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BOOK of ABSTRACTS

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THE COMPOSITION OF THE GUT VIROME IS ASSOCIATED WITH THE LATER DEVELOPMENT OF COELIAC DISEASE: RESULTS OF A PROSPECTIVE FOLLOW-UP OF TWO NEONATAL COHORTS

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Celiac disease (CD) develops in only a tiny fraction of individuals who carry susceptible HLA genotypes and consume gluten. This has prompted the search for environmental triggers or accelerators, including the realm of viruses. The objective of this study was to investigate whether gut virus exposure in early life differs between children later developing celiac disease, compared to tightly matched CD-free controls.

Two newborn cohorts preselected by HLA screening were investigated: the Norwegian MIDIA and Finnish DIPP. Cases of CD were identified by testing in late childhood, and stool samples from infancy were retrieved from the repositories. Each case of CD was matched to two CD-free controls by date and place of birth. Stool samples collected monthly between the age of 3 and 36 months were subjected to unbiased virome metagenomic sequencing. A total of 2043 viromes from 41 case-control trios were characterised. Previously unknown viruses were identified by cross-assembly and sequence-based classification. The association of the gut virome with the subsequent CD was evaluated by comparing results of standard machine learning techniques (partial least squares model and naive Bayes model) between actual data, and their variants with random permutations of the case-control labels.

In total, more than 9,000 previously unknown bacteriophages were newly classified and their genomes were annotated. The composition of the viromes differed significantly between children who later developed CD versus their matched controls (kappa statistics = 0.11, $P=10^{-14}$, Figure 1). This indicates an etiological involvement of phages or their bacterial hosts very early in the CD pathogenesis. Although the signal is clear, the magnitude of the effect is minute, and no single virus signature could be identified that would explain the association.

In a proof-of-concept study, we demonstrated that common gut bacteriophages significantly affect the risk of later non-infectious immunopathological disease, in a manner analogous to that observed for e.g. asthma.

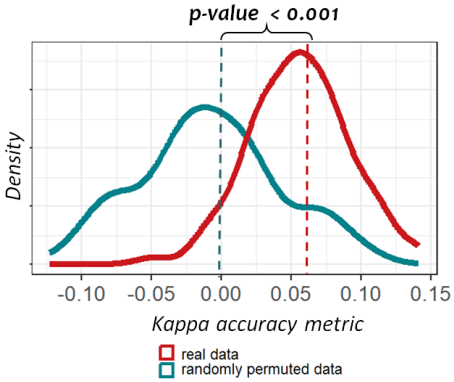

Fig. 1. **The accuracy metric of coeliac disease autoimmunity prediction by virome data as compared to permutations with random assignment of the case-control status**

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