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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 80,961 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; RHD*weak D type 4.0* linked to *RHCE*ceVS.02 and RHCE*ce (c.48C, c.105T, c.733G, c.744C, c.1025T)*. Among the samples with RhCE variants, 10·6% predict partial c, partial e, hr^B- and/or hr^S- 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^B *and* hr^S *antigens.*

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

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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, E, c 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 antigens can make alloantibodies corresponding to the epitopes missing from the altered antigen (Hue-Roye *et al.*, 2011; Noizat-Pirenne & Tournamille, 2011; Westhoff *et al.*, 2013b) 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^B and hr^S, contributing to Rh alloimmunization (Noizat-Pirenne & Tournamille, 2011). Therefore, transfusion dependent patients of African origin can make complex antibody specificities, such as anti-hr^S and anti-hr^B, 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*ceTI* is frequently *in cis* to *RHD*DIVa-2* (Westhoff *et al.*, 2013a), *RHCE*ceAR* or *RHCE*ceEK* are inherited with *RHD*DAR* (Hemker *et al.*, 1999), *RHCE*ceMO* is often found with *RHD*DAU0* (Westhoff *et al.*, 2013b), *RHCE*ceBI* is linked to *RHD*DOL* (Roussel *et al.*, 2012) and *RHCE*ce48C,733G,1006T* is usually associated to *RHD*DIIIa* (Westhoff *et al.*, 2010).

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