Trends in Genetics

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Opinion

Genetic suppressors as new therapeutic targets for Mendelian diseases

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Most Mendelian diseases lack effective treatments, with current options often limited to symptomatic care rather than addressing the underlying genetic defect. In this opinion article, we argue that genetic suppressors, a specific class of modifier variants that can counteract the effects of disease-causing mutations, can identify promising new avenues for therapeutic intervention. We discuss the prevalence of potential suppressors across Mendelian diseases, describe approaches for their systematic identification, and consider their therapeutic relevance. As genome-wide screening technologies and machine learning methods continue to advance, we expect suppressor identification to accelerate in the near future. These suppressors present exciting opportunities for expanding our therapeutic arsenal and improving outcomes for individuals with inherited disorders.

Highlights

Most Mendelian diseases lack effective treatments.

Suppressor genes, which, when mutated, rescue the detrimental effects of a disease mutation, can encode promising alternative drug targets.

Recent years have seen increased development of drugs targeting suppressors.

Genetic suppressors are common and may exist for many Mendelian disease genes.

Systematic identification and validation of suppressor variants could transform therapeutic strategies for rare genetic diseases.

Most Mendelian diseases lack effective treatments

While most **Mendelian diseases** (see Glossary) are individually rare, they collectively affect over 400 million people worldwide [1]. Over the past few decades, remarkable progress has been made in identifying the genetic causes of these disorders [2]. Yet, this knowledge has not translated into more effective therapies. For more than 95% of Mendelian diseases, available treatment options remain limited, with care often centered on managing symptoms rather than addressing the underlying genetic defect [3].

Identifying a drug target is generally a crucial first step in developing a new therapy. In cases where the disease is caused by gain-of-function mutations—resulting in excessive activity or expression of the encoded protein—directly inhibiting the mutated protein can have therapeutic potential, and the protein encoded by the disease gene is thus an obvious drug target. The majority of Mendelian diseases, however, result from loss-of-function mutations [2,4], leading to the absence or dysfunction of the encoded protein. Restoring protein function with small molecules is much more challenging in these cases. Occasionally, the mutated protein retains some residual function and may be amenable to modulation, such as in the case of cystic fibrosis [5]. However, for the majority of Mendelian disorders, pharmacological correction of the mutated protein is currently not possible [3]. Although gene therapy could be used to introduce a functional copy of the mutated gene, the considerable costs, delivery difficulties, and safety concerns associated with such treatments remain major obstacles in their development, particularly for rare diseases [6,7].

Suppressors as alternative drug targets

Genetic suppressors can reveal promising alternative drug targets. Genetic suppressors are a specific class of **modifier variants** that partially or completely alleviate the phenotype caused by

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another mutation, a phenomenon that has been extensively studied in model organisms [8–14]. Suppression interactions can be intragenic, occurring between two mutations within the same gene, or extragenic, involving mutations in different genes [15]. Extragenic suppressors of disease mutations are of particular interest, as they reveal biological mechanisms that mitigate the disease (Box 1), which may be leveraged for new therapeutic approaches. Here, we focus on extragenic loss-of-function suppressors of disease genes, as their effect may be mimicked by small molecules or antibodies that target the encoded protein.

A well-known example of a disease suppressor is a loss-of-function variant in *BCL11A*, which encodes a transcriptional repressor of the fetal hemoglobin subunit γ, that is protective against severe sickle cell disease [20]. When expressed in adults, the fetal γ subunit of hemoglobin can replace the β subunit, which is mutated in sickle cell patients. This finding led to the development of Casgevy, a highly effective therapy targeting *BCL11A* [21,22] (Table 1, Key table). While this therapy still relies on the genetic inactivation of *BCL11A*, in other cases, small molecules are being developed to inhibit a suppressor protein, potentially leading to affordable and effective therapies for the suppressed disease (Table 1).

Box 1. Mechanisms of suppression

Genetic suppressors can be classified into different mechanistic categories based on the functional relationship between the suppressor gene and the suppressed disease gene [8,16]. Approximately one third (36%) of suppression interactions that have been reported to date occur between genes that are annotated to the same biological process, such as those encoding members of the same protein complex or pathway (Figure I). For instance, gain-of-function variants in the γ hemoglobin subunit gene can suppress sickle cell disease by circumventing the need for the mutated β subunit [17]. Suppression can also occur through more general mechanisms. Suppression of partial loss-of-function alleles can result from mechanisms that enhance expression of the mutated disease gene or improve stability of its gene product, thereby increasing the levels of the mutated but partially functional protein (16% of interactions). This is illustrated by cystic fibrosis, which is caused by mutations in *CFTR* that often lead to misfolding and subsequent degradation of the encoded ion channel. Many unstable cystic fibrosis transmembrane conductance regulator (CFTR) mutants retain function, and in such cases, changes in *CFTR* transcription or translation, chaperone levels, or activity of the protein degradation machinery, can (partially) restore ion transport [16]. Finally, 19% of reported interactions involve altered signaling or stress response processes, such as signaling cascades, apoptosis, and the immune response. Genes with a role in signaling or the response to stress can suppress defects associated with mutation of genes involved in diverse biological processes. For example, variants that attenuate cytokine signaling can reduce symptoms of both cystic fibrosis and sickle cell disease [16]. This underscores the critical role of inflammation in both disorders, despite distinct underlying pathologies [18,19]. Collectively, these mechanistic classes account for 70% of reported suppression interactions and provide insights into common mechanisms through which suppression of disease mutations can occur.

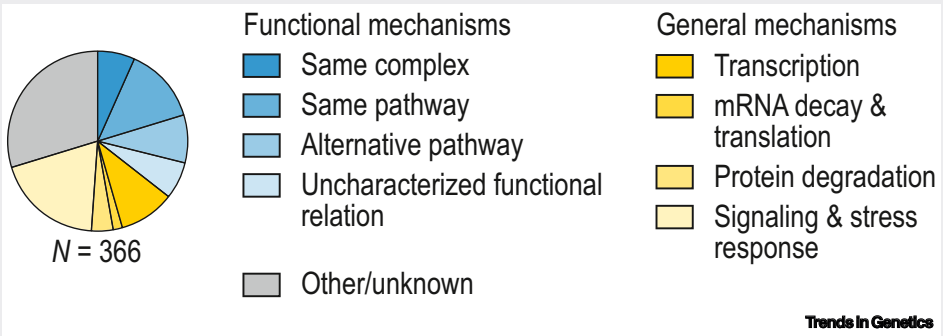

Figure I. Mechanistic classes of suppression. Distribution of suppression interactions across mechanistic classes for suppressors identified in patients, cultured human cells, or animal models. There are no significant differences in the distribution of interactions between interactions identified in patients and those identified in cellular or animal models (not shown). Classification was performed as described previously [16] using an updated list of literature-curated suppression interactions.

Glossary

Dominant: a genetic variant is considered dominant if a single copy of the allele carrying the variant is sufficient to produce an observable trait or effect, overriding the influence of other alleles of the same gene.
Genetic suppressor: a genetic variant that counteracts or reduces the harmful effects of another mutation, such as a disease-causing mutation.
Genome-wide association study (GWAS): a research approach that involves comparing genetic variants present in different groups of individuals to identify associations with specific traits or diseases.
Incomplete penetrance: penetrance refers to the proportion of individuals carrying a particular genetic variant who exhibit the associated phenotype. Incomplete penetrance occurs when not all carriers of a disease-associated mutation display symptoms.
Mendelian disease: a disorder caused by mutations in a single gene, typically following inheritance patterns described by Gregor Mendel (autosomal dominant, autosomal recessive, X-linked, etc.).
Modifier variant: a genetic variant that alters the phenotype associated with another mutation, potentially influencing disease severity, symptoms, or age of onset.

Key table

Table 1. Therapies targeting suppressor genes that are in various stages of clinical development

Disease	Disease gene	Suppressor gene	Clinical development stage	Identification method	Key Refs
Sickle cell disease and β-thalassemia	*HBB*	*BCL11A*	Approved (Casgevy)	GWAS	[20–23]
Familial hypercholesterolemia	*LDLR*	*PCSK9*	Approved (Evolocumab, Alirocumab)	Family studies	[24–26]
Glycogen storage disorders	*GAA*, *GBE1*, *EPM2A*, and *NHLRC1*	*GYS1*	Completed Phase 1 (MZE001)	Mouse model	[27–30]
Niemann–Pick disease type C	*NPC1*	*PLA2G15*	Investigational	Cultured mammalian cells	[31]
Barth syndrome	*TAFAZZIN*	*ABHD18*	Preclinical	Cultured mammalian cells	[32,33]

Despite successes, such as Casgevy, the identification of suppressors is not yet commonly pursued as a strategy for discovering drug targets in Mendelian diseases. This is likely due to a combination of limited awareness of their existence, technical challenges in their discovery, and uncertainty about their therapeutic applicability across the wide spectrum of genetic disorders. In the following sections, we explore how many genetic diseases may be suppressible, approaches for identifying these suppressors, and considerations for targeting suppressors in a therapeutic setting.

How many disease alleles can be suppressed?

Although we currently lack definitive data on how many disease alleles can be suppressed, suppressors have been reported for many of the more common Mendelian diseases—including sickle cell disease, β-thalassemia, cystic fibrosis, Huntington's disease, Duchenne muscular dystrophy, and spinal muscular atrophy [16]. The relative scarcity of reports on the suppression of rarer disorders likely reflects limited patient numbers and ascertainment rather than a true absence of suppressors. This is supported by systematic studies in model organisms, which show that genetic suppression is remarkably common [12–14,34]. For example, in budding yeast, the proportion of detrimental alleles that can be suppressed ranges from ~20% for lethal deletion alleles to more than 95% for deleterious missense mutations [8,34–36]. Lethal deletion mutants, in which a gene is completely absent in a haploid genome, are more challenging to suppress because this requires bypassing the need for the missing protein. In contrast, deleterious missense mutations that retain some residual protein expression or activity are more amenable to suppression. In these cases, suppression often involves boosting or adapting to the reduced protein activity, which can be achieved through multiple mechanisms (Box 1). According to recent estimates, ~35% of human loss-of-function disease alleles carry missense mutations [37]. If we assume that, similar to yeast, suppressors exist for 95% of missense mutations and for 20% of the remaining alleles, about half ($0.95 \times 35 + 0.20 \times 65 = 46\%$) of all loss-of-function disease alleles may be rescued by a genetic suppressor. Although this calculation rests on several assumptions and the actual fraction of suppressed disease alleles may differ, given the high frequency of suppression observed for common Mendelian diseases, it is not unreasonable to expect that many human disease genes can likely be rescued by a genetic suppressor.

How many suppressor genes exist per disease gene?

Not all suppressor genes are likely to yield good drug targets, and it would thus be advantageous for drug development purposes if a disease allele had multiple suppressor candidates to explore.

Suppressors have been reported in the scientific literature for ~100 different human disease genes [16]. For most of the disease genes queried, between one and four suppressor genes have been described [16]. Some of these interactions, however, were found in underpowered or hypothesis-driven studies that may have only tested or reported one suppressor gene, while additional suppressors may exist. Despite this bias, the reported numbers are consistent with findings from systematic screens in yeast and mouse, which typically identify about two to four strong suppressors per allele [8,13,35,38]. Importantly, ~80% of reported human suppressors with a known functional effect are loss-of-function variants [16], indicating that these suppressors could potentially be mimicked by drugs that inhibit the encoded protein.

How can suppressor genes be identified?

Given the likelihood that suppressors exist for a wide range of disease alleles, how might we find these genes? In some cases, there are indications that suppressors are present in a patient population, particularly when there is notable variation in disease severity or when a disease allele shows **incomplete penetrance** (Box 2). Under these circumstances, association or linkage analyses can help pinpoint the suppressor gene (Figure 1). **Genome-wide association studies (GWASs)** are especially powerful for identifying common genetic variants that suppress a

Box 2. How common are resilient individuals?

Resilient individuals, who are healthy despite carrying mutations associated with a highly penetrant, severe, early-onset Mendelian disorder [39–41], may carry protective suppressor variants that compensate for the detrimental effects of the disease-causing mutation. But how common is genetic resilience? Several studies have identified potentially resilient people that appeared to carry a severe, highly penetrant, early-onset Mendelian disease-causing mutation in large cohorts of healthy individuals [39–42]. Despite differences in methodology and included diseases, these four studies find remarkably similar rates of ~1–3 resilient individuals per disease gene per 10 million individuals (Table I). Their resilience could not be explained by for example sequence or annotation errors, escape of nonsense-mediated mRNA decay for premature termination codons, exon skipping, or rescue by modifying variants within the same gene. Although some resilient candidates carried mutations linked to relatively common genetic diseases, such as cystic fibrosis, about half of the individuals harbored mutations associated with a disease affecting fewer than one in a million live births. Given that most of the candidate resilient individuals were unavailable for recontacting, it is possible that some of the identified individuals show disease symptoms or that somatic mosaicism for deleterious mutations could explain the absence of phenotypic expression. These studies, however, have focused on highly penetrant deleterious mutations that have ages of onset less than 2 years of age, so even if some individuals are not completely resilient, their cases remain noteworthy. Overall, this body of work shows that candidate resilient individuals can be readily identified, even in relatively small cohorts of 10 000 healthy individuals (Table I).

Table I. Number of resilient individuals found in biobank searches

Biobank size	Examined disease genes	Resilient individuals identified in study	Resilience prevalence per disease gene	Refs
589 306	162	10[a]	1.0×10^{-7}	[39]
60 706	924	5[b]	8.9×10^{-8}	[41]
807 162	77	17[c]	2.7×10^{-7}	[40]
9637	1606	3[d]	1.9×10^{-7}	[42]

[a]Out of 13 potentially resilient individuals, three were excluded due to carrying a disease mutation for which variable phenotypes had been reported.
[b]From 18 candidate resilient individuals, 13 were excluded who carried a mutation that possibly occurred at a low-quality site or that was present in fewer than 35% of reads for heterozygous mutations, or fewer than 100% of reads for homozygous mutations.
[c]Out of 33 severe, highly penetrant, early-onset disease mutations detected in healthy adults, 16 were excluded that were affected by genotyping or mapping errors, that occurred in part of a gene that is excluded in most transcripts, or that could have escaped nonsense-mediated mRNA decay. As the number of individuals carrying a mutation was not indicated, we assume that each mutation was found in a single individual.
[d]Among nine candidate resilient individuals, five were excluded due to reported cases of rare, adult-onset presentations of the condition and one was excluded due to their young age (12 years old).

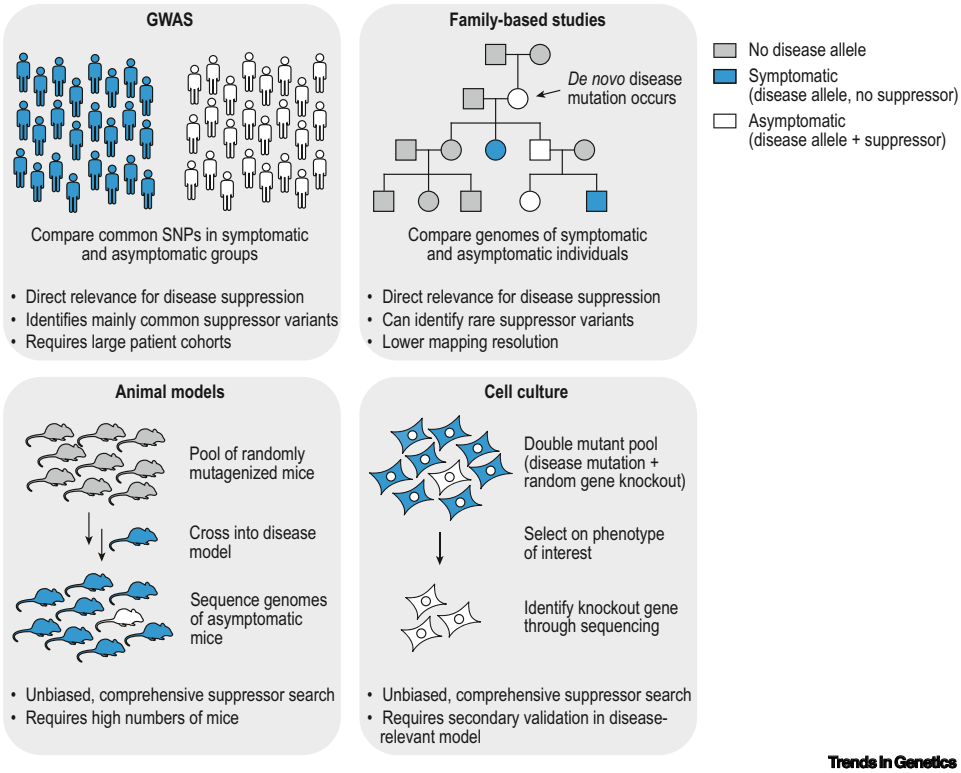

Figure 1. Approaches for identifying suppressor genes. Genome-wide association studies (GWASs) compare large cohorts of patients with varying disease severity to identify common suppressor variants associated with milder or absent disease phenotypes. Family-based studies involve sequencing affected and unaffected relatives carrying disease alleles to find rare suppressor variants that segregate with disease resilience. Mouse screens use pools of mutagenized mice crossed into disease models to unbiasedly search for suppressors that rescue disease phenotypes. Cell culture screens employ genome editing in human cells to create pools of double mutants, all carrying the disease mutation and one other mutation (often gene knockout) elsewhere in the genome, followed by selection for rescue of phenotypes caused by the disease mutation, enabling systematic identification of suppressor genes. For each approach, key advantages and limitations are summarized in the figure. For simplicity, disease and suppressor alleles are assumed to be dominant in this illustration, but the same principles apply to recessive alleles. SNPs: single nucleotide polymorphisms.

disease. Most study designs compare thousands of individuals who share a disease-associated allele but differ in how severely the disease manifests. Suppressor variants will be overrepresented in individuals with mild or no disease. This approach has identified suppressor variants in *BCL11A* that are protective against severe sickle cell disease [20], as described earlier.

For genetic diseases that are too rare to assemble cohorts of thousands of patients, suppressors can sometimes be identified in affected families (Figure 1). In these cases, segregating suppressor variants rescue disease phenotypes in some family members. By sequencing relatives who show differences in disease severity, suppressor variants can be uncovered. While GWASs are typically limited to finding common variants, family-based studies have the added advantage of being able to identify rare suppressor variants. Family studies have, for example, identified *MTMR4* as a suppressor of long QT syndrome, which is characterized by prolonged cardiac repolarization and an increased risk of life-threatening arrhythmias. Across 13 families affected by the disease, 10 individuals were identified who were asymptomatic despite carrying a **dominant** disease-associated mutation that destabilizes the potassium channel KCNQ1 [43]. The asymptomatic family members carried loss-of-function variants in *MTMR4*, which reduced the activity of E3

ubiquitin-protein ligase Nedd4L, thereby limiting degradation of KCNQ1 and normalizing cardiac repolarization [43]. Suppressor variants can sometimes also occur somatically, a mechanism that is particularly relevant for hematopoietic disorders due to the continuous accumulation of mutations in hematopoietic stem cells [44]. For example, one copy of the *EIF6* gene is frequently lost or inactivated in bone marrow cells of patients with Shwachman–Diamond syndrome who have a relatively benign clinical course [45–48]. Deficiency of the Shwachman–Diamond syndrome protein impairs the release of eIF6 from 60S ribosomal subunits during their final maturation [49–51], thereby reducing translation efficiency, which can be restored by loss of eIF6.

When there are no indications of suppressors occurring in patients, animal models offer an alternative means to identify them (Figure 1). If the molecular mechanisms underlying the disease pathology are well known, hypothesis-driven experiments can be used to validate suppressor candidates. For example, based on the central role of glycogen synthase GYS1 in glycogen accumulation, investigators tested whether the loss of *GYS1* could suppress disease phenotypes in a mouse model of Lafora disease—a disorder characterized by the accumulation of glycogen aggregates in the brain and skeletal muscle [27–29]. *GYS1* deficiency prevented glycogen build-up and fully rescued neurodegeneration and seizure susceptibility in these mice [27,28,52], and a GYS1 inhibitor is currently being tested in the clinic (Table 1). In the absence of directly testable hypotheses, unbiased genetic screens in animal models can be a powerful way to identify suppressors. A systematic screen of ~3000 chemically mutagenized mice engineered to model Rett syndrome, a neurodevelopmental disorder, revealed five suppressors that ameliorated disease symptoms [13]. Although such screens can identify suppressor candidates, screening thousands of mice is a substantial undertaking that is typically restricted to specialized research facilities.

High-throughput screens in cultured human cells that test thousands of mutant combinations in a single experiment can provide an alternative way to identify suppressor mutants that rescue cellular defects caused by disease mutations (Figure 1). Such screens typically rely on clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 genome editing or insertional mutagenesis in haploid cells to inactivate every gene in the human genome in pairwise combinations with a disease gene of interest. In addition to fitness, readouts such as fluorescence, cellular morphology, or transcriptome profiling [53–55] can be used in *in vitro* screens to identify suppressors of clinically relevant phenotypes. After identification, the suppressor candidates will need to be validated in disease-relevant models. For example, a genome-wide knockout screen found that inactivation of *ABHD18* fully rescued the proliferation defect of a cellular model of Barth syndrome, a mitochondrial disorder caused by an accumulation of monolysocardiolipins [32]. Knockout of *ABHD18*, which encodes a monolysocardiolipin-producing enzyme, fully rescued embryonic lethality, reversed weight loss, and restored cardiac function in a Barth syndrome mouse model, highlighting the therapeutic potential of inhibiting ABHD18 [32] (Table 1). Together, these complementary approaches enable the systematic discovery of suppressor genes across diverse genetic disorders.

Considerations for clinical targeting

Despite the promise of suppressors as therapeutic targets, several factors should be considered when developing a therapy that targets a suppressor. Not every identified suppressor will make an ideal drug target, as is the case with more traditional approaches to target identification. Suppressor genes are sometimes associated with diseases themselves and are significantly depleted of deleterious mutations in healthy individuals [16], suggesting that the beneficial effects of suppressor variants may only be apparent in the presence of the disease mutation. This should be considered when testing for the toxicity of new therapeutic agents targeting suppressors.

However, if a suppressor has been identified through a family-based study and individuals carrying the variant are healthy, this provides evidence that the suppressor is not inherently harmful.

Suppressors may also be tissue-specific, rescuing only a subset of symptoms. For instance, a patient with Shwachman–Diamond syndrome carrying a rare germline *EIF6* suppressor variant, rather than the somatic *EIF6* variants described earlier, exhibited mild hematological symptoms but still suffered from pancreatic insufficiency, neurodevelopmental challenges, and short stature [56]. While it is possible that EIF6 was not sufficiently inactivated in the affected organs, another possibility is that inactivation of *EIF6* only suppresses hematological symptoms. Similar tissue-specificity has been observed for suppressors of cystic fibrosis [57].

Furthermore, suppressors may only rescue particular disease alleles. As discussed earlier, loss-of-function variants in *MTMR4* limit the degradation of KCNQ1 channel protein variants associated with long QT syndrome [43], thereby suppressing the disease phenotype. However, this suppression will likely only rescue *KCNQ1* alleles that retain channel function, which account for about half of the disease-associated alleles [58], and will have no effect on disease alleles that fully disrupt KCNQ1 function. Conversely, some suppressors have broad clinical relevance beyond the particular genetic disorder for which they have been identified. A well-known example is *PCSK9*: loss-of-function variants in this gene can lower LDL-cholesterol in patients with familial hypercholesterolemia caused by mutations in *LDLR*, as well as in individuals with nongenetic forms of hypercholesterolemia [24,59]. Similarly, *GYS1* deficiency is not only protective against Lafora disease, as discussed earlier, but also against other glycogen storage disorders [29,30,52].

Finally, the timing of intervention can play a critical role, as delayed treatment may not reverse established pathology. For example, in the mouse model of Lafora disease mentioned earlier, knockout of *GYS1* at 4 months of age fully restored disease phenotypes. However, knockout at 6 months or later was less effective; although disease progression was halted, existing glycogen aggregates in the brain persisted, and neuroinflammation remained [60,61]. Similarly, in amyotrophic lateral sclerosis, genetic or pharmacological inhibition of Epha4 early in development could suppress disease phenotypes in mice and zebrafish models [62,63], but inhibiting the protein in pre-symptomatic adults failed to rescue [64–66].

Taken together, these considerations illustrate the importance of a carefully tailored approach to suppressor-based therapies that accounts for timing, toxicity, and allele specificity to maximize therapeutic benefit. Nonetheless, with thoughtful design and patient stratification, targeting suppressors holds great promise for advancing precision medicine in genetic diseases, as exemplified by the suppressors listed in Table 1.

Concluding remarks and future perspectives

Nearly all Mendelian diseases still lack an effective treatment [3], underscoring the urgent need for novel therapeutic approaches. Because suppressors generally act by modulating disease pathways rather than directly restoring the function of a mutated disease gene, they can represent tractable and affordable targets for new drug development based on small molecules or antibodies. Given that suppressors have been described for most common Mendelian diseases [16] and exist for nearly every deleterious point mutation in model systems [35,36], suppressors may exist for many genetic diseases. Nonetheless, for the vast majority of genetic disorders, no suppressors are currently known. We highlighted different strategies that can be taken to identify suppressor genes in such cases, ranging from systematic association studies in patient cohorts for more common diseases [20,67] to hypothesis-driven or screening approaches in model

Outstanding questions

What are the most effective approaches for discovering clinically relevant suppressor genes in rare Mendelian diseases, where patient cohorts are limited?

To what extent can loss-of-function suppressor mutations be mimicked pharmacologically?

How conserved is suppression among genetically distinct individuals?

Are there tissue-specific constraints on the effectiveness of suppressors?

systems [13,27,32] (Figure 1). The rescue phenotype of several suppressors, such as *ABHD18* in Barth syndrome and *EIF6* in Shwachman–Diamond syndrome, is conserved from yeast to humans [32,46,48,50,68], illustrating the relevance of model systems in finding suppressor genes.

Although we focused here on noncancerous disorders, suppressors may also prevent tumor formation in individuals with high-risk cancer driver alleles. For example, knockdown of the epidermal growth factor receptor gene *EGFR* largely prevented tumor development in a mouse model of the cancer predisposition syndrome neurofibromatosis type I [69]. Furthermore, while loss-of-function suppressors provide a more straightforward approach for drug targeting, gain-of-function suppressors can be informative for drug development purposes by revealing biological mechanisms of compensation that may be indirectly replicated by therapeutics. For instance, gain-of-function variants that increase expression of the fetal hemoglobin gene *HBG1* can reduce the severity of sickle cell disease, a mechanism that is mimicked clinically by inactivation of *BCL11A* [21,22,70]. Similarly, drugs that mimic activation of *RELN1* may be beneficial in familial Alzheimer's disease [71].

A decade ago, the use of resilient individuals, who are healthy despite carrying a disease-associated mutation, was laid out as an alternative path to drug discovery [72]. It was proposed that mining genotype and health data from existing biobanks could identify apparently healthy adults carrying highly pathogenic, fully penetrant mutations (Box 2), and that such discoveries could provide an alternative pathway to drug discovery for rare genetic diseases if one could identify their underlying genetic suppressors. However, determining which of the millions of variants in the genome of a resilient individual is responsible for the suppression phenotype is not trivial. Since that time, the emergence of machine learning tools has made this more feasible. Variant effect predictors and genomic language models, such as AlphaMissense and Evo2, make the identification of loss-of-function variants in genomes far more scalable [73,74]. Moreover, systematic studies have defined common mechanisms of suppression (Box 1), such as a tendency of suppressor genes to affect stress signaling or to function within the same biological process as the disease gene they suppress. Together, these variant effect predictors and established suppression mechanisms provide valuable training data for machine learning models designed to rapidly and accurately predict suppressor variants in resilient individuals [16].

As large-scale genetic resources, genome editing screens, and machine learning approaches continue to evolve, the systematic identification and characterization of human suppressors are expected to accelerate, yielding new avenues for therapeutic intervention for genetic disorders. Although the clinical approval of suppressor-based therapies (Table 1) has illuminated a path forward, much work remains to translate suppressor discovery into routine clinical practice (see Outstanding questions). Collaborative efforts spanning basic research, clinical genomics, and drug development will be essential for realizing the promise of suppressors as therapeutic targets. Ultimately, integrating suppressor identification into the therapeutic pipeline offers hope for transforming the lives of individuals and families affected by inherited disorders.

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Declaration of interests

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