Screening viral host dependency factors and human loss of function polymorphisms to identify broad-acting host directed antiviral targets against HIV and other viruses

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Introduction: Viruses require host cell components to establish and maintain infection. Multiple genome-wide knockout/knockdown studies of HIV and other viruses have identified sets of host dependency factors (HDFs) that are essential for viral replication. Although these factors may be candidates for development of novel antivirals, defining targets that do not lead to drug toxicity is challenging. One opportunity to identify good targets is to define which HDFs harbour homozygous loss of function (LoFs) polymorphisms in healthy people.

Methods: We performed a literature review to identify genome-wide studies of viral HDFs for multiple viruses. We identified 27 studies covering HIV, Hepatitis C, Hepatitis D, SARS-CoV-2, SARS-CoV, Ebola, Influenza A, Zika, Dengue and West Nile virus. These HDFs were intersected with the genome aggregation database (gnomAD), a resource containing >125,000 human exome and >15,000 whole-genome sequences, to identify HDFs that harbour homozygous LoFs in healthy individuals.

Results: We identified 2898 unique HDFs across all viruses. 326 of these were implicated in more than 1 virus and 2 HDFs were implicated in 5 viruses. Using gnomAD data, we found that HDFs implicated in more than one virus tend to be highly intolerant to a LoF mutation suggesting they are highly conserved within the host. Six candidate HDFs that intersect with HIV were narrowed down for CRISPR gene editing, as potential broad-acting drug targets (Table 1).

Conclusion: *In silico* and *in vitro* screening of HDFs harbouring homozygous LoFs in healthy people may aid in the development of novel broad acting antivirals.

Supporting Document

Table 1: Six candidate HDFs that intersect with HIV for future CRISPR knockout testing with viral infection assays, to verify HDF non-essentiality for the host and to confirm a reduction in viral infection

Top HIV HDF candidates	Viruses sharing the HDF	Loss of function variant from gnomAD	Type of loss of function mutation	Number of Homozygous Loss of function in control individuals
RABEPK	HIV + Hepatitis C	p.Pro135HisfsTer44	Frameshift	3
KRBA2	HIV + Ebola	p.Arg183Ter	Stop gained	1
PI4KA	HIV + Hepatitis C	p.Leu1952CysfsTer45	Frameshift	1
MYEF2	HIV + Hepatitis D	c.1138+1G>T	Splice donor	1
USP6	HIV + West Nile	p.Arg522LysfsTer12	Frameshift	5
ERN2	HIV + Influenza A	p.Cys694TrpfsTer8	Frameshift	2