# HerpesDRG: a comprehensive resource for human herpesvirus antiviral drug resistance genotyping

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**Abstract**

The prevention and treatment of many herpesvirus associated diseases is based on the utilization of antiviral therapies, however therapeutic success is limited by the development of drug resistance. A comprehensive point of truth of resistance conferring mutations has been missing but would be important to aid the development of antiviral drugs and in management of infections. We therefore developed HerpesDRG, a drug resistance mutation database for all the known important genes and current treatment options, built from a systematic review of available genotype to phenotype literature. The database is released along with an R package to provide a low barrier of entry to variant resistance annotation and clinical implication analysis from common sanger and NGS sequence data. This represents the first openly available and community maintainable knowledgebase of drug resistance mutations for the human herpes viruses (HHV), developed for the community of researchers and clinicians tackling HHV drug resistance.

**Key words**

HCMV, HSV, VZV, resistance, database, Ganciclovir, Letermovir, Acyclovir, Cidofovir, Amenamevir

**Availability**

The HerpesDRG database is available at github.com/ojcharles/herpesdrg-db. The R package for resistance genotyping data is available at github.com/ojcharles/herpesdrg. A user-friendly webserver is available at cmv-resistance.ucl.ac.uk/herpesdrg

## Introduction

Herpesviruses and their associated diseases are a major health problem worldwide for immunocompromised patients. The prevention and treatment of human cytomegalovirus (HCMV) and herpes simplex virus (HSV) disease for example are essential in management of solid organ transplant (SOT) & hematopoietic stem cell transplant (HSCT) recipients (Ariza-Heredia et al., 2014; Emery, 2001; Lee et al., 2019; Limaye, 2002). Although a handful of treatment options are available such as Acyclovir, Ganciclovir and Letermovir, emergence of resistance causing mutations are now found for all approved drugs and pose a significant threat due to aggressive disease course and a greater mortality risk (Bacon et al., 2003; Kakiuchi et al., 2017; Komatsu et al., 2014; Lurain and Chou, 2010; Patel et al., 2014).

Drug resistance in a clinical setting is often diagnosed by sequencing followed by variant annotation (genotyping), rather than isolating and phenotypically characterising (phenotyping) due to cost and time benefits (Gu et al., 2019; Russell, 2018). Genotyping does however require that any variants present have previously been phenotyped (Lurain and Chou, 2010). In these experiments a single novel mutation is transferred into a reference virus, or a clinical isolate is found with similar characteristics. The impact of this mutation on drug sensitivity can then be determined by a plaque reduction assay (PRA), Bacterial Artificial Chromosome (BAC) reporter assay or similar, returning an $IC_{50}$ against a given drug. It is typical to report the mutations impact on antiviral sensitivity as a fold change relative to the control strain $IC_{50}$, where HCMV is currently

49 the only human herpes virus (HHV) with consensus guidelines relating fold change to a "resistant"
50 or "susceptible" phenotype (Kotton et al., 2018; Danve et al., 2002; Chou et al., 2005; Sauerbrei et
51 al., 2011).

52 An issue is that those previously phenotyped data are published in a disparate collection of
53 reports. This has meant that researchers often must perform a review of the scientific literature
54 for identified mutations in a viral isolate, which is time consuming, especially when there are
55 several reports for a given mutation (Paolucci et al., 2021; van der Beek et al., 2013, p. 20).
56 Therefore there have been published efforts to collate this data previously such as in reviews,
57 however the data contained is not updateable and requires reformatting for informatics (Lurain
58 and Chou, 2010; Sauerbrei et al., 2016). Advancing our toolbox such as by developing a
59 comprehensive mutation phenotype map that is community maintainable and in an open format
60 would solve these data requirement problems for genotypic methods. Further, it could play an
61 important role in developing improved antiviral therapies (Chou, 2020; Razonable et al., 2020).

62 User-friendly tools are also important to enable researchers to make use of such databases
63 (Chevillotte et al., 2010; Hayer et al., 2013). Any such tool built to analyse HHV sequence data
64 should support both sanger consensus sequence outputs, as this is still widely adopted, as well as
65 modern Next Generation Sequencing (NGS) variant outputs (Streck et al., 2023). NGS has become
66 a popular option and provides advantages such sensitivity to low-level variants that helps in early
67 decision making (Chin et al., 2013; Garrigue et al., 2016; Guermouche et al., 2020) and evidence
68 that accumulation of low-level variants may be associated with poor clinical outcome (Houldcroft
69 et al., 2016; Venturini et al., 2022). Additionally there is interest in sequencing wider than just
70 DNA polymerase (HSV1/2:UL30, HCMV:UL54, varicella-zoster virus (VZV):ORF28) and kinase
71 (HSV1/2: UL30, HCMV:UL97, VZV:ORF36) genes as the number of antiviral targets has grown
72 (Kawashima et al., 2017; Lurain and Chou, 2010; Serris et al., 2022). For example HCMV mutants
73 in UL27, UL51, UL56 and UL89 are not sequenced in many diagnostic labs (Kotton et al., 2018).

Here we present an open-source comprehensive database that links HHV mutations to impact on drug sensitivity phenotypes that is interrogatable and maintainable by the community. The database is released along with analytical tools suitable for resistance annotation of modern sequence data from HCMV, HSV1, HSV2, VZV and HHV6.To the best of our knowledge published comparable resources are comparatively affected by issues such as not covering all genes affecting current clinically relevant drugs, inability to update data after publication and closed-source databases that cannot be community verified (Chevillotte et al., 2010; López-Aladid et al., 2019; Lurain and Chou, 2010; Sauerbrei et al., 2016).

**Database Construction**

Literature regarding mutation resistance phenotype were identified by a comprehensive PubMed ("Database resources of the National Center for Biotechnology Information," 2018) search with key terms "Cytomegalovirus [Title] AND resistance [Title/Abstract]", likewise for the other HHVs. Papers were inspected with regular expressions to detect the occurrence of mutations, from where literature article data was manually extracted. Each entry in the database represents the relationship between a mutation, study, control species, assay method, metadata, and fold change, where fold change values are stored for 11 currently clinically important drugs. Multiple entries may be present for the same variant where either a single publication provides different test methodology to produce independent sensitivity results, or where the same variant is tested across multiple publications. This Fold-change values come in the form of a numeric decimal value if fold changes are possible to extract, or as a string "Resistance" or "Polymorphism" if only a phenotype is described. Study reference data comes in the form of a title, a HTTP link and a DOI. Assay information columns record the method of strain generation, i.e., "marker transfer", or "isolated strain", the test method such as "PRA" or "dye uptake assay" and the control strain used to generate a fold change. For some well-studied mutations, co-occurring mutations have been observed to amplify resistance and are recorded where relevant (Chou, 2015; Chou et al., 2016).

99 Finally, any metadata such as when the entry was created, any notes and a status flag. Only rows
100 with the status "A" for active are returned in the R package and webserver.

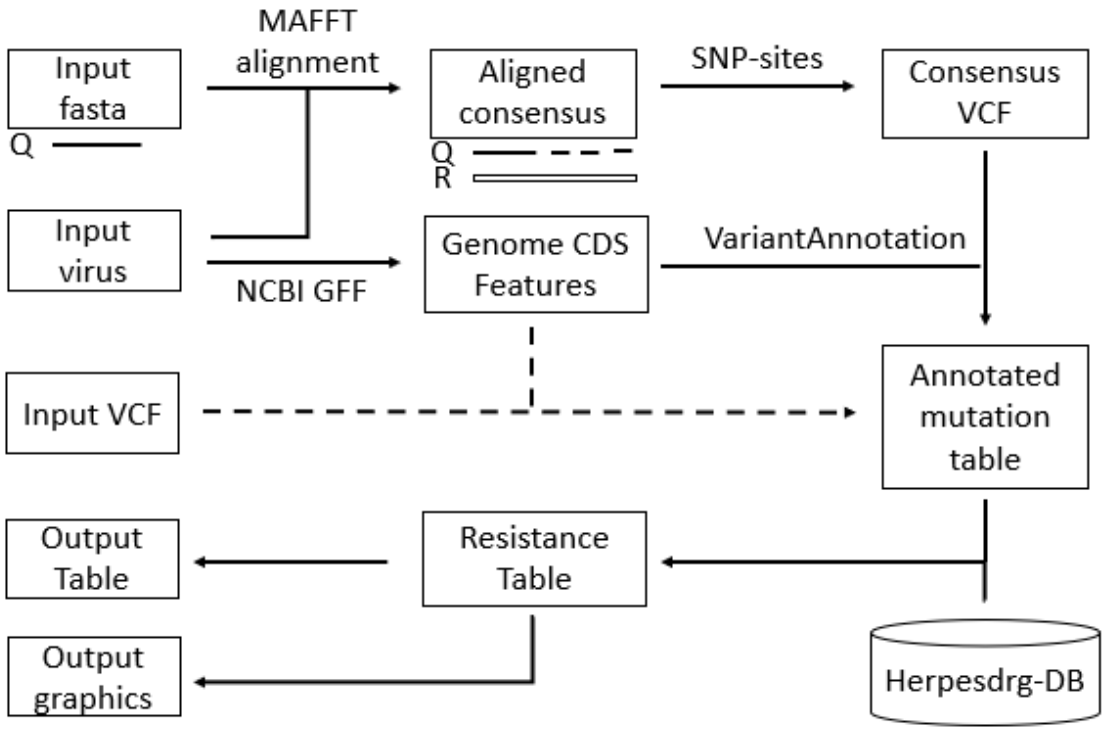
101 It is well understood that a single key mutation is almost always the causative agent that results
102 in drug resistance for the HHV's, while any other mutations are often neutral polymorphisms. In
103 this database there are entries from isolates with multiple co-occurring mutations, often clinical
104 isolates. We use the following rules when including these entries: a) If the strain is sensitive in
105 vitro, any uncharacterised mutations are accepted as polymorphisms. B) Where a strain has a
106 single uncharacterised mutation, and the others are known polymorphisms, the single unknown
107 mutation is entered with the strains fold change. C) If there are multiple uncharacterised
108 mutations the entry is recorded along with co-mutations and set the status "O" for obsolete, it will
109 not feature in processes. d) If at a later date with new data only a single uncharacterised mutation
110 now is present for an entry as in (c), the entry is re-looked at and treated as in (b).

111 **Drug resistance genotyping**

112 To facilitate the resistance annotation of virus sequence data we developed Herpes Drug
113 Resistance Genotyping "HerpesDRG", a R package that enables the assessment of resistance
114 mutations present from variant VCF or FASTA sequence data (Figure 1). FASTA format sequences
115 are aligned to the selected viruses reference genome with MAFFT (Katoh and Standley, 2013)
116 using the "—add –keeplength" parameters, such that both whole genome sequences or genetic
117 fragments (e.g. UL23, UL54) can be inputted. SNP-sites is used to extract SNP's and downstream
118 functions identify indels (Page et al., 2016). For detection of low frequency mutations Variant Call
119 Format (VCF >= version4.0) and default Varscan2 output file are accepted, where the data has
120 been mapped to the relevant NCBI reference strain (Koboldt et al., 2012). All input formats are
121 converted to a variant which is processed using the VariantAnnotation package to predict their
122 effect on coding regions (Obenchain et al., 2014; R Core Team, 2014). The HerpesDRG
123 "call_resistance" function produces the key output, an annotated variant table including

124 resistance data present in the database. In the case of a mutation present having multiple entries
125 in the database, all relevant entries are returned.

126




127

128 Figure1: Graphical representation of the HerpesDRG annotation pf FASTA sequence input or VCF
129 inputs (dashed lines). Q – Query sequence, R – NCBI Reference sequence.

130 A concise clinical output can then be generated from this table using the "make_clin_table"
131 function (Figure 2). Here for each drug HerpesDRG identifies the mutation of maximal fold change
132 found in the sample present at greater than 10% frequency, then allocates a category to that drug
133 accordingly: High level (maximum fold change above 15), Moderate level (maximal fold change
134 between 5-15), Low level (the maximum fold change between 2-5), Polymorphism (less than 2,
135 or recorded as such), Resistant (only anecdotal resistant data was returned), NA (no mutations
136 returned) and evidence strength as: "Good, in vitro", or NA (no evidence). These fold change cut-
137 off values are in line with recommendations from 'The Third International Consensus Guidelines

138 on the Management of Cytomegalovirus in Solid-organ Transplantation' (Kotton et al., 2018)
139 which we use consistently across all viruses.

| | Ganciclovir | Aciclovir | Cidofovir | Foscarnet | Brincidofovir | Letermovir | Brivudine | Pencyclovir | Tomeglovir | Maribavir | Cyclopropavir |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Resistance Phenotype | Low level | NA | Low level | Moderate level | NA | NA | NA | NA | NA | High level | Low level |
| Evidence Strength | good, in vitro | No Evidence | good, in vitro | good, in vitro | No Evidence | No Evidence | No Evidence | No Evidence | No Evidence | good, in vitro | good, in vitro |

140

141 Figure2: Clinical overview table produced by the "make_clin_table" function for the example data
142 A10.vcf. Example code on GitHub.

143 **Usage**

144 Install HerpesDRG by running the R command: devtools::install_github("ojcharles/herpesdrg").
145 This will take care of installing other dependencies and the database. Inputs for the
146 "call_resistance" function takes as input any of the aforementioned file types, along with which
147 virus to genotype against and flags for whether to return all synonymous / non synonymous
148 mutations (default is only resistance mutants). The above examples were all based on HCMV for
149 consistency but work equivalently for the other herpesviruses.

150 **User interface**

151 The HerpesDRG toolset is accessible through a user-friendly web interface included in the R
152 package and available at cmv-resistance.ucl.ac.uk/herpesdrg/. Here users upload sequence data
153 as described above and select the virus of interest from the drop-down list. There the full
154 resistance mutations table, the simplified clinical overview and additional graphics are generated
155 automatically. Specific terms of use for the hosted instance are included with the shiny
156 application. The application was developed using the shiny framework (Chang et al., n.d.). We
157 include example files for whole genome analysis (VCF, varscan tab, FASTA), and specific gene
158 regions FASTA.

159 **Conclusion**

160 We have developed a database that comprehensively captures known drug resistance mutations
161 and their impact on antiviral sensitivity for the antiviral treated Humen Herpes Viruses. The
162 database is released in an open-source format such that it can be community maintained acting
163 as a point of truth for future research and informatic tools. We release this database with an
164 associated tool that allows a low barrier to analysing presence of resistance in sequencing data.

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169 **Conflicts of interest**

170 None declared.

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