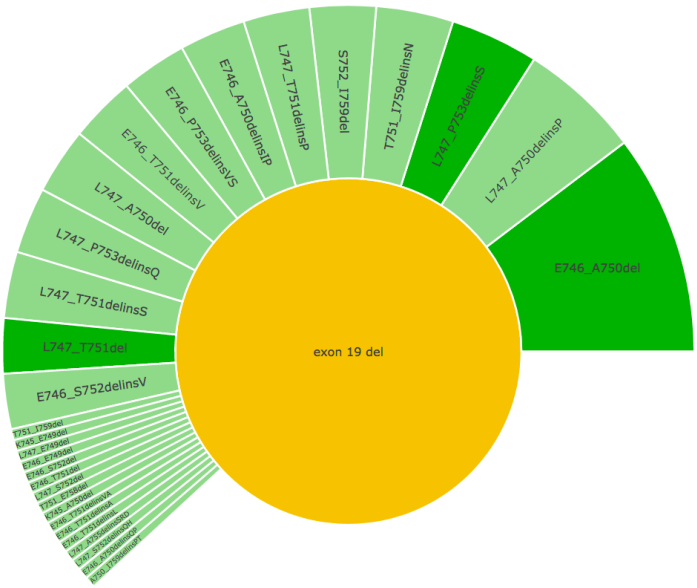
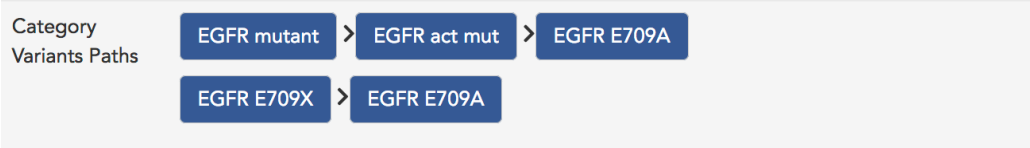
CKB Category Variants

Purpose – One consequence of trying to reduce complexity in molecular diagnostics is that many publications, professional guidelines, drug labels, and clinical trials will only mention a general category of a gene variant class and fail to name the specific variant entity. CKB standard operating procedures require curation to the named variant in the reference and does not make inference to actual gene variants, if not specifically defined. For example, if a reference only mentions "EGFR exon 19 deletion, CKB curates to the category variant of "EGFR exon 19 del". In order to connect a specific EGFR exon 19 deletion variant (i.e., EGFR E746_A750del) to the EGFR exon 19 del data, we have created category (parent) terms to walk the data bidirectionally.

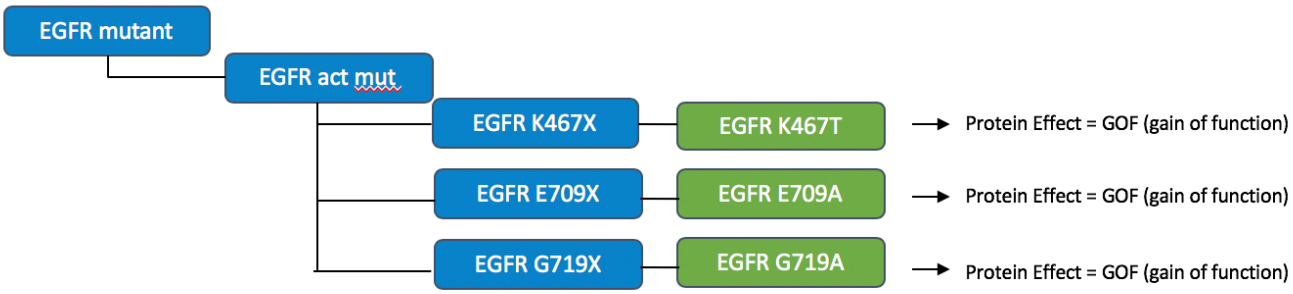
Our CKB BOOST™ subscribers can navigate these relationships through our patent-pending technology for visual rendering:



Our CKB FLEX™ customers can walk the hierarchy to enrich content queries for clinical reporting. For example, if a patient's tumor profile has the gene variant, EGFR E709A, efficacy evidence data can be walked up the path to pull relevant data from EGFR E709X or EGFR act mut:



These data in CKB represent example paths shown here:



Category Definitions – CKB has established a set of category variants that are descriptive classes for gene variants that are similar, either by protein position or function. An example for function is the category variant of "inact mut", which organizes all the variants of a gene annotated with "loss of function" or "loss of function – predicted" under the same umbrella. An example of position is the category variant defined as amino_acid_X, which organizes all the variants of the protein at amino acid position X under the same umbrella. We also define non-specific variant and synthetic categories.

Category Variants

variant_entry	***definition***
Category Variants	*Category variants are variants that can be considered a parent variant to a group of other variants. These are typically used when a type or group of variants is indicated, but the specific variant is not.*
act mut	Indicates that the variant results in a gain of protein function. This can be considered a category containing any variant that results in a gain of function. In some cases, such as with small GTPases, this may indicate that the variant results in a loss of intrinsic function, resulting in activation of downstream signaling. In these cases, this can be considered a category that contains loss of function and/or gain of function variants resulting in downstream pathway activation.
fusion	Indicates a fusion of the gene, but the fusion partner is unspecified. This can be considered a category containing any fusion in which the specified gene is a partner.
inact mut	Indicates that the variant results in a loss of protein function. This can be considered a category containing any variant that results in a loss of function.
mutant	Indicates an unspecified mutation in the gene. This can be considered a category containing any missense, indel, nonsense, or frameshift variant in the gene.
rearrange	Indicates an unspecified rearrangement of the gene. This can be considered a category containing rearrangement of the specified gene.
exonX	Indicates a mutation in the specified exon. This can be considered a category containing any variant within the specified exon.
Xaa#(X)	Indicates that the variant results in the replacement of the amino acid at the specified position by another amino acid. The can be considered a category containing any variant resulting in an amino acid substitution at the specified position. An example would be 'BRAF V600X'.
exon X del	Indicates a deletion in the specified exon of the gene. This can be considered a category containing any variant resulting from a deletion in the specified exon. An example would be 'EGFR exon 19 del'.
exon X ins	Indicates an insertion in the specified exon of the gene. This can be considered a category containing any variant resulting from an insertion in the specified exon. An example would be 'FLT3 exon 14 ins'.
del exonX	Indicates a deletion of the entirety of the specified exon. This can be considered a category containing any variant that results in the deletion of the specified exon, but not resulting in deletion of other exons. An example would be 'MET del exon14'.

Non-specific Variants

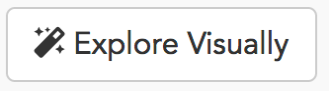
Non-specific Variants	*Non-specific variants are variants that are not attributed to a specific change in the amino acid or genomic sequence, and are not considered categories.*
amp	Indicates an increased number of copies of the gene and is used in association with CNV
dec exp	Indicates decreased expression of the mRNA and/or protein
del	Indicates a deletion of the gene and is used in association with CNV
high	Indicates a high level. For example, MSI high indicates a high level of microsatellite instability.
loss	Indicates loss of the gene, mRNA, and protein
low	Indicates a low level. For example, MSI low indicates a low level of microsatellite instability.
negative	Indicates a lack of expression of mRNA or protein
over exp	Indicates overexpression of the mRNA and/or protein
positive	Indicates the presence of the gene, mRNA, and protein
wild-type	Indicates that no mutation has been detected within the gene

"Synthetic" Categories

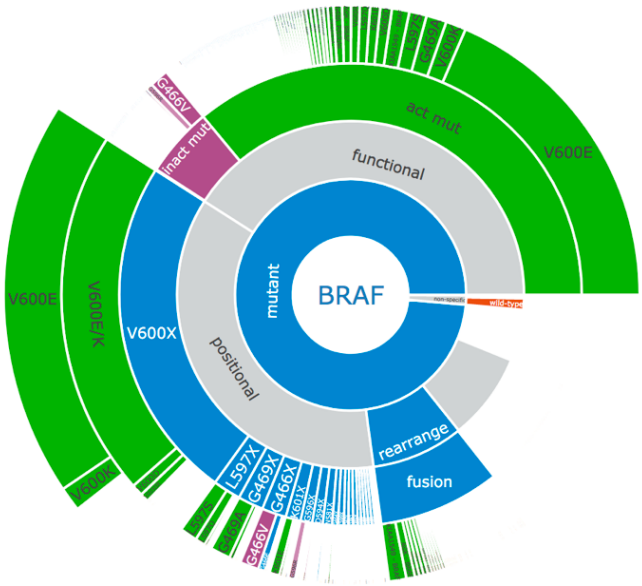
Synthetic Categories	*Synthetic categories are for navigation purposes only*
functional	Indicates gene mutations that alter protein activity
postional	Indicates variants grouped by their positional location, such as exon or amino acid. Examples include commonly mutated amino acid positions that are considered "hotspots".
mutant	Indicates gene mutations that have not yet been classified by function or position
non-specific	See above or help docs for non-specific category definitions
blank or empty	Indicates unclassified gene variants

Navigating Category Visuals

Start the navigation by clicking on the icon:

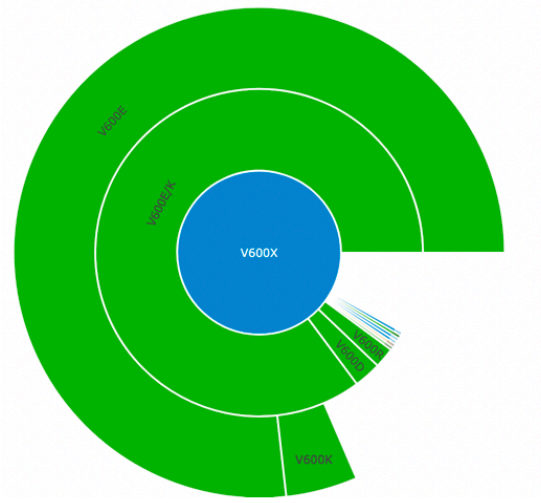


This will render the visual for navigation:



Hovering over a gene variant will show the number of associated efficacy evidence (EE) annotations and the variant will highlight in **yellow,** if it is found in both Functional and Positional synthetic categories. The size of each variant wedge is relatively proportional to the number of efficacy annotations.

Clicking on a category or variant will drill down into the hierarchy visual and display the annotation and category paths on the right:



Gene	BRAF
Variant	V600X
Impact List	missense
Protein Effect	unknown
Gene Variant Descriptions	BRAF V600X indicates any Braf missense mutation that results in replacement of the the valine (V) at amino acid 600 by a different amino acid. BRAF V600 mutations are hotspot mutations that often result in increased Braf kinase activity (PMID: 15035987).
Associated Drug Resistance	
Category Variants Paths	BRAF mutant > BRAF V600X

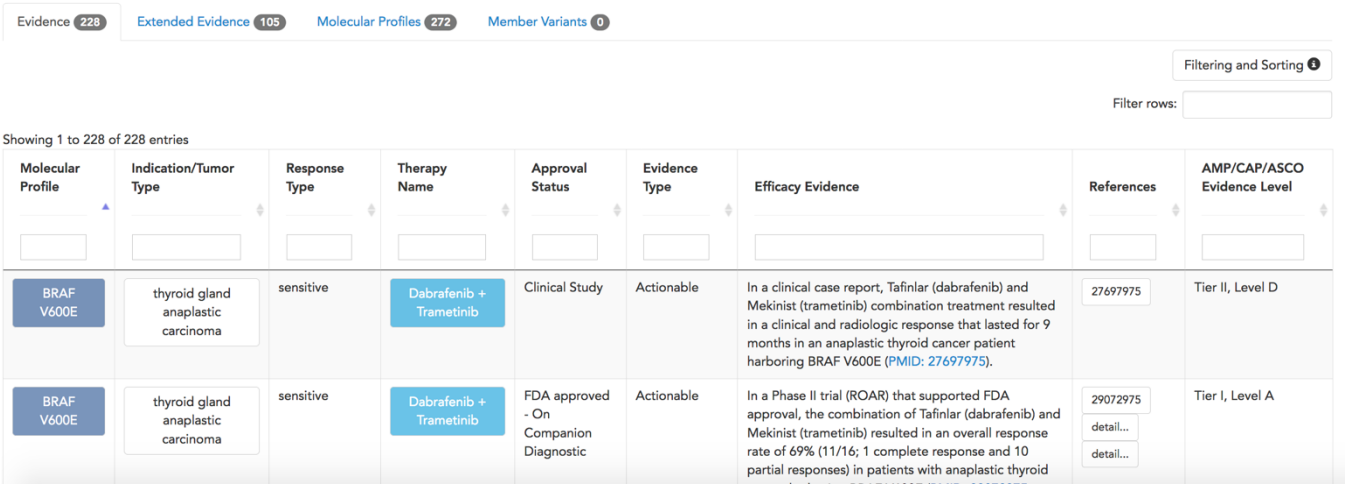
The visual can be increased or decreased in size with these buttons:

Increase Size | Decrease Size

To go back to the root level, click:

Zoom Out

Scroll down to see related efficacy evidence:



To see annotations and category paths for a variant without drilling down into the plot, hold down “h” while clicking on the variants.