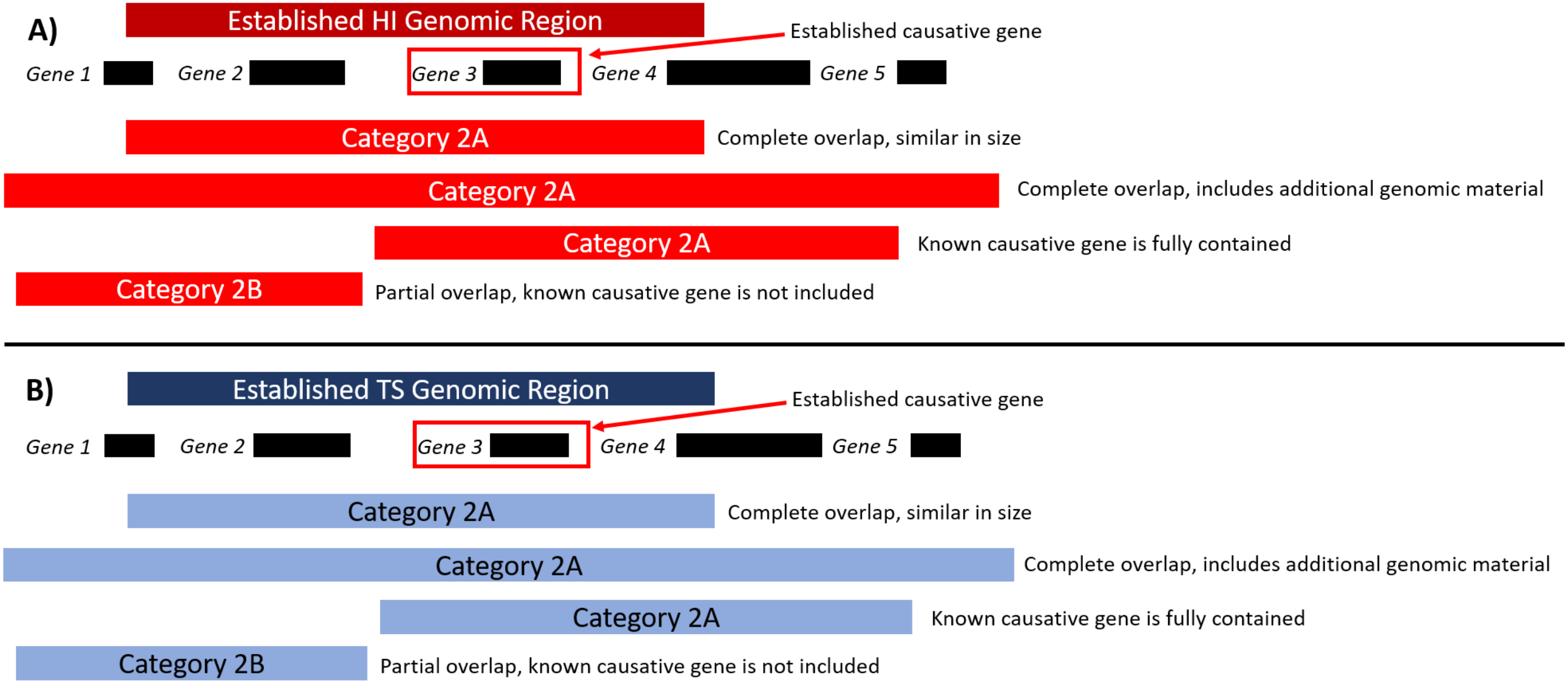
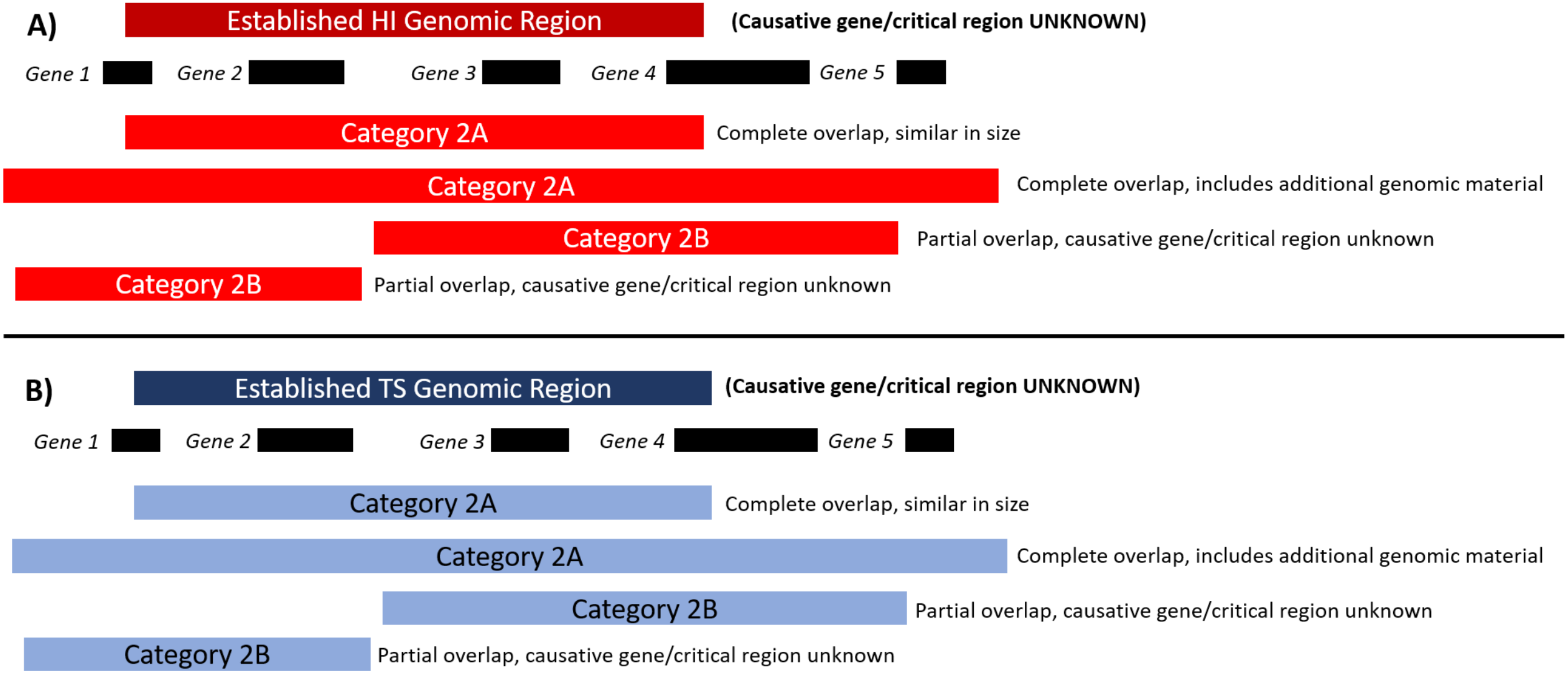
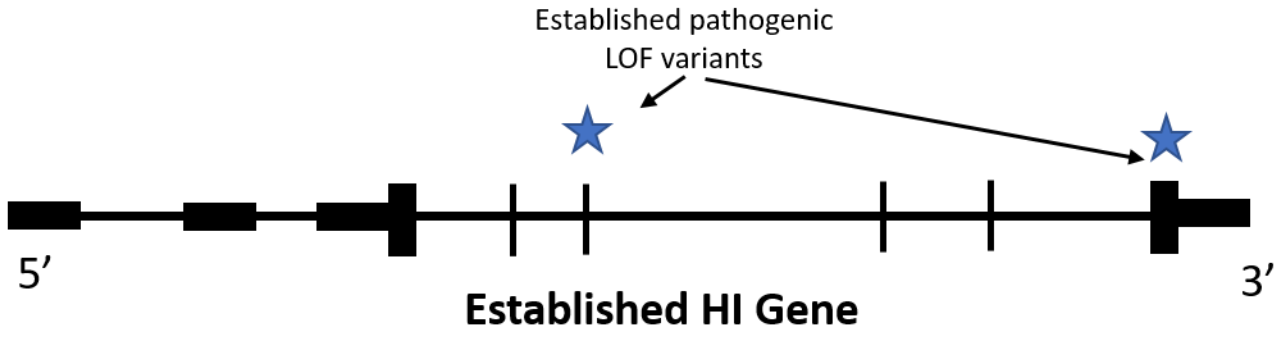


Supplemental Figure 1.1: Illustrations of gain and loss scoring metric categories 2A-2B (overlap with established HI or TS region, causative gene/critical region known). A) A theoretical established haploinsufficient genomic region is shown in the context of several genes, one of which has been established as the main contributor to the phenotype associated with loss of this region. Example overlapping deletions are shown below, each representing a scenario described in the loss scoring metric (Table 1, Main Document). **B)** A theoretical established triplosensitive genomic region is shown in the context of several genes, one of which has been established as the main contributor to the phenotype associated with gain of this region. Example overlapping duplications are shown below, each representing a scenario described in the gain scoring metric (Table 2, Main Document). Red boxes represent deletions, blue boxes represent duplications. HI = haploinsufficient; TS = triplosensitive.



Supplemental Figure 1.2: Illustrations of scoring metric categories 2A-2B (overlap with established HI or TS region, causative gene/critical region unknown). A) A theoretical established haploinsufficient genomic region is shown in the context of several genes. In this example, no single gene or critical region has been established as the main contributor to the phenotype associated with loss of this region. Example overlapping deletions are shown below, each representing a scenario described in the loss scoring metric (Table 1, Main Document). **B)** A theoretical established triplosensitive genomic region is shown in the context of several genes. In this example, no single gene or critical region has been established as the main contributor to the phenotype associated with gain of this region. Example overlapping duplications are shown below, each representing a scenario described in the gain scoring metric (Table 2, Main Document). Red boxes represent deletions, blue boxes represent duplications. HI = haploinsufficient; TS = triplosensitive.



Category 2C-1 Overlap with 5’ end, coding sequence involved

Category 2C-2 Only 5’ UTR is involved

Category 2D-1 Only 3’ UTR is involved

Category 2D-2 Only the last exon is involved; other established pathogenic variants have been reported in this exon

Overlap with 3’ end; includes other exons in addition to the last exon; nonsense-mediated decay expected to occur — Category 2D-4

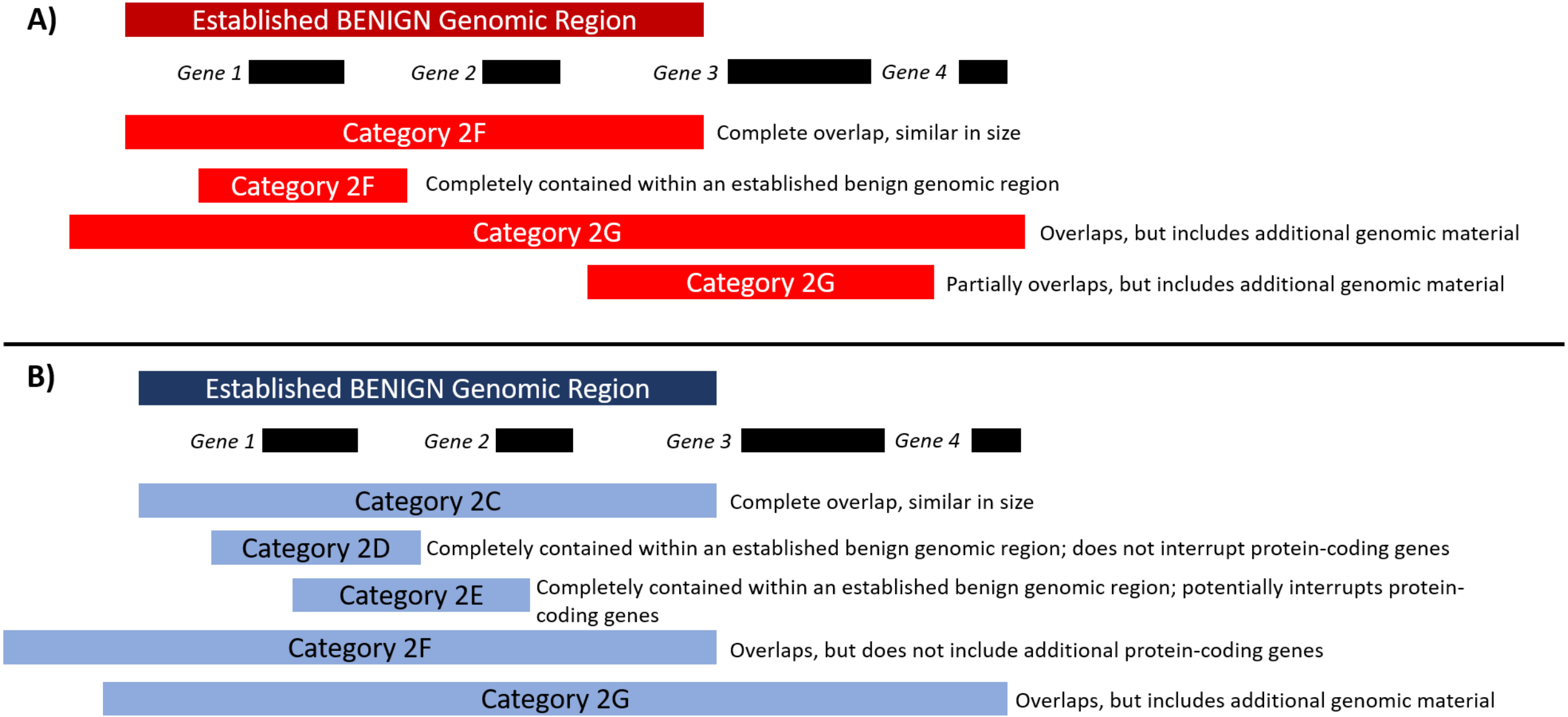
Category 2E Both breakpoints are within the HI gene

Category 2H HI gene fully contained within observed copy number gain

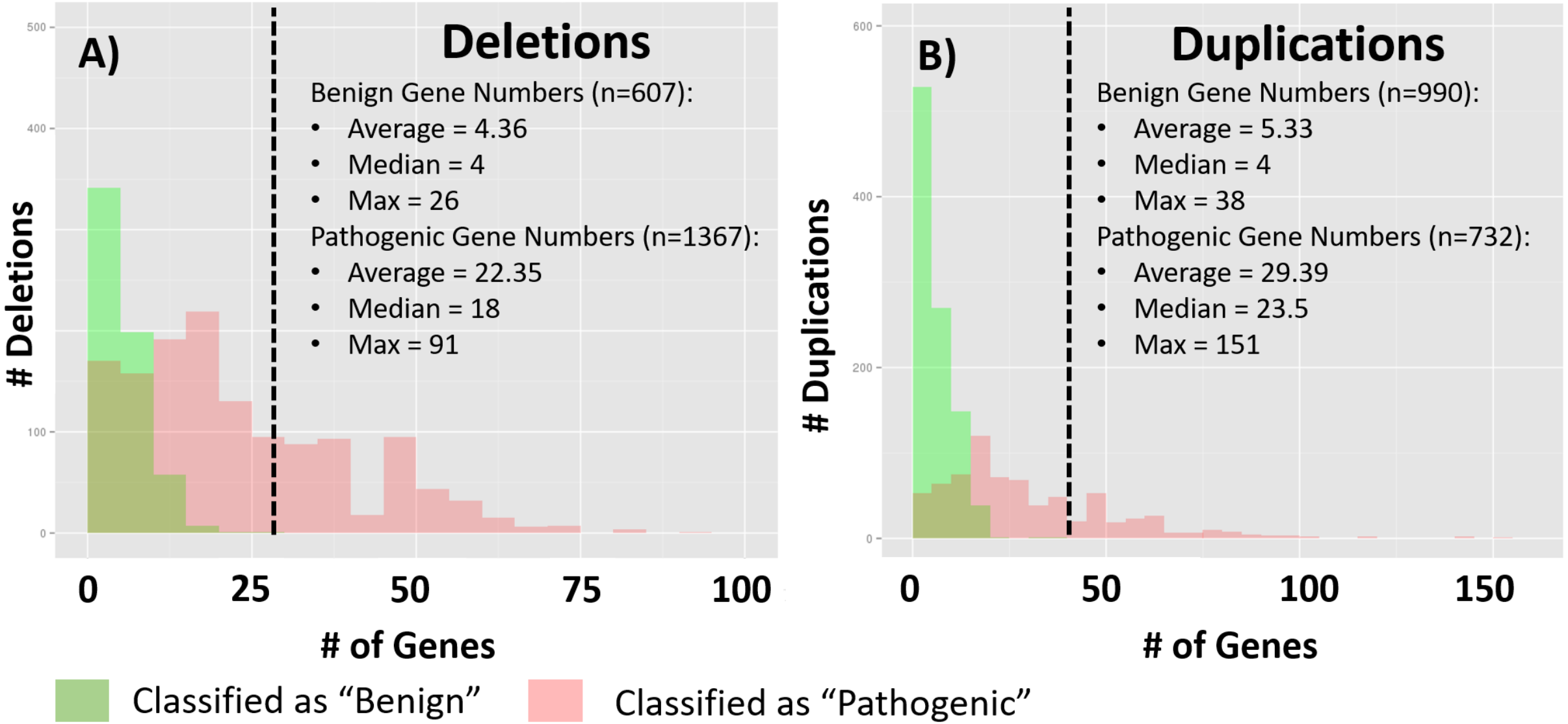
Category 2I Both breakpoints are within the HI gene

One breakpoint within the HI gene — Category 2J or 2K

Supplemental Figure 1.3: Illustrations of scoring metric categories 2C-2E (loss metric) and 2H-2K (gain metric) - overlap with established haploinsufficient genes. A theoretical haploinsufficient gene is shown at the top. Example overlapping copy number variants are shown below, each representing a scenario described in the loss (Table 1, Main Document) or gain (Table 2, Main Document) scoring metric. Red boxes represent deletions, blue boxes represent duplications. HI = haploinsufficient; LOF = loss of function; UTR = untranslated region.



Supplemental Figure 1.4: Illustrations of scoring metric categories 2F-2G (loss metric) and 2C-2G (gain metric) - overlap with established benign genomic regions. A) A theoretical established benign genomic region is shown in the context of several genes. Example overlapping deletions are shown below, each representing a scenario described in the loss scoring metric (Table 1, Main Document). **B)** A theoretical established benign genomic region is shown in the context of several genes. Example overlapping duplications are shown below, each representing a scenario described in the gain scoring metric (Table 2, Main Document). Red boxes represent deletions, blue boxes represent duplications.



Supplemental Figure 1.5: Analysis of gene content across clinically-classified copy number variants (CNVs) in dbVar. CNVs involving autosomes with clinical classifications between 200 kb-5Mb within dbVar studies nstd37 and nstd101 were analyzed for gene content. Those CNVs involving known dosage sensitive genes or genomic regions (as documented in dbVar study nstd45) were excluded. Gene arrays and non-protein-coding genes were not included in gene counts. The average, median, and maximum number of genes noted within benign (green) and pathogenic (red) deletions (A) and duplications (B) are depicted.