Restoring Healthy Phenotypes in Juvenile Idiopathic Arthritis Through Targeted Manipulation of the HLA-DRB1 Gene

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Abstract

Juvenile Idiopathic Arthritis (JIA) is a chronic autoimmune disease with poorly understood genetic factors and often life-lasting treatment and implications. This review investigates the potential of gene editing on the Human Leukocyte Antigens (HLA-DRB1) gene, particularly on altering amino acids 11 and 13 to restore a healthy phenotype in JIA patients. Genetic associations, JIA pathophysiology, and therapeutic implications were evaluated by conducting a literature review of papers from PubMed, Science Direct, and National Institutes of Health (NIH). Key findings include that positions 11 and 13 significantly influence peptide binding grooves and antigen presentation that lead to JIA, yet editing these genes for therapeutic purposes is highly theoretical. The hyperpolymorphic nature of HLA genes, difficulty of editing precisions, challenges with delivery, and ethical concerns mean clinical application with current gene editing technologies is not yet feasible for JIA. However, progress with technologies like CRISPR and PRIME editing shows that what remains currently unattainable may become a realistic possibility in the future.

Introduction

Juvenile Idiopathic Arthritis (JIA) is a chronic, relapsing, inflammatory disease that affects the joints of children and adolescents, causing pain, swelling, and stiffness. JIA is an autoimmune disease, meaning that the immune system mistakenly attacks its own healthy organs and tissues. JIA is the most common type of arthritis in children, affecting about 1 in 1,000 children (roughly 300,000 children total) in the United States.[1] While there are several subtypes of JIA that differ by number and pattern of joints affected, presence of extra-articular features (skin, eyes, organs), and underlie immune and genetic associations, most share the same baseline symptoms: persistent joint pain, swelling, warmth, and stiffness. Often, these symptoms are worse in the morning and after a nap or prolonged setting.[2]

JIA is not limited to joint pain; JIA's chronic nature can substantially impair a child's ability to play, learn, and participate in daily life. Without timely treatment with immunosuppressive / immunomodulatory agents, JIA can cause serious complications including irreversible joint damage, deformities (including joint contractures, finger deformities, bone fusion, growth disturbances), spinal or facial abnormalities and even eye inflammation. In the same cases, it can even lead to life threatening complications of macrophage activation syndrome.[3]

While the clinical challenges of JIA are significant to patients, the financial strain of treatment is equally profound. Direct medical costs for JIA often exceed those for adult chronic arthritis. For

example, direct costs reached $32,446 in the UK, $15,949 in the Netherlands, and $10,830 in the USA, compared to $1,862–$20,262 for adult rheumatoid arthritis worldwide.[4] This price difference is driven by pediatric specific dosing and monitoring being more costly than those for adults, the smaller patient population of JIA causing less spread of drug development which keeps prices higher, costs from lifelong treatment, need for multidisciplinary care across medical specialties, and slower entries of biosimilars for youth population. These expenses placed a substantial financial burden on affected children and their families.

Early diagnosis and treatment of JIA are critical. Aggressive use of biologic treatments can help control inflammation, prevent joint damage, optimize growth, and improve the child's ability to participate in daily activities and maintain a good quality of life.[5] Yet, even with treatment, the impact is still profound: studies show JIA can cause long-term psychological, emotional, and social challenges such as anxiety and depression, and reduced participation in peer activities. Nearly half of the patients continue to experience disease activity and physical and social limitations into adulthood.[6]

The prevalence, lifelong implications, and gaps in existing understanding of disease pathophysiology of JIA raises a significant medical challenge to patients. To address these concerns, it is important to understand the biological causes of JIA in the human body. Mutations in the HLA-DRB1 gene are strongly associated with JIA, particularly amino acid changes in position 11 and 13, which alter the peptide binding groove and disrupt immune recognition. Yet, targeted manipulation of this gene remains incompletely understood. The present research question arises from this gap in knowledge:

Does targeted genetic manipulation of amino acid in positions 11 and 13 in the HLA-DRB1 gene lead to a restored phenotype in the context of JIA?

Methods

This paper is a literature review conducted using databases like PubMed, Science Direct, and National Institutes of Health (NIH) resources. Search terms include combinations of "Juvenile Idiopathic Arthritis", “JIA pathophysiology”, “HLA-DRB1”, “MHC Class II”, “Amino Acid Position 11”, “Amino Acid Position 13”, “CRISPR in autoimmune disease”, etc. Studies published between 2005-2025 were considered with highest priority alongside high-impact factor journals that were focused on rheumatology, autoimmunity, and genetics. Articles not available in English or lacking primary data were excluded. Sources were analyzed based on recurring themes across immunogenetics, current therapies, and emerging genetic factors. Particular attention was given to studies highlighting the molecular role of HLA-DRB1 positions 11 and 13 and their potential targets for therapeutic invention.

Section 1: Glossary

- Major Histocompatibility Complex (MHC) - A group of genes that code for proteins found on the surfaces of cells that help the immune system recognize foreign substances. MHC molecules present antigens to particular T cells, triggering an immune response.
    - MHC Class I - on surface of all nucleated cells in body with purpose to present endogenous antigens (proteins created within the cell like viral or cancer proteins)
    - MHC Class II - on surface of only specialized immune cells (antigen presenting cells like macrophages, B cells, & dendritic cells) to present exogenous antigens (environmental or bacteria particles)
- Human Leukocyte Antigens (HLA) - gene family human leukocyte antigen which helps immune system distinguish body's own proteins (self) from proteins made by foreign invaders (non-self)
    - HLA-DRB1 - Helps immune system distinguish body's own proteins from foreign proteins (created by bacteria, viruses, etc)
        - MHC Class II
    - HLA-B27 - Helps immune system distinguish body's own proteins from foreign proteins (created by bacteria, viruses, etc)
        - MHC Class I
- TNFα - protein that triggers inflammation; recruits neutrophils and macrophages to inflammation site & activates them; signals for more cytokines with further amplifies immune response
- Cytokines (IL-18, IL-6, IL-1) - diverse group of signaling proteins that communicate and regulate immune responses

Section 2: JIA Pathophysiology

Juvenile Idiopathic Arthritis (JIA) is a group of chronic, inflammatory arthritis conditions that affect children under the age of 16. Like Rheumatoid Arthritis (RA) in adults, JIA occurs when the body's immune system mistakenly attacks its own tissues, particularly the lining of joints, leading to persistent inflammation.

Table 1: Shows key features and additional details of the seven recognized subtypes of Juvenile Idiopedic Arthritis.[2]

Subtype	Key Feature(s)	Additional Details
Oligoarticular JIA	Affects ≤4 joints	Most common type; often knees/ankles
Polyarticular JIA (RF-)	≥5 joints; rheumatoid factor negative	Similar to adult RA but RF test negative
Polyarticular JIA (RF+)	≥5 joints; rheumatoid factor positive	More aggressive; mimics adult rheumatoid arthritis

Enthesitis-Related JIA	Inflammation at entheses (tendon/ligament attachments)	Often lower limb & spine involvement
Psoriatic JIA	Arthritis + psoriasis	⅓ of children with psoriasis develop arthritis
Systemic JIA	Affects joints + organs (heart, lungs, liver, spleen, lymph nodes)	May cause fevers, rash, systemic inflammation
Undifferentiated JIA	Does not fit other categories	Underlying cause not identified, broader group until more features emerge

Biologically, a healthy immune system operates through coordinated innate and adaptive responses. In the innate immune system, macrophages and neutrophils detect pathogens via pattern recognition and trigger the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. This process promotes vasodilation (expanding of blood vessels), vascular permeability (transfer of small molecules, nutrients, water and cells), and immune cell recruitment, causing the characteristics of redness, warmth, and swelling of inflammation. Dendritic cells present the antigens to helper T-cells, killer T-cells, and B-cells which attack the pathogen. Once the pathogen is cleared, regulatory T-cells shut down the immune response, damaged tissues repair themselves, and inflammation comes to a stop.[7]

In JIA, immune cells inappropriately target healthy joint tissues as if they were pathogenic, activating an immune response to self. Since there is no actual infection to resolve, immune cells continue to release proinflammatory cytokines. This subsequently leads to more immune cell recruitment and T cell activation coordinated by antigen presenting cells. Subsequently, this inflammatory state feeds forward in a vicious cycle that is difficult to disrupt and allow for restitution.[8]

JIA Genetic & Environmental Factors

JIA is caused by complex interactions between genetic and environmental factors. The genetic factors stem from the MHC region, a gene cluster in chromosome 6 that encodes proteins to recognize foreign versus self. HLA-DR (Human Leukocyte Antigen) is a protein found on the surface of immune cells like lymphocytes and macrophages that has a role to recognize and present virus/bacteria proteins to the immune cells. Particularly, amino acids 11 and 13 on the HLA-DRB1 gene have been associated with proteins immune recognition and autoimmune activation.[9]

Environmental influences have also been investigated. A study by PubMed Central found that infectious disease, smoking, stressful life events, and prenatal characteristics like breastfeeding had previously been associated with JIA. Conditions like B19, EBV, HIV have been linked to arthritis but not chronic disease like JIA.[10] Science Direct also found some associations with stress and JIA. Data on 88 children with JIA were studied and found no significant association with any of these environmental factors and JIA except for premature delivery but even that requires further studies. Another study published in Autoimmunity Reviews found that exposure to viral infections like influenza A, rubella,compared with 2952 geographically matched controls aiming to elucidate characteristics that may participate in the disease etiology. The rate of adoption was more than three times higher in the patients than in the controls. Half of these events (divorce, separation, death or adoption) occurred close to the onset of JIA. Similar findings were previously reported of significant life stress events occurring within a year before disease onset in 37% of JIA patients.[11] This connection is plausible because stress is a known stimulator of the sympathetic nervous system, and has shown to increase the production of interleukin 6, one of the most important inflammatory cytokines in JIA.

Section 3: Current JIA Treatments

JIA treatment starts with NSAIDs with subsequent escalation to DMARDs and corticosteroids as patients continue to experience symptoms / prove refractory to treatment. Corticosteroids are synthetic hormones mimicking adrenal steroids. Physical and occupational therapy which are structured exercises and adaptive training, and surgeries which are rare medical procedures to repair joints. Beyond pharmacological therapy there is physician and occupational therapy to address mobility or movement concerns. In rare cases, surgery can be performed to repair joints that are significantly damaged.

NSAIDs

NSAID (nonsteroidal anti-inflammatory drugs) have the ability to inhibit biosynthesis (creation) of prostaglandins (body chemicals that cause pain, swelling, and fever) at the level of the cyclooxygenase enzyme. Some therapeutic benefits of NSAID include improvement in pain and stiffness, they are widely available and fast acting, and they are highly effective in pain relief due to PG production in peripheral tissues in the CNS. Some limitations of NSAID include digestive and bleeding risks alongside kidney and cardiovascular concerns.

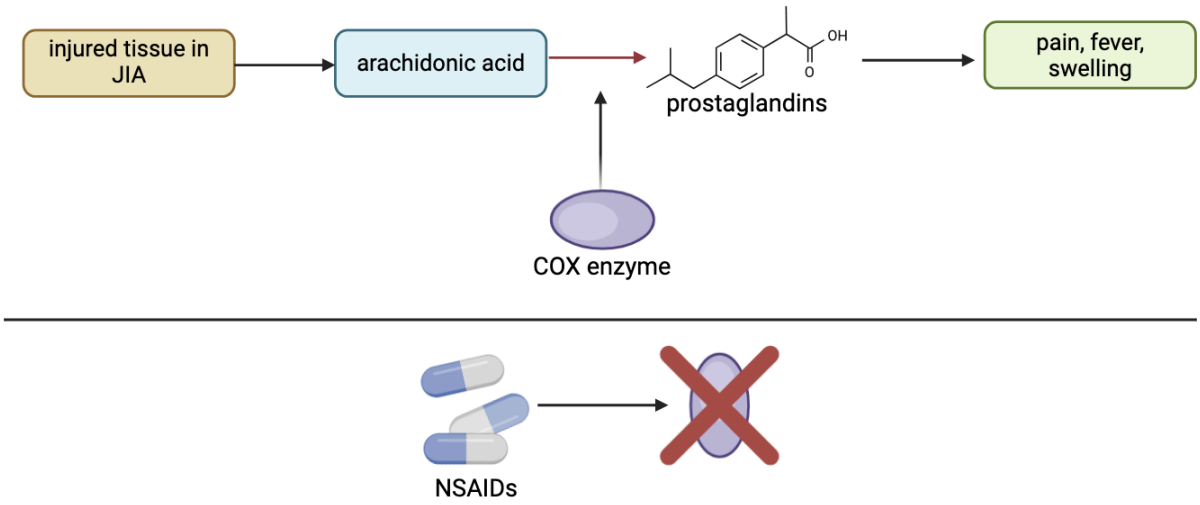


Figure 1: Mechanisms of NSAIDs in JIA. Injury in JIA triggers arachidonic acid, which is converted by cyclooxygenase (COX) enzymes into prostaglandins, leading to pain, fever, and swelling. NSAIDs inhibit COX activity which reduce prostaglandin synthesis and provide relief. *Created with BioRender.com.*

DMARDs (Biological Agents)

Biologic agents are types of DMARDs that target key components of the dysregulated immune response. Examples are proteins that will block TNF receptors, pegylated antibody fragments, cytokines, Il-1 receptors, and more key agents in JIA. Yet, these agents are also important to maintain normal immune homeostasis and carry an array of normal physiological effects so their blockage can lead to adverse effects such as impaired immune function, non-immunological function, immune imbalance syndrome, autoimmunity, etc. Due to biologics being relatively recent, there is still a lack of evidence supporting long term evidence.

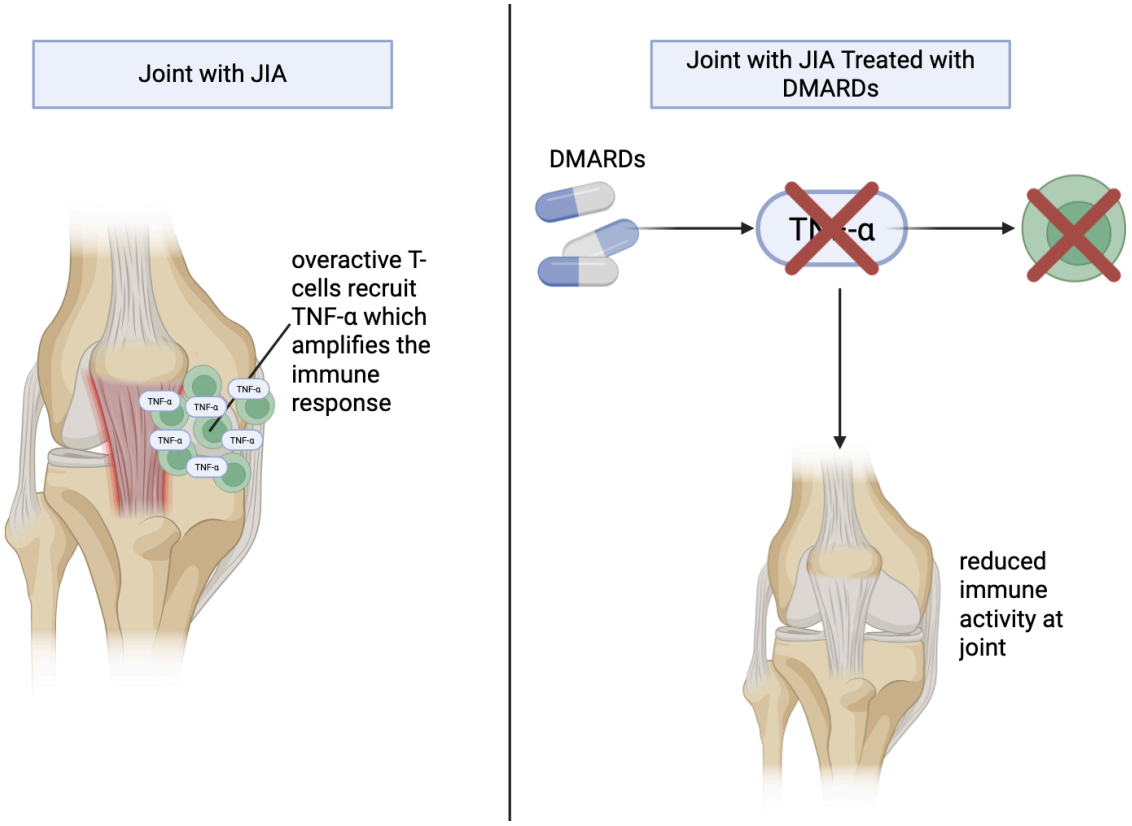


Figure 2: Mechanisms of DMARDs in JIA. Injury in JIA triggers overactive T-cells to recruit TNF-α to further amplify immune response. DMARDs treatment inhibits TNF-α, limiting an amplified immune response. *Created with BioRender.com.*

Etanercept and adalimumab are both TNF-α inhibitors that block the effects of TNF-α. Etanercept was the first specific anticytokine therapy (biologic) approved for treatment of RA. Etanercept has a distinct structure from other TNF inhibitors due to its composure being of human protein sequences which leads to it triggering fewer anti-drug antibodies causing better long term effectiveness. Some of its known benefits are stable immune modulation, lower immunogenicity, and additional benefits such as preventing muscle atrophy and improving life span. Some of etanercept limitations include inability to bind effectively to TNF embedded in cell membranes, injection reaction risk, and many side effects.[12] Adalimumab has similar benefits with reducing inflammation and also similar side effects, commonly injection site reactions and more rare include worsening/initiation of congestive heart failure, lupus like syndrome, promotion of lymphoma, etc.[13]

CLIPPER and CLIPPER 2 were a ten year clinical study to analyze the safety and benefit of etanercept treatment for JIA. CLIPPER was the first two years of this study that tested the drug efficiency, finding that the use of etanercept led to substantial improvement due to less joints with detected arthritis and lower disease activity. In fact, data showed that between the first

injection to six months using etanercept, disease activity decreased significantly. CLIPPER 2 was the 8 year extension to CLIPPER and was meant to study the etanercept long term effects, withdrawals, and sustained efficiency. In regards to TEAEs (treatment emergent adverse effects), the most frequently reported were headaches, arthralgia, pyrexia, diarrhea, and leukopenia. Over the course of 10 years, TEAEs significantly decreased from 193 reported in year 1 to 9 reported in year 10. However, after withdrawal 57% of participants reported flare ups with a median relapse time of 190 days.[14]

Another addressed the long term safety of adalimumab in 23458 patients from global clinical trials for RA, JIA, AS, psoriatic arthritis, Ps, and CD. The study found there are SIEs (serious adverse effects) such as pneumonia, cellulitis, TB, and more. The study found the rate of serious infection in JIA was 2 out of 100 patients. The malignancies were the same as the general population and mortality was the same or lower than the general population. The trial was most focused on safety but continued long term use, low discontinuation rates, and disease-specific approvals indicate positive clinical outcomes with adalimumab.[15]

Yet, biologics work by suppressing a part of the immune system, which ultimately reduces the body's ability to fight off other infections. Additionally, the CLIPPER study identified both short term and long term side effects which pose ongoing challenges for patients. Biologics and NSAIDs are also not permanent solutions as many patients relapse once removed from the medication. The next step in treatments is to find a permanent cure to JIA, allowing patients to completely stray away from side effect filled medications. The best way to do so is by addressing the root of the problem: genetic and environmental triggers. Since the environmental triggers are less explored and because gene editing treatments are now growing more common, editing the genes that cause JIA is the next step to finding a permanent cure for the disease.

Section 4: Genetics in JIA

Genetic Structure Overview

HLA are a gene family in the human leukocyte antigen, located on chromosome 6, which helps the immune system distinguish the body's own proteins (self) from proteins made by foreign invaders (non-self). HLA-DRB1 are beta chain proteins which combine with alpha chain structures to create hemoglobin, T-cell receptors, and cytokine receptors. It correlates to MHC Class II by providing instructions for making proteins present on the surface of immune cells like lymphocytes, macrophages, and neutrophils. HLA contributes to JIA at a rate around 20%. Some of the phenotypes of HLA-DRB1 include *01:01 - associated with RA; *03:01 - linked to type I diabetes; *04:01 - strongly associated with RA; and *15:01 - associated with multiple sclerosis (MS).[9]

HLA-DRB1 positions 11/13, 71, and 74 are associated with inflammation level, disease activity, and the health assessment questionnaire score in patients with inflammatory polyarthritis.[16]

While this is not specific to JIA, it indicates that positions 11 and 13 show significance in JIA. A reason for this is because position 11 and 13 are in the peptide binding groove in the HLA-DR molecule that hold and present antigen fragments. Changes, like substitution, of the amino acids in these grooves can cause the immune system to misrecognize itself as foreign, causing T-cell activation, cytokine release, and chronic inflammation. Each position contains amino acids.

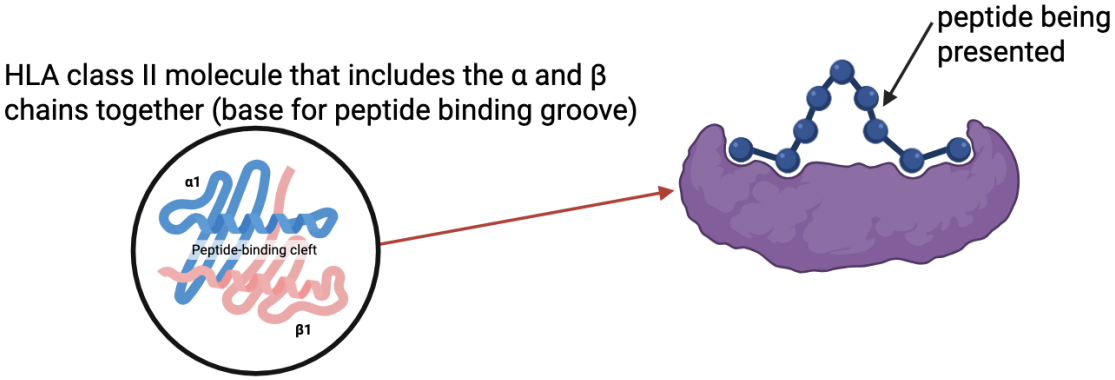
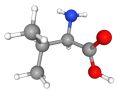
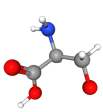
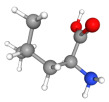
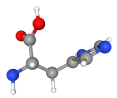
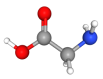


Figure 3: Structure of HLA molecule highlighting the peptide binding groove. The HLA class II molecule is formed by an α-chain (blue) and a β-chain (pink) that together form the peptide-binding cleft. Within this groove/cleft, antigenic peptides (blue) are held and presented to T-cell receptors. In JIA, amino acid substitutions in amino acid 11 and 13 can alter peptide binding, leading to misrecognition of self as foreign, and trigger downstream T-cell activation and chronic inflammation. *Created with BioRender.com.*

Amino Acids

Table 2: Shows key features of critical amino acids regarding structure, size, charge, polarity, essential vs non essential, and JIA risk. Position 11 contains amino acids valine, lucine, and serine. Position 13 contains histidine and valine. *Images from PubChem.*

Amino Acid & Position	Image	Function	Size	Charge	Polariity	Essential	JIA Risk
Valine (11 & 13)		critical for protein synthesis, muscle growth, and regulating blood sugar	medium	Neutral	non-polar	Essential	Strong risk (creates pocket that is favorable for self-binding)
Serine (11)		critical for protein synthesis, cell function, and brain signaling	Small	Neutral	polar	Non-essential	low risk (Less favorable for self-antigen presentation)

Leucine (11)		critical for protein synthesis, muscle growth, and wound healing	Medium	Neutral	non-polar	Essential	Moderate risk (creates pocket that is favorable for self-binding)
Histidine (13)		Protein synthesis, enzyme activity, histamine precursor (immune response)	Medium	Positive (at physiological pH can carry partial + charge)	polar	Essential	Strong risk (position 13 substitution associated with JIA)
Glycine (11)		Protein synthesis, collagen stability, neurotransmission	Very small (smallest amino acid)	Neutral	non-polar	Non-essential	Normal/no risk (protective at position 11)

Amino acids that favor JIA structurally create a groove that is favorable for self-binding with immune cells like T-cells which causes inflammation and JIA. Based on the data table, larger, non-polar amino, hydrophobic amino acids tend to increase JIA risk. This could be because they create deeper, more stable binding pockets within the binding groove. These pockets make it easier for self-peptides to bind and present to T-cells, increasing likelihood of misrecognition and autoimmunity. Similarly, histatide at position 13 carries the same risk because its partial positive charge allows it to form greater hydrogen bonds which causes greater stability. This stability with peptides in the groove again increases the presentation of self-antigens that drive T-cell activation.

In contrast, the data table shows smaller, polar amino acids like serine and glycine less associated with JIA risk. Their small size disrupts the formation of deep, hydrophobic binding grooves which makes self-binding less favorable.

Taken together, the JIA risk seems to be the highest when positions 11 and 13 are occupied by medium-sized hydrophobic or positively charged residues that stabilize peptide binding to MHC molecules. Risk is the lowest when the MHC molecule is made up of small, polar amino acids that destabilize or loosen peptide interactions. This pattern highlights how subtle changes in amino acid positing can significantly shift immune recognition from tolerance to autoimmunity, therefore inducing JIA development.

Section 5: Gene Editing as Therapeutic Treatment for JIA

Types of Gene Editing

Gene therapies work by modifying a person's genes to treat or cure disease (FDA). This can be implemented through multiple mechanisms such as replacing a disease causing gene with a healthy copy of the gene; inactivating a disease causing gene that is not working properly; or introducing a new or modified gene to the body to help treat disease.

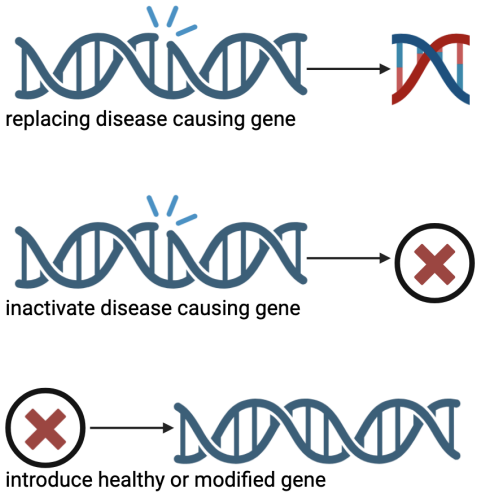


Figure 4: Types of gene editing. *Created with BioRender.com.*

There are many gene editing methods, the most common being CRISPR Cas9. It works by using a guide RNA (gRNA) with a sequence complementary to the target DNA sequence that acts like a GPS coordinate for Cas9. The gRNA is bound to the Cas9 protein, creating a search and cut mechanism. Once the matching DNA is identified, the Cas9 makes a cut next to the DNA tag called the PAM (Protospacer Adjacent Motif) sequence. Then Cas9 makes a double stranded break, making a break in the DNA at the target site. This allows scientists/cells to correct the DNA at the target site using non-homologous end joining or Homology-Directed Repair (HDR).[17]

Some other types of gene editing include ZNFs which consist of identifying a specific DNA strand and then cutting and replacing both DNA strands. TALENs are engineered proteins that bind specific DNA sequences and use nuclease to cut the DNA at the site, allowing for the cell to repair its DNA at the site. PRIME editing pegRNA nicks DNA at target sequence and then creates edited strand and unedited strand. One part of the original DNA strand is removed and replaced with an edited strand. Because of the mismatch in the DNA, the cell's mismatch repair mechanism incorporates the edited strand into the DNA of the cell. This method is even more specific and has fewer off-targets than CRISPR but PRIME is relatively new technology which limits its therapeutic usages.[18]

Genetic Editing Vehicles

There are 3 main vehicles to deliver gene editing systems: physical delivery, viral vectors, non-viral vectors.[19] A common physical delivery method is the microinjection method is a needle that carries DNA plasmid, mRNA w/Cas9 directly to the cell of interest. Using microscope and 0.5–5.0 μm diameter needle, a cell membrane is pierced and cargoes are delivered directly to a target site within the cell. Microinjections around cellular barriers such as cellular membrane, etc

and directly into the DNA/nucleus and most importantly have been successful with CRISPR-Cas9.

Viral delivery vectors include specifically engineered adeno-associated virus (AAV), and full-sized adenovirus and lentivirus vehicles. Particularly, scientists repurpose viruses (stripped of pathologic genes) and use their natural cell-entry and nuclear delivery machinery in order to enter cells. This method has been very successful with delivering CRISPR Cas9, and is in fact the most common CRISPR Cas9 delivery method. For JIA, though, this may not be the best method. Because of the virus, viral delivery can often stimulate the immune system which can cause issues for autoimmune patients.

Non-viral methods are not as prominent as viral methods but they carry advantages such as much lower immunogenicity, minimal risk of insertional mutagenesis, and the transient expression is easier to control and stop. They work by using synthetic/physical carriers to carry the CRISPR cargo (mRNA, plasmid DNA, etc) to make their way into cells.

Gene Editing Clinical Trials

CRISPR/Cas9 has been approved to treat sickle cell disease. Casgevy utilizes CRISPR/Cas9 to direct targeted DNA areas which are then edited (removed, add, replace). Sickle cell disease is created by a mutation in the HBB gene. Casgevy doesn't edit the mutation in the HBB gene but instead uses CRISPR/Cas9 to edit another gene in patients own stem cells to increase production of fetal hemoglobin. Scientists collect stem cells from patients, do CRISPR editing in the lab, put patients through high-dose chemo to destroy existing bone marrow cells which makes room for new cells, and infuse high levels of edited cells.[20]

In another clinical study at CHOP (Children's Hospital of Philadelphia), a single injection of CRISPR/Cas9 was used to treat patients with inherited blindness. Participants showed improvements in the measures: best corrected visual acuity, dark adapted full field stimulus test, visual function navigation, and visitation related quality of life.[21]

Genetic editing has also been used with immune genes in the past. Genetically modifying immune cells is being used to create living drugs for blood based cancers. CAR-T therapy is a form of cellular immunotherapy where doctors take patients T-cells, use viral vectors to insert a transgene encoding a chimeric antigen receptor (CAR), expand those modified cells, and reinfuse them. The CAR allows the T cells to recognize a specific tumor marker (like CD19) and kill cancer cells. This is often called a "living drug" because the infused cells persist, expand, and actively fight disease inside the body. This process is not editing of the genome like CRISPR, but it relies on gene transfer to insert the CAR transgene. This causes semi-random insertion unlike CRISPR which is very precise.[22]

In 2020, report on a clinical trial for using CRISPR-engineered T-cells in patients with refractory cancer. The goal of the trial was to measure safety and feasibility of genetic engineering in the immune system, not providing cancer remission.[23] During the trial, they targeted three genes: TRAC and TRBC (endogenous T-cell receptor chains) and PDCD1 (encoding PD-1). The process considered drawing blood from patients, isolating T cells, and introducing Cas9 protein + guide RNAs into the T cells as a ribonucleoprotein (RNP) complex. These guides target the three genes and edit them by removing the natural TCR and knock out PD-1 to boost T-cell function by resisting tumor-mediated "shut-down." After CRISPR knockout, the cells were transduced with a lentiviral vector carrying a synthetic TCR that recognizes NY-ESO-1, a tumor antigen expressed in some myelomas and sarcomas. The modified T cells were expanded in the culture until there were billions of cells. Before infusion, patients received lymphodepleting chemotherapy which clears space in the immune system so cells can engraft and expand. Then, the cells were infused back into the patient and thrive as a living drug.

Experts highlighted there was no evidence of immune rejection against the edited cells, suggesting CRISPR edited T cells can persist in a healthy, functional memory state in some patients. This opens the possibility of using precision immunotherapy as a long term therapy for treating many cancers. But since the evidence is based on a single patient and doesn't include tumor samples, we can't conclude how general or effective this treatment will be for all patients across all tumor environments.

Overall, this study demonstrated many benefits of editing immune genes. For example, immune gene editing treatments carry high potential for fighting cancer effectively and also have broad applications across genetic disease, including JIA. Other benefits this article found includes being precise and non-disruptive and effective based on these early clinical trials. Yet, some challenges include risking off-target mutations and chromosomal damage, facing challenges with delivery, having low efficiency for complex editing, being high cost, and having ethical implications.

Positive Implications of Editing Immune Genes

Some positive implications of gene editing of positions 11 and 13 include potential breakthroughs in autoimmune treatment because in theory, editing these genes should reduce autoimmune risk by altering peptide treatment. For JIA or RA this could mean moving from immune overactivation to immune tolerance. Editing these genes goes beyond JIA and into precision medicine as HLA genes could be tailored for immune recognition. This could be useful for transplant tolerance or cancer immunotherapy too. Further, if HLA editing is possible, it opens the door toward treating more, polygenic immune-mediated disease.

Negative Implications of Editing Immune Genes + Polymorphism

Yet, there are also many limitations of this concept. The MHC complex contains most polymorphic genes in human genome and is now considered hyperpolymorphic.[24] Polymorphic genes refer to genes with two or more different forms (alleles) present within a population, each occurring at a rate of at least 1%, ultimately meaning they have high genetic variation. Hyperpolymorphic is the state of having an extremely high level of genetic polymorphism, or variation, within a species or population.

Some common assumptions with polymorphic genes include: Polymorphic genes have many variants so guide RNA or peg RNA that works on one allele might not bind properly to another.[24] Gene editing has to be personalized, at least to alleles. For HLA genes, polymorphism is not just single nucleotides, but a combination of amino acids across positions that shape function. Therefore, correcting positions 11 and 13 is valuable only if surrounding haplotype context is favorable. Otherwise, the effect may not restore function or reduce risk. Polymorphic genes often mean two different alleles so editing one allele might disrupt the balance with the other, causing new antigen presentation. This is different from monogenic disease where altering one faulty gene will restore function. Polymorphic HLA genes don't have a single “healthy” version; they have adaptive diversity. Editing will shift immune repertoire but whether that shift helps or harms depends on disease context, infection exposure, etc. Most HLA editing works to remove rather than fix expressions. Polymorphic genes might require mutli-site editing which would require a highly precise and multifarious delivery tool.

Other limitations with editing positions 11 and 13 on chromosome 6 include risk of overcorrection or unintended effects. Changing antigen presentation might stop autoimmunity, but it could also weaken immune defense against infections or tumors. Could trigger new, unintended autoimmune responses if the peptide-binding repertoire shifts too far. Further, editing immune genes (bone marrow stem cells) to reprogram lifelong immune tolerance.

Section 6: Clinical Feasibility & Limitations

Clinical Feasibility

The clinical feasibility of gene editing for JIA remains highly experimental and limited, though early progress in the field provides optimism. Existing trials using CRISPR edited immune cells, such as T-cells engineered for cancer immunotherapy, demonstrate that gene manipulation can be safe for patients and functional for treatment uses. However, translating this to JIA would be more complex, as it would require editing hyperpolymorphic immune genes like HLA-DRB1 within hematopoietic stem cells to reprogram long term immune tolerance. Editing of these genes have been edited in preclinical studies but precise editing has not been tested yet. Delivery remains a major challenge. While viral vectors have proven to be effective in delivering CRISPR Cas 9, they risk stimulating unwarranted immune responses in autoimmune (JIA) patients. Non-viral methods are less immunogenic but also less effective. Furthermore, polymorphism in the HLA complex means edits must be allele specific and context aware,

making universal treatment unlikely. While the concept holds promise for permanent solutions beyond biologics and NSAIDs, currently the feasibility is restrained by low efficiency for complex edits and limited clinical evidence.

Addressing Research Gaps

Addressing key research gaps can make genetic editing in the HLA complex more feasible. Firstly, allele specific targeting can address the gap that current CRISPR and PRIME tools are not optimized for highly polymorphic genes like HLA. The development of allele-aware, personalized editing strategies (guide RNA libraries or computational design pipelines) to reliably target diverse HLA-DRB1 haplotypes would address this issue.

Next, a safer and more effective delivery method is required. Editing hematopoietic stem cells to permanently reprogram immune tolerance is difficult and viral delivery could trigger immune activation. Improved delivery vehicles, that have the efficiency of viral vectors but lower immunogenicity, are required.

Another concern is genetic editing risks towards unintended outcomes such as off-target mutations, chromosomal rearrangements, or harmful immune imbalance. More precise editing systems are needed to combat these risks and a method to monitor long-term editing for safety and stability.

Since HLA diversity has developed to protect populations from infections, editing one allele might disrupt the balance with another allele and reduce pathogen defense. Mis-edits could weaken the immune system even more than it would be under biologic side effects, making it an non-viable treatment. What is needed is system level studies that model how altering amino acids 11 and 13 would affect antigen presentation, infection sustainability, and autoimmune risks across populations.

Currently, most discussion of HLA editing is focused on cancer immunotherapy and transplant tolerance. Ethical frameworks and clinical trial guidelines are needed that are tailored towards autoimmune applications, particularly for the pediatric populations.

Ethical Concerns

Gene editing carries many ethical concerns. Bioethical issues in genome editing by CRISPR-Cas9 technology risks off target effects and mosaics are strong risks and individuals and embryos shouldn’t be put at harm.[25] Others argue that genetic therapies should be allowed to cure genetic disease as it is a moral imperative. Yet, others see it as a slippery slope to being used for non-therapeutic and enhancement purposes. Many people hold moral and religious obligations towards using embryos for research. Further, embryos are unable to provide consent but the argument against that is that parents are already making decisions that impact a child’s

future for them. Genes can also be transferred between species, which can cause unintended population effects in the environment.

Finances play into further ethical concerns. Some argue that gene editing would cause inequity since it would only be accessible to the wealthy. Further, federal funds don't fund any research that involves creating or destroying embryos. With lack of research, the full effects of gene editing will remain unknown which leads to further risks. There is worry that modifying human embryos can lead to long-term unintended genetic changes and effects being passed down to children.

Section 7: Conclusions

Juvenile Idiopathic Arthritis (JIA) represents a complex and costly challenge, both medically and socially. While current treatments such as NSAIDs and biologics can provide meaningful relief, they are not curative and come with relapse and long-term side effects. Gene editing offers a permanent cure that shifts away from managing symptoms and instead focuses on addressing the underlying genetic drivers of arthritis. In particular, treating positions 11 and 13 on chromosome 6 is a novel and promising idea because of their known association with autoimmune activation.

As of right now, the solution remains highly theoretical. The hyperpolymorphic nature of HLA genes, difficulty of editing precisions, challenges with delivery, and ethical concerns mean clinical application with current gene editing technologies is not yet feasible. However, the progress with technologies like CRISPR and PRIME editing shows that what remains currently unattainable may become a realistic possibility in the future. Continued research into allele specific editing, safer delivery vehicles, and system level immune modeling are key steps.

Ultimately, exploring genetic editing in JIA is not only valuable for this one disease but opens the door to many more broad autoimmune diseases. Though far from clinical reality, it represents an exciting future possibility that can shift the treatment of autoimmune disease from therapy to permanent cure.

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