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Promises and Challenges of Precision Medicine in Rare Neurodevelopmental Disorders

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Abstract

Rare deleterious variants with large effect sizes offer a unique opportunity to understand the pathophysiology of neurodevelopmental and psychiatric disorders and provide insights into mechanism-based therapies. Single gene disorders may, in particular, be addressable with gene-based technologies even in cases where we may not understand the pathophysiology completely, as has been the case for spinal muscular atrophy. This chapter reviews the therapeutics development process in several modalities, including small molecules, antisense oligonucleotides, and viral vector-mediated gene replacement using examples of rare genetic disorders such as tuberous sclerosis complex, Fragile X syndrome, Rett syndrome, and Angelman syndrome. Finally, a strengths, weaknesses, opportunities, and threats (SWOT) analysis is included to guide the use of rare genetic variants to develop treatments. Identification of rare genetic variants has changed the landscape of research in this field; however, to translate these discoveries into rational, mechanism-based, safe, and effective treatments for neurodevelopmental and psychiatric disorders will require building and sustained support of networks/consortia that work closely with patient communities and industry partners.

Introduction

It is now well established that many psychiatric neurodevelopmental disorders (NDD), such as autism spectrum disorder (ASD, schizophrenia, and bipolar disorder, have high heritability (Hebebrand et al. 2010). Advances in genetics and genomics, in particular the wider application of exome and genome sequencing to ever larger cohorts of individuals with ASD, have revealed that both common and rare variants contribute to autism risk. Most of the genetic risk for ASD is accounted for by the presence of multiple common variants (Gaugler et al. 2014) that individually have small effect sizes. In contrast, rare

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deleterious variants with large effect sizes can be the primary determinant in specific individuals; these variants are often associated with intellectual disability. According to a Swedish epidemiological database (the Population-Based Autism Genetics and Environment Study or PAGES), up to ~27% of individuals with ASD have pathogenic or likely pathogenic rare variants (Mahjani et al. 2021). Recent meta-analyses have recommended the use of exome or genome sequencing as first line testing for neurodevelopmental disorders such as ASD (Manickam et al. 2021; Srivastava et al. 2019). In this chapter, I will evaluate current understanding of the NDD genetic landscape from the perspective of therapeutic development and provide a strengths, weaknesses, opportunities, and threats (SWOT) analysis to guide the use of rare genetic variants to develop treatments.

Genetic Landscape of Autism Spectrum Disorder

Individuals who suffer from ASD can harbor rare disruptive variants in genes that are intolerant of loss of function and/or variation in the broader population. This finding has enabled statistical analysis of genetic variants in large ASD cohorts compared to the general population. Analysis of ever larger research cohorts has increased the number of genes for which we have high confidence from 65 in 2015 (Sanders et al. 2015) to 102 with FDR <0.01 in 2020 (Satterstrom et al. 2020) to 183 genes with FDR <0.05 in 2022 (Fu et al. 2022). According to these statistical analyses, the odds ratio of carrying one of these variants can be 10- to 20-fold higher in the ASD cohort compared to the general population. These estimates are based, however, on small numbers of individuals in the ASD cohort and even smaller or none in the control cohort. Therefore, clinical confirmation of such findings is extremely important. There is a strong ascertainment bias in these types of studies; therefore, learning the full phenotype and penetrance of the genetic variants will almost always require the collection of a larger number of individuals with that variant identified through clinical testing and potentially population-level analyses using birth cohorts or health system registries (Sanders et al. 2019).

Much research in neuropsychiatric disorders has focused on copy number variants (CNVs). For many CNVs, it has been difficult to identify a single critical gene within the chromosomal region that is driving the effect. In fact, for many recurrent CNVs, multiple genes with smaller individual effect sizes seem to contribute to the overall risk. For example, the typical 22q11.2 deletion, a CNV associated with variable and complex behavioral and medical syndromes including autistic features, encompasses around 50 genes, 10 of them intolerant to haploinsufficiency. Taken together, single gene disorders are likely to be easier to address with gene-based therapies than multigenic CNVs.

The assertion that a gene is implicated in syndromic versus nonsyndromic intellectual disability or ASD is often based on methods of ascertainment

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and extent of detailed phenotyping. A syndrome is a group of traits that tend to occur together and characterize a recognizable disease. Some syndromes (such as FXS, Rett syndrome, and tuberous sclerosis) have been recognized for decades. Several genes, initially implicated in syndromic conditions, were later reported in subjects with nonsyndromic forms of intellectual disability (e.g., *ARX, CASK, JARID1C, FGD1*, and *ATRX*). There has also been some debate about whether there is sufficient evidence for "autism-specific" genes (Buxbaum et al. 2020; Myers et al. 2020a, b; Satterstrom et al. 2020). Regardless, it is unequivocally clear that there is a significant overlap between "ASD-predominant" and "ASD with NDD" genes from both a statistical and a clinical genetics perspective. For the purposes of therapeutics, this debate is not particularly productive.

Before considering the advantages and disadvantages of targeting rare genetic variants for therapeutics development, one needs to briefly review the process of drug development in neuroscience. The translational pipeline necessary to bring a therapy to the clinic requires several steps: correct target, correct molecule, correct dose, correct duration of drug treatment, correct subset of patients, correct stage of disease, correct sample size, correct endpoints, and acceptable side effect profile. There is potential for failure at each of these steps (Figure 6.1). Even if every step is successful, the traditional drug discovery process (from target discovery to approval) can take 10–17 years (Ashburn and Thor 2004). Recently, alternative drug development approaches have come to the forefront. One of them, drug repurposing, can reduce the time to approval. Another is gene-based therapies for genetic disorders. The application of each of these approaches to rare genetic variants will be discussed below with representative examples.

Therapeutic Modalities

Small Molecules

The drug industry has traditionally focused on small molecules, although the drug discovery toolbox has grown from protein-based therapeutics (proteins, peptide, and antibodies) to, more recently, gene-based therapies: antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), gene replacement, and gene editing. Small molecules remain the most well-established platform and have many advantages, including low cost and scale of synthesis, multiple routes of administration, bioavailability, controlled dosing, and stability. Small molecules could theoretically target all tissues, although exposure depends on the chemical structure, especially for penetrating the blood–brain barrier. Certain targets, such as G protein-coupled receptors or kinases, have proven tractability with small molecules, but recently other mechanisms, such as correction of misfolding/trafficking (e.g., CFTR protein in cystic fibrosis)

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Figure 6.1 Stages in the traditional drug discovery process and potential pitfalls. The probability of success is ~10%. Absorption, distribution, metabolism, excretion, and toxicity (ADMET), European Medicines Agency (EMEA), Food and Drug Administration (FDA), intellectual property (IP), Ministry of Health, Labor, and Welfare (MHLW).

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or modulation of splicing (e.g., *SMN2* gene in spinal muscular atrophy), have proven successful. One of the unique advantages of rare genetic diseases for small-molecule drug development is the ability to perform phenotypic screens, including the possibility of drug repurposing. A case in point is amyotrophic lateral sclerosis (ALS): a phenotypic screen performed in iPSC-derived ALS motor neurons demonstrated that retigabine, an FDA-approved drug for epilepsy, decreased hyperexcitability and increased survival of human motor neurons. This drug is now in Phase II trial for ALS patients (Wainger et al. 2014).

Both whole animal and cell-based disease models can play crucial and complementary roles in the development of therapeutics (Figure 6.2). Although animal models are necessary to study behavior, their relevance in brain disorders has been an area of rigorous debate (Howe et al. 2018; Pankevich et al. 2014). One point of agreement, though, is that for findings to be translationally impactful, better pharmacokinetic/pharmacodynamic studies need to be encouraged in animal models (Kleiman and Ehlers 2016). Using iPSCs can circumvent species-related issues, but the promise of using iPSCs for drug discovery also comes with some caveats; most importantly, variability and reproducibility. Several recent papers have analyzed these important issues and provided recommendations for accelerating translation (Anderson et al. 2021; Engle et al. 2018; Germain and Testa 2017; Volpato et al. 2018). The consensus is that both animal and human neuronal models can represent part

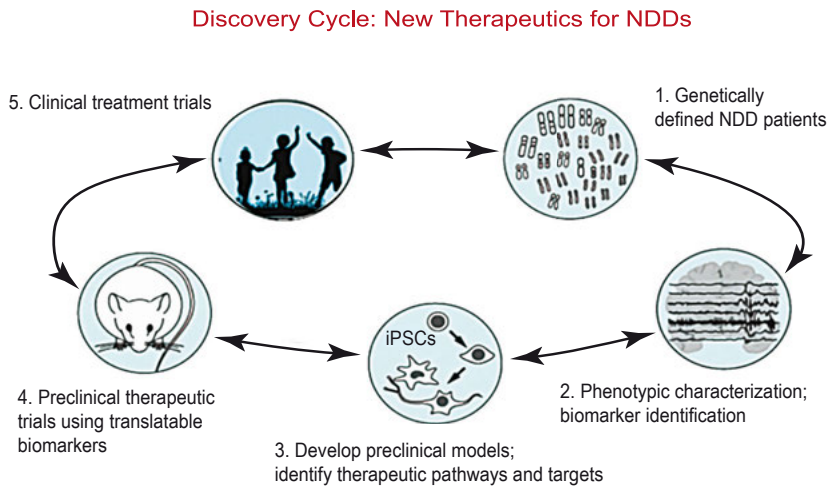

Figure 6.2 The translational cycle for precision therapies in neurodevelopmental disorders (NDDs): (1) identification of patients, (2) phenotypic characterization, (3) cellular models, (4) animal models, and (5) clinical trials. Successful development of safe and effective treatments is likely to take several cycles. Modified from Sahin and Sur (2015).

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of the evidence for target validation, but neither alone is sufficient to predict success before starting proof-of-concept clinical trials, as long as the experimental compounds are safe.

mTOR Inhibitors and Tuberous Sclerosis Complex

Rapamycin is a natural compound that was first identified in soil samples from Easter Island in 1964 as a potential fungicidal compound. Rapamycin turned out to have immunosuppressant and antiproliferative properties and in 1999 received FDA approval as an immunosuppressant for organ transplants. Everolimus (Afinitor®, Novartis), an analog of rapamycin, was approved for the treatment of patients with advanced renal cell carcinoma. Around 2002, several groups around the world discovered that loss of function of *TSC1* or *TSC2* genes, which are the causal genes in tuberous sclerosis complex (TSC), leads to hyperactivation of mTOR (mechanistic Target of Rapamycin, a protein kinase that controls cell growth, proliferation, and survival). The first open-label clinical trial, performed by David Franz and colleagues, treated six patients who had a rare type of brain tumor (SEGA) seen in TSC patients with rapamycin. All the tumors stopped growing or shrank (Franz et al. 2006). This was followed by a Phase II trial with everolimus, another drug targeting mTOR, in 28 patients; similar results were shown, leading to approval of everolimus for SEGA (Krueger et al. 2010).

Epilepsy, another major symptom in TSC, was the next indication, and detailed preclinical pharmacokinetic/pharmacodynamic studies as well as treatment trials on several different mouse models of TSC supported the notion that mTOR inhibitors could rescue the seizure phenotype in mice (Meikle et al. 2008; Zeng et al. 2008). Clinical evidence required a double-blind placebo-controlled trial with over 300 patients (French et al. 2016). The response rate in the placebo arm was ~15%, while the response rate in the low-dose and high-dose everolimus arms were ~30% and ~40%, respectively, leading to approval of everolimus for refractory epilepsy.

Two clinical trials (one in the U.S.A., the other in Europe) were performed to test whether mTOR inhibitors could also improve neurocognitive deficits in TSC patients (Krueger et al. 2017; Overwater et al. 2019). Neither study demonstrated superiority of mTOR inhibitors over placebo. One potential reason for the failure to demonstrate improvement in neurocognitive deficits may have been the timing of treatment onset. In fact, in an animal model of TSC, early mTOR inhibitor treatment (postnatal day 7) prevented both social interaction deficits and repetitive behaviors (Tsai et al. 2012). In contrast, treatment later in life (6 weeks of life) rescued the social deficits but not the repetitive behaviors. Treatment beyond 10 weeks rescued neither outcome (Tsai et al. 2018). Based on such preclinical as well as clinical data, there are now two trials testing the hypothesis that early pharmacological intervention can improve neurocognitive outcomes in TSC (NCT05104983, NCT02849457). Another

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outstanding question is whether cellular pathways such as mTOR signaling or translational regulation (see below) may be a point of convergence among different genetic causes of ASD (Figure 6.3). True testing of this concept will only be possible by applying interventions successful in one disorder to others and seeing if they succeed.

The Metabotropic Glutamate Receptor Theory of Fragile X Syndrome

Fragile X syndrome (FXS) is one of most common monogenic disorders associated with intellectual disability and ASD. In almost all cases, FXS arises from a CGG trinucleotide repeat expansion in the 5′ untranslated region of the *FMR1* (Fragile X messenger ribonucleoprotein 1) gene, which silences the production of its protein product, Fragile X messenger ribonucleoprotein (FMRP). There are at least two major functions of FMRP in neurons: (a) regulation of protein synthesis and (b) interaction with ion channels. Most of the focus has been on alteration in protein synthesis, which has led to the "metabotropic glutamate receptor (mGluR) theory of fragile X." This theory is based on the observations that mGluR activation leads to the rapid protein synthesis in the postsynaptic dendrites and that protein synthesis is exaggerated in the absence of FMRP. Large numbers of studies in multiple animal models of FXS have demonstrated that diverse phenotypes thought to model aspects of disease can be corrected by inhibiting a subtype of mGluR, mGluR5 (Bhakar et al. 2012). Despite preclinical successes, early clinical trials in adolescents and adults with FXS have not shown efficacy (Berry-Kravis et al. 2016). These

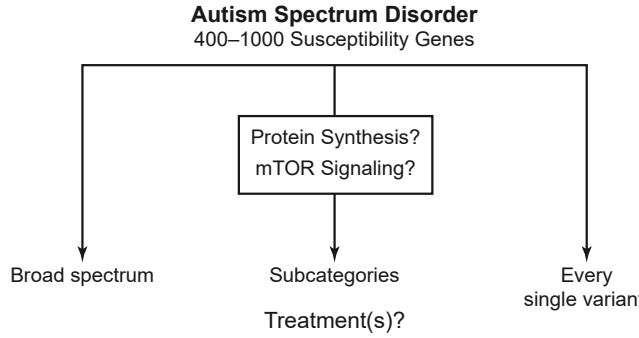

Figure 6.3 The scenario of "convergence" among the etiologies underlying ASD. In terms of the development of treatments, one can think of several scenarios. One possibility is that a single treatment will work for all etiologies (unlikely, especially for conditions where either under- or overexpression of a gene results in symptoms). Another scenario is that we will have to develop a unique treatment for each gene or even each variant (highly labor and resource intensive). A potential opportunity may arise if certain conditions have a shared pathophysiology such that a treatment developed for one condition may be effective in several similar etiologies. Such convergence may occur at the level of cellular or circuit functions.

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trials have raised critical questions in the field about optimal clinical trial design, whether younger individuals should be treated, whether the trials should be performed with longer treatment duration and longer placebo run-ins, and whether biomarkers could help assess behavioral and cognitive benefits earlier and in more objective and reproducible ways. To address some of these issues, another mGluR5 inhibitor trial is currently being funded by the NIH in younger children in combination with a language-based intervention and an EEG-based biomarker (NCT02920892).

For both TSC and FXS, the studies reviewed above are based on the repurposing of small molecules, initially developed for other indications. The advantage of this approach is that these drugs have well-known safety and dosing profiles, reducing risks and development times (Ashburn and Thor 2004). NIH has an initiative, entitled "Discovering new therapeutic uses for existing drugs" that aims to accelerate this approach.

Oligonucleotide Therapies

In recent years, there has been considerable interest in oligonucleotide-based therapeutics that alter gene function at the level of the RNA molecule. The most extensively investigated of these are ASOs and siRNAs, which can bind to complementary RNA and lead to its degradation. ASOs can also be used for other manipulations, including exon skipping, cryptic splice restoration, and alternative splicing. One major advantage of oligonucleotides is that their specificity is based on gene sequence such that theoretically any gene could be targeted. Sequence specificity, however, can also be a disadvantage, such as when different patients with the same disease have different gene sequences and therefore require different oligonucleotides. Another drawback for the treatment of NDD is that oligonucleotides do not cross the blood–brain barrier, so they need to be introduced into the cerebrospinal fluid (CSF), e.g., by lumbar puncture, and require repeated dosing every few months.

The most successful use of ASOs has been for spinal muscular atrophy. An ASO, nusinersen, was shown to increase expression of SMN protein and improve neurological symptoms in spinal muscular atrophy, a disease that is often fatal in early childhood (Finkel et al. 2017). The success of nusinersen has opened the possibility of rapid development of "n-of-1" treatments for rare variants (Kim et al. 2019). Acceleration of ASO applications in the clinical trial setting has also uncovered adverse events that were unanticipated under certain cases (Stoker et al. 2021). Previous studies have, for example, documented sequence-specific pro-inflammatory effects of phosphorothioate modified ASOs (Bennett et al. 2017; Krieg 2006).

Angelman syndrome provides a unique opportunity for the use of ASOs. It occurs due to defects in the maternally derived *UBE3A* gene, which is imprinted exclusively in the brain. The paternally derived copy of *UBE3A* is normally silenced by an antisense transcript (*UBE3A-ATS*) but could be

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reactivated by targeting the antisense Ube3a-ATS transcript using ASOs. In a UBE3A-deficient mouse model, treatment with ASOs that were designed to absorb the *UBE3A-ATS* transcript resulted in increased UBE3A production in neurons throughout the brain (Meng et al. 2015). There are now several initiatives to test this strategy in a clinical trial. The first, being developed by GeneTx, had shown promising results in a few patients, but the Phase 1/2 open label had to be paused due to a severe side effect, acute inflammatory polyradiculopathy (Davidson et al. 2022).

Viral Vector-Mediated Gene Replacement

In theory, for monogenic diseases with loss-of-function variants, the delivery of a wild-type copy of the mutated gene to cells which lack functional protein represents the most curative approach. There are two major types of gene delivery: *ex vivo* and *in vivo*. A common *ex vivo* gene delivery approach is to use lentiviruses to genetically modify extracted patient cells (e.g., hematopoietic stem cells) prior to re-infusion. Inherited metabolic disorders affecting lysosomal and peroxisomal metabolic activity are amenable to *ex vivo* therapies. Altered progeny of hematopoietic stem cells, including microglia, overexpressing the gene of interest that has been introduced by a lentivirus can achieve stable levels of the missing enzyme in the mouse brain (Matzner et al. 2005). There are now ongoing trials for X-linked adrenoleukodystrophy (X-ALD), metachromatic leukodystrophy (MLD), mucopolysaccharidosis (MPS) type I and type III, and Fabry disease (Eichler et al. 2017; Ellison et al. 2019; Fumagalli et al. 2022; Gentner et al. 2021). It is not yet clear whether *ex vivo* gene therapy can be used more broadly for NDDs that are not metabolic in origin.

For most forms of gene delivery in NDDs, the target is likely to be neurons, which will require *in vivo* gene delivery. For that application, a different method will be required to deliver genetic payloads. Recombinant adeno-associated virus vectors (rAAVs) are the most widely used in the neuroscience community. In mouse models, AAV-mediated gene therapy appears remarkably successful. AAV-mediated UBE3A expression rescued the cognitive deficits in a mouse model of Angelman syndrome (Daily et al. 2011). Several papers have reported improvement in the phenotype of mouse models of Rett syndrome by re-expression of *Mecp2,* the gene missing in Rett syndrome (Gadalla et al. 2013; Sinnett and Gray 2017; Tillotson et al. 2017). However, both Angelman and Rett syndromes are representative of conditions where the level of gene expression seems to have a narrow physiological range and either down-regulation or up-regulation of gene expression can result in a neurodevelopmental disorder, posing a considerable dosing challenge.

Rett syndrome (RTT) is one of the most common monogenic causes of intellectual disability and is an X-linked disorder predominantly affecting girls. The main cause is a deleterious mutation of the *MECP2* gene on one of the X

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chromosomes. Classic RTT is characterized by a brief period of stagnation after normal or near-normal development up to 6–18 months, followed by rapid loss of skills before stabilization or slowing of regression. The phenotype can be affected by skewed X-inactivation, leading to more or less X chromosomes with the intact *MECP2* gene to be active in patients. *MECP2* duplication syndrome predominantly affects males, but females who carry the duplication on one X chromosome (heterozygotes) may exhibit some signs of the disorder. This syndrome is characterized by global developmental delay, recurrent respiratory infections, epilepsy, and progressive spasticity. *MeCP2* has been implicated in a wide range of molecular functions, including transcriptional repression and activation, chromatin architecture, alternative splicing, miRNA processing and translational regulation, thus similar to *TSC1/2* genes and FMRP, it also modulates the expression of a large number of proteins.

Although the exact pathways are unknown, deficient brain-derived neurotrophic factor (BDNF) expression has been proposed to be involved in RTT pathogenesis, leading to the hypothesis that restoration of BDNF function might treat the disorder. BDNF, however, does not cross the blood–brain barrier. A related growth factor, insulin-like growth factor 1 (IGF-1), can cross the blood–brain barrier and like BDNF can promote the development and maintenance of neural circuits. IGF-1 administration reversed some RTT-related phenotypes in a mouse model of RTT but failed to improve neurological symptoms in girls with RTT. A large number of therapeutic trials have been pursued in preclinical and clinical studies in RTT (Leonard et al. 2017). Recently, trofinetide, a synthetic analog of a naturally occurring neurotrophic peptide, which is the terminal tripeptide of IGF-1, was approved by the FDA for RTT. Some of these have targeted the neurotransmitter systems disrupted in RTT; others have involved growth factors, cell metabolism, and homeostasis. However, given the very large number of proteins whose expression is regulated by MECP2 and the many cellular processes that are aberrant in MECP2-deficient cells, it is difficult to imagine that targeting one particular neurotransmitter system or growth factor will be sufficient to change the natural history of this disorder. Therefore, more recently, attention has turned to gene-based therapies.

The fact that healthy brain development appears to require just the right amount of MECP2 expression creates a daunting challenge to development of a treatment for this X-linked disorder. Brains of girls affected with RTT contain a mosaic of wildtype and reduced MECP2 expression based on X-inactivation in each cell. Therefore, re-expression of MECP2 may rescue some cells from too little MECP2 expression to the normal range while being toxic for other cells which were expressing MECP2 in the normal range prior to treatment. Therefore, controlling deleterious overexpression of MECP2 is a crucial goal in gene therapy development for RTT. Several approaches have been developed in preclinical models to overcome this obstacle. One approach is to add a miRNA target cassette to the transgene to regulate the expression of the exogenous MECP2, which could regulate gene expression levels on a cell-by-cell

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basis (Sinnett et al. 2021). When MECP2 is overexpressed, it would increase the levels of certain miRNA that would in turn bind to the 3′UTR of the transgene and reduce its expression.

While RTT is a particularly difficult disorder to treat with AAV-mediated gene delivery due to X-inactivation and a narrow physiological window of expression, the rate-limiting step in the development of successful AAV gene therapy is biodistribution. Although certain AAV9-derived variants (e.g., PHP.B or PHP.eB) can cross the blood–brain barrier and transduce neurons in mice, the receptor that mediates their transport across the blood–brain barrier is not expressed in primates. Therefore, AAV9 delivery into the CSF is often used. Recent quantitative studies compared biodistribution of AAV9 associated expression of green fluorescent protein (GFP) in juvenile cynomolgus macaques either infused intrathecally via lumbar puncture or the intra cisterna magna. In both cases, GFP expression was observed primarily in perivascular astrocytes in the brain, but relatively little in neurons (Meseck et al. 2022). Therefore, developing novel AAVs or other delivery systems that have improved central nervous system (CNS) cell tropism after direct or peripheral delivery is a major ongoing effort (Chen et al. 2022; Davidsson et al. 2019; Deverman et al. 2016; Lin et al. 2020; Lukashchuk et al. 2016; Nonnenmacher et al. 2021; Wang et al. 2019).

Aside from the issues of toxicity due to overexpression, there are also other risks with AAV-mediated gene delivery. A major issue is the low efficiency of gene delivery to the CNS by viral vectors that requires large vector doses and consequently brings the risk of immune reaction. The presence of preexisting neutralizing antibodies can also be a problem (Foust et al. 2009; Gray et al. 2011). Moreover, while AAV vectors typically remain outside of the host genome in a stable, episomal form, the AAV genome can sometimes integrate into the host at low frequency. If it is inserted into the DNA in the wrong location, it could possibly cause harmful mutations to the DNA (Donsante et al. 2007), although this seems to be rare in human genome (see discussion in Wang et al. 2019). A more common problem with AAV administration into the CSF has been dorsal root ganglia (DRG) toxicity, which may affect spinal cord function. DRG toxicity has been reported in both preclinical and clinical studies (Hinderer et al. 2018; Hordeaux et al. 2018; Mueller et al. 2020).

A number of additional gene therapy platforms are being tested in preclinical studies, though none have yet reached clinical testing for CNS disorders. These approaches include (a) gene editing that alters nucleotide sequence in the genome directly, such as CRISPR, base editing, prime editing (Chen et al. 2021; Koblan et al. 2021; Wolter et al. 2020), and (b) gene activation or deactivation by using small molecular drugs or CRISPR and other technologies (Matharu et al. 2019; Monteys et al. 2021). In conclusion, the therapeutic armamentarium for rare genetic diseases affecting the CNS is likely to expand even further in the near future.

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SWOT Analysis of Rare Variants

Strengths

The advances in mechanism-based therapies for rare genetic disorders discussed above highlight several of the advantages of using these variants to develop therapies (Figure 6.4). The scientific knowledge base regarding underlying genetic mechanism, mutational spectrum, and tolerance to haploinsufficiency or overexpression provides a significant advantage over less well characterized "idiopathic" and heterogeneous conditions such as ASD. In theory, for loss-of-function recessive disorders, re-expressing the correct sequence in the right cells at the right time at the right doses should provide a marked improvement in the phenotypes. Spinal muscular atrophy is an example of such success, even though we still do not fully understand the cellular function of SMN protein.

Such knowledge about the genetics also enables the creation of cell-based and animal models, another opportunity often missing in "idiopathic" conditions. These models allow for experiments aimed at clarifying the neurobiology underlying these disorders as well as the testing of therapeutic approaches *in vitro* and/or *in vivo* before clinical testing, providing some confidence about the safety and potential efficacy of the approach. Unbiased phenotypic screens can also be used in such models, enabling genome-wide investigations or very large, small-molecule compound library screens.

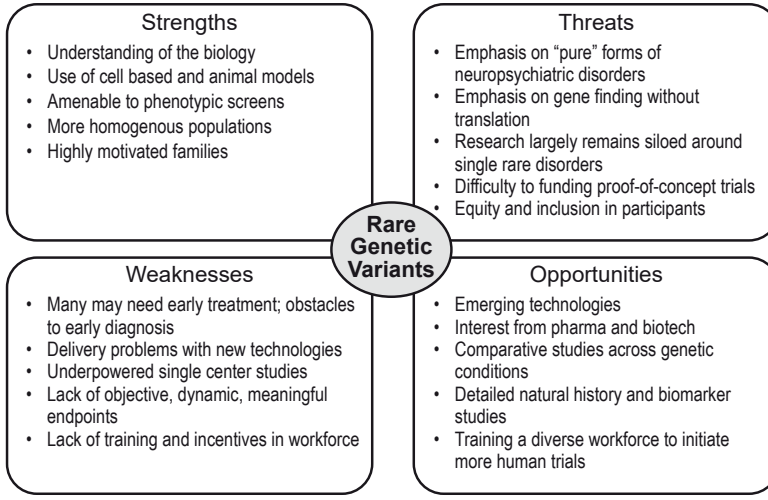

Figure 6.4 SWOT analysis for using rare genetic variants in development of precision therapies.

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In terms of translation to clinical trials, rare genetic variants also provide a more homogenous cohort of participants to enroll, potentially reducing the variability in response to the intervention and correspondingly increasing statistical power.

Weaknesses

Despite the promise noted above, research in rare genetic variants in neurodevelopmental and psychiatric disorders has not yet produced as many successes as anticipated. One potential reason is that these variants are by definition rare and can be difficult to identify. This challenge is especially acute since treatments for many of these variants would need to be delivered in the early postnatal period. There are many systemic obstacles to access to genetic testing for such conditions, creating lengthy "diagnostic odysseys." Partially, but not exclusively, because of these challenges, many of the proof-of-concept trials have been performed in very small cohorts and at single centers. While such open-label trials often yield promising results, subsequent larger, controlled clinical studies frequently fail.

Some of the new technologies available for delivery of therapeutics are hampered by limited bioavailability. Even for small molecules, evidence that they engage brain targets may be limited. Another significant obstacle in clinical trials is the lack of sensitive, quantitative, and meaningful outcome measures to gauge the success of the intervention. Finally, the diverse workforce needed to perform such trials has not been developed in clinical settings, and the incentives to develop such a workforce are not well aligned with academic careers.

Opportunities

The combination of emerging technologies with disease-modifying potential, a better understanding of the underlying mechanisms to limit the risk of therapeutics development, and the incentives provided for the industry by the Orphan Drug Act provide an opportunity for major progress in rare genetic disorders. What could accelerate such progress are detailed natural history cohorts developed by multi-center networks that are well coordinated and use standardized acquisition/analysis. Remote assessment may be a way to be more inclusive in the populations studied, reducing obstacles to access. Translational biomarkers can also be tested and validated in multiple disorders and at multiple centers, providing tools for stratification of participants and/or assessing target engagement (Sahin et al. 2018). To realize the full promise of using rare genetic variants to develop treatments for neurodevelopmental and psychiatric disorders will require integration and sustained support of networks/consortia that work closely with patient communities and industry partners.

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Threats

There is a list of external factors that have limited the impact of therapeutics based on rare genetic variants. First of all, certain groups and funding agencies have excluded syndrome forms of disorders (i.e., those that arise from specific rare variants) when seeking to understand and investigate the more common forms of neurodevelopmental disorders. Others have focused predominantly on gene-finding studies with little or no support for clinical translation. Such approaches have made it extremely difficult for investigators to initiate proof-of-concept trials and test hypotheses in rare disease populations. Furthermore, there is insufficient convergence of approach and of knowledge across different specific rare genetic conditions. Partly, this is because much of the research is supported by patient advocacy groups focused on a specific condition. Finally, research cohorts typically lack representation from medically underserved communities, limiting the impact of the research and posing a challenge to the equitable application of medical advances. Taken together, this analysis clearly highlights the fact that rare genetic diseases provide a unique opportunity for both understanding the pathophysiology of neurodevelopmental disorders and developing mechanism-based therapies in the near future. By addressing the weaknesses and threats outlined above, the investigators, patient advocacy groups and funding agencies will further enhance this opportunity and help improve the lives of individuals and families affected with these disorders.

Disclosures

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