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A Comparison Between Nerve Decompression Surgery and Injection Procedures for Treatment of Primary Headache Disorders

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Introduction

Although often perceived as minor ailments, headaches have a profound global impact—affecting over 3 billion individuals worldwide—and represent a significant public health concern. People with headache disorders often suffer from debilitating pain, leading to a significantly reduced quality of life. According to the World Health Organization's (WHO) Global Health Estimates from 2019, headache disorders are the third leading cause of disability worldwide. Despite their widespread impact on individual health, society, and the economy, headache disorders are often incorrectly diagnosed or underdiagnosed (World Health Organization, 2024). When misdiagnosis occurs, ineffective treatment resulting in negative patient outcomes can occur. Studies from the American Headache Society and other scientific organizations reveal that misdiagnosis is incredibly common, with about 50-80% of migraine patients initially misdiagnosed with other headache disorders such as sinus, stress, and tension-type headache, as well as sinusitis and cervical pain (Halsey, 2025; Kim et al., 2024). Contributing factors that lead to misdiagnosis include insufficient objective screening tools, a limited understanding of migraines among healthcare providers, and lack of provider expertise in migraine management (Kim et al., 2024). Even when correctly diagnosed, medication

management alone has proven insufficient in most cases, highlighting the need for more comprehensive treatment approaches.

To develop more effective and individualized treatment strategies, it is essential to understand how headache disorders are classified. Treatment is typically determined after the specific headache disorder has been categorized as either primary or secondary. The two are differentiated in that primary headache disorders are the direct cause of headaches, while secondary headache disorders result from an underlying condition—often a serious or life-threatening medical condition—that triggers their onset (Hernandez et al., 2024). Migraines and tension-type headaches are the most common primary headache disorders, while intracranial tumors and subarachnoid hemorrhage are typical examples of secondary headache disorders. However, it is possible for medication-overuse headache (MOH), a secondary headache disorder, to occur simultaneously with primary headache disorders (Ahmed, 2012).

This overlap between primary and secondary headache disorders emphasizes the importance of tailored treatment approaches. While guidelines for the management of primary headache disorders vary between adults and children, current recommendations often advise providers to treat patients conservatively with pain-relief medications or minimally invasive procedures (*Clinical Practice Guidelines*, 2024). For migraines, this often includes over-the-counter (OTC) medications such as ibuprofen and aspirin, other NSAIDs like naproxen and diclofenac, and triptans for those who do not benefit from the first-line treatments. Preventive measures for primary headache disorders include onabotulinumtoxinA (Botox) injections, beta-blockers such as propranolol, antidepressants, herbal medications, cognitive behavioral therapy (CBT), and acupuncture—especially for migraines—although these treatments have also been used for other primary headache disorders, such as cluster and tension headaches. Children

under the age of 18 are usually limited to oral medications and preventive measures that exclude injections, although off-label use of these injections is sometimes considered in adolescents with headaches unresponsive to other treatments (Ahmed, 2012). Additional treatment modalities include intravenous (IV) infusion therapy and autoinjectors, both of which exhibit similar mechanisms of action to oral pharmacologic agents. Neurostimulation, including neuromodulation techniques such as deep-brain stimulation (DBS), represents an alternative therapeutic option; however, its utilization remains limited due to the intensive nature of the procedures, associated high costs, and restricted availability (Miller et al., 2016).

The similarities shared by different headache disorders and the age-related treatment limitations indicate a need to evaluate procedural interventions within the broader scope of headache disorders. While prior reviews have examined headache disorders as a whole, this paper aims to provide a holistic overview of primary headache types and analyze procedures to treat these disorders. Recent clinical trials have demonstrated the use of more invasive techniques, specifically injection therapies and nerve decompression surgeries targeted at headache trigger sites, as effective treatment methods for primary headache disorders. A comparison between nerve decompression procedures and various injections demonstrates that injection-based treatments offer a more individualized approach, allowing for tailored management based on a patient's specific needs. Moreover, they represent an appropriate first-line treatment option, irrespective of whether surgical intervention is being considered.

Methods

This review examines peer-reviewed scientific literature published within the past 15 years and focuses exclusively on the study of primary headache disorders. It centers on a comparative analysis of nerve decompression and neurolysis versus injection-based treatment modalities.

Studies were excluded if they addressed secondary headache disorders or other headache types, were published prior to 2010, or investigated treatment approaches other than nerve decompression, neurolysis, or injections. Relevant literature was identified using the following keywords: 'headache disorders,' 'headache types,' 'primary versus secondary headaches,' 'medication overuse headache,' 'surgical interventions for primary headache disorders,' 'headache treatment,' and 'headache procedures.'

Results

Accurate diagnosis of the various primary headache disorders is critical to ensuring that patients receive effective and appropriately specialized treatments beyond standard pharmacological interventions. Emerging evidence suggests that more invasive therapeutic approaches may lead to improved patient outcomes; however, the choice of procedure is contingent upon the specific type of primary headache disorder identified. This highlights the importance of accurate diagnosis, particularly given the overlap in clinical presentation among various primary headache disorders. Common primary headache disorders that tend to overlap in clinical presentation include tension headache, migraine, cluster headache, and exertional cephalalgia.

Primary Headache Disorders

One of the most common primary headache disorders is tension headaches, which are classified as bilateral, recurrent headaches that are mild to moderately intense and last between thirty minutes to seven days. Patients with tension headaches often describe the pain as a dull, pulseless pressure and/or tightening pain that feels like a band around the head. While tension headaches typically cause mild to moderate discomfort, migraines often progress through distinct stages and can be significantly debilitating. Migraine headaches are typically unilateral (but can

be bilateral), produce pain that is throbbing, pulsating, and/or pounding, and are accompanied by additional symptoms including nausea, vomiting, and sensitivity to light, sound, or smell. Migraines consist of four stages known as the prodrome, aura, headache, and postdrome phases. The prodrome and postdrome stages often result in symptoms such as changes in mood and energy levels before and after the migraine attack. Some people may experience an aura phase preceding the head pain, which can cause visual or sensory disturbances such as colorful spots, flickering lights, a narrowed or darkened visual field, and numbness or tingling in the limbs. Of those who have experienced an aura before a migraine attack, this phase may not always be present between the prodrome stage and onset of head pain. Migraine pain may last anywhere from less than twenty-four hours to more than three days, depending on the severity.

Primary headache disorders that are less prevalent than tension-type and migraine headaches but are characterized by a more sudden and rapid onset include cluster headaches and exertional cephalalgia. Cluster headaches are associated with trigeminal nerve overexcitation and indicated by intense unilateral pain of the head and face. This pain is thought to be triggered by the descent of inflammation down the nerves. Confirming diagnosis of cluster headache through a neurological exam requires the patient to be actively experiencing an episode. They present as daily attacks that persist for weeks to months followed by remission periods that can go on for years. These attacks generally last less than three hours, but can recur more than once in the same day, whereas exertional cephalalgia occurs exclusively during or after physical activity. Exertional cephalalgia causes bilateral throbbing head pain associated with physical activity, including coughing. This type of headache is often more acute and evaluated in critical care settings. Primary headaches from coughing can present with additional symptoms; patients may

report nausea or vertigo. Headaches following physical exertion can be exacerbated by external factors such as hot weather and high altitudes.

For all these primary headache disorders, it is important to note that flares may present more severely and differ in clinical presentation. Headache episode frequency can range from less than one day per month to fifteen or more days per month. Confirming a diagnosis involves ruling out other conditions, including through assessment of past medical history and current signs and symptoms. Additionally, certain symptoms of these headache disorders are very similar to those of secondary headache disorders (Hernandez et al., 2024).

Primary Headache Disorder Treatment Options

Once the primary headache disorder has been classified by assessing patient symptoms and analyzing results from objective screening tools, targeted procedural treatment options can be considered for further pain management. Providers generally recommend more conservative invasive treatment options such as injection therapy prior to considering surgical interventions requiring anesthesia. Prominent examples of these treatment modalities include intracranial injections (such as nerve blocks and Botox) and nerve decompression and neurolysis techniques. Both treatment approaches enhance the patient experience in managing primary headaches by targeting the nerves involved in headache-triggering pathways. The primary distinction between these two treatment modalities lies in the minimally invasive approach and transient modulation of nerve function, which render injection therapy an appropriate initial intervention. In contrast, nerve decompression and neurolysis provide sustained relief through the permanent correction of structural nerve pathology.

Injection Therapies

For patients who require or prefer less invasive treatment modalities, injection-based therapies constitute a widely utilized and clinically effective approach to pain management, particularly in the treatment of headache disorders. The primary types of injections used for this purpose include nerve blocks, trigger point injections, and onabotulinumtoxinA (Botox) injections. Nerve blocks involve the administration of a local anesthetic—commonly lidocaine or bupivacaine—to temporarily numb specific nerves (admin, 2021). These procedures serve both diagnostic and therapeutic purposes: diagnostically, they help identify the nerves responsible for pain; therapeutically, they provide targeted pain relief. The pharmacokinetic properties of different local anesthetics influence their onset and duration of action. In some cases, epinephrine is added to the anesthetic to prolong its effects. Additionally, corticosteroids are frequently included to reduce local inflammation; however, their effects are temporary and symptoms often recur within a few days to several months (admin, 2021). Trigger point injections target hyperirritable muscle bands or soft tissue areas that contribute to pain. These injections typically contain a local anesthetic, with or without a corticosteroid, aimed at modulating and blocking local pain signals (“trigger points”) to achieve significant relief. The frequency and number of both nerve block and trigger point injections are tailored to the specific headache disorder and the anatomical targets involved.

For patients who may benefit from trigger point injections but are allergic to anesthetic agents, an alternative approach known as "dry needling" may be utilized. This technique involves the insertion of a needle without any accompanying medication, potentially providing additional pain relief by mechanically disrupting muscle fibers, thereby facilitating their relaxation and lengthening (Kuruvilla & Robbins, 2017). A comparable approach that achieves muscle relaxation and pain relief through pharmacologic means is the use of onabotulinumtoxinA

(Botox) injections. Intramuscular injection of onabotulinumtoxinA is approved by the U.S. Food and Drug Administration (FDA) as a preventive treatment for chronic migraine (*HIGHLIGHTS of PRESCRIBING INFORMATION*, 2010). Given that migraine pain is believed to originate from the meninges, the administration of Botox typically involves injections into the scalp, forehead, bridge of the nose, temples, occipital region, and neck. OnabotulinumtoxinA may also be utilized as a nerve block or trigger point injection. Evidence from several studies suggests that targeting specific nerves—particularly the greater occipital nerve—or relaxing certain muscle groups can be effective in alleviating both acute and long-term pain in patients with chronic headaches.

Off-label use of onabotulinumtoxinA has demonstrated efficacy in the management of various other headache disorders. These include primary headache disorders such as episodic migraine, tension-type headache, new daily persistent headache, cluster headache, and nummular headache, as well as secondary headache disorders including cervicogenic headache, post-traumatic headache, chronic post-craniotomy headache, and low cerebrospinal fluid (CSF) pressure headache. In these contexts, Botox has been associated with reductions in headache frequency, muscle spasms, and muscle stiffness (Talbet & Elnahry, 2022).

Given its therapeutic benefits, the administration of Botox—along with other interventional techniques such as nerve blocks and trigger point injections—has become a practical option in clinical settings since it can be done in a physician's office and does not require general anesthesia or sedation (*Botox Injections: Side Effects and Tips for Managing Them*, 2022; Kuruvilla & Robbins, 2017; Sim, 2011). Providers generally inject into the nerves perceived to be most affected at that time to determine which injection site produces therapeutic benefit (admin, 2021). Common side effects of injections include localized pain, redness, swelling, numbness, bruising, bleeding, and infection. Repeated steroid injection may also cause

localized hair loss at the injection site. Less common side effects of these injections may include dizziness, vertigo, and lightheadedness (*Botox Injections: Side Effects and Tips for Managing Them*, 2022; Kuruvilla & Robbins, 2017; Levin, 2010; Sim, 2011). Uncommon side effects of Botox injections may include headaches, facial asymmetry, eyelid drooping, and temporary dysphagia. In rare cases, Botox can cause allergic reactions, muscle weakness, double vision, or difficulty speaking. (*Botox Injections: Side Effects and Tips for Managing Them*, 2022; Sim, 2011).

Nerve Decompression and Neurolysis

Due to the transient nature of injectable treatments and the need for repeated administration, some patients may be more suitable candidates for a single surgical procedure offering longer-term results. For these patients, surgical intervention may provide a more long-lasting and effective alternative. Nerve decompression surgery is typically performed on an outpatient basis under local anesthesia, with the patient awake. The procedure involves the surgical release of compressed peripheral nerves that may contribute to primary headache disorders, especially migraine headaches. In certain cases, achieving adequate decompression may require the disruption or removal of surrounding elements such as muscle tissue, scar tissue, bone, or blood vessels. Neurolysis, on the other hand, is a procedure intended to interrupt transmission of pain by deliberately damaging or disrupting nerve tissue, often through the injection of a chemical agent that coagulates the nerve. Although the two techniques are frequently used in combination, neurolysis is generally considered a less invasive alternative to nerve decompression (Bajaj & Munakomi, 2020; Rosa, 2022).

During nerve decompression surgery, various anatomical headache trigger sites may be targeted to improve clinical outcomes. These trigger sites—commonly located in the frontal,

temporal, occipital, and peripheral regions—are areas where nerve irritation or entrapment can initiate or exacerbate headache symptoms. Specific nerves associated with each trigger site are identified and located using various approaches. For the frontal trigger site, the supraorbital and supratrochlear nerves are accessed via an endoscopic or transpalpebral technique. The auriculotemporal nerve, responsible for the temporal trigger site, is typically located using a hand-held Doppler device. Access to the greater and lesser occipital nerves at the occipital trigger site is achieved through blunt dissection of nearby muscle structures, including the occipitalis, trapezius, semispinalis, splenius, and sternocleidomastoid muscles. Peripheral trigger sites, involving the zygomaticotemporal and auriculotemporal nerves, are usually approached using endoscopic or Doppler-guided methods, although alternative surgical techniques may also be employed depending on the case (Bajaj & Munakomi, 2020; Rosa, 2022).

Once the target nerves and related anatomical structures have been located, a small incision—generally between 2 to 6 centimeters, depending on the site—is made to expose the nerves, muscles, and neuromuscular components involved. Blood vessels in close proximity to the nerve are coagulated as needed, after which nerve decompression and/or neurolysis are performed. The procedure concludes with suturing of the incision (Bajaj & Munakomi, 2020; Rosa, 2022). Following closure of the surgical site, postoperative outcomes were generally favorable. Resulting complications, including numbness, paresthesia and itching of the operation site, were minor, short-lived, and lasted between one and several months. Additionally, patients were informed that deactivating a migraine headache trigger site may trigger secondary sites in about 60% of patients, potentially leading to additional surgeries. Overall, the specific techniques applied to the trigger site(s) during the surgery produced significant benefits and minimal complications (Rosa, 2022).

Treatment-specific Patient Outcomes

Based on a study that included 375 eligible patients, 131 patients receiving dual intervention (onabotulinumtoxinA injections and peripheral nerve blocks) were compared to 131 patients treated with onabotulinumtoxinA injections alone, and 104 patients receiving dual intervention were compared to 104 patients treated only with peripheral nerve blocks. Analysis of the study results concluded that 11.5% of patients (12 out of 104) from the dual intervention group and 29.8% of patients (31/104) from the peripheral nerve block group, respectively, were diagnosed with neuralgia (Anderson et al., 2024). This demonstrates a significant correlation between diagnosis of neuralgia and patients that received peripheral nerve blocks, especially given that patients in the peripheral nerve block group were 30% more likely to be diagnosed with neuralgia. While all patients received between 1 milliliter and 18 milliliters of anesthetics, the dual intervention group received an average of 7.8 milliliters of anesthetics, whereas the peripheral nerve block group received an average of 6.6 milliliters of anesthetics (Anderson et al., 2024). Significant findings show that there is a 1.5% chance that the difference in the dosage of anesthetics needed is due to random, unexplained factors, and that for each additional milliliter of anesthetics administered, it is 10% more likely that a patient is receiving dual intervention than peripheral nerve blocks alone (Anderson et al., 2024).

In a separate clinical trial consisting of patients who underwent nerve decompression surgery of the greater occipital nerve, overall improvement was reported by 18 out of 20 patients (Eskilsson et al., 2021). Additionally, 4/7 migraine patients reported a decrease in headaches and 2/7 migraine patients reported no headaches and were symptom-free. In patients who were also affected by other symptoms, 12/22 patients reported reduced neck pain, 10/20 patients reported increased neck mobility, 5/15 patients reported reduced dizziness or perceived instability, and

9/17 patients reported improvement in their ability to read text (Eskilsson et al., 2021). The surgical procedure was associated with improved engagement in social activities in 11/22 patients, improved mood in 14/22 patients, and increased physical ability in 11/22 patients. Moreover, 8/21 patients decreased their intake of analgesics, patient work capacity increased by 18% from 36% to 54%, and the amount of sick leave taken by patients of working age reduced in frequency by 19% from 64% to 45% (Eskilsson et al., 2021). Another study that collected data from 1071 patients who received primary trigger point deactivation surgery evaluated a failure rate of approximately 12% as a main result of incompletely deactivating primary trigger points (Saffari et al., 2024). A notable limitation from the study includes the possibility of secondary trigger points emerging after addressing primary trigger points occurring in 17.8% of patients (Saffari et al., 2024).

Although nerve decompression surgery has not yet become a standard treatment method for primary headache disorders compared to traditional medication use, additional factors further prevent patients considering this more invasive intervention from undergoing the surgery. With the availability of nerve decompression surgery and even injection therapy being limited as a result of geographic accessibility to these medical interventions, variance in criteria used to determine patient eligibility for surgery, continuous increase in the cost of treatments until surgery, lack of specialists (particularly surgeons), and lack of familiarity with headache surgery among providers who treat headache disorder patients (neurologists and primary care providers), the condition of headache patients only worsens as healthcare costs for interventions with the ability to resolve this issue keep rising. According to a study evaluating the delay in surgical management of headache disorder patients, patients experience headache disorder symptoms for an average of 20 years prior to undergoing surgery, with this duration for patients from the study

ranging between 8.2 and 32 years (Merel H.J. Hazewinkel et al., 2023). Over the 20-year period, the mean cost of surgery was $989,275.65, but ranged from $618,677.31 to $1,331,073.99, despite the mean cost of the surgery itself being $11,000 at the time. A remarkable finding of the study highlights that delayed treatment for nerve decompression surgery decreased the days per month pain is experienced by 0-25 days (median of 16 days), reduced pain intensity by 2-7 (median of 4) on the visual analog scale (VAS), decreased pain duration by 0-22 hours (median of 11 hours) (Merel H.J. Hazewinkel et al., 2023). Given that nerve decompression surgery is a less common intervention, the limited availability of post-procedure patient data may further prolong delays in surgical treatment.

Discussion

While studies on injections and nerve decompression and neurolysis have been conducted to evaluate the individual efficacy of these treatment methods, determining which treatment is the best option for a patient is ultimately the choice of the individual receiving the treatment when weighing the benefits and detriments of the treatments in relation to their personal situation. This review of nerve decompression and neurolysis versus injection-based treatment modalities focuses on primary headache disorders, as both treatment options directly target headache trigger sites when they are the underlying cause or sources of pain. Given the overlap among various primary headache disorders in clinical presentation, with common ones including tension headache, migraine, cluster headache, and exertional cephalalgia, accurate diagnosis is critical to selecting an appropriate therapeutic approach. Although current guidelines describe headache disorders according to the specific type of pain, symptoms, and duration of the headache, perhaps also classifying headache disorders by outlining specific indicators found in a patient's medical

history would provide an even more clear and comprehensive set of guidelines in addition to analyzing results from neuroimaging and other screening tests and assessing patient symptoms.

To effectively implement these refinements in the classification and diagnostic criteria for headache disorders, it is essential to remain consistently informed of current research and relevant literature. Continuous and comprehensive review of the existing literature is imperative to advancing our understanding of headache disorders. Evaluation of cumulative headache research enhances diagnostic accuracy, facilitates the development of individualized treatment plans, and ultimately improves patient outcomes. Moreover, it contributes to the creation of innovative therapeutic approaches, leads to advancements in treatment, and critically challenges conventional methodologies to promote the integration of more effective, evidence-based interventions. Nevertheless, in spite of these advancements, the scope of current research predominantly focuses on migraines as opposed to addressing all headache types, limiting our understanding of headache disorders, impeding accurate diagnosis, and preventing thorough assessment of all potential treatment modalities for patients.

Upon comparing injection therapy to nerve decompression and neurolysis techniques, injections appear to be favored for their minimal invasiveness and minor side effects including localized pain, redness, swelling, numbness, bruising, bleeding, and infection (*Botox Injections: Side Effects and Tips for Managing Them*, 2022; Kuruvilla & Robbins, 2017; Levin, 2010; Sim, 2011). The three injection types analyzed (nerve blocks, trigger point injections, and Botox) require repetitive administration to maintain their effects (Bajaj & Munakomi, 2020; Rosa, 2022). However, injection therapy offers more versatility with treatment than nerve decompression surgery since patients can choose to receive a single or dual injection intervention. Due to the 1.5% chance that a variety of factors may influence a change in the dosage of anesthetics a patient

receives, a patient may also request for their anesthetic dosage to be increased if needed (Anderson et al., 2024).

Given the correlation between various diagnoses related to headache disorders and the amount of patients that receive single or dual intervention with injection therapy, patients can decide which intervention may produce better results for them based on their past diagnoses. This is likely to substantially impact the efficacy of injection-based treatments among individual patients. In support of this claim, the same study found that 29.8% of patients (31/104) from the peripheral nerve block group were diagnosed with neuralgia, making them 30% more likely to be diagnosed with neuralgia than the dual intervention (onabotulinumtoxinA injections and peripheral nerve blocks) group (Anderson et al., 2024). In the event that the patient cannot tolerate the effects of the injection or experiences an adverse reaction in response to a particular injection, the dose of the anesthetic can be decreased or discontinued.

On the other hand, nerve decompression and neurolysis are less conservative treatments due to their invasive surgical methodology and increased potential to cause serious adverse effects, but they are often considered by patients seeking a long-lasting alternative to injection therapy because of their permanent effects (Bajaj & Munakomi, 2020; Rosa, 2022). It is usually a one-time surgery, but a second surgery may be performed if necessary and safe to do. In a study consisting of 1071 patients who received primary trigger point deactivation surgery, the possibility of a second surgery was suggested since incomplete deactivation of the primary trigger points occurred in 12% of patients, and secondary trigger points emerged in 17.8% of patients post-surgery (Saffari et al., 2024). However, in another study that performed nerve decompression surgery of the greater occipital nerve on patients whose headaches had caused them to experience other symptoms such as neck pain, dizziness, or decreased physical activity, or even resulted in

missing work or unemployment, multiple patients reported significant improvement and reduced symptoms (Eskilsson et al., 2021).

Although nerve decompression surgery has been studied using a statistically significant sample size—considering it is a less common intervention—fewer clinical trials have been conducted as compared to injection therapy research. As a result, there is less post-procedure patient data available for nerve decompression and neurolysis. For patients concerned about the potential risks of surgery, it is important to recognize that, like any invasive procedure, it carries the possibility of causing irreversible damage. In such cases, an alternative treatment approach may involve starting with injection therapy before deciding whether to pursue surgery. It is also important to recognize that the efficacy of injection therapy may vary depending on the specific primary headache disorder being treated and the anatomical sites targeted. Furthermore, nerve decompression surgery, with or without neurolysis, can be technically challenging when involving certain peripheral nerves. Although studies have demonstrated that both injection therapy and nerve decompression with neurolysis can yield significant outcomes when assessed independently, determining the most appropriate treatment is ultimately up to the patient, who must carefully evaluate the potential benefits and risks of each option in light of their individual circumstances.

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The Effects of Ultraviolet Radiation on the DNA of Aquatic Species

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Introduction

Over the course of the past 25 years, aquatic species have been more challenged than ever to survive in their environments due to the worsening of Ultra Violet (UV) radiation. As the O-zone layer (a layer of protection, preventing high amounts of UV radiation from reaching the surface of the earth) slowly depletes, with the ongoing presence of global warming, more plants and species than ever are impacted by this extreme environmental change. This extreme change in aquatic species' lives has severely impacted the composition of their DNA, which in turn affects the way species are able to thrive in the sea. To combat the genetic damage, aquatic organisms have adopted molecular defense mechanisms and DNA repair systems. This paper will analyze the ways in which these cellular defenses and repair processes function within aquatic organisms to oppose the threat of increased UV radiation exposure.

Types of UV Radiation

To understand the molecular defenses and repair of DNA, it is essential to differentiate the types of UV radiation and consider the ways in which they impact aquatic species. UV radiation can have negative effects, and it has been found that although all UV radiations can have a negative impact on marine species, the different types of UVR has the ability to affect organisms at different rates, depending upon the molecular and genetic make up of that organism (Dahms & Lee, 2010). There are three types of UV radiation: UV A, UV B, and UV C. The A, B,

and C found within the title of each subclass of UV radiation indicates its severity. UV C is the most powerful type of radiation, as it has shorter wavelengths, making it more harmful to an organism (Nishigori, Yamano, Niskiaki-Sawada, et al., 2023). Compared to this, UV B has a slightly larger wavelength, measuring about 280-320 nm, and UV A has the largest wavelength, which measures around 320-400 nm (Williamson, C.E., Neale, et al., 2001). Evidently, it has been shown that UV radiation variants with smaller waves have a more harmful effect on ecosystems compared to those with larger waves, which are deemed to be less damaging to organisms.

Molecular Defenses Used to Prevent UV Induced DNA Damage

Prior studies have suggested that marine organisms have a molecular resilience to them, permitting them to combat DNA damage. Although there are several types of molecular defense mechanisms, this paper will focus exclusively on the quenching of reactive oxygen species (ROS), mycosporine-like amino acids (MAA), and oxidative stress markers.

Radical Scavengers

ROS are chemically reactive molecules with a negative charge. They are natural byproducts of cellular metabolism, especially during aerobic respiration in mitochondria. These ROS molecules are damaging, as they could negatively impact an organism's DNA, lipids, and proteins (Zorov, D.B., Juhaszova, et al., 2014). This ultimately leads to dysfunction in the cells found within the organism.

Aquatic organisms normally produce ROS at low levels, but their production can significantly increase under stressful conditions such as UV exposure, pollution, or infection. In fact, aquatic organisms have a mechanism that prevents excessive amounts of ROS from reaching an aquatic organism’s body through its gills (Dahms & Lee, 2010). Aquatic species’ cells contain free radical scavengers, which aid in the organism’s ability to counteract the effects of ROS.

Radical scavengers such as vitamin A, copper, zinc, and superoxide dismutase reduce the presence of ROS by neutralizing the negatively-charged ROS molecules.

Mycosporine-like amino acids (MAA)

MAAs are secondary metabolites made primarily by photosynthetic organisms like cyanobacteria, algae, fungi, lichens, and some marine animals. MAA's function as antioxidants to combat oxidative stress markers like ROS resulting from UV exposure. They do this by absorbing UV radiation and converting it into a harmless heat. This ultimately protects cells from UV induced damage.

Oxidative Stress Marker

An oxidative stress marker is a biochemical indicator, a molecule, or measurable change that reflects the presence and intensity of oxidative stress in an organism. Some studies have found that these markers are elevated in the kidneys and livers of fish inhabiting environments of high UV radiation (Hader & Sinha, 2005).

Similar to MAAs, these markers indicate to an organism's nervous system when an increased level of oxidative stress is present. These signals communicate with the brain to activate the organism's molecular defense mechanisms against harm from UV radiation exposure. This will allow the brain to get the organism's body ready to fight off the UV radiation exposure (which triggers the signal) by either creating ROS or MAA's.

Synthesis of Molecular Defenses

Along with this, MAAs are compounds found within the cells of marine organisms that absorb UV radiation by turning it into heat, preventing harmful ROS from being created within the aquatic organism's body. Lastly, oxidative stress is typically induced by pollutants, which are very similar those seen in the ever-evolving environment of aquatic organisms (Valavanidis).

These markers are so positive because they monitor the status of various types of antioxidant defense mechanisms that protect against free radicals (Dellinger & Khachatryan, 2011).

The quenching of ROS, the presence of MAAs, and having oxidative stress markers allows organisms to molecularly combat some of the inflictions UV radiation imposes on organisms. In order to eliminate the presence of ROS, which form severe threats upon organisms, the organism's body has a mechanism that decreases the diffusion of exogenous ROS through the gills and permits excretion of internal hydrogen peroxide through the gills to the surrounding environment (Dahms & Lee, 2010). UV radiation has been found to create these harmful ROS within organisms, so by having a molecular mechanism that extinguishes them, organisms are able to experience less harm when facing UV radiation. Along with this, the molecular defense mechanism of withholding mycosporine-like amino acids is very helpful to marine life, as these acids are UV-absorbing compounds found within countless aquatic organisms that help transfer UV radiation into a harmful heat. By having these amino acids present within marine species, organisms are able to lighten the effects of UV radiation severely, by transforming the harmful waves into a less harmful heat. Lastly, oxidative stress markers have become a very important aspect of marine organisms, indicating to them when their bodies are out of balance.

Types of DNA Damage Caused by UV Radiation Exposure

When marine species are introduced and exposed to UV radiation, their DNA ultimately gets affected by it. The DNA damage is caused by the combination of UVR and PAR, which increases the production of toxic ROS and the flow of hydroxyl radicals that create a disruption to the cell, causing cellular damage (Svanfeldt, Lundqvist, Rabinowitz, et al., 2013). Henceforth, UV radiation is harmful because it creates reactive oxygen species, which can destroy organisms functioning systems, needed within them in order for survival. Some of the more specific damage

found within organisms exposed to UV radiation with an increased amount of reactive oxygen species are the fragmentation of DNA and the creation of pyrimidine dimers (Rastogi, Richa, Kumar, et al. 2010).

Both the fragmentation of DNA and the creation of pyrimidine dimers are products of ample amounts of UV radiation exposure within an ecosystem. DNA fragmentation is the process in which there is “extensive damage” found “to chromatin and DNA cleavage” within any organism exposed to UV radiation (Lesser, Kruse, & Barry, 2003). Essentially, DNA fragmentation could cause ample amounts of mutations within an organism, as DNA is being left as incomplete.

Along with this, the creation of pyrimidine dimers within organisms is also a significant product of UV exposure. The creation of these dimers occurs once UV-photoproducts makes DNA bases bond together, which ultimately creates the damaging pyrimidine dimers. The creation of pyrimidine dimers disrupts the normal base pairings of thymine and cytosine building blocks, ruining the patterns of the DNA while also disrupting the DNA replication process. The formation of pyrimidine dimers is very similar to DNA fragmentation, in the sense that when present, both processes hold very poor impacts on organisms. DNA is the building block of all organisms, hence when it's disrupted even in the slightest manner, immense amounts of problems can arise.

Taken together, the evidence presented in this paper shows how the effects the DNA undergoes leads to significant cellular damage. The combination of UV radiation and photosynthetically active radiation results in the product of ROS. These reactive molecules are harmful because they can overwhelm the cellular defense systems, causing oxidative stress that compromises vital cellular functions. One of the most serious consequences of this oxidative

damage is DNA fragmentation, where DNA strands are severely cleaved, resulting in extensive damage to the chromatin and genetic material of the organism. This fragmentation can lead to mutations and the loss of important genetic information needed for survival. DNA fragmentation has a serious implication for cellular integrity, as even small disruptions in the DNA structure can trigger widespread problems within the organism. Since DNA is the fundamental blueprint for all biological functions, any damage to it can result in profound consequences for an organism's survival and overall health, showing that UV radiation is a significant environmental threat to aquatic species.

DNA Repair Mechanisms

To counteract the UV damage imposed on an organism's DNA, marine organisms have evolved a suite of DNA repair mechanisms, including base excision repair (BER), nucleotide excision repair (NER), and recombination.

Base Excision Repair (BER)

The BER pathway plays a crucial role in protecting marine species from the damaging effects of UV radiation, specifically by repairing small DNA lesions that can arise from oxidative stress and UV-induced damage (Kuper, J., Kisker, & et al. 2013). When UV radiation leads to the formation of ROS, these highly reactive molecules can modify DNA bases often leading to oxidative damage. The BER pathway is responsible for identifying and repairing such damage by recognizing altered bases.

The BER process is very significant to aquatic organisms who are battling increased UV radiation exposure. When UV radiation is combined with increased photosynthetically active radiation, the oxidative stress can overwhelm the DNA repair mechanisms, including BER, resulting in genomic instability. Failed repair through BER can allow mutations to accumulate,

leading to defects in key genetic functions necessary for survival. Over time, the failure of BER to fix even minor base alterations could lead to cellular dysfunction, further endangering the survival of species in UV-exposed environments. Therefore, the efficiency and capacity of the BER system in aquatic organisms are critical for maintaining genetic integrity and ensuring the long-term viability of populations exposed to increasing UV radiation (Kuper, J., Kisker, & et al. 2013).

Nucleotide Excision Repair (NER)

NER is a critical DNA repair pathway that specializes in removing bulky, helix-distorting lesions, such as cyclobutane pyrimidine dimers (CPDs), which are commonly caused by UV radiation (Kisker). CPDs form when two adjacent pyrimidine bases (usually thymine or cytosine) become bonded as a result of UV exposure, creating a distortion in the DNA helix (Kuper, J., Kisker, & et al. 2013). The distortion interferes with the normal structure of the DNA, obstructing processes like replication. This structural disruption is extremely severe, meaning that CPDs are harmful to the cell if left unrepaired//untreated. They are so harmful, as they can ultimately lead to errors in DNA replication, mutations, and apoptosis. The NER pathway is designed to recognize and remove these types of bulky lesions to preserve the health of genomes.

This efficient repair mechanism ensures that DNA can be restored to its normal, functional state. However, in environments with elevated UV exposure, such as in aquatic ecosystems experiencing increasing UV radiation, the ability of NER to repair CPDs becomes complicated. If the NER process is overwhelmed by the amount of damage, the accumulation of CPDs can lead to mutations, genomic instability, and increased risk of cancer or cellular apoptosis (Kuper, J., Kisker, & et al. 2013). That being said, NER plays a vital role in maintaining the

health of organisms exposed to UV radiation, ensuring that genetic material remains intact for proper cellular function and survival.

Recombination

Recombination is a vital DNA repair mechanism that plays a central role in maintaining healthy, genomic stability by fixing double-strand breaks (DSBs). Recombination focuses on fixing the more complex DNA damage that NER and BER are unable to repair (Kowalczykowski 2000). Double-strand breaks are one of the most dangerous types of DNA damage, as they involve the breaking of both strands of the DNA helix. This leads to the complete disruption of the DNA molecule. If left unrepaired, DSBs can result in chromosomal rearrangements, mutations, or cell death, all of which have serious consequences for cellular function and organismal health (Kowalczykowski, 2000). Since DSBs cannot be easily fixed by removing damaged bases or bulky lesions, the cell relies on recombination to restore the health of the DNA.

There are two main forms of recombination that are used to repair DSBs: homologous recombination (HR) and non-homologous end joining (NHEJ) (Grindley, Whiteson, & Rice, 2006). Homologous recombination is the more accurate of the two, as it uses a sister chromatid (an identical copy of the chromosome) as a template to repair the break, ensuring that the genetic sequence is restored without introducing errors. On the other hand, non-homologous end joining (NHEJ) is a quicker but more error-prone mechanism that directly joins the broken ends of the DNA together, often with the insertion or deletion of a few nucleotides (Grindley, Whiteson, & Rice, 2006). Without recombination, cells would be at a greater risk of undergoing mutations or apoptosis. Therefore, recombination serves as a crucial backup system that helps maintain the integrity of the genome when other repair mechanisms are not sufficient.

Apoptosis

If none of the previously mentioned processes occur within the cell, it will undergo apoptosis. Apoptosis is a form of "programmed" cell death, meaning that cell death is regulated within the organism's body. Despite there being regulation present when apoptosis typically occurs, this is not always the case. A cause of apoptosis is UV radiation exposure. As UV radiation levels are dramatically increasing and being forced upon aquatic species, apoptosis is occurring more frequently (Fiandalo & Kyprianou, 2013). When the rate of apoptosis increases, there is no longer assurance of knowing that these dead cells will regenerate in a manner suitable for the organism's body.

Apoptosis is a very important mechanism within all organisms body's, except for when the process is occurring too frequently. By killing off more cells than the body can generate, organisms can undergo tissue damage, compromised organ function, and ultimately, the breakdown of physiological processes within an organism (Fiandalo & Kyprianou, 2013). In the case of aquatic species, increased apoptosis due to elevated UV radiation may result in the loss of crucial cells in the skin, immune system, or other tissues, which can impair their ability to regenerate and adapt to environmental stressors. Moreover, as these cells die off, their removal could hinder essential biological functions. This continuous cycle of excessive cell death and insufficient regeneration can lead to long-term health declines. This will ultimately impact the stability of various populations and exosystems.

Therefore, while apoptosis serves as an important safeguard against damaged or mutated cells, its mismanagement—especially in response to increasing UV exposure—poses a significant threat to the survival of these species and the balance of their ecosystems.

Significance of DNA Repair Mechanisms

The presence of DNA repair mechanisms is crucial in preventing apoptosis because UVR can cause significant damage to the cell's DNA. If this damage is left unaddressed, it can lead to cellular malfunction or worse, apoptosis.

Conclusion

By analyzing the impact of UV radiation on aquatic species, it has become clear that the ongoing depletion of the ozone layer, caused by global warming, must end. As the ozone layer gets smaller and smaller, the less protection there is from the earth's surface and the sun. This in turn means that more UV radiation from the sun is able to seep onto the earth's surface. Countless organisms have poor responses to UV radiation, especially when introduced in larger amounts. As shown throughout this paper, UV radiation has a very poor impact on life, as DNA can be altered when exposed. Therefore, maintaining the ozone layer to reduce UV radiation exposure is essential for supporting aquatic life survival, especially as the environment continues to deteriorate.

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Adapting self-attention algorithms to chemogenomic spaces to predict antimicrobial resistance and accelerate antibiotic discovery

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Abstract

Antimicrobial resistance (AMR) is a critical global health threat, directly responsible for an estimated 1.27 million deaths and in- directly linked to another 4.95 million in 2019, according to the World Health Organization. By 2050, AMR could claim 10 million lives annually and cause $3.4 trillion in yearly GDP losses. Traditional antimicrobial drug discovery remains time-consuming and costly, relying on extensive in vitro testing. Recently, machine learning has emerged as a powerful alternative, with two distinct approaches: one relies on bacterial DNA to calculate resistance scores; the other focuses on the chemical structures of compounds. Both require new assay testing for novel antibiotics or pathogens. This work proposes a method that combines bacterial DNA sequences with antimicrobial chemical structures to predict activity with- out additional in vitro tests. Using a self-attention-based transformer algorithm, the model identifies key patterns in both DNA and chemicals. Trained on E. coli data, it can predict the activity of new antibiotics against unfamiliar pathogens, pinpoint AMR-related gene locations, and assist drug discovery.

Keywords: antimicrobial resistance · transformers · drug discovery

Introduction

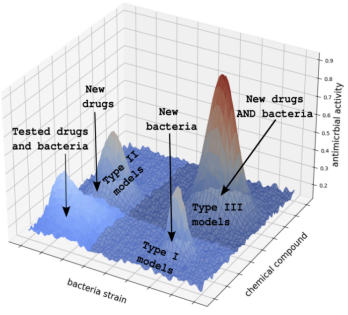
This project addresses the problem of antimicrobial resistance (AMR) [1]. A traditional approach to AMR prediction involves antimicrobial susceptibility testing (AST), which is accurate but time-consuming and costly. Recently, several computational methods have been proposed to reduce the need for laboratory testing. These methods can be grouped into two categories. The first group ("Type I") [2, 5] uses a fixed antibiotic compound and treats the pathogen genome as a vari- able. After ASTs are performed on pathogens with a given

compound, machine learning is applied to predict AMR for similar pathogens. The second group ("Type II") [3,4] uses a fixed pathogen and tests it against multiple chemical compounds. After ASTs, a machine learning model is trained to predict AMR for structurally similar chemicals against the same pathogen. Both approaches support knowledge transfer from experimental data to unseen data, but each has limitations: Type I generalizes to new pathogens but not new compounds, while Type II generalizes to new compounds but not new pathogens.

In this work, we propose a combined approach—"Type III"—which enables prediction for both new chemicals and new pathogens, covering a cross-domain input space (Fig. 1). Simply combining encoders used in Type I and II meth- ods is insufficient: such a model cannot effectively capture interactions between DNA segments and chemical substructures. Modern language models based on self-attention (transformers) [8] excel at identifying dependencies in textual data. While DNA and chemical structures are not natural languages, applying transformer-based models to their combined representations is a promising di- rection. In the following sections, we describe how transformers can be adapted to build a Type III AMR prediction system and present results from a working prototype.

Method	Bacterial DNA	Antimicrobial compound chemical structure	In vitro assay and model retraining
Type I	Used as a training/prediction variable	Not used	Required each time a new antibiotic candidate emerges
Type II	Not used	Used as a training/prediction variable	Required each time a new pathogen emerges
Type III (our proposal)	Used as a training/prediction variable	Used as a training/prediction variable	Required to build the model, not required for new pathogen/new compound

(a) Types of algorithms



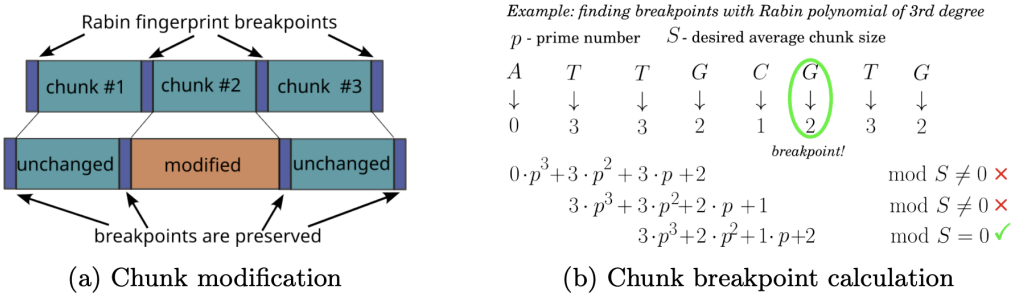
(b) Solution space coverage

Fig. 1: AMR prediction methods comparison

System design

To apply a transformer to both DNA and chemical structures, each must be represented as a sequence of "words." For chemicals, the SMILES representation is a natural choice, with each symbol's encoding learned during training. DNA is more challenging. A full genomic sequence consists of millions of nucleotides from only four base types, which provide limited information individually. Genes would be better "words," but are not always annotated. As a compromise, we split the genomic sequence into chunks, hoping some capture meaningful traits. However, fixed-size chunks are fragile: a single deletion or insertion can shift all boundaries, resulting in dissimilar representations for similar sequences.

To address this, we use a technique from document search—splitting char- acter sequences into pseudo-random chunks using Rabin fingerprints [6]. This method tolerates insertions and deletions by creating more stable chunk bound- aries. For example, if we split a 100-character string into fixed-size chunks of 10 characters, we get 10 segments. Inserting a character at the beginning shifts all chunks, replacing all 10. In contrast, Rabin-based chunking would still pro- duce about 10 chunks on average, but most would remain unchanged, preserving similarity. Applied to DNA, this produces a more language-like structure, where recurring segments can retain meaning across sequences (Fig. 2). Once tokenized, the input can be processed with self-attention (Fig. 3) to identify patterns and relationships that traditional algorithms may miss.



(a) Chunk modification (b) Chunk breakpoint calculation

Fig. 2: Splitting data with Rabin fingerprints

Testing

We built a simple proof-of-concept neural network to evaluate our approach (Fig. 4). We used public data from [5], comprising 1934 E. coli strains tested against 12 antibiotics: cefotaxime (CTX), ceftazidime (CTZ), ampicillin (AMP), amoxi- cillin (AMX), amoxicillin-clavulanate (AMC), piperacillin-tazobactam (TZP), cefuroxime (CXM), cephalothin (CET), gentamicin (GEN), tobramycin (TBM), trimethoprim (TMP), and ciprofloxacin (CIP). DNA sequences were downloaded from the European Nucleotide Archive, encoded as 4 nucleotides per byte, and split into pseudo-random chunks of approximately 128 bytes.

For each antibiotic, the following procedure was used:

1. Exclude all ASTs involving the selected compound.
2. From the set of pathogens tested with that compound, exclude 5%. 3. Train the model on the remaining data for 50 epochs.
3. Test the model on the excluded pathogen-compound pairs.
4. Repeat steps 2–4 using 20-fold cross-validation.

For comparison, we also evaluated Random Forest and Support Vector Ma- chine models (Fig. 5). Despite limited training data, our transformer-based model demonstrated successful knowledge transfer and outperformed the baselines.

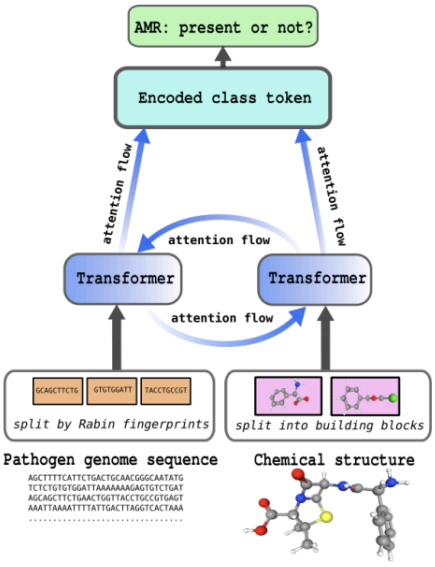


Fig. 3: Basic concept

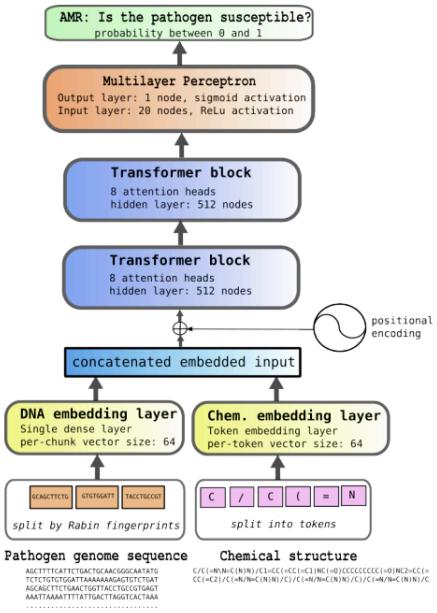


Fig. 4: Implementation details

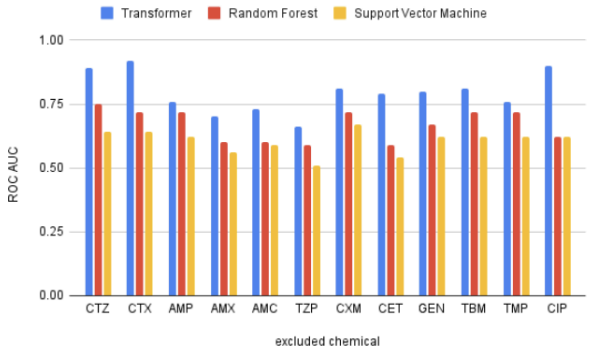


Fig. 5: AMR prediction accuracy for 12 chemicals

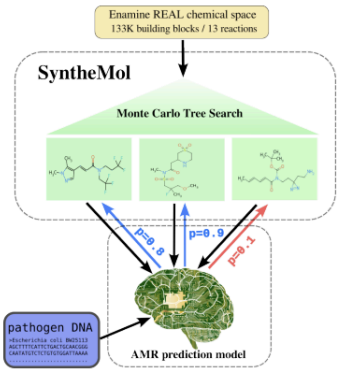


Fig. 6: Integration with SyntheMol

Applications

We envision three applications of our approach: drug repurposing, novel drug discovery, and AMR gene exploration. To evaluate these, we retrained the model on the full dataset.

For drug repurposing, we used a balanced set of AST results for the BW25113 strain of E. coli [4], which was not part of the training data. We selected com- pounds with Tversky similarity >0.5 to the training set (due to its limited size), resulting in 26 test cases where both the pathogen and compounds were unseen. The model correctly predicted 21 responses (80%), a promising result for a proof-of-concept.

For drug discovery, we combined our model with SyntheMol [7], a generative AI tool (Fig. 6). It generated several thousand drug candidates predicted to be active against BW25113. Without synthesis capabilities, we approximated vali- dation by comparing to known antibiotics. From 6000 compounds tested against BW25113 [4], we identified 18 with Tversky similarity >0.8 to any generated candidate. All 18 were effective, supporting the model's predictive validity.

An additional benefit of self-attention models is the availability of attention maps, which highlight important input regions. In genomic data, these may correspond to AMR-related genes. We extracted the top 100 positions with the highest attention scores and found that at least 11 overlapped with known AMR- associated gene locations. While this requires further investigation, it indicates that the attention maps can assist in the discovery of other AMR-related genes.

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