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ORIGINAL ARTICLE

Using reported pathogenic variants to identify therapeutic opportunities for genetic diseases

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Abstract

Purpose: Drug development strategies for genetic diseases depend critically on accurate knowledge of how pathogenic variants cause disease. For some well-studied genes, the direct effects of pathogenic variants are well documented as loss-of-function, gain-of-function or hypermorphic, or a combination of the two. For many genes, however, even the direction of effect of variants remains unclear. Classification of Mendelian disease genes in terms of whether pathogenic variants are loss- or gain-of-function would directly inform drug development strategies.

Methods: We leveraged the recent dramatic increase in reported pathogenic variants to provide a novel approach to inferring the direction of effect of pathogenic variants. Specifically, we quantify the ratio of reported pathogenic variants that are missense compared to loss-of-function.

Results: We first show that for many genes that cause dominant Mendelian disease, the ratio of reported pathogenic missense variants is diagnostic of whether the gene causes disease through loss- or gain-of-function, or a combination. Second, we identify a set of genes that appear to cause disease largely or entirely through gain-of-function or hypermorphic pathogenic variants.

Conclusions: We suggest a set of 16 genes suitable for drug developmental efforts utilizing direct inhibition.

KEYWORDS

autosomal dominant, drug development, gain-of-function, missense variants, therapeutic inhibition

1 | INTRODUCTION

Determining whether a genetic disorder is due to a gain, loss or change of protein function is a critical first step in effective drug discovery. For many recessive disease genes, including many inborn errors of metabolism, pathogenic variants have been clearly identified as loss-of-function (LoF). Similarly, for a number of dominant disease genes, careful functional characterization of variants found in patients has provided clear evidence of variantal effects. For example, dominant pathogenic variants in the NSD1 gene have been shown to reduce or eliminate the function

of NSD1 (Choufani et al., 2015; McClelland et al., 2016), whereas nearly all apparently pathogenic variants in SCN8A and KCNT1 have been clearly shown to be variants that increase channel current (Lopez-Santiago et al., 2017; Milligan et al., 2014; Pan & Cummins, 2020; Quraishi et al., 2019). Furthermore, some disease genes have been clearly shown to carry both pathogenic gain-of-function and LoF variants. For example, after the identification of loss of SMCHD1 function is causative for a form of muscular dystrophy (Lemmers et al., 2012), later research identified gain-of-function variants in SMCHD1 as responsible for rare syndrome BAMS (Gurzau et al., 2018), a distinct genetic disease. Overall, although many recessive genes are classified as due to LoF variants, and a subset of dominant genes are classified as haploinsufficient, meaning that disease is due to loss of activity of one of the two alleles, many dominant genes remain not clearly classifiable as due to either loss- or gain-of-function variants. The secure identification of which of these unclassified genes cause disease because of variants that increase or change the activity of the encoded protein would have immediate implications for drug development.

Over the past decade, a wide range of approaches have been used to infer the functional impact of pathogenic variants (Dong et al., 2014; Li et al., 2019; Liu et al., 2015). Attempts to identify LoF and gain-of-function variants have leveraged existing bioinformatic tools like genetic tolerance sorting (SIFT), polymorphism phenotyping (PolyPhen) (Flanagan et al., 2010), and conservation-based Hidden Markov Models (Liu et al., 2014). Additionally, highly supervised approaches that manually examine variants suggested to be GoF within OMIM have been attempted (Chen & Altman, 2017). Despite these advances, identifying a subset of genetic diseases well suited for therapeutic inhibition has yet to be well established. Surprisingly, no one has yet attempted to use the distribution of reported pathogenic variants to infer whether pathogenic variants are strictly gain- or loss-of-function, or some combination. The intuition behind this approach is straightforward. Genome wide has been estimated that approximately 20% of missense variants are significant hypermorphic or LoF variants (Kryukov et al., 2007). In addition, on average, the proportion of variants in a human gene that are missense versus nonsense variants has been estimated to be about 1.05 (Gorlov et al., 2006). This means that for genes that cause disease due to haploinsufficiency, the proportion of pathogenic missense to all missense and LoF variants should be approximately 0.21. This intuition is clearly supported by considering the well-known examples of NSD1 and KCNT1. Of all reported pathogenic (mostly de novo) variants in NSD1, the proportion of missense variants is 0.27 (88 missense, 242 LoF), whereas KCNT1 has 38 reported pathogenic missense variants and no known pathogenic LoF variants. Based on this intuition, we have developed an evaluation of the proportion of variant type in all autosomal dominant genes in order to infer the direction of effect of pathogenic variants. Specifically, we seek to find a threshold on the proportion of variants that are missense versus LoF that is diagnostic of whether the gene causes disease due to loss- or gain-of-function/hypermorphism. For convenience, hereafter, we will refer to both the gain-of-function and hypermorphism as "gain-of-function" (GoF), without attempting to distinguish between the two.

2 | METHODS

To develop a pipeline to distinguish genes that cause disease due to LoF or GoF, we first extracted all pathogenic and likely pathogenic variants from ClinVar's GRCh37 weekly VCF file with minor allele frequencies of 0 in all three of Exac, GO-ESP, and GMAF (Figure 1). We hypothesized autosomal dominant variants will predominantly cause disease via haploinsufficiency or GoF. Thus, we focused our analyses on known Haploinsufficient genes (n = 361) and OMIM annotated autosomal dominant ("AD") genes (n = 219).

We then categorized variants as "likely LoF" if they were annotated as "nonsense", "frame-shift," or "stop-loss" and as "missense" if they were annotated as "missense." All other variant types were not binned as either missense or likely LoF variants and were not include in ratio calculations. On the occasions where the same variant was annotated as both "likely LoF" and "missense," the variant was excluded from downstream analyses.

To assess whether the variant ratio is generally diagnostic of how variants caused disease, we first considered a set of genes that have been defined previously as haploinsufficient. To this end, we leveraged two separately generated lists of genes. First, we considered a list of genes ("Dang") generated through Dang et al.'s robust database-mining of OMIM and PubMed (Dang et al., 2008). We additionally considered ClinGen's manually curated and reviewed list of 312 genes ("ClinGen") determined to have "sufficient evidence of haploinsufficiency." Out of these gene lists, a total of 361 unique haploinsufficient ("HI") genes had more than 10 P/LP variants. Of these 361 entries, 93 were shared, 63 were unique to Dang and 205 were unique to ClinGen. We considered both lists in order to identify a threshold on the variant ratio for autosomal dominant genes not annotated as haploinsufficient. Noting that genes that cause more than one Mendelian disease can have different directions of effects for different diseases, we also separately distinguished genes responsible for only one Mendelian disease.

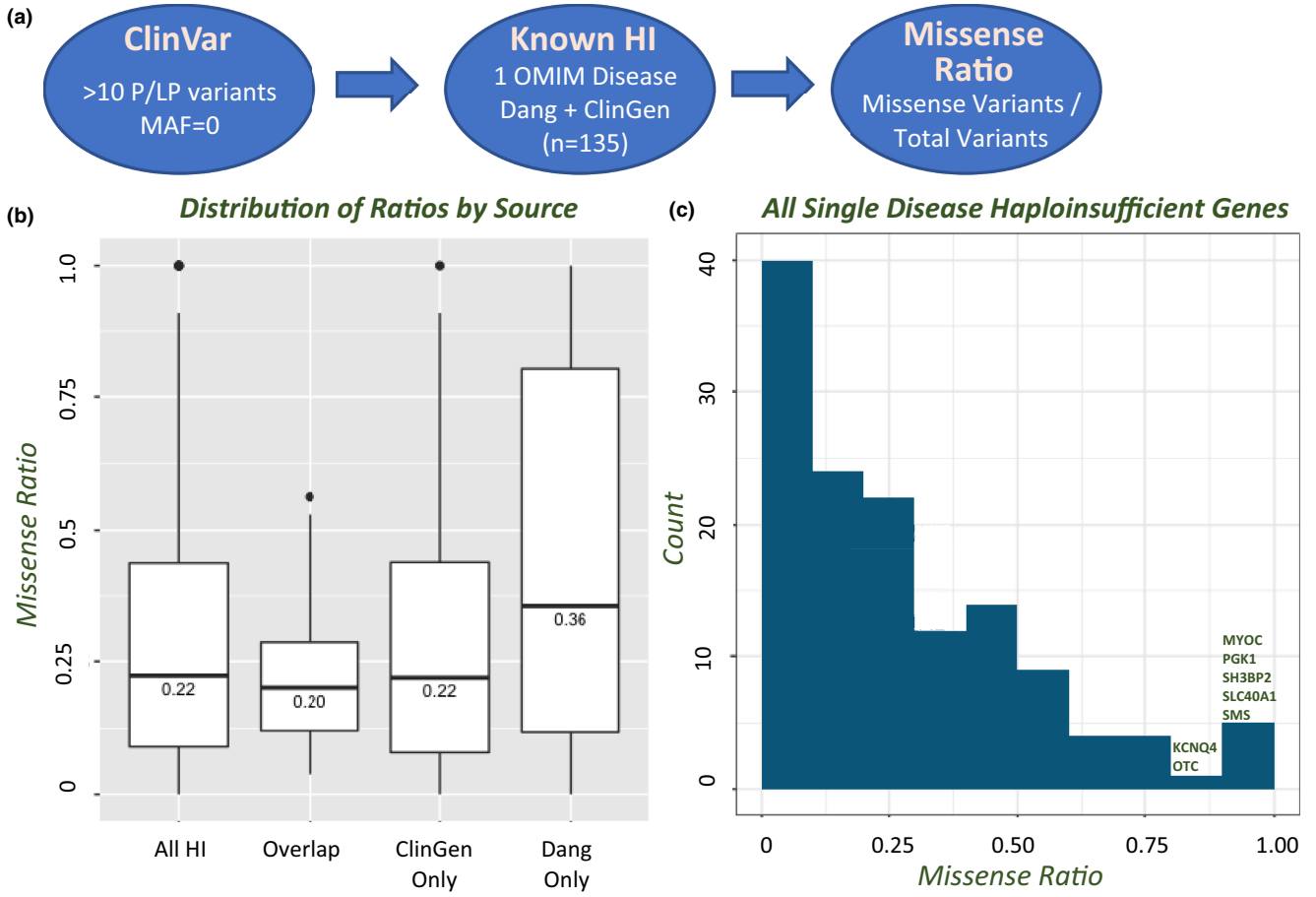

FIGURE 1 Identification of non-HI threshold. (a) Schematic of ratio identification. All pathogenic/likely pathogenic variants with minor allele frequency of 0 were used to generate a ratio of missense variants for known haploinsufficient genes associated with a single OMIM disease. (b) Box plot generated for known HI genes separated by source with median ratio values displayed. Overlap genes are in both ClinGen and Dang. (c) Histogram of all missense ratios for all single disease HI genes with outliers above HI- threshold highlighted.

3 | RESULTS

3.1 | Autosomal dominant genes enriched for missense variants

In all genes considered (HI = 361, OMIM autosomal dominant, 'AD', = 219), we identified pathogenic or likely pathogenic variants classified as either missense or LoF (Figure 1). We first evaluated the ratio of missense to all pathogenic variants for HI genes that are associated only with a single Mendelian disease (Figure 1). We found that for known HI genes associated only with a single Mendelian disease, 95% of all HI genes have a missense ratio less than 0.8 (128/135) and the median missense ratio for all haploinsufficient genes is 0.22, nearly identical to the a priori predicted ratio of missense variants. Importantly, since the generation of Dang's list of HI genes, more recent research has clearly demonstrated haploinsufficiency is not the predominant mechanism of disease for variants of, MYOC and SH3BP2, while additional pathogenic GoF or dominant-negative variants have been identified in KCNQ4 and SLC40A1 (Kamada et al., 2006; Kim et al., 2001; Reichenberger et al., 2012; Shepard et al., 2007; Zhang et al., 2019). Further, the three HI genes from ClinGen surpassing a threshold of 0.8 (OTC, PGK1, SMS) are all found on the X-chromosome. Importantly, a simple threshold may identify more false positives when the total number of variants is lower. Thus, we alternatively considered the lower bound of a 95% binomial confidence interval and did not find a significant enhancement of signal (Figure S1). Given similar results when considering a binomial lower bound and the successful exclusion of haploinsufficiency, a simple threshold is sufficient to exclude haploinsufficiency as a likely mechanism for AD genes.

Based on this finding, we considered all AD genes not known to be HI that are associated with only a single Mendelian disease, and we find 51 out of 110 applicable AD genes that appear to cause disease through GoF. Among this set of genes with variant ratios indicative of GoF, we find genes well known to cause disease due to GoF, such as GFAP and RIT1 (Figure 2a).

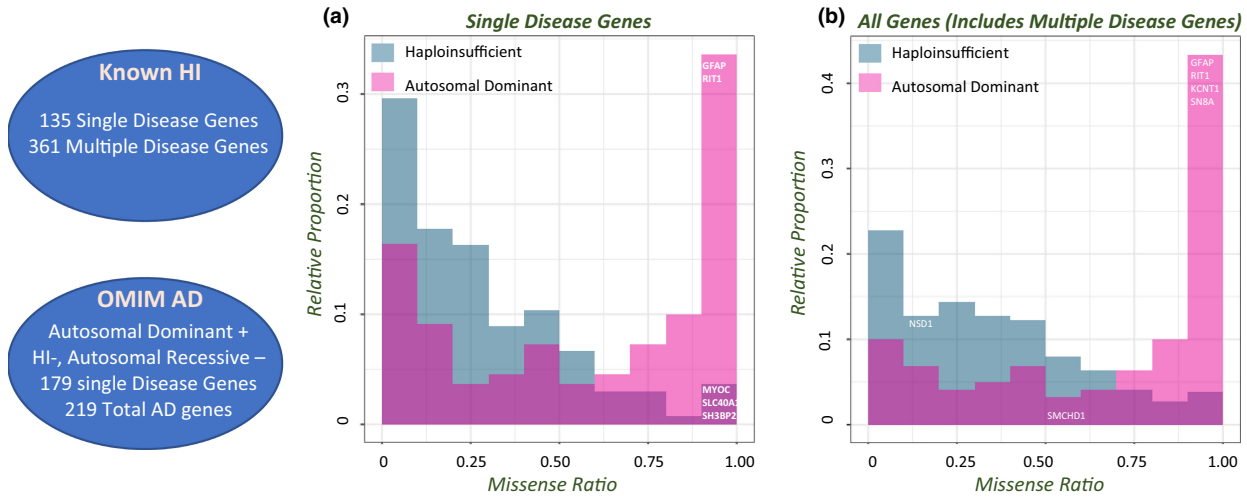

FIGURE 2 GoF AD genes. The relative frequency of missenseratios for known HI and AD genes are displayed alongside annotations of notable genes. Enrichment of AD genes with higher missense ratios for both single disease genes (a) and all genes (b).

We then investigated whether or not our HI- threshold could be extended to all genes with at least one disease annotated as AD, including those that cause multiple Mendelian conditions. We found similar enrichment of AD genes and absence of HI genes above our threshold (Figure 2b). Using our HI- threshold and more permissive inclusion criteria, we generated a list of 121 AD genes (Table S1) likely to act through a gain-of-function. Importantly, we find the presence of aforementioned known GoF genes such a KCNT1 and SCN8A within this gene list.

Finally, we sought to examine the topological distribution of missense variants in GoF AD genes, given GoF variants in the aggregate tend to be more spatially clustered (Lelieveld et al., 2017). As hypothesized, AD genes tended to be more clustered than known HI genes and autosomal recessive OMIM genes (Figure S2). However, the distributions of clustering were overlapping and a clear way to incorporate clustering to complement a simple missense threshold was not apparent.

3.2 | Identifying GoF genes for drug targeting

Once we generated a threshold capable of reliably identifying likely GoF genes, we aimed to determine a subset of genes well suited for therapeutic inhibition. To assess whether inhibition is likely to be well tolerated, we considered whether the genes are under strong selection against LoF variants. To this end, we only considered GoF genes highly tolerant to LoF variants (Lek et al., 2016) (pLI <0.1).

When considering all AD and HI genes, lower pLI scores are correlated with increasing ratio of missense variants. However, the strength of correlation is minimal. Further, the distributions of AD genes and HI are not cleanly distinguished and 11 of the 35 genes with pLI <0.1 are known HI genes, including two genes, PKD2 and TRAPPC2, that are found in both HI sources (Figure 3). Thus, the addition of pLI is not redundant and complementary to our missense ratio threshold.

Among the AD genes that appear to act through a GoF based on missense ratio, we identified 36 that show no evidence of strong selection against LoF variants in the human population. Finally, we manually cross-referenced our list with "The Drug Gene Interaction Database" (Cotto et al., 2018) to identify a set of genes known to be therapeutically accessible. Following curation, we identified a list of 16 druggable, LoF tolerant, likely GoF genes (Table 1).

4 | DISCUSSION

Identifying causal GoF disease genes tolerant of reduced dosage would provide therapeutic targets of immediate interest. Further, publicly available drugs are more often inhibitors than activators, suggesting enhanced therapeutic potential for downregulation (Law et al., 2014). Identifying likely GoF genes has proved relatively difficult, as displayed by the distribution of pLI scores for known haploinsufficient genes and significant reduction in performance of Polyphen and SIFT compared to prediction of LoF variants (Flanagan et al., 2010). Despite these difficulties, several groups have developed methods to identify likely GoF variants, but a definitive list of GoF genes remains elusive. Here, we leveraged the increasing number of known pathogenic/likely pathogenic variants to generate a HI- threshold that identifies likely GoF

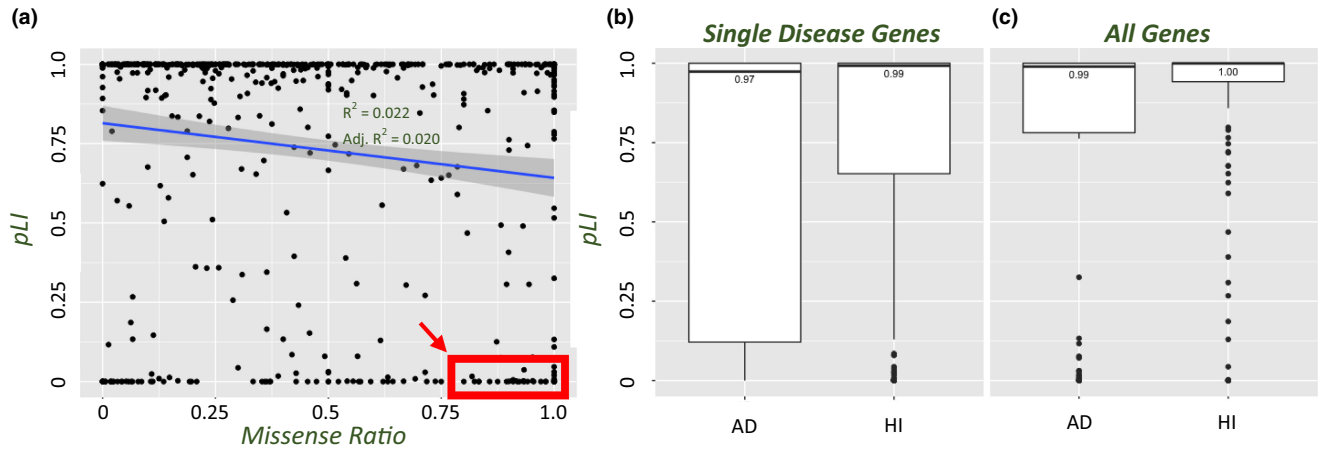

FIGURE 3 pLI threshold complementary to HI- threshold. Scatterplot with linear regression line of pLI versus missense ratio. Likely GoF genestolerant to LoF variants shown in red box. (a) and (b) show the distribution of pLI scores for known AD and HI genes alongside median values for single diseasegenes and all genes including multiple disease genes, respectively.

TABLE 1 GoF genes suitable for therapeutic inhibition

Gene ID	Variants	OMIM diseases	Missense ratio	Missense ratio lower bound (95% CI)	pLI score	Druggable?
ABCC9:10060	22	3	0.95	0.77	9.4 E-09	Y
APP:351	18	2	1	0.81	0.047	Y
AVP:551	17	1	0.88	0.64	0.074	Y
COMP:1311	45	2	0.93	0.82	1.3 E-09	Y
ELANE:1991	29	2	0.93	0.77	0.0012	Y
FN1:2335	15	2	1	0.78	0.0014	Y
KCNA1:3736	21	1	0.95	0.76	0.076	Y
KCNT1:57582	38	2	1	0.91	2.8 E-05	Y
LRRK2:120892	10	1	0.8	0.44	2.6 E-30	Y
NOD2:64127	12	3	0.83	0.52	2.0 E-30	Y
PCSK9:255738	16	2	0.87	0.62	2.7 E-17	Y
PIK3R2:5296	11	1	0.81	0.48	0.016	Y
TNNT2:7139	47	4	0.91	0.80	0.0020	Y
TRPC6:7225	13	1	0.92	0.64	3.0 E-07	Y
TRPV4:59341	55	11	0.98	0.90	2.2 E-16	Y
UMOD:7369	34	3	0.97	0.85	3.2 E-17	Y

Note: All genes have missense ratios > 0.8, pLI < 0.1 and are in the druggable genome. Number of known OMIM Mendelian diseases listed alongside genes for reference.

genes. We further parsed these likely GoF genes to identify a subset of targets that were both therapeutically accessible and LoF tolerant.

Well-characterized GoF genes, such as SCN8A, SOS1, and KCNT1 are present in the list of likely GoF genes, alongside mischaracterized "known haploinsufficient genes" like MYOC and SH3BP2. However, these genes all have been relatively robustly assessed in vitro, while many pathogenic variants have very limited functional evidence in the literature and can benefit particularly from a hypothesis on functional mechanism. Further, our list of likely GoF genes with low pLIs includes GFAP, which when targeted with antisense inhibition, has shown the potential benefit of utilizing drug inhibition on candidate genes (Hagemann et al., 2018).

Importantly, within our analyses, we did not attempt to distinguish between hypermorphic variants and other GoF mechanisms. Similarly, we did not consider whether or not a variant may act through a dominant negative mechanism. Such genes may be present within our GoF list and additional strategies would be required to confidently exclude them.

Finally, as publicly available datasets continue to increase in size, the list of genes with more than 10 variants that surpass HI-threshold will continue to increase. Thus, the list of therapeutically accessible likely GoF genes will expand and may provide important context when considering which treatment candidate to prioritize in vitro when investigating novel causal variants. Furthermore, recent work from our laboratory and others has leveraged published RNA sequencing data to identify downregulators of gene targets (Shukla et al., 2020; Wang et al., 2020). A similar approach in this context would be complementary and may lead to rapid successful drug repurposing capable of providing direct benefit to patients.

AUTHOR CONTRIBUTIONS

A.K.R and D.B.G contributed to conception, design, analysis and interpretation of data. A.K.R drafted the manuscript and D.B.G revised the manuscript.

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None.

CONFLICT OF INTEREST

D.B.G is a founder of and holds equity in Praxis and Actio, serves as a consultant to AstraZeneca, and has received research support from Janssen, Gilead, Biogen, AstraZeneca and UCB. A.K.R declares no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that supports the work within this manuscript is publicly available on ClinVar's weekly GRCh37 weekly vcf file (https://ftp.ncbi.nlm.nih.gov/pub/clinvar/vcf_GRCh37/weekly/) and through OMIM's data downloads (Online Mendelian Inheritance in Man, OMIM®, 2020) (https://omim.org/downloads/%3F%3F%3F/mimTitles.txt). The work within this manuscript is up to date as of August 3, 2021.

ETHICS STATEMENT

No animal subjects or human samples were used for this study and work was performed in adherence to Columbia University Medical Center's ethical standards.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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