FUNCTIONAL CHARACTERIZATION OF NOVEL NON-SYNONYMOUS ALTERATIONS IN CD46 AND FACTOR H FOUND IN ATYPICAL HEMOLYTIC UREMIC SYNDROME PATIENTS

Dorottya Csuka[1]

Frida C. Mohlin[2], Sara C. Nilsson[2], Anna M. Blom[2]Tanja Kersnik Levart[3], Ema Golubovic[4], Krisztina Rusai-Heindl[5], Thomas Müller-Sacherer[5], Klaus Arbeiter[5], Éva Pállinger[6], Nóra Szarvas[1], Ágnes Szilágyi[1], Zoltán Prohászka[1]

[1]3rd Department of Medicine, Semmelweis University, Budapest

[2]Department of Laboratory Medicine, Lund University, Malmö

[3]Department of Pediatric Nephrology, University Medical Centre, Ljubljana

[4]Clinic of Pediatrics, Clinical Center, Medical Faculty, University of Nis, Nis

[5]Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna

[6]Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a disease of complement dysregulation and is characterized by hemolytic anemia, thrombocytopenia and acute renal failure. Mutations in the complement inhibitors (factors H and I, CD46), are major risk factors of aHUS, although environmental trigger factors also contribute to the development of aHUS in genetically predisposed subjects.
The aim of this study was to investigate whether two novel alterations found in CD46 (E142Q, G259V), together with a previously reported factor H alteration (Q950H), would change the protein expression and/or function and thereby contribute to the disease.
Methods: To determine if the alterations affect the function of the proteins, both the factor H and CD46 mutants, as well as the wild type proteins were expressed recombinantly. Degradation assays were performed to determine if the alterations found in factor H or CD46 affect their cofactor activity to factor I. The ability of factor H to inhibit complement activation on the cell surface was also determined.
Results: We identified two novel heterozygous non-synonymous CD46 alterations (E142Q and G259V). These mutants were expressed recombinantly and the results demonstrated that G259V had decreased protein expression on the cell surface and in the cell lysate compared to wild type (wt). Functional analysis revealed that G259V had a substantially impaired ability to act as a cofactor to factor I, in the degradation of C3b and C4b. The E142Q mutant showed neither decreased expression nor impaired function. In two of our patients a rare heterozygous non-synonymous alteration in factor H (Q950H) was identified, which has been reported previously in aHUS patients but not functionally tested. This mutant had a somewhat decreased expression and complement inhibitory function on cell surface compared to wt.
Conclusions: Taken together, we report a novel CD46 alteration (G259V) showing both decreased protein expression and substantially impaired cofactor function. A factor H variant (Q950H) with moderate functional effects was also observed.
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