identifying the locations of no less than six genes whose expressions play a significant role in causing the conditions that bring about preterm birth.

Because of its breadth, depth and potential for sparking further research, this study marks the beginning of using human populations to understand the human genome in a robust way to find genetic triggers that cause preterm birth. This approach, called a “genome-wide association study,” is the culmination of decades of scientific research, the application of the latest innovations in genetic technology, and global cooperation.

One of the breakthroughs that made this study possible was initiated by Dr. Muglia when he sent an email to 23andMe, the genetic testing company. It turned out that 23andMe had collected a rather large data set, 43,568 women of European ancestry, to be exact, who had all answered the question, “How long was your first pregnancy?” This large data set formed the basis for the genome-wide association study in which gestational length was used as a continuous trait and either term or preterm birth was the dichotomous outcome.

The women in this data cohort were called the discovery set. But because all the information was self-reported, data from follow-up cohorts were needed to associate, replicate and validate the results. And for these, Dr. Muglia, in partnership with Dr. Jacobsson, relied on long-standing relationships he had built with
researchers in the Scandinavian countries and their governments. Working with various agencies in Norway, Sweden, Denmark and Finland, he obtained replication studies that included three Nordic data sets, for a total of 8,643 women. This dataset was used to test for the replication of genomic loci that were associated with those in the discovery set.

“When you’re comparing more than a million genetic variants over a large population, the first thing you worry about is a false positive. And so you always need a second, independent group to know that those results are robust,” Dr. Muglia said. “We didn’t know how accurate the self-reporting in discovery group was, so we needed a second group where the data was very carefully and precisely documented. Although it’s a smaller sample size, we were able to use that data to validate the data from the discovery group.”

Using data from these Scandinavian countries was important for several reasons: First, the rates of preterm birth in those countries are relatively low, around 7 percent or less, which likely reduces environmental factors leading to prematurity. And second, these countries have very well developed health registries, which have been meticulously collecting detailed health and genetic information for years, so it was readily obtainable and most important for a replication cohort, extremely reliable.

“The technology to perform this study has existed for the last 15 years or so. But we lacked the populations upon which to build a strong statistical foundation,” said Dr. Muglia. “In total, we analyzed over 50,000 pregnancies, and when you get into those kinds of numbers, you’re establishing a foundation secure enough to base future investigations on. Now, for the first time in history, we have that foundation.”

The Results and What They Mean.

In both the discovery and replication sets, six gene areas and their variants were associated either with gestational length, preterm birth or both, in various ways.

“Overall, genetics probably contributes to between 25 percent and 40 percent of all preterm births, and the genes we identified probably represent an even smaller percentage of that, but individually, they might increase—or decrease—a woman’s chances of having a preterm birth by 10 to 20 percent,” said Dr. Muglia.

“These findings also help us understand the pathways genes affect. For instance, one of the genes we identified regulates a selenium, a micronutrient. But we did not how that particular micronutrient was important for pregnancy. So we have identified risk factors for how selenium is handled, but for certain populations, might the micronutrient itself be deficient? Would supplementing it benefit certain populations in preventing preterm birth? We think that’s fairly likely and we’re just embarking on studying that further,” he said.
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“Forthmore, people have been looking at the same pathways over and over again—hormone signaling and inflammatory and the genes that they’ve been looking at have not really been revealing to date,” he said. “We now know that the genes we’ve identified have variants that are contributing to preterm birth, but they are not ones we would have predicted ahead of time. They make sense in retrospect, but they’re not where you would necessarily start. Until you get evidence like this.”

What Comes Next?

Dr. Muglia sees two new avenues of research based on this research. First, we need to understand more about the genes we’ve identified.

“We just identified six super exciting targets, these regions of the genome, but we don’t know exactly how each variant is altering gene expression to cause a change in pregnancy outcomes,” he said. “So we need to very carefully characterize those causal polymorphisms: what genes are they regulating, and how do they affect pregnancy?”

“We have some ideas about the capacity of some of these genes—many of them affect the lining cells of the uterus, a tissue that is important for pregnancy but hasn’t been the main focus in the past. Other genes are expressed in many different cell types in the immune system, or in mother’s metabolic pathways, so we don’t know how those are working and for us to be able to design the kinds of interventions we need, that are based on mechanisms that are disruptive to pregnancy, we need to understand that,” he said. “But now that we know the regions to look at and how to study them, we intend to collaborate very closely with the March of Dimes Prematurity Research Center University of Chicago-Northwestern-Duke because they’re studying expression of genes and are going to be an important partner on this, and we’re also going to be working with the Prematurity Research Center-Stanford University School of Medicine to make this information, along with other findings, part of the GEneSTATION and other data repositories.”

“Second, we’ve shown the power of large sample sizes in genetics and we need to continue increase our sample size so we can discover even more genes, not only in the mother’s genome, but in the baby’s as well. We also want to expand to cohorts that are not of European ancestry—there are huge racial and ethnic disparities in other populations and we need to understand if genetics is a substantial contributor, he said.”
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“The Path Forward is Clear.

Thanks to the pioneering work done by Drs. Muglia, Zhang and their colleagues around the world, we now have conclusive proof that genetics has a profound impact on human preterm birth, and there is a great potential to discover new interventions based on new genetic pathways this solid evidence shows.

This work would not have been possible without the extraordinary collaboration that crossed continents and oceans. Vital information was provided by the participants in Finland, Denmark, Sweden and Norway. The University of Iowa and Vanderbilt shared important information with Dr. Muglia’s team, while Yale University and Children’s Hospital in Cincinnati provided critical analysis that showed how one of the regions identified contained a DNA change that altered the ability of estrogen receptor to bind in the region and regulate gene expression. And other March of Dimes Prematurity Research Centers, especially those at Chicago-Northwestern-Duke and Stanford University School of Medicine, will play important roles in disseminating this research to the other centers as fuel for their researchers and by extension, the rest of the world.

As always, we’re limited by resources, not by ideas.

The March of Dimes has supported Dr. Muglia’s work since 2004, and was the driving force behind this latest breakthrough. But we were not the only ones who invested in his vision. The Gates Foundation was instrumental in funding as well as the Scandinavian governments and philanthropic societies.


I want to thank all the people and organizations that worked on this project. We complement each other’s skills, and without everyone’s contributions, we wouldn’t have made this progress. The sustained investment is really starting to pay off.”

Louis J. Muglia, M.D., Ph.D.

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