

## Enrichment Of Variations In KIR3DL1/S1 And KIR2DL2/L3 Among H1N1/09 Icu Patients: An Exploratory Study

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### Abstract:

BACKGROUND: Infection by the pandemic influenza A (H1N1/09) virus resulted in significant pathology among specific ethnic groups worldwide. Natural Killer (NK) cells are important in early innate immune responses to viral infections. Activation of NK cells, in part, depend on killer-cell immunoglobulin-like receptors (KIR) and HLA class I ligand interactions. To study factors involved in NK cell dysfunction in overactive immune responses to H1N1 infection, KIR3DL1/S1 and KIR2DL2/L3 allotypes and cognate HLA ligands of H1N1/09 intensive-care unit (ICU) patients were determined. METHODOLOGY AND FINDINGS: KIR3DL1/S1, KIR2DL2/L3, and HLA -B and -C of 51 H1N1/09 ICU patients and 105 H1N1-negative subjects (St. Theresa Point, Manitoba) were characterized. We detected an increase of 3DL1 ligand-negative pairs (3DL1/S1(+) Bw6(+) Bw4(-)), and a lack of 2DL1 HLA-C2 ligands, among ICU patients. They were also significantly enriched for 2DL2/L3 ligand-positive pairs ( $P < 0.001$ ,  $P_c < 0.001$ ; Odds Ratio:6.3158, CI95%:2.481-16.078). Relative to St. Theresa aboriginals (STh) and Venezuelan Amerindians (VA), allotypes enriched among aboriginal ICU patients (Ab) were: 2DL3 (Ab>VA,  $P = 0.024$ ,  $P_c = 0.047$ ; Odds Ratio:2.563, CI95%:1.109-5.923), 3DL1\*00101 (Ab>VA,  $P < 0.001$ ,  $P_c < 0.001$ ), 3DL1\*01502 (Ab>STh,  $P = 0.034$ ,  $P_c = 0.268$ ), and 3DL1\*029 (Ab>STh,  $P = 0.039$ ,  $P_c = 0.301$ ). Aboriginal patients ligand-positive for 3DL1/S1 and 2DL1 had the lowest probabilities of death (R(d)) (R(d)=28%), compared to patients that were 3DL1/S1 ligand-negative (R(d)=52%) or carried 3DL1\*029 (R(d)=52%). Relative to Caucasoids (CA), two allotypes were enriched among non-aboriginal ICU patients (NAb): 3DL1\*00401 (NAb>CA,  $P < 0.001$ ,  $P_c < 0.001$ ) and 3DL1\*01502 (CA<NAb,  $P = 0.012$ ,  $P_c = 0.156$ ). Non-aboriginal patients with ligands for all three KIRs (3DL1/S1, 2DL2/L3, and 2DL1) had the lowest probabilities of death (R(d)=36%), compared to subjects with 3DL1\*01502 (R(d)=48%) and/or 3DL1\*00401 (R(d)=58%). CONCLUSIONS: Specific KIR3DL1/S1 allotypes, 3DL1/S1 and 2DL1 ligand-negative pairs, and 2DL2/L3 ligand-positive pairs were enriched among ICU patients. This suggests a possible association with NK cell dysfunction in patients with overactive immune responses to H1N1/09,