Causes and Treatments for Various Phenotypes Among Autistic Individuals

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Abstract

This paper surveys genetic and non-genetic causes and emerging treatments for individuals with autism with challenges including stress, social, functional, emotional, and behavioral difficulties. Genetic treatments consist of methods to replace and edit DNA, along with reducing translation of mRNA that may have mutations, which would encode defective proteins. A key challenge with genetic treatments is finding a dosage amount that is not toxic to patients. Non-genetic treatments consist mainly of behavioral therapies and medications. Although these treatments can help to improve communication and decrease stress for some individuals, the medications may have some side effects, and improved behavior from behavioral therapies is not guaranteed, which would not always make these treatments excellent options. This paper also includes concerns about treatments including treatment delivery, ethical concerns about a certain behavioral therapy, treatment progressions in the long-term, treatments for coexisting conditions, and access and affordability of treatments. This paper concludes with an ethical discussion about genetic treatments using an Islamic framework.

Keywords: Autism, Genetic, Non-Genetic, Causes, Treatments, Challenges, Phenotypes

1. Introduction

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5-TR), autism spectrum disorder (ASD) consists of various observable behavioral phenotypes (traits) that can be present in individuals. Autism is also heterogeneous, meaning there are various factors influencing the prevalence of autism in individuals including sex, environment, and genetic mutations either in one gene, or multiple genes. These traits include trouble with being socially active and with being flexible with doing new activities. Depending on the severity of autism in the individual, behavioral challenges like stress management and social interactions of the individual can range from mild to severe. To treat genetic mutations, there are various evolving genetic treatments to replace and edit genes or silence mRNA from being translated into proteins. To treat phenotypes influenced by environmental factors, there are behavioral therapies and medications to reduce the severity of behavioral challenges.

This paper is a survey of certain research literature and summarizes genetic and non-genetic causes and evaluates the benefits and limitations of some genetic and non-genetic treatments for autism. Given the variety of behaviors in the autism spectrum and the evolving field of genetics and biotechnology, this review is worth writing to analyze many treatments for genetic disorders like autism. These evaluations would be beneficial for geneticists, therapists, bioethical scholars, autistic patients and their families for considering which treatments are the most effective for the patients and would complement the ongoing autism research of causes and treatments. This paper explores some genetic and non-genetic causes and treatments for individuals with autism with challenges including stress, as well as social, functional, emotional, and behavioral difficulties.

2. Literature Review

2.1 Causes for Expressed Phenotypes Associated with Autism

Various genetic causes have been associated with autism through research studies. There are two main types of genetic mutations that cause autism, the first being monogenic autism (i.e., one mutated gene significantly increases the risk of having autism) (Figure 1) and the second being polygenic autism (i.e., one or more mutated genes can increase the risk of having autism) (Figure 2). Furthermore, there are non-genetic causes like environmental factors related to autism.

Genetic Causes: Causes For Expressed Phenotypes Associated with Autism

There are various monogenic causes of autism which can impact neuronal communication. Neuronal communication occurs in neurons (brain cells) (Harper, 2024). This process, which is neurons sending messages to other neurons, occurs by neurotransmitters (chemical signals) crossing from one neuron's synapses to the dendrites of the next cell's cell body (Harper, 2024). This cell body then sends electrical impulses to and through the axons to the cell's synaptic terminals (Harper, 2024). Then, the synaptic terminals, which have neurotransmitters, communicate the message to the following neuron's dendrites, and the process repeats (Harper, 2024). But challenges with neuronal communication can cause messages to not cross from one neuron to the next, which can alter messages being sent throughout the brain. This challenge can be caused by various genetic mutations, like single-gene mutations.

An example of monogenic autism is the genetic deletion of the *ANKRD11* gene or the *SHANK3* gene (Xu et al., 2023). According to a study on mouse models of autism, the *SHANK3* genetic deletion can impact neurons' functioning resulting in social, emotional, and functional challenges among mice (Xu et al., 2023). These mutations can modify neuronal communication, and lack of neuronal strength, which can cause alterations with brain function among individuals with autism (Xu et al., 2023). But there can be more than one mutation that occurs and increases the risk of having certain phenotypes.

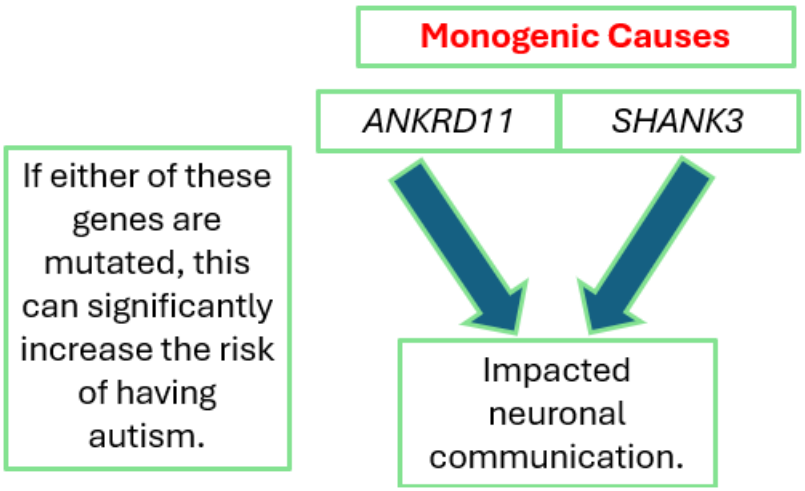

Figure 1. How a monogenic mutation can directly relate to a neuronal impact in the autistic brain

There are various polygenic causes of autism which can impact neuronal structure. Proper neuronal structure and development are necessary for the brain to function effectively. Neuronal development includes fully formed parts of neurons which help to communicate messages

throughout the brain like the myelin sheath and dendritic spine (Hu et al., 2018). Neuronal structure is influenced by various genes like the *MAP* gene family which influences the development of microtubules (Hu et al., 2018). Microtubules, which are part of the cytoskeleton, give neuronal cells structure, shape, and help to prevent neuronal cells from being degraded. But alteration with microtubule development can cause atypical brain function (Hu et al., 2018).

An example of polygenic autism impacting neuronal structure is genes like the *MAP1A* and *MAP6* genes that encode protein families like the microtubule-associated protein family (*MAP*) and can cause autism (Hu et al., 2018). If these genes are mutated, the defective proteins that the genes encode can influence the alteration or lack of neuronal functions and proper structure. These challenges can lead to various behavioral abnormalities associated with autism, like hyperactivity and atypical emotional expression. As mentioned in a research study about BTBR (Black and Tan Brachyury) mice (Blanchard and Meyza., 2017), the *MAP1A* and *MAP6* genetic mutations in the *MAP* gene family can cause deficiencies in neuronal development, stability, and transmission of messages (Hu et al., 2018).

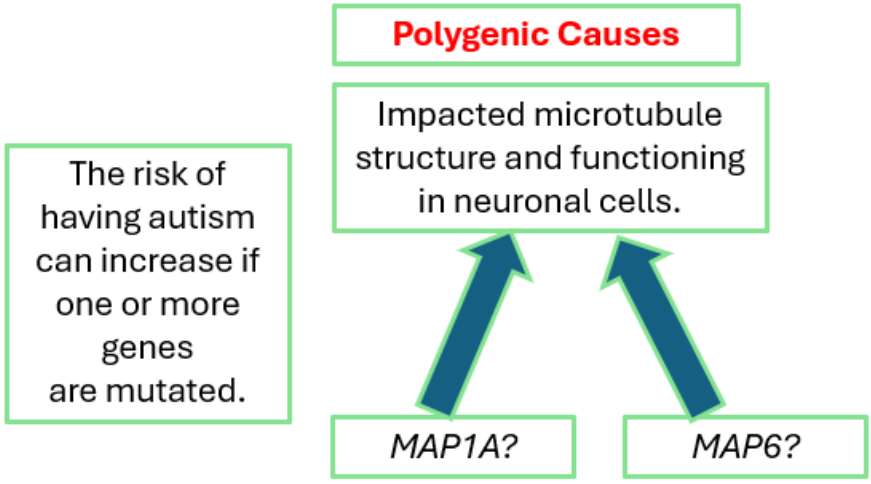

Figure 2. How a neuronal impact in the autistic brain cannot be linked to only one mutation

Environmental and Sporadic Causes of Autism

In addition to genetic causes, there are some non-genetic factors resulting in neuronal efficiency challenges in individuals with autism. Specifically, maternal frequent stress during pregnancy (Figure 3) can cause hormonal imbalances like excess amounts of the stress hormone cortisol and low testosterone levels in autistic children (Pervanidou et al., 2022). One cause of changed neuronal function is due to the time when an embryo is becoming a fetus is when low levels of testosterone and excess cortisol can impact the offspring's hypothalamic-pituitary-adrenal axis (HPA axis). The HPA axis is a part of the body's stress system, and it facilitates stress hormonal responses that circulate through bodily glands, and the brain's adrenal cortex as well as receptors when stress triggers are present (Pervanidou et al., 2022). Additionally, if the levels of the fetus's glucocorticoid (fat) hormone (which is within the cortisol pathway) are altered, this can result in altered neuronal function and stress hormonal responses. This can lead autistic children to have excess stress and anxiety for extended periods of time, which can impact their neuronal functioning (Pervanidou et al., 2022).

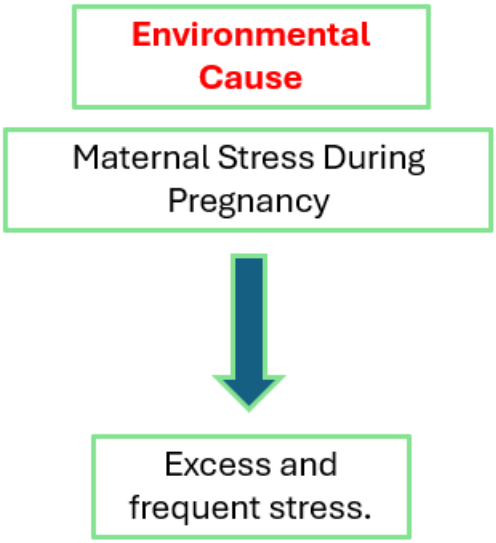

Figure 3. How excess maternal stress can impact stress management in the autistic brain

2.2 Genetic and Non-Genetic Treatments

There are various emerging genetic treatments for monogenic autism. These treatments include transducing foreign DNA into cells within one's CNS and RNA Knockdown to decrease amounts of mRNA that are translated into proteins that could be defective and influence behavioral and functioning challenges in individuals with autism. Furthermore, there are treatments like editing proteins influencing autistic traits for polygenic autism. Additionally, there are non-genetic treatments for autism, including chemical compounds as medications to alter neuronal receptors' atypical functions that contribute to the presence of autistic phenotypes. All the genetic and non-genetic treatments can be referred to in both (Figure 4) and (Figure 6). Some of the genetic and non-genetic treatments have been tested on mouse models of autism and are potentially applicable for treating autistic humans' phenotypes.

Genetic Therapy Treatments for Monogenic Autism

Emerging genetic therapies can help reactivate certain neuronal pathways that were impacted by genetic mutations, to help fix the stress and anxiety phenotypes in individuals with autism. Treatments include replacing genes, editing genes, and knocking down genes for monogenic autism (which only occurred in roughly 5 to 10% of individuals with autism who participated in a research article relating autism and genetic factors (Anna et al., 2019).

The first treatment for monogenic autism is recombinant adeno-associated viruses (RAAVs). This treatment is the primary delivery-method into the CNS that can edit single-gene mutations, which were performed during studies on mouse models of autism. A challenge with RAAVs is if non-targeted cells become intoxicated due to toxic dosage levels (Mazarakis et al., 2018). To fix dosage toxicity in non-targeted cells and improve CNS-transduction, RAAVs could be intravenously injected along with promoters that target specific cells into one bodily area to fix some if not all behavioral challenges (Mazarakis et al., 2018). But one's immune system rejecting the transduction of foreign DNA via antibodies being present at the site of transduction is still a

concern (Mazarakis et al., 2018). Although mutated genes can be replaced, they also can be blocked from being translated into defective proteins.

In addition to adding foreign DNA to fix mutations that cause a lack of proteins, knocking down mutated genes that are in excess can prevent them from being translated. RNA Knockdown inactivates certain mRNA from being translated into proteins within dysregulated neurons within neuronal circuits in the brain's hippocampus, corpus callosum, and the cerebellum so these genes that contribute to autistic phenotypes cannot be translated (Mazarakis et al., 2018).

RNA Knockdown can be applied in several ways. First, antisense oligonucleotides (ASOs) and short interfering RNA (siRNA) can help to bind mRNA transcripts to prevent their translation. The nucleic acids that make up the RNA can be used to halt RNA degradation and inflammation (Mazarakis et al., 2018). ASOs and siRNA are applicable as a treatment choice for restoring either partial synaptic function by using microRNA which is partially complementary to various targeted mRNA strands to knockdown or by using siRNA which is fully complementary to targeted mRNA to knockdown. This can be accomplished while not editing non-targeted synapses' functions. Another method is hyper-knockdown of lots of mRNA but receiving such high dosage levels would result in patients becoming neuronally intoxicated (Mazarakis et al., 2018). So, RNA Knockdown may be beneficial for treating patients with monogenic autism (or treating a few genes at a time). However, extremely small dosages would be inconvenient due to the frequency patients would receive treatment. Instead, a vector dosage range along with frequency of treatment appointments should be made for preventing neuronal intoxication. Thus, the challenge of dosage toxicity to provide sufficient intra-CNS (central nervous system) transduction lies with both RAAVs and RNA Knockdown (Mazarakis et al., 2018). But genes can also be edited without replacing them or decreasing their expression.

Mutated genes can also be edited, without replacing or silencing them with the help of the gene-editing tool clusters of regularly interspaced short palindromic repeats (CRISPR). Although CRISPR has yet to edit only targeted genes and has not been administered in high dosage quantities, CRISPR being used with RNA Knockdown to silence genetic targets may reduce dosage toxicity in mouse models of autism (Mazarakis et al., 2018). Therefore, CRISPR is a potential treatment for editing autistic phenotypes. To elaborate, CRISPR can edit mutations by using recombinant DNA or joining ends of non-homologous DNA to silence genes (Mazarakis et al., 2018). Additionally, if CRISPR and RNA Knockdown are used together, they can help nullify toxicity associated with foreign DNA (Mazarakis et al., 2018). However, more research is necessary to understand how to only deliver gene editing processes and edit only targeted genes (Mazarakis et al., 2018).

Genetic Therapy Treatments for Polygenic Autism

If individual genes that are mutated cannot be identified, proteins that influence phenotypes can be edited. One therapy is to fix structural errors among proteins for treating polygenic autism which is common in most individuals with autism (Mazarakis et al., 2018). Such genetic mutations that affect amino acid sequences in regions, like the brain's amygdala, which assist social interactions and understanding new concepts, along with other mutations affecting synaptic functioning were discovered (Mazarakis et al., 2018). Fixing synaptic functioning modifications related to environmental circumstances is difficult, but correcting the impacts of proteins on synaptic functioning and phenotypes like social interactions is doable, which will make editing proteins an effective treatment for phenotypes rooted in polygenic causes of autism (environmental circumstances) (Mazarakis et al., 2018). For example, if the *NLGN3* gene (within

a class of adhesion molecules) is mutated, then the gene being knocked down in mice shows synaptic plasticity modifications related to Fragile X Syndrome (Mazarakis et al., 2018). This reveals how either the overexpressed *FMRP* gene or the PI3K-AKT-mTOR pathway can be knocked down to fix the behavioral differences in mice (that are broadly linked to autism) (Mazarakis et al., 2018). These mutations can be treated by correcting influential proteins' expression influencing translation circuits (Mazarakis et al., 2018).

Another therapy for treating specific mutations that may be unknown is to fix phenotypes that can be due to an amino acid deficiency by replacing proteins. For example, intra-CNS transduction of branched chain amino acids (BCAAs) can help restore function of the blood brain barrier solute carrier transporter 7a5 and the lack of BCAAs in the CNS within mice (Mazarakis et al., 2018).

Non-Genetic Treatments: Chemical Compounds

Some modern ways to treat behavioral challenges among individuals with autism include pharmacological treatments which use chemical compounds including propranolol, aripiprazole, and risperidone.

The compound propranolol is well-known, affordable, and typically used for lowering blood pressure. It has been studied in autistic children with anxiety. Over three months, autistic children taking propranolol showed a significant decrease in anxiety at doctor check-ups. Unfortunately, in this study, propranolol did not improve individuals with autism' social interaction skills (Kanne et al., 2024). To summarize, although the inexpensive medication propranolol addressed anxiety symptoms, propranolol did not fix the root cause of some autistic peoples' stress which was social interactions. This may be a challenge if social difficulties cause extreme anxiety for some individuals with autism, and they must take propranolol at high doses. However, there are other medications to treat anxiety difficulties as well.

Two other medications used to treat autism-related phenotypes are aripiprazole and risperidone which are both FDA-approved antipsychotics that control the Serotonin 2C receptor, which has a key role in growth of the cerebral cortex including regulating synaptic functions like pruning (to filter important and current information from synapses storing old information) (Iris et al., 2023). To add on, the Serotonin 2C receptor is regulated by the Serotonin (5 HT), which controls neuronal development, formation, migration, and differentiation. However, if the Serotonin (5 HT) regulator is not regulated, then individuals may have autism and challenges with anxiety and intellect (Iris et al., 2023).

These medications also result in similar outcomes among individuals with autism, such as less severe behavioral challenges and improved social interactions (Madrid et al., 2023). These medications may help individuals with autism who are socially inactive but understand social cues and how to communicate with others. However, these medications are not ideal for inactive or hyperactive individuals with autism due to side effects like potential weight gain, unresponsiveness, and uncontrollable actions (Feder, 2023). Therefore, individuals with autism' activity levels should be at a moderate level and should be tracked to see benefits from taking risperidone and aripiprazole. This may help to manage individuals with autism' side effects. But there is one more medication that was used in a study on mice that may help treat anxiety.

As for medications for treating behavioral differences in mice, the compound CDPPB manipulates neuronal receptors' functions, which helps treat functional problems with anxiety and social mingling. In a study performed with mouse models of autism, the compound CDPPB weakened the brain's defective mGluR5 receptor via negative allosteric modulation (substances

bind to receptor to alter receptor's function when facing stimuli) and made the defective mGluR5 receptor do the reverse of its function, which is regulating synaptic communication (Sahin et al., 2017). This resulted in partially improved social interactions, memory, and less severe anxiety-related phenotypes (Sahin et al., 2017). Thus, CDPPB can be included as a potential treatment for inhibiting the mGluR5 receptor's function. Additionally, because treatment from mice may be applicable to autistic humans as mentioned earlier in the genetic treatments section, CDPPB may help to eliminate or reduce phenotypes like social challenges and anxiety in individuals with autism.

Non-Genetic Treatments: Therapies

There are also modern non-pharmacological therapies to improve executive functioning in individuals with autism. One therapeutic potential treatment to address social interactions as a root cause of stress in individuals with autism is hyperbaric oxygen therapy (HBO) which was used in a study on mouse models of autism. HBO, which involves a pressurized environment with increased oxygen, was beneficial for helping the mice socially interact and function more effectively. Researchers found that this therapy significantly improves social interactions of mice. This led to neuronal alterations like less inflammation of neurons in the cortex of the brain and more executive functioning abilities (Barak et al., 2022). However, although this is an evolving treatment that brings hope to improve executive functioning among mouse models of autism, more research is needed to learn about the effects of HBO on autistic humans (Barak et al., 2022). To add on, the main disadvantage expressed in the study about HBO and its effects on mice was that behavioral therapies did not improve behavior of mice. Specifically, social interactions, expressing and processing emotions, and learning customs when socially interacting all increase the amount of depression, anxiety, and stress that autistic people face (Barak et al., 2022). But aside from HBO, there are other treatments for autistic phenotypes that can be implemented in the lifestyles of individuals with autism.

Some other non-pharmacological treatments, such as therapy for social and executive functioning challenges, may be beneficial for individuals with autism who struggle with communicating. To elaborate, herbs, various dietary supplements, and vitamins, along with music, social, and oral therapies help to improve some behavioral challenges in individuals with autism (Xu et al., 2023). However, more research needs to be done regarding the efficiency of these specific non-pharmacological treatments aimed at improving these traits (Xu et al., 2023). Furthermore, there may be some disadvantages to these therapies if they do not work for some individuals with autism' behavioral challenges. First, some therapies like music may not help individuals with autism who dislike music. Second, dietary assistance depends on individuals with autism' food choices and current diet and vitamin intake. Thus, although some therapies may not help autistic individuals, there are some behavioral therapies which may help improve phenotypes.

The first therapy is applied behavior analysis (ABA). It helps to understand and utilize an individual's environment and life events to change the phenotypes that influence the individual. A main benefit of ABA is if young individuals frequently receive ABA for improving many skills at an early age like 3 to 4 years old for a long period of time (Möllmann et al., 2023). But the initial uncertainty if autistic children's behavior will improve can cause parents lots of stress. To add on, although parental stress decreases if autistic children's symptoms' severity decrease, parental stress increases if they must intervene frequently in their child's ABA sessions (Möllmann et al., 2023).

The second therapy is cognitive behavior therapy (CBT). It helps to alter an individual's thought process and emotions from negative thoughts to more positive thoughts. To add on, CBT helps individuals with autism to control their stress when in social situations and to be more metacognitive of their feelings and thought processes (Yao et al., 2021).

To summarize, dietary, social, and behavioral therapies like ABA and CBT may improve some autistic individuals' executive functioning and communication skills. However, these treatments may not be effective if autistic individuals are not flexible to lifestyle changes or the type of therapy.

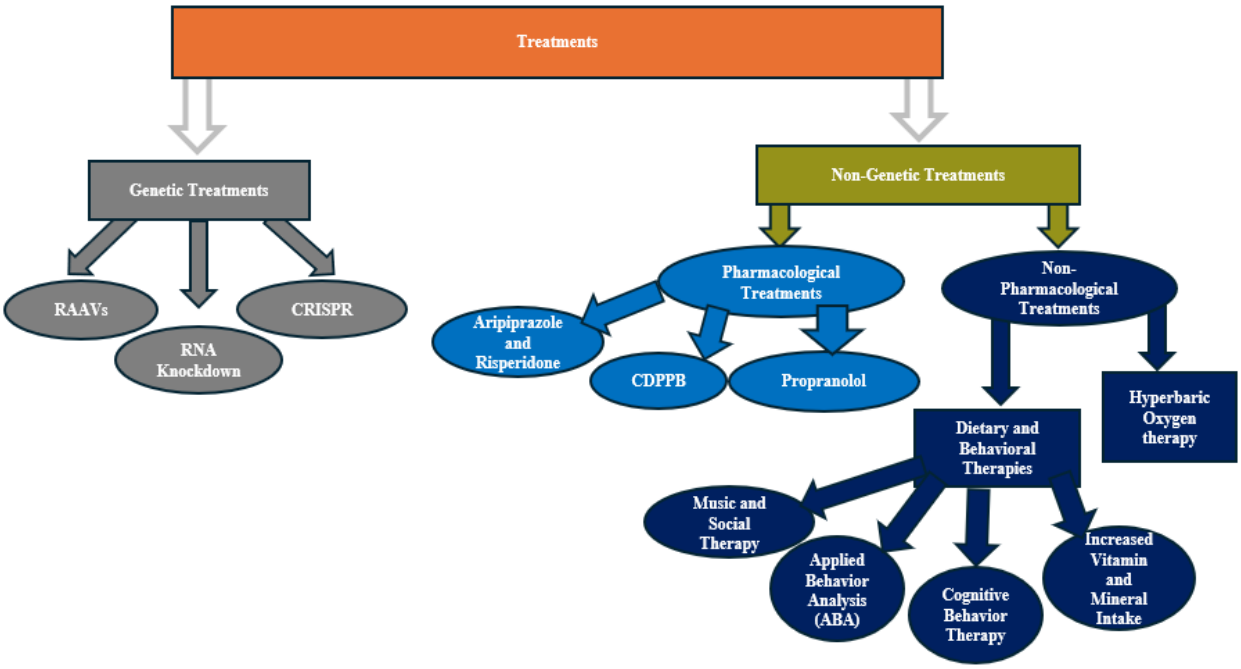

Figure 4. Genetic and non-genetic treatments

3. Discussion

3.1 Administration of Treatments

There is a potential concern aside from dosage toxicity levels and bodily tissue rejecting foreign DNA when administering genetic treatments to treat monogenic autism, as well as administering the compound CDPPB for autism treatment in a non-genetic manner. If individuals with autism do not want to receive treatment intravenously due to potential skin sensitivity or anxiety when seeing needles in front of them, then individuals with autism may receive the treatment intrathecally (via spinal injection) so the treatment can get to the brain. However, if some individuals with autism have such phobias towards needles (even if the individuals could be sedated), then injecting CRISPR, RAAVs or the compound CDPPB may not be possible for them. This is a field to be further explored for long-term treatment plans. In addition to insights for future delivery of genetic treatments, there are also considerations to be made about evolving non-pharmacological therapies.

3.2 Ethical Concerns About ABA

A significant concern about ABA is about ABA therapists making autistic individuals consistently comply with their wants because they believe neurotypicals constantly comply (Khosrowshahi et al., 2022). This highlights the necessity for ABA therapists to understand that some behaviors among autistic individuals may be different from neurotypicals, but these behaviors should not be seen as being wrong and something to cure. For example, behaviors that shape an autistic individual's identity like their religion should not be viewed as wrong because they are autistic, but the individual's actions are part of who they are and not what needs to be fixed.

3.3 Long-Term Graduation Path for Treatment

Depending on individuals with autism' improvement with their phenotypes, further therapeutic, pharmacological, and genetic treatment may vary. This is a field to be further explored for long-term treatment plans, and this includes considerations for individuals with autism with undiagnosed disorders.

3.4 Treatment Processes for Co-existing and/or Undiagnosed Disorders

For treatment processes for patients with co-existing or undiagnosed disorders, monitoring of symptoms and creating plans for genetic and non-genetic treatment (therapies and chemical compounds) may help to manage symptoms of autism and of other disorders that might not have been diagnosed (Butler and Genovese, 2020; Butler and Genovese, 2023; Wang et al., 2024). Creating plans may be beneficial especially when considering the high costs and access to these emerging treatments.

3.5 Treatment Access, Mobility, and Affordability

High costs of genetic treatment are a concern for treating genetic disorders, especially diseases that are rare and require urgent treatment. However, there are more payment strategies, technology, and information about health insurance to cover such costs for genetic diseases (Bradshaw and Carr, 2016; Dabbous et al., 2021). If certain patients' families cannot afford various treatments, there should be increased insurance coverage of payments.

4. Conclusion

This paper has reviewed that mutations can occur in genes among all the chromosomes across an organism's genome, including genes that make up proteins among protein families. These mutations can cause neuronal functioning differences which can result in individuals with autism having challenges with stress and social interactions. Furthermore, an autistic individual's expressed behavioral challenges may be due to not only genetic causes as stated above, but also due to environmental factors. All the genetic and non-genetic causes can be referred to in (Figures 4 and 6).

There are different genetic, pharmacological, and non-pharmacological treatments from research studies (some with autistic mouse models) to extend these treatments to various challenges individuals with autism have like anxiety and communication challenges. To recap the treatments, although monogenic autism treatments like editing or replacing genes can correct

some differences, the primary challenge is finding effective, adequate, and non-toxic dosage levels for autistic patients. For polygenic autism treatments, correcting problems with synaptic function because of environmental influences is difficult, but can be done, making this a potential treatment choice for individuals with autism. Pharmacological non-genetic treatments which are chemical compounds, may be at least partially effective for fixing hormonal imbalances and defective neuronal circuits in the brain. Non-pharmacological treatments like behavioral therapies and altering individuals with autism' diets may partially improve actions like communication. Thus, there are some benefits to improving various individuals with autism' phenotypes using genetic, pharmacological, and non-pharmacological treatments. All the genetic and non-genetic treatments along with treatment concerns can be referred to in (Figure 7).

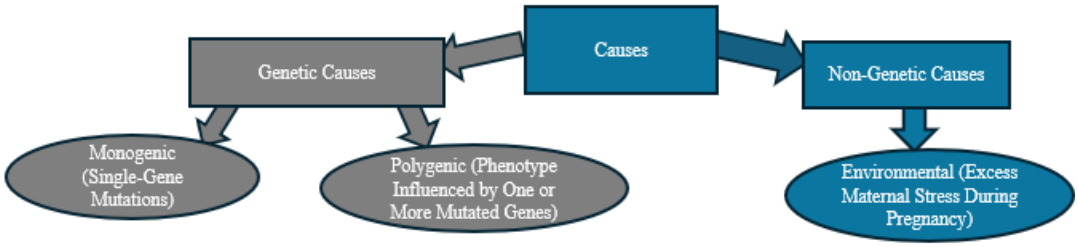

Figure 5. Genetic and non-genetic causes

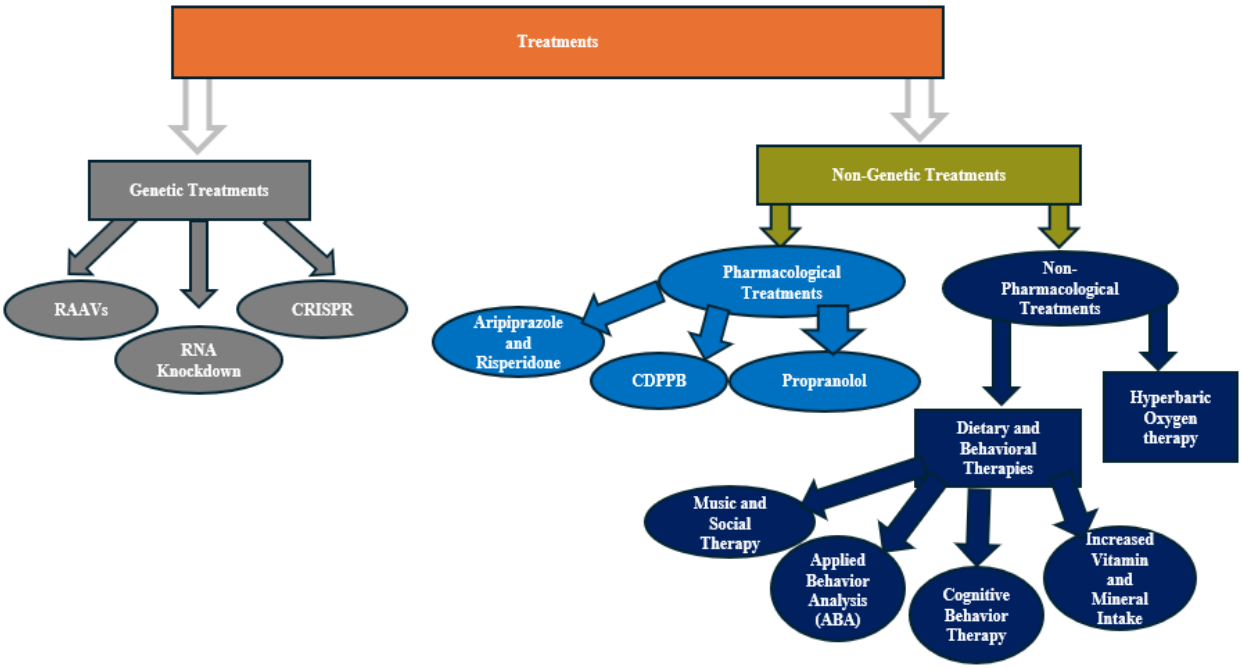

Figure 6. Genetic and non-genetic treatments

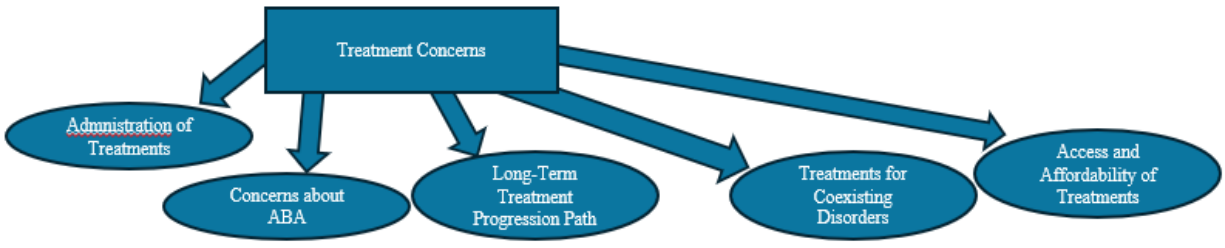

Figure 7. Treatment concerns

5. Appendix

5.1 Bioethical Concerns About Genetic Treatments for Genetic Disorders from an Islamic Perspective

The author of this paper, Abdullah Ali, as a Muslim who is an aspiring geneticist, is interested in genetic treatment and bioethical concerns from an Islamic approach to evaluating the validity of various genetic treatments. Many Muslim scholars are interested in genomic editing, as it aligns Islamically with understanding more about God's creation.

There are various conditions for assessing the validity of a genetic treatment according to an Islamic framework. Based on this, Islamic scholars should urgently address any bioethical problems for autistic patients who receive any unsafe or unnecessary genetic treatment for non-medical reasons (Ghaly, 2019). Specific Islamic concerns about gene editing treatment that may arise include if the gene editing treatment is medically necessary, safe, and will be done to the 22 pairs of non-sex chromosomes somatic cells and not sex chromosomes (Ghaly, 2019). These reasons are tied back to Islamic values to evaluate if such genetic treatment does not break Islamic law (*Shari'a*) (Ghaly, 2019). For example, Muslim scholars explain that editing genes to enhance traits for unnecessary and non-medical purposes means scientists would be changing features of God's creation (Ghaly, 2019). This is because Islamically there is wisdom behind why and how God creates his creation, and that would make the genetic treatment Islamically unethical (Ghaly, 2019). Therefore, genetic treatments should occur if individuals with autism need to have their traits genetically changed urgently for medical needs.

5.2 About the Author

Abdullah Ali is autistic and struggles with stress, anxiety, and executive functioning challenges. Additionally, Abdullah is fascinated about the vast range of genetic and environmental causes, and evolving treatments for treating different behavioral obstacles individuals with autism face. Furthermore, Abdullah is a Muslim who is interested in bioethical concerns regarding gene editing through an Islamic perspective, and how that can be applied to biology in the future.

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