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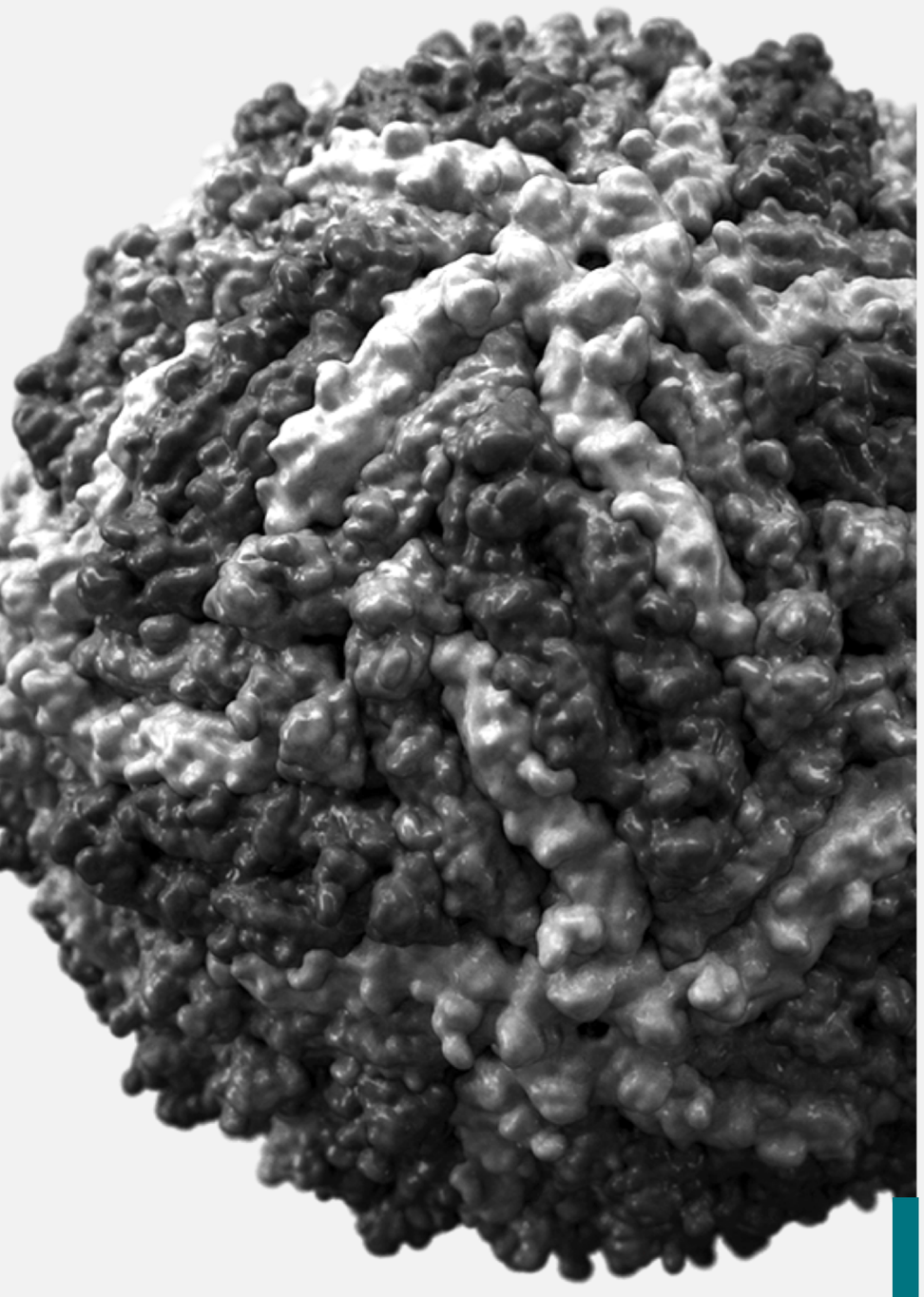
Rare variants

in antiviral response genes drive severe viral respiratory infections in children

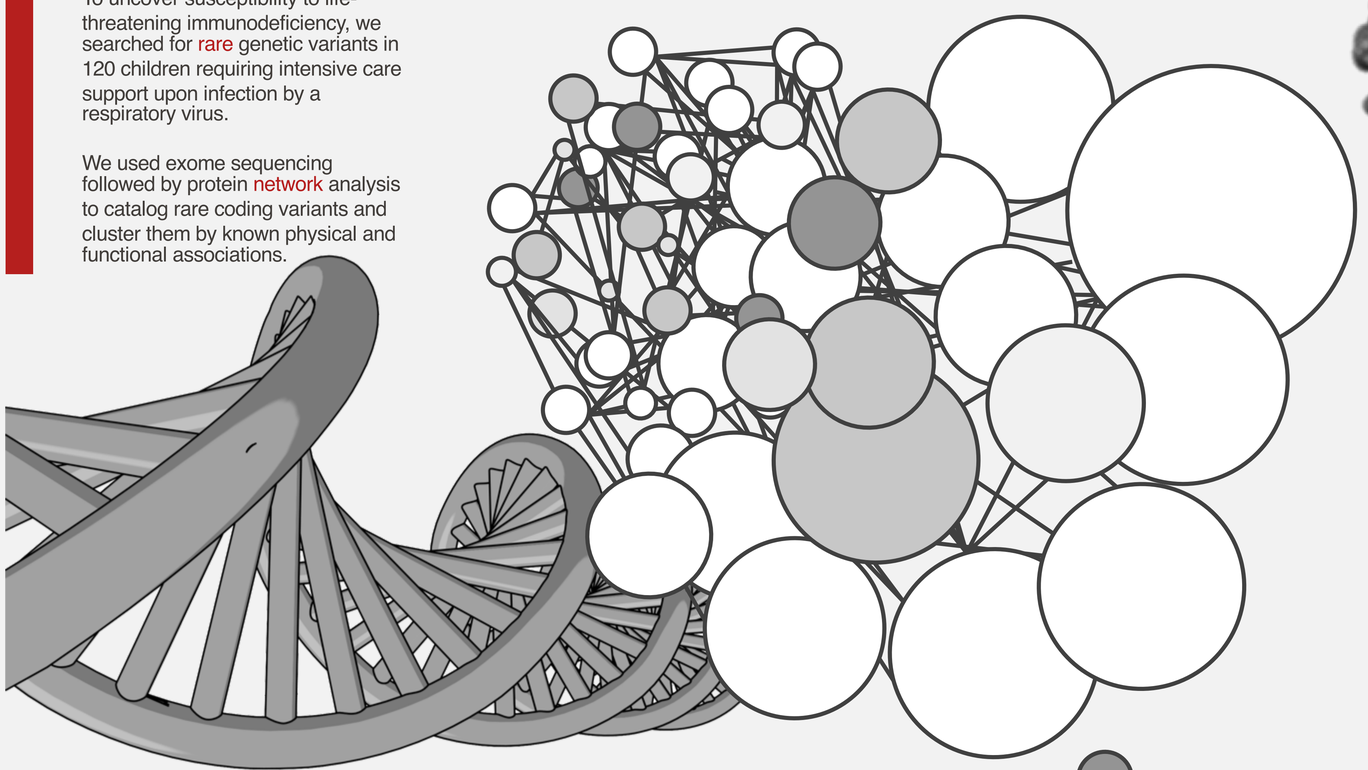


Introduction

A robust and self-limiting immune response is required for clearance of viral respiratory infections.

To uncover susceptibility to life-threatening immunodeficiency, we searched for rare genetic variants in 120 children requiring intensive care support upon infection by a respiratory virus.

We used exome sequencing followed by protein network analysis to catalog rare coding variants and cluster them by known physical and functional associations.



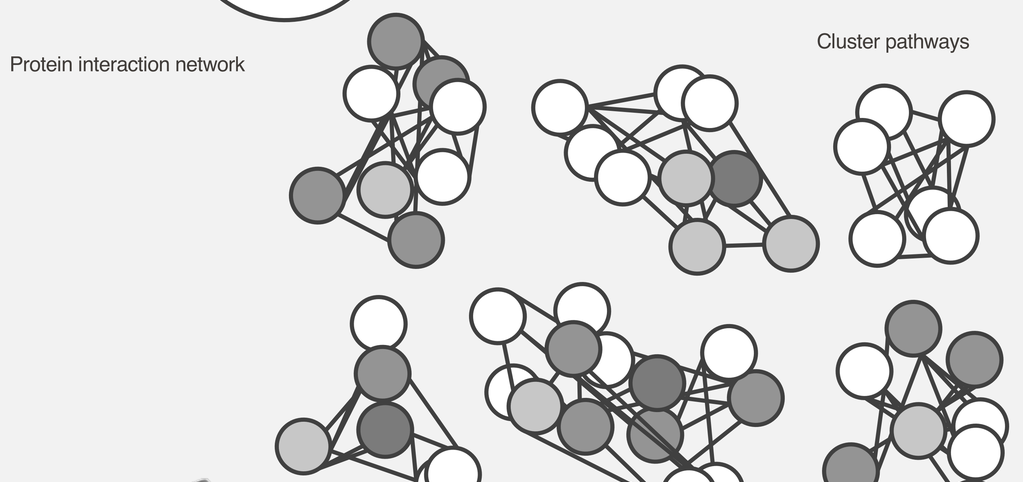
Results

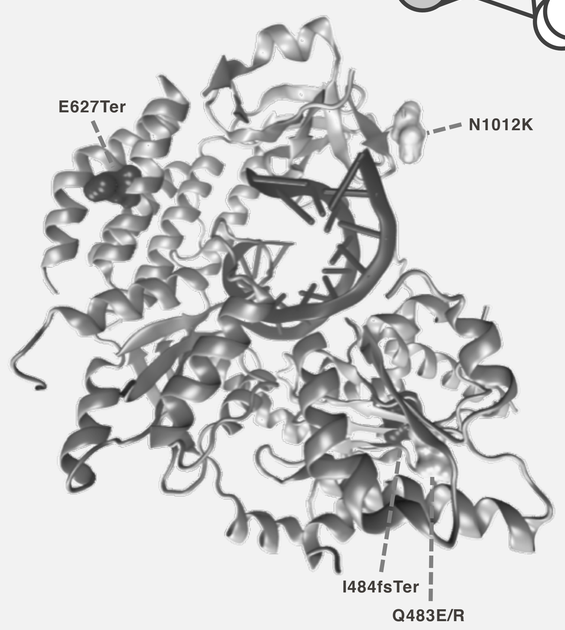
We identified pathway-specific variant enrichment in genes involved in proinflammatory response and viral nucleic acid detection, including *DDX58* and *IFIH1,* encoding RIG-I and MDA5, respectively.

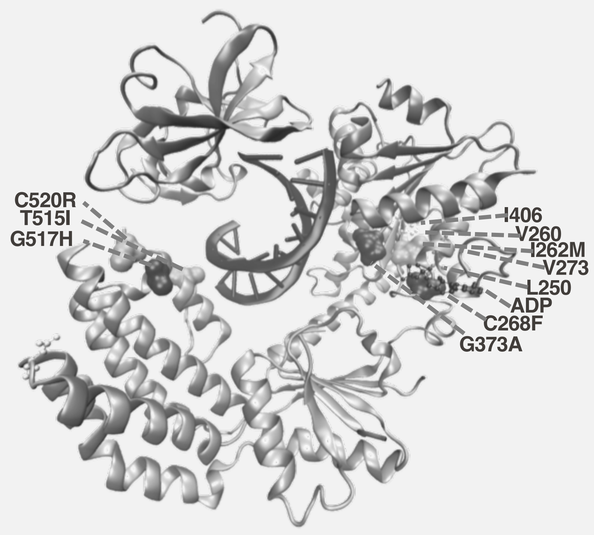
Both proteins share a common mechanism of RNA recognition and signal repression. In the absence of viral infection, each is maintained in an autoinhibited state, where the effector domain (CARD) and the ATP-binding helicase homology domain are masked by the C-terminal repressor domain (CTD). Binding of viral dsRNA at the CTD relieves repression and results in a proinflammatory cascade.

Three loss-of-function variants in *IFIH1* were previously reported for this cohort. A further four patients had helicase / ATP-binding domain variants in *IFIH1*, and one patient with a rare CTD variant. Rare variants were found in *DDX58* affecting the RNA binding motif; one patient harbored a variant predicted to disrupt the ATP-binding helicase.

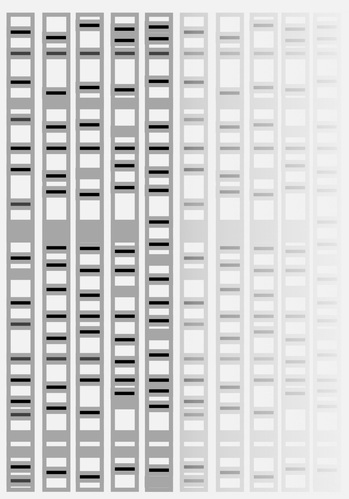
In total we identified 10 rare variants in 15 patients and several further candidate genes.







Pathway analysis



Rare disease cases and controls exome sequenced; 240 in total. GATK best practices for exome analysis[1] with joint genotyping and custom filtering[2]. Genes harboring rare predicted LoF variants were grouped based on protein-protein interactions[3]. A Markov cluster algorithm[4] separated protein networks. Variant enrichments identified networks of relevance. Case-control testing was performed on each protein pathway cluster for total rare variant load. Multiple testing correction identified significantly enriched protein pathway of immune viral detection.

Summary

We present a primary immunodeficiency resulting in extreme susceptibility to common respiratory RNA viruses, due to genetic variants in a common pathway that severely impairs viral recognition.

A new method was developed for the unbiased detection of a protein network, driving disease, based on potential loss of function variants.

1. GATK; A framework for variation discovery and genotyping using next-generation DNA sequencing data. DePristo M, et al. Nat Gen '11
2. VCFhacks; David A. Parry, https://github.com/gantzgraf/vcfhacks
3. Franceschini, A et al, STRING: protein-protein interaction networks, with increased coverage and integration. Nucleic Acids Res '13.
4. Markov cluster algorithm; Stijn van Dongen, Graph Clustering by Flow Simulation. University of Utrecht, '00.

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