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Forward and reverse inheritance — the yin and the yang

J. Lee Nelson and

Clinical Research Division, Immunogenetics, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, Seattle, Washington 98109, USA; and at the Department of Medicine, University of Washington, Seattle, Washington, USA

Nathalie C. Lambert

Aix-Marseille University, INSERM, Gènes HLA-DR, 163 Avenue de Luminy, 13288 Marseille cedex 09, France

Standfirst

The theory of Mendelian inheritance states that half our genes are maternal and half are paternal. This view is incomplete, as maternal–fetal exchange creates a legacy of non-native cells within an individual that can affect their health for better or worse, including contributing to their risk of developing autoimmune disease.

In common with other autoimmune diseases, rheumatoid arthritis (RA) has an increased prevalence in females and strong HLA-associated genetic risk factors. A 2017 study by Cruz *et al.*¹ reveals that the risk of a woman developing RA is influenced by the specific HLA alleles carried by any children born to her before disease onset. HLA molecules have a central role in the immune system, presenting foreign antigens and self-antigens as part of a network that, during health, is tolerant to normal self-antigens. The specific HLA molecules associated with risk of RA are well-defined, with the best known RA-risk factor being a series of similar sequence motifs at positions 70–74 of the HLA-DRβ1 chain (QKRAA, QRRAA or RRRAA), encoded by some allelic variants of *HLA-DRB1* (for example, *04:01, *04:04, *04:05, *04:08, *01:01, *14:02 and *10:01). These sequence motifs are known as the ‘shared epitope’. Overall, Cruz *et al.*¹ found that the risk of developing RA was increased among women who had given birth to a child with an allele encoding the shared epitope (adjusted for the mother’s status as a carrier of RA-risk alleles; OR 3.0, 95% CI 2.0–4.6).

Bidirectional exchange of cells between the mother and fetus during pregnancy creates a long-term legacy. A mother’s cells persist in her progeny into adult life, and cells of fetal origin are present in women for many years following a pregnancy, potentially persisting for a lifetime (FIG. 1). These small populations of naturally occurring immigrant cells carry a complement of genes that differ from the individual who acquires them, a phenomenon known as microchimerism, and can confer benefits or risks to that individual’s long-term

Correspondence to J.L.N. Inelsonlab@fredhutch.org.

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health². This potential for a child's genetic makeup to influence maternal health later in life can be considered akin to 'reverse inheritance'.

Two previous studies provided evidence that women with RA who are negative for the shared epitope more frequently harbour shared epitope-positive microchimerism than healthy women^{3,4}. When Cruz *et al.*¹ stratified patients according to their shared epitope status, shared epitope-positive mothers with RA were more likely to have had a shared epitope-positive child than matched healthy women. Surprisingly, the corresponding results were not statistically significant for shared epitope-negative mothers, although the number of shared epitope-negative mothers among cases was low (31 shared epitope-negative cases among the 170 total cases). Stratified analysis did, however, indicate that having a child or children who carry alleles encoding lysine at position 71, essentially representing *HLA-DRB1*04:01*, conferred a risk of developing RA in both risk-allele carrier and non-carrier mothers ($P = 0.01$ and $P = 0.001$, respectively).

These observations bring to mind an intriguing aspect of RA immunogenetics, namely that there is a hierarchy of RA-risk⁵ depending on the HLA genotype of an individual, and that the three different shared epitope sequences are not equivalent. At the top of the hierarchy is *HLA-DRB1*04:01*, which confers risk irrespective of the second haplotype, whereas the other shared epitope sequences are most potent in specific combinations, a phenomenon referred to as compound heterozygosity. Consideration of this hierarchy provides a potentially analogous explanation for the observations of Cruz *et al.* Briefly, carrying a child with the strongest shared epitope sequence (QKRAA, *HLA-DRB1*04:01* with a lysine at position 71) will be sufficient to confer risk, but carrying a child with any of the other shared epitope sequences will only be sufficient to confer risk if they are present in the context of another shared epitope sequence. Lending support to this interpretation, Rak *et al.*³ observed a higher occurrence of *HLA-DRB1*04*-positive microchimerism in *HLA-DRB1*01*-positive patients with RA than *HLA-DRB1*01*-positive microchimerism in *HLA-DRB1*04*-positive patients with RA. In this study³, it was assumed that *HLA-DRB1*04* and *HLA-DRB1*01* microchimerism primarily consisted of shared epitope-encoding alleles. In a subsequent study, QKRAA and QRRAA microchimerism was directly demonstrated⁴. Neither study^{3,4} distinguished the source of shared epitope-positive microchimerism.

Non-inherited maternal HLA alleles can also have long-lasting effects on her progeny. The sequence DERAA, encoded at the same amino acid positions as the shared epitope but by other *HLA-DRB1* alleles, is considered to be RA-protective in most studies. As discussed by Cruz *et al.*¹, a previous study in patients with RA showed a deficit of non-inherited maternal alleles encoding DERAA compared with non-inherited paternal alleles. In light of this evidence, the finding of an increased risk of RA among women with a child who had a DERAA-encoding allele was unexpected¹. Although the explanation for this finding is unknown, one consideration is that the effect of maternal cells acquired during fetal life (when the immune system is developing) can be expected to differ from that of fetal cells acquired by an adult woman (when the immune system is mature). Functional studies have not yet addressed this subject, although other kinds of unexpected outcomes in the maternal-fetal relationship have been described. For example, children born to mothers with type I

diabetes mellitus were less likely to develop the disease when islet-specific autoantibodies were present in cord blood than when they were absent, contrary to expectations⁶. Also, variable results were reported in studies that evaluated RA risk according to whether the non-inherited maternal HLA allele encoded a shared epitope sequence⁷. What is missing is a study that evaluates the effect of both the non-inherited maternal HLA allele and the paternally transmitted HLA allele of children born before disease onset in women with RA.

Another variable that could affect results is gravidity without parity. The majority of studies have found an overall decrease in RA risk in parous women, as compared with nulliparous women^{8,9}. Both spontaneous and induced abortion can also result in microchimerism²; however, gravidity without parity seems to confer no protection against RA⁸. Other sources of microchimerism include a recognized or unrecognized twin and, potentially, previous microchimerism from an older sibling or maternal miscarriage, passed along with maternal cells to a child born later in the mother's life² (FIG. 1). Together, these microchimeric cells might be likened to a patchwork within the individual, creating increased genetic diversity in women and having variable effects depending on the source of the cells and the timing of acquisition, among other factors.

Naturally acquired microchimerism can be tissue-specific or haematopoietic, and harbouring multiple microchimeric 'grafts' across generations in women is of special interest, as highlighted by experimental studies¹⁰. Much can be learned from elucidating the long-term consequences of forward and reverse inheritance; in terms of both the benefits and the risks that can be accrued from our immigrant cell populations, acquired as a natural form of 'mini-gene transfer'.

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References

1. Cruz, G.I., et al. Increased risk of rheumatoid arthritis among mothers with children who carry DRB1 risk-associated alleles. *Ann Rheum Dis*. 2017. <http://dx.doi.org/10.1136/annrheumdis-2016-210662>
2. Nelson J.L. The otherness of self: microchimerism in health and disease. *Trends Immunol*. 2012; 33:421–427. [PubMed: 22609148]
3. Rak J.M., et al. Transfer of shared epitope through microchimerism in women with rheumatoid arthritis. *Arthritis Rheum*. 2009; 60:73–80. [PubMed: 19117368]
4. Yan Z, Aydelotte T, Gadi V.K., Guthrie K.A., Nelson J.L. Acquisition of the rheumatoid arthritis HLA shared epitope through naturally acquired microchimerism. *Arthritis Rheum*. 2011; 63:640–646. [PubMed: 21360493]
5. Balandraud N, et al. HLA-DRB1 genotypes and the risk of developing anti citrullinated protein antibody (ACPA) positive rheumatoid arthritis. *PLoS ONE*. 2013; 8:e64108. [PubMed: 23737967]
6. Holm B.C., et al. Evidence for immunological priming and increased frequency of CD4+ CD25+ cord blood T cells in children born to mothers with type 1 diabetes. *Clin Exp Immunol*. 2006; 146:493–502. [PubMed: 17100770]
7. Guthrie K.A., Tishkevich N.R., Nelson J.L. Non-inherited maternal human leukocyte antigen alleles in susceptibility to familial rheumatoid arthritis. *Ann Rheum Dis*. 2009; 68:107–109. [PubMed: 18684745]

8. Guthrie KA, Dugowson CE, Voigt LF, Koepsell TD, Nelson JL. Does pregnancy provide vaccine-like protection against rheumatoid arthritis? *Arthritis Rheum.* 2010; 62:1842–1848. [PubMed: 20309863]
9. Guthrie KA, Gammill HS, Madeleine MM, Dugowson CE, Nelson JL. Parity and HLA alleles in risk of rheumatoid arthritis. *Chimerism.* 2011; 2:11–15. [PubMed: 21547030]
10. Kinder, JM., Stelzer, IA., Arck, PC., Way, SS. Immunological implications of pregnancy-induced microchimerism. *Nat Rev Immunol.* 2017. <http://dx.doi.org/10.1038/nri.2017.38>

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Figure 1. Forward and reverse inheritance from microchimerism of maternal and of fetal origin Maternal–fetal exchange creates a long-term legacy of a small number of cells in an individual that have a different genetic makeup, known as microchimerism. The individuals AC and EH in the middle generation harbour microchimerism from their mothers (AB and EF, respectively). In addition, AC can acquire cells from her children (AE, CH and AH) as a result of her own pregnancies. Other possible sources of microchimerism include a twin (including a vanished twin), pregnancies not resulting in a birth, and, potentially, previous microchimerism from maternal miscarriages or an older sibling that is carried with maternal cells to a later pregnancy (the latter illustrated as microchimerism from AE in AH).