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## Molecular and laboratory characteristics of recessive von Willebrand Disease 2N anno 2018

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**Introduction**: The FVIII binding site on von Willebrand factor (VWF) is located in the D' (766-864) and D3 (1054-1060) regions of the VWF gene. The cysteine residues in the D' domain Cys767-Cys808;Cys776-Cys804;Cys810-Cys821 form disulfide bridges between two D' trypsin-inhibitor-like (TIL') and E' regions, which are of critically importance for the binding between Til'E' and FVIII.

**Aims:** To study the genotype phenotype relationship of VWF in von Willebrand disease (VWD) 2N

**Methods:** We critically analyzed the molecular and laboratory characteristics of VWD 2N reported in the literature and describe experiences from three VWF Research Centers in Europe.

**Results:** Homozygous non-cysteine R854Q/R854Q mutation and of R854Q double heterozygous with non-cysteine E787K, T791M and R816W mutations in the D' domain result in a mild FVIII binding defect (FVIII:BD) (about 30%) featured by mild to moderate hemophilia A with normal bleeding time and normal VWF functions and multimers. The FVIII:BD is markedly decreased (less than 10%) in E787K, T791M, R816W, 869 and C1060 either homozygous or double heterozygous with a null allele. FVIII:BD due to 2N non-cysteine mutations in the D' domain of VWF gene and FVIII mutations in the C1 and C2 domain in FVIII gene have no influence on synthesis, storage, secretion and multimerization of VWF. The VWD type 2N cysteine mutations C788R/Y; Y795C and C804F in TIL'; C858C/F in E' are associated with aberrant multimerization, poor secretion and reduced FVIII binding to VWF. Homozygous R760W/R760 (D2 domain) and R788/R788 (D' domain) induce a pronounced secretion and multimerization consistent with recessive VWD 2C in which a mild FVIII:BD of about 35% does not contribute to the severity of bleeding phenotype. The combination of R854Q and R760 in the D'D2 domains produce VWD type 2N with a smeary pattern of VWF multimers due to a mixture of normal VWF and of proVWF. Heterozygous R763/WT mutated VWD type 1 and VWD 2N double heterozygous for R854Q and R763 (Furin cleavage site) show a smeary VWF multimeric pattern due to a mixture of normal VWF and pro-VWF protein. The homozygous C1060R/C1060R and the double heterozygous D879N/null, C1060R/R854Q and C1060R/null mutations in the D3 domain are associated with a hybrid phenotype of 2N/2E VWD.

**Conclusion:** Classical VWD 2N due to the homozygous non-cysteine mutations in D' Domain of the VWF R854Q and R816W impair the binding of FVIII capacity of VWF (FVIII binding defect: FVIII-BD) but do not impair the multimeric structure of VWF. The cysteine mutations inside the D' domain C788R/Y, C788T and C804F in TiL', and C858S/F in E' and outside the D' domain C760C in D2, R763C Furin cleavage site only produce VWD 2N when combined with the R854Q mutation and are associated with aberrant multimerization of VWF. Homozygous C1060R/C1060R mutation in the D3 domain, and the double heterozygous D879N/null, C1060R/R854Q or C1060//null mutations are associated with a hybrid phenotype of 2N/2E VWD.

### Speaker Biography

Jan Michiels Professor of Nature Medicine & Health Blood Coagulation & Vascular Medicine Center in Netherlands. He also serves as an Editorial board member for many scientific journals.

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