RHCE variants inherited with altered RHD alleles in Brazilian blood donors

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SUMMARY

Background: The high homology and opposite orientation of RH genes promote rearrangements between them and generate a large number of RHD and RHCE variants which can be inherited together. Searching of RHD-CE genotypes predicting partial antigens in donors is of interest in order to find more closely matched donors for African descent patients. This study aimed to evaluate a molecular approach to search for RhCE variants in a cohort of individuals with altered expression of D antigen and determine the association of RH variant alleles in Brazilian blood donors.

Methods: From 80,561 blood samples tested, 421 with atypical D typing results were studied. The samples were phenotyped for C, c, E, e antigens. Rh variants were identified using molecular techniques.

Results: All 421 samples had altered RHD alleles, being 56.3% of them partial D. Among them, 94.9% presented variant RHCE*ce and the most common associations were: RHD*weak: D type 4.2.2 with RHCE*ceAR; RHD*DAR linked to RHCE*ceVS:02; and RHD*weak: D type 4.0 linked to RHCE*ceVS:02 and RHCE*ce (c.488C, c.1057T, c.733G, c.744C, c.1025T). Among the samples with RhCE variants, 10.6% predict partial c, partial e, hr+ and/or hr− and 100% express low prevalence antigens.

Conclusion: Targeting individuals with altered expression of D antigen can be a good strategy for finding donors with RhCE variants. In our study 94.9% of the partial D samples revealed altered RhCE variant alleles and 5.7% of the samples with altered RHD allele predicted partial c, partial e and the lack of the high prevalence hr+ and hr− antigens.

Key words: blood group genotyping, partial RhD, Rh variants, RHCE alleles.

Rh system is one of the most important and complex blood group systems (Flegel, 2007; Westhoff, 2007), which is composed by two homologous genes, RHD and RHCE, encoding the RhD and RhCE proteins. Approximately 50 antigens in addition to the five major Rh antigens (D, C, c, E and e) are encoded by these genes. The large number of antigens is attributable to the complex genetic basis of RH genes (Flegel, 2007), including the position on the chromosome and the high similarity between them, that promotes gene rearrangements (Okuda et al., 2000; Suto et al., 2000), besides single nucleotide polymorphisms (SNPs), deletions and insertions which may give rise to a large number of variant RhD and RhCE proteins.

Over 200 RHD and 80 RHCE alleles were reported (http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/). Altered RH alleles may lead to weak expression, loss of epitopes and expression of new antigens. Variant RHD and RHCE alleles are prevalent in individuals of African descent with alleles encoding altered (partial) antigens. Patients with partial Rh antigen can make alloantibodies corresponding to the epitopes missing from the altered antigen (Huc-Roye et al., 2011; Noizat-Pirenne & Tourmann, 2011; Westhoff et al., 2013a) and these Rh antibodies can be clinically significant (Chou et al., 2013; Sippert et al., 2015).

Many variant RHCE*ce alleles encoding partial e antigens have been described expressing low-prevalence antigens (e.g. V and VS) and lacking high-prevalence antigens, such as hr+ and hr−, contributing to Rh alloimmunization (Noizat-Pirenne & Tourmann, 2011). Therefore, transfusion dependent patients of African origin can make complex antibody specificities, such as anti-hr+ and anti-hr−, and present a challenge with regard to finding compatible blood for them (Reid et al., 2014).

Another level of complexity occurs when the variant RHCE is inherited with an altered RHD. Some combinations are more common than others, e.g. RHCE*ce77 is frequently cis to RHD*DVA:2 (Westhoff et al., 2013a), RHCE*:ceAR or RHCE*:ceEK are inherited with RHD*DAR (Hemzer et al., 1999), RHCE*:ceMO is often found with RHD*D10A (Westhoff et al., 2013b), RHCE*:ceBi is linked to RHD*DOL (Rousset et al., 2012) and RHCE*:ce48C,733G,1006T is usually associated to RHD*D10L (Westhoff et al., 2010).