How Mom May "Inherit" RA Risk From Baby - Or Dad

December 11, 2014 | Rheumatoid Arthritis [1]
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Microchimerism ("blending" of cells) during pregnancy can confer genetic risks for rheumatoid arthritis in unexpected ways, according to this research on women with the disorder. It may also affect the risk for some men. **Source: Rheumatology Network**

Rheumatoid arthritis (RA) affects three times more women than men. For this reason, female-specific factors such as exposures related to pregnancy are suspected to be involved in the disease. Traditionally, the father’s genetic makeup has been viewed as relevant only to his child’s health. We have found that a father’s family history can become part of the mother’s history, influencing her predisposition to RA, passed indirectly through the fetus. This can happen via the two-way exchange of cells between fetus and mother during pregnancy, which is a form of microchimerism (MC), the presence of cells in one organism that originated in another.\(^1\) Pregnancy can expose both fetus and mother to MC cells with elements deriving from each other.

- In most pregnancies, **fetal material can be identified in the mother’s blood** as early as 6 weeks after conception, and is cleared soon after delivery.
- However, fetal DNA **can remain in the mother’s body for decades.** The causes of persistence remain unknown. Because the fetus can be seen in some senses as a foreign graft, HLA haplotypes may play a role.
- MC **can occur among individuals who have not actually borne a child,** through: spontaneous and induced abortions, gestating in the same uterus as a twin, indirect exposure in the mother’s blood from an older sibling, or blood transfusion.
- The presence of **fetal MC is more common in women with RA** than in women who do not have the disease.\(^2,3\) MC cells **have been identified in affected tissue** such as rheumatoid nodules and synovial fluid.
- MC cells are **thought to have stem cell-like properties,** as engraftment has been found in various organs, perhaps creating graft-like conditions. Some autoimmune conditions have similarities to graft-versus-host disease.\(^4\)

MC could affect RA and other autoimmune conditions in one of two ways:
1. Microchimeric antigens are presented to the mother’s T cells, or
2. Fetal T cells attack maternal antigens.

**Mothers with RA are more likely to have children with HLA profiles associated with RA risk.** One of the most polymorphic regions in the genome, HLA is associated with the strongest genetic risk in RA. We have investigated whether children of mothers with RA are more likely to carry HLA risk alleles than are those born to mothers without RA.

- The **highest risk of RA is associated with HLA alleles collectively referred to as the “shared epitope” (SE),**\(^5\) alleles encoding specific amino acid sequences at positions 70-74 of the 3rd hypervariable region of HLA-DRB1. SE alleles are strongly associated with seropositive or anticitrullinated protein autoantibody (ACPA) positive RA.\(^6\) One SE allele appears to confer a 4-fold increase in RA risk and 2 alleles an 11-fold increase, compared to healthy persons who do not carry any SE alleles.\(^7\)

- **Mothers with RA are twice as likely as unaffected control mothers to have children who carry SE alleles,** our research shows--after taking into account the mother’s own HLA risk status, including the SE. (We compared the frequency of mothers with children carrying HLA risk...
alleles such as the SE, and alleles encoding the five high-risk amino acids reported by Raychaudhuri and colleagues.)

► **Mothers might also be susceptible to long-term MC, analogous to a foreign graft.** We investigated this possibility by inquiring whether mothers with RA were more likely to have children who were more similar to themselves at each of the classical HLA genes. We found no evidence of increased similarity. (It remains possible that other HLA and non-HLA relationships between mother and child could predispose to long-term MC.)

The finding that a child's genes are independently associated with risk of RA in the mother **could have implications for how we assess risk in the clinic.**

► A father's family history could change the *a priori* probability of RA, especially for women who lack traditional risk factors for the disease. Identifying patients at high risk can lead to earlier treatment and improvement of patient quality of life.

► These findings **could be relevant to women with any history of pregnancy**, regardless of the pregnancy outcome.

► For both men and women, MC could also contribute to the **well-known association between blood transfusion and RA risk.**

**References:**


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