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Allo- and auto-anti-D in weak D types and in partial D

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Pham et al.¹ published findings on the nature of anti-D among individuals carrying weak D types 1 or 2. By evaluating 121 weak D type 1 and 99 weak D type 2 individuals and documenting 12 examples of auto-anti-D, they present arguably the largest study to address, but not the first study to resolve, the nature of allo- and auto-anti-D in these two most prevalent weak D types. Pham and coworkers imply consequences for transfusion and pregnancy, which are in full accordance with recommendations published in 2000.² The current study lacks data on transfusion and pregnancy, which previous studies did address. There must have been transfusions and pregnancies in the 220 patients and many involving exposure to D positive blood. But how many exposures occurred under which specific circumstances? These data would strengthen their publication. Without such data, critical evidence for their clinical recommendations, which we fully support, is unfortunately lacking.

Pham et al. stated that their serologic data for anti-D are “in accordance with the incomplete serologic data obtained”¹ by one of the undersigned authors.² Because data, conclusions and recommendations in the 2011 paper¹ are in accordance with our study published in 2000, our data² cannot be labeled “incomplete”. Limitations imposed by the format of this Letter do not allow reference to all additional corroborating data published since 2000, specifically in 2006³ and continuously updated online (<http://www.uni-ulm.de/~wflegel/RH/RIR/rirres.html>). Pham et al. should cite these references that provide data supporting their conclusions.

There is no surprise that more extensive testing¹ and larger numbers of observations¹ have been made in the decade since the definition of weak D types⁴ was published in 1999. Such corroborating data are important, very welcome and enhance our knowledge. Despite abstracts and oral communications claiming allo-anti-D, there has been no publication to date substantiating such claims of allo-anti-D in prevalent weak D types 1, 2, 3 and 4.0. Even if one or more case reports in the future were to prove allo-anti-D unambiguously, the current clinical recommendations for prevalent weak D types might not be affected. Based

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on the extensive study by Pham et al.,¹ our conclusions from 2000 seem to have sustained the test of time.

The terms “partial D” and “weak D type” were coined by groups in France in 1984⁵ and in Germany/Austria in 1999.⁴ It is worthwhile to revisit the definition for partial D: “All partial D people may produce anti-D, this is not the case of true D^u persons.”⁶ Many D variants are routinely termed “partial D” today, for which no anti-D has ever been observed. One can justifiably doubt that they have a much increased propensity to become anti-D immunized, despite their lack of some D epitopes. Because “partial D” is accepted without any evidence of allo-anti-D (in violation of the original definition, of course), how should we know who is a “true” weak D (D^u) person? Although our use of “partial D” constantly violates the original definition, no one takes issue with the term “partial D”. Pham et al.¹ endorse this common misconception by not applying the “weak D type” and “partial D” definitions as rigorously as the scientific process requires:

The more recent “weak D type” terminology⁴ is based only on structural features, including the D antigen and the nucleotide sequence of the *RHD* gene, unavailable in 1984. This finally resolved in 1999 the somewhat circular definition of partial D from 1984 and allowed to separate by more rigorous scientific criteria “true” weak D types from partial D at the time of their first observation. An anti-D immunization event or lack thereof has never been part of the weak D type terminology, as it is not a mandatory feature of the partial D terminology used today.

The term “weak D type” for a distinct D variant is not invalidated if later an anti-D is observed, no matter if it is allo or auto in nature. Introducing anti-D immunization events as defining criteria into the terminology, as proposed by Pham et al.¹ and others, is a step backwards. We regularly transfuse many partial D patients, like those carrying DVII, with D positive blood; and no one takes issue. Conversely, there are patients with distinct weak D types who can produce anti-D and must be transfused with D negative blood; we should get used to this approach as well.

It will be an interesting lead for research in immunology, if a propensity is found for many weak D types to develop low titer, clinically benign auto-anti-D after exposure to D positive blood. Pham et al.¹ cannot exclude an observation bias in their study, like recruiting weak D individuals with anti-D preferentially. Although 12 auto-anti-D among 220 individuals with weak D types 1 and 2 may be a correct representation, we conclude that the occurrence of auto-anti-D in these two most prevalent weak D types in Caucasians is a rare event.

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