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Title: Rare variants in the IFIH1 gene and severe viral respiratory infections in early childhood
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Introduction:
Virtually all infants experience viral respiratory infections, and most recover well without medical attention. However, around 1-2% of infants are hospitalised with more severe infections, and of those, 10% require treatment in a paediatric intensive care unit. Many of these severely affected infants are otherwise healthy, and possess no known risk factors, suggesting the possibility of a genetic basis of susceptibility to infection.

A recent study (Asgari *et al.*, In press) has provided emerging evidence that rare genetic variants in the IFIH1 gene may contribute towards this increased susceptibility in sick infants. In this study, three loss-of-function genetic variants in IFIH1 were identified at a higher frequency in those who experienced severe viral respiratory infections as infants, compared with a healthy control population.

IFIH1 (Interferon Induced with Helicase C domain 1), also known as MDA5 (Melanoma Differentiation-Associated protein 5), functions to detect long, double stranded viral RNA in the event of a cellular infection and subsequently triggers a type-I interferon immune response.

Aim:
During this pilot study, the hypothesis we sought to test was that rare, loss of function variants in the IFIH1 gene are more common in those who experienced severe viral respiratory infection as infants, compared with a control group with no such history. Genetic analysis methods were established and validated, before applying these methods to analyse the IFIH1 gene of the 13 participants from the Christchurch Health and Development Study (CHDS) with early life hospital admission records for severe viral respiratory illness.

Impact:
Recent studies have suggested that rare, damaging variants in the IFIH1 gene may compromise the immune system of affected infants, leading to an increased incidence of severe viral respiratory illness. Our pilot study has been carried out in order to ascertain whether these findings are relevant to New Zealand infants.

Method:
Participants from the Christchurch Health and Development Study with early life hospital admission records for respiratory illness were selected. To analyse genetic variation in the IFIH1 gene, several laboratory assays were developed. These included:

1. Assays (PCR and Sanger sequencing) for analysis of the coding regions of IFIH1, with a focus on the three IFIH1 variants recently implicated in susceptibility to viral respiratory infections.
2. A similar assay for examining variation in the promotor region of the gene, which has not yet been studied in this context.
3. Assays (digital PCR) to analyse copy number variation of the IFIH1 gene.

Laboratory assays were implemented for genetic analysis of selected participants from the Christchurch Health and Development Study to determine the distribution of IFIH1 variants amongst those with early life severe respiratory viral illness versus those with no such history.

Results:
Bioinformatic analyses of sequencing traces revealed that one of the 13 selected Christchurch Health and Development Study participants possesses a rare, loss of function variant in IFIH1. This genetic variant (rs35337543), one of the three identified by Asgari and her colleagues, is an in-frame splice site variant that causes skipping of exon 8 during pre-mRNA processing. This results in the protein lacking a section of the conserved helicase 1 domain which is necessary for unwinding invading viral RNA. This variant occurs in approximately 1% of Europeans in the control group.

Genetic variation in the promoter region was not observed, nor was copy number variation of IFIH1, however, analysis in this area is ongoing.

Conclusion:
This project has established and validated genetic analysis methods for the IFIH1 gene.

Applying these methods to analysis of Christchurch Health and Development Study participants with the relevant phenotype identified a rare, loss of function variant in one individual. Whether this is truly an enrichment of the variant in the study population cannot be concluded due to the small sample size.

Further studies involving the recruitment of more cases with well-defined severe viral respiratory infection will reveal whether analysis of IFIH1 variants could be useful in identifying susceptibility to severe viral respiratory infections during early childhood.