*Journal of Health Disparities Research and Practice*

*Volume* 12, *Issue* 4 2018 *Article* 18

2019 STEP-UP SPECIAL ISSUE

# The Interaction between Nef Protein and ABCA1 Mutants in Tangier Disease

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## Abstract

The genetic disorder Tangier Disease is characterized by mutations at a chromosomal locus, 9q31, which affect proper function of the cholesterol transporter ATP-Binding Cassette A1 (ABCA1). Individuals with mutant ABCA1 have very low levels of high-density lipoprotein and are at high risk for development of neuropathy and atherosclerosis. Two of the ABCA1 mutations, Q597R and R587W, lead to retention of ABCA1 in the endoplasmic reticulum (ER) in a pattern that is reminiscent of a previously reported ABCA1 inactivation by HIV-1 protein Nef. The mechanism of that inactivation involves Nef binding to an ER chaperone calnexin, which disrupts the interaction between calnexin and ABCA1 preventing proper maturation of ABCA1. As a result, ABCA1 is retained in the ER and not transported to the plasma membrane where its main activity takes place. Thus, we speculated that the underlying mechanism of retention of ABCA1 in the ER of patients with Q597R and R587W mutations is caused by a weakened interaction between mutated ABCA1 and calnexin. However, our preliminary data suggests that it is actually an abnormally strong interaction between these two molecules that leads to the retention of ABCA1 in the ER. The main aim of my research is to attempt to use HIV-1 Nef to decrease the strength of interaction between these mutants and calnexin, which may enable the transport of ABCA1 molecules to cellular membrane, thus restoring the cholesterol efflux from the affected cells. If successful, this approach could lead to a potential therapeutic treatment for Tangier disease using Nef-mimicking peptides.

**KEYWORDS:** ABCA1; HIV-1 Nef; Calnexin

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*The STEP-UP HS program is supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, Grant number: R25DK113659.

**Journal of Health Disparities Research and Practice**
**Volume 12, STEP-UP Special Issue, Summer 2019, pp. 30**

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## ABSTRACT

The genetic disorder Tangier Disease is characterized by mutations at a chromosomal locus, 9q31, which affect proper function of the cholesterol transporter ATP-Binding Cassette A1 (ABCA1). Individuals with mutant ABCA1 have very low levels of high-density lipoprotein and are at high risk for development of neuropathy and atherosclerosis. Two of the ABCA1 mutations, Q597R and R587W, lead to retention of ABCA1 in the endoplasmic reticulum (ER) in a pattern that is reminiscent of a previously reported ABCA1 inactivation by HIV-1 protein Nef. The mechanism of that inactivation involves Nef binding to an ER chaperone calnexin, which disrupts the interaction between calnexin and ABCA1 preventing proper maturation of ABCA1. As a result, ABCA1 is retained in the ER and not transported to the plasma membrane where its main activity takes place. Thus, we speculated that the underlying mechanism of retention of ABCA1 in the ER of patients with Q597R and R587W mutations is caused by a weakened interaction between mutated ABCA1 and calnexin. However, our preliminary data suggests that it is actually an abnormally strong interaction between these two molecules that leads to the retention of ABCA1 in the ER. The main aim of my research is to attempt to use HIV-1 Nef to decrease the strength of interaction between these mutants and calnexin, which may enable the transport of ABCA1 molecules to cellular membrane, thus restoring the cholesterol efflux from the affected cells. If successful, this approach could lead to a potential therapeutic treatment for Tangier disease using Nef-mimicking peptides.

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## ACKNOWLEDGEMENTS

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