“Candidatus Neoehrlichia mikurensis”- a new agent of tick-borne infectious disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen, Klinisk Mikrobiologi, Guldhedsgatan 13A, Göteborg,
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Av
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Fakultetsopponent: Professor Anders Sjöstedt Institutionen för klinisk mikrobiologi, Umeå Universitet

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IV. Grankvist A, Sikora P, Wennerås C. Complete reference genome of a clinical isolate of Candidatus Neoehrlichia mikurensis and comparison with two additional Swedish isolates In manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR INFEKTIONSSJUKDOMAR
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Abstract
“Candidatus Neoehrlichia mikurensis” (Ca. N. mikurensis) is a tick-borne bacterial pathogen that can cause disease particularly among immune compromised persons. This new infectious disease is called neoehrlichiosis. The clinical picture of neoehrlichiosis is characterized by fever, migrating pain, and vascular/thromboembolic complications. The bacterium received its name in 2004, after its discovery in ticks and rodents on the Japanese island of Mikura. This thesis have four main aims 1) Map this new infectious disease with respect to what types of patients that are afflicted, the clinical picture displayed by the patient categories, and the pattern of laboratory findings seen in infected patients. This is described in paper I; where clinical data of six patients participating in the “NEO-VÄST study” are described together with additional cases from Europe. 2) Determine if Ca. N. mikurensis is an opportunist that only afflicts immune compromised patients? In paper II we describe two immune competent patients who had raised levels of Ca. N. mikurensis DNA in the blood accompanied by a cytokine response for several months. The patients were diagnosed after PCR screening of plasma samples from 102 tick-bitten persons in Sweden who participated in the Tick-Borne Disease Study called STING. A PCR assay for clinical use was developed in this study and the cytokine levels were measured with multiplex technology. 3) Establish if Ca. N. mikurensis strains in Europe vary genetically. Paper III describes the development and use of a multilocus sequence analysis (MLSA) protocol to investigate the genetic diversity of clinical Ca. N. mikurensis strains in Europe. A low genetic diversity was seen among the strains, all of which were derived from immune compromised patients. Unexpectedly, Ehrlichia ruminantium was found to be the closest relative of Ca. N. mikurensis within the family of Anaplasmataceae. 4) Perform de novo whole-genome sequencing of Ca. N. mikurensis to characterize the bacterium. In paper IV we determined the complete reference genome sequence of Ca. N. mikurensis, sequenced directly from the blood of three immune suppressed patients. We also compared these sequences with those of other whole-genome sequenced relatives of Ca. N. mikurensis. The sequencing strategy relied on library preparation using a new type of technology called 10X Chromium followed by Hiseq Illumina sequencing, sequence assembly and de novo annotation. Our studies have yielded more knowledge about this anonymous emerging pathogen but much remains to be resolved, the work continues!

Keywords: Tick-borne, Candidatus Neoehrlichia mikurensis, infectious disease, human, neoehrlichiosis

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