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Aggressive Behaviour and Autism Spectrum Disorder – Focusing on the Genetic Landscape

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Abstract: *Aggressive behaviour is a complex behavioural phenotype influenced by the dynamic interaction of genetic, environmental, and epigenetic factors. Genetic studies identified key genes, including SHANK3, MAOA, SLC6A4, and genes encoding oxytocin and arginine-vasopressin receptors, involved in neurotransmitter systems processes. Variations in these genes can lead to behavioural disturbances. Environmental factors influence the complexity of gene–environment interactions in the regulation of aggressive behaviour. The epigenetic research has revealed diverse factors and mechanisms that can alter gene expression patterns associated with aggressive behaviour. The zebrafish (Danio rerio) is increasingly being used as a model organism for studying these mechanisms, due to their high genetic homology with humans and suitability for complex behavioural assays. The aim of this narrative review is to integrate, synthesise and enhance the understanding of the interplay between genetic, epigenetic, and environmental regulation of aggressive behaviour, while highlighting how zebrafish models offer valuable insights into the molecular and neural basis of aggression, with potential translational relevance to neurobehavioural disorders.*

Keywords : *autism; zebrafish; genetics; epigenetics; valproic acid.*

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1. Introduction

Apart from the universal behaviour exhibited for survival and evolution, aggressive behaviour could commonly be associated with mental disorders, such as autism spectrum disorder (ASD), schizophrenia, and psychopathy (Cho et al., 2019; Moise et al., 2025). The basic survival instinct could be naturally driven by competitive behaviour for food, territory, and mating. In this way, aggressive behaviour can be innate, proactive, or reactive, proposing survival instincts (Fritz et al., 2023).

However, in some cases, the impaired interaction between individual and environmental stimuli could lead to altered responses that often include aggressive behaviour. In ASD, pathological aggressive behaviour could be seen in both adult and infant patients and could be directed at others or self. Self-injurious behaviour (SIB) episodes, commonly identified in children with ASD, consist of persistent self-injurious behaviour in response to numerous external factors (Genovese &Butler, 2023). The aggressive behaviour is observed in approximately 28% of children with ASD, and its intensity tends to decrease with age. Furthermore, 17% to 56.5% of adolescents diagnosed with ASD exhibit a tendency towards physically aggressive behaviour and increased social anxiety (Baweja et al., 2023). In adults, the lack of aggressive behaviour management could affect the quality of life and lead to alienation, unemployment, property destruction, and increased criminality (Im et al., 2021; Gohari et al., 2024). Sensory overload, high susceptibility to repetitive behaviours, and low resilience to changes in routine mainly contribute to the occurrence of aggressive behaviour in ASD patients (van den Boogert et al., 2021; Martin et al., 2024). Other stimuli including social interaction and psychological discomfort could also contribute to reactive aggressivity (Moise et al., 2025). Moreover, Baweja et al. (2023) observed a significant correlation between misconduct and irritability in adolescents with ASD often developing aggressive behaviour (Baweja et al., 2023).

The aim of the present narrative review is to integrate and synthesise current evidence regarding the genetic, epigenetic, neurobiological, and environmental mechanisms underlying aggression in ASD. In addition, the manuscript aims to highlight the relevance of zebrafish models in studying the molecular and behavioural correlates of aggression in ASD and to integrate the available evidence to better explain how molecular alterations may contribute to aggressive behaviour.

2. Methodology

For the preparation of this narrative review, electronic databases including PubMed and Google Scholar were consulted. The literature search was conducted using combinations of the following keywords: “aggressive behaviour”, “autism spectrum disorder and aggressive behaviour”, “aggressive behaviour genetics”,“aggressive behaviour epigenetics”,“aggressive behaviour neurobiology”, “valproic acid aggressive behaviour”, “aggressive behaviour in zebrafish”, “aggressive behaviour in zebrafish genetics”, “aggressive behaviour in zebrafish epigenetics”.

The review included original research articles, review articles, and systematic meta-analyses published in English and relevant to the genetic, epigenetic, neurobiological, and behavioural mechanisms associated with aggression in autism spectrum disorder in both humans and animal models.

Articles published in languages other than English and articles without full-text content availability were excluded. The literature search was conducted between October and December 2025.

3. Genes Associated to ASD Aggression

Recent studies documented more than 800 genes with clinical relevance in ASD pathology. While the implication of genetic alterations in idiopathic ASD is complex and not fully understood, syndromic ASD has been associated with various genetic defects, such as gene and chromosomes abnormalities, polymorphisms, deletions, and duplications (Butler et al., 2015; Genovese &Butler, 2023; Sauer et al., 2021; Koyama et al., 2024).

Moreover, the ASD-specific behaviour involves an imbalance between excitatory and inhibitory neurotransmission along with dysfunctions and imbalances of several neural pathways including neurotransmitters and neuropeptides such as dopamine, serotonin, noradrenaline, GABA, vasopressin, oxytocin and monoamine along with the influence of environmental factors (Sener et al., 2019; Marotta et al., 2020; Martin et al., 2024). Furthermore, the reactive type of aggression involves neural pathways such as the amygdala, hypothalamus, prefrontal cortex, and septum, while the instrumental aggression includes cortical functions (Martin et al., 2024). Previous studies reported that polymorphisms located on the promoter region of *MAOA* (monoamine oxidase A enzyme activity) lead to low activity of the gene, resulting in increased cerebral cortical volume as well as increased white and grey matter volumes, findings that have been associated with ASD (Davis et al., 2008).

The influence of *MAOA* polymorphism on behaviour was associated with aggressive behaviour, antisocial behaviour and low intelligence quotient (IQ) (Davis et al., 2008). Moreover, similar results regarding the low activity of *MAOA* polymorphisms were associated with impairments of social communication and aggressive behaviour in ASD and fragile X syndrome (Wassink et al., 2014).

The neurixine family member *CNTNAP2* (contactin-associated protein-like 2) is associated with an increased risk of ASD symptomology (Peñagarikano & Geschwind, 2012). The loss of function of *CNTNAP2* was associated with ASD behavioural symptomology, hyperactivity, and epilepsy (Peñagarikano & Geschwind, 2012). The scaffold protein genes *SHANK1*, *SHANK2*, and *SHANK3* are involved in the formation of synapses, glutamate transport, and signal transmission. Abnormalities present at *SHANK3* and *SHANK2* structural levels were associated with intellectual and cognitive disabilities (Sato et al., 2012; Huang et al., 2023).

Meanwhile, the *SHANK3* alterations are involved in cognitive impairment (Sato et al., 2012). Antisocial behaviour such as aggressive behaviour and mild self-injurious behaviour was also linked to *SHANK3* alterations (Huang et al., 2023).

Similarly, the polymorphic variability of several genes regulating oxytocin and arginine-vasopressin neurometabolic processes implicated in social interaction and aggression (Miller et al., 2013) was reported in ASD pathophysiology. Several polymorphic variants of the oxytocin receptor gene (*OXTR - rs237887, rs2268491 and rs225429, rs2254298, rs7632287*) were associated with ASD risk, impaired social interactions, increased amygdala volume, anxiety, and depression (Cataldo et al., 2018).

Moreover, a key correlation between ASD, the arginine-vasopressin system, and aggressive behaviour was reported by several studies describing social recognition deficiencies and premature activation of the amygdala in individuals with increased expression of a polymorphic variant of the arginine-vasopressin receptor 1A gene (*AVPR1a*) (Knafo et al., 2008; Francis et al., 2016; Cataldo et al., 2018).

For instance, Sener et al. (2019) previously documented the correlation between aggressive behaviour and pain sensitivity and reported that the expression of several genes regulating emotional behaviour and response to pain stimuli (i.*e. OPRL1*, an opiate receptor; *TACR1*, a neurokinin receptor; and *HTR1E*, a serotonin receptor) is also correlated with the occurrence of aggressive behaviour (Sener et al., 2019) (Table 1).

Table 1. Genes with clinical relevance in ASD pathology

Gene	Biological functions	Genetic alterations	Relevance in ASD	Reference
MAOA promoter polymorphism	*MAOA* plays a role in neurotransmitter metabolism in the brain and regulates the levels of catecholamines and serotonin.	Low activity of *MAOA* allele in the brain.	Increased aggression; impairments of social cognition.	Davis et al., 2008; Wassink et al., 2014
CNTNAP2	grouping of K+ channels in the juxtaparanode region of Ranvier nodes.	increased expression in brain regions related to ASD, absent expression in peripheral lymphoblasts, and disrupted CNTNAP2 transcript.	Language impairment, cognitive delay, social delay.	Bakkaloglu et al., 2008; Peñagarikano & Geschwind, 2012
SHANK3	encodes a scaffold protein of the postsynaptic density and excitatory synapse in the brain.	significantly down - regulated gene expression and low mRNA level of the *SHANK3* gene.	aggressive behaviour, mild self-injurious behaviour, impaired associative learning, cognitive impairments, intellectual disability.	Bai et al., 2021; Huang et al., 2023
SHANK1, SHANK2	encodes a scaffolding protein located at synapses in the brain.	deletions of *SHANK1*. *SHANK2* was moderately and highly expressed in the human brainstem and spinal cord, respectively neuropil *SHANK2* expression.	cognitive impairment and social anxiety, enhanced anxiety.	Sato et al.,2012; Woelfle et al., 2023
OT/ OXTR (oxytocin receptor); rs7632287, rs237887, rs2268491, and *rs2254298 rs547238576; rs3536969C* in *OXTR.*	*OXTR* activation regulates the timing of the excitatory-to-inhibitory GABA switch.	decreased levels of plasmatic oxytocin, alteration of gene expression of oxytocin and a strong association with ASD pathology.	single nucleotide polymorphisms were associated with aggression and fear responses, lower social skills; especially *rs3536969C* with aggression in children; *rs2254298* with social impairments; *rs547238576* with social withdrawal.	LoParo & Waldman, 2015; Francis et al., 2016; Li et al., 2024
AVPR 1B/1A (arginine-vasopressin receptor)	associated with animal territoriality and "defensive" behaviours, the reactions transporter in the sympathetic nervous system and hypothalamic-pituitary-adrenal axis.	-	Single-nucleotide polymorphisms of *VPR1B* were associated with social communication and restrictive/ social behaviour; restricted repetitive behaviours and childhood aggression.	Francis et al.,2016; Cataldo et al., 2018

3.1. Functional Neurobiological Pathways Associated with Aggression

The dopaminergic and serotonergic systems are involved in multiple processes and have a strong anatomical and physiological connection including motor control, reward, cognitive processing, and in the modulation of aggressive behaviour (Marota et al., 2020; Martin et al., 2024; Speranza et al., 2025). Moreover, genetic profiling studies of aggressive behaviour have shown that

there is a possible connection between dopamine and serotonin function and ASD through their genes and receptors (Martin et al., 2024). Previous studies reported that the polymorphisms located in the dopamine receptor gene DRD4 could influence aggressive behaviour. Several alterations were found in DRD4 mRNA gene expression, revealing high levels of DRD4 in peripheral blood lymphocytes but lower levels of it when the whole blood was analysed (Figure 1) (Gadow et al., 2010; Sener et al., 2019). Furthermore, several signaling molecules, such as dopamine, could also influence aggressive behaviour when their regulatory activity is impaired. Furthermore, commonly aggressive behaviour-associated mutations of the dopamine transporter gene (*SLC6A3*) were reported to alter the reuptake of dopamine from the synaptic cleft, leading to social impairment, anxiety, and stereotypical behaviour (Neumann et al., 2010; Geng et al., 2023; Li et al., 2025). Furthermore, mutations of another member of the same solute transporter family, *SLC6A4*, were previously associated with brain serotonin reuptake dysfunctions and were reported in ASD-like behavioural manifestations, such as repetitive behaviour and comorbid anxiety (Adamsen et al., 2011). Specifically, certain polymorphic variants of SLC6A4 were associated with aggressive behaviour patterns and phenotypes alongside increased cranial volume and neural circuits connecting processes (Schuch et al., 2016; Altiok et al., 2025). It is also well established that the mutation encoded by *SLC6A4*, the *Gly56Ala* variant, is responsible for serotonin reuptake and ASD-specific behaviour such as aggression and insensitivity to pain (Adamsen et al., 2011;Sener et al., 2019) (Figure 1). In addition, the interaction between dopaminergic and serotonergic systems in the prefrontal cortex could regulate aggressive behaviour (Altiok et al., 2025). The impairments of GABA transmission associated with serotonergic imbalance could be associated with social impairment, repetitive behavioural patterns, and other ASD-specific behaviours (Bamicha et al., 2025).

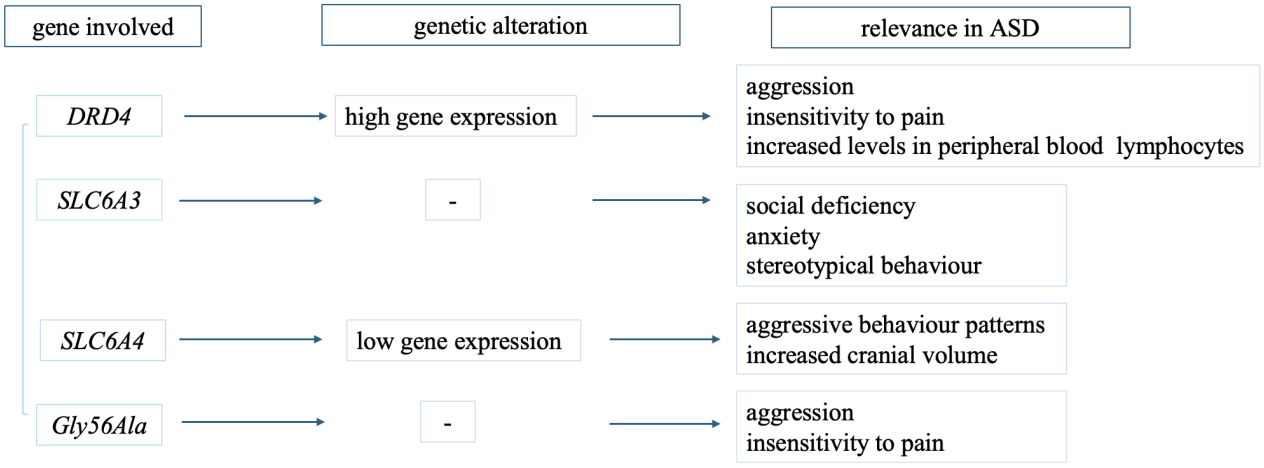

Figure 1. Gene alternations of SLC6A4 (serotonin transporter, modulator of serotonin reuptake from the synaptic cleft), DRD4 (dopamine D4 receptor), Gly56Ala (serotonin transporter) lead to aggression and insensitivity to pain, peripheral blood lymphocytes, macrocephaly, rigid compulsive behaviour

3.2. Genetic and Neurobiological Basis of the 'Fight or Flight' Response

The genetic basis of the 'fight or flight' response involves the disruption of neurotransmitter systems and the genes involved in their regulation (Adamsen et al., 2011). By definition, the 'fight or flight' response is the reaction of survival/adaptation to perceived danger, aiming at restoring homeostasis. It involves activating the central nervous system where the stimulus is processed in the brainstem, followed by activation of the sympatho-adrenomedullary system and the hypothalamic–pituitary–adrenal axis (Adamsen et al., 2011; de Abreu et al., 2021). The hypothalamic–pituitary–adrenal axis could be activated or inhibited. The key brain regions include the amygdala, hippocampus, and the prefrontal cortex de Abreu et al., 2021). The cognitive

processing of stimuli is carried out by the frontal regions (especially the prefrontal cortex). The reactivity of the amygdala is influenced by genes of the serotonergic system: *HTR (1A -3A); TPH2; MAOA; SLC6A4.*

The important dopaminergic system in amygdala reactivity was identified in the dopamine transporter *DAT1, DRD2* (Adamsen et al., 2011). At the same time, the 'fight or flight' response leads to increased cardiovascular activity and respiratory and cutaneous responses. Low heart rate reactivity has been associated with the *S5-HTTLPR* allele of the serotonergic system. The muscle reaction may be exaggerated in mental disorders as it was associated with the activity of the serotonergic system (Sumner et al., 2016) and the dopaminergic system (Adamsen et al., 2011). In the context of ASD, the sympathetic branch of the autonomic nervous system shows dysregulations that lead to behavioural disorders, increased heart rate and anxiety (Panju et al., 2015).

4. Aggressive Behaviour in ASD Zebrafish Models

Zebrafish (*Danio rerio)* are valuable animal models for neurobehavioural research due to their genetic and physiological similarities with mammals (Li et al., 2024). The zebrafish genetic model shows approximately 70% similarity to the human genome, which makes it a valuable study tool for understanding the genetic basis of multiple diseases (Choi et al., 2021).

Furthermore, as the behavioural patterns have been thoroughly described, zebrafish also exhibit complex behavioural responses to aversive stimuli, i.e., aggressive behaviour, when faced with competition for food, territory, and mating hierarchies (Filby et al., 2010; Jones &Norton, 2015). The response to aversive stimuli is processed in zebrafish similarly to mammals. Sensory perception activates the central nervous system, which triggers the neuroendocrine stress response axis and behavioural responses (Khalid &Vijayan, 2025). These behavioural patterns, often reported as reactive aggressive behaviour responses, include approach, fin raising, undulating body movements, mouth opening, charging, biting, chasing, and circling (Kalueff et al., 2013). Specifically, the most evident aggressive behaviour is mouth opening and biting. Also, 'alarm reaction' behaviours, such as zig-zagging swimming and freezing, were described (Kalueff et al., 2013).

Similarly to humans, the zebrafish aggressive behaviour pathways involve serotonergic, dopaminergic, GABAergic, and neuroendocrine regulation (Jones &Norton, 2015). Despite the fact that the evidence regarding the contribution of dopaminergic, noradrenergic, glutamate, and GABA signaling toward zebrafish aggressive behaviour is rather scarce, Jones and Norton (2015) explained the highly conserved, across species, serotonergic modulation. The inverse relationship between serotonin and aggressive behaviour as well as the genetic homology between human and zebrafish serotonin pathways (including serotonin reuptake transporter, serotonin receptors, and tryptophan hydroxylase 2 genes) have been documented. Previous studies on zebrafish models reported that polymorphic variants of serotonin receptor 1A and tryptophan hydroxylase 2 genes contributing to decreased serotonin production or synaptic reuptake could be associated with aggressive behaviour patterns (Jones & Norton, 2015). Filby et al. (2010) also studied serotonergic and dopaminergic pathways genes expression and their relation with aggressive behaviour modulation and reported that dominant males exhibit aggressive behaviour at increased rates and have increased expression of *avpl* (arginine-vasopressin-like), *oxtl* (isotocin), *tph* (tryptophan hydroxylase) genes, while only *th* (tyrosine hydroxylase) and *slc6a3* (dopamine transporter) genes of the dopaminergic pathway were associated with increased aggressive behaviour. Furthermore, *3c1* (glucocorticoid receptor) and *npy* (neuropeptide Y) genes related to hypothalamic-pituitary-interrenal axis, were over-expressed and associated with aggressive behaviour in both dominant and subordinated fish (Filby et al., 2010).

However, modelling aggressive behaviour in zebrafish could be rather difficult despite the increased structural and genetic similarity to humans (Meshalkina et al., 2018; Rea & Van Raay, 2020; Tayanloo-Beik et al., 2022). The modulation of aggressive behaviour in ASD zebrafish models is not fully understood. Most of the ASD zebrafish models exhibiting aggressive behaviour

were obtained by transgenesis rather than through other classical methods (Liu et al., 2018; Weinschutz et al., 2023; Gabellini et al., 2023; Kareklas et al., 2023; Tatzl et al., 2025). Mutant zebrafish ASD models for the risk gene *CNTNAP2* (loss of gene function) were created using the zinc finger nucleases and crossedbreeding. The results showed increased night-time locomotor activity and a reduction in GABAergic neurons (Hoffman et al., 2016). Decreased aggressive behaviour along with increased anxiety was noted in the *shank3a* and *shank3b* mutant zebrafish model (Li et al., 2024). Additionally, decreased social behaviour and increased anxiety were reported (Li et al., 2024). Similarly, knockout of *lrrtm4l1* (zebrafish orthologue of human *LRRTM4* - leucine-rich repeat transmembrane proteins) in both larval and adult zebrafish led to decreased aggression and increased anxiety (Kim et al., 2017). On the other hand, *oxtr* and *oxtrl* receptor knock-out of a zebrafish did not alter aggressive behaviour but reduced social preference (Karimi et al., 2023). The same method was used for adult zebrafish with *slc6a3* gene knockout for studying the dopamine disruption in relation to ASD (Li et al., 2025). Loss of *slc6a3* gene function results in decreased social behaviour and increased anxiety (Li et al., 2025). Contrary, increased social impairment together with altered anxiety-like and social behaviour were noted after knockout of *dyrk1aa* (human orthologue of *DYRK1A*) in the zebrafish ASD model (Gemmer et al., 2022)(Table 2).

Table 2. Gene alterations and behavioural effects in zebrafish ASD models

Animal model	**Gene**	**Genetic alteration**	**behavioural effect**	**Reference**
zebrafish embryo	gene expression of *hrt1aa, slc6a4* and *oxtr.*	decreased mRNA expression of *hrt1aa and oxtr*, and transient up-regulation of *slc6a4*.	↓ defensive behaviour, ↓ social behaviour ↓ shoaling ↑anxiety.	Parker et al., 2014
adult zebrafish	*shank3b* gene deficiency.	The expression of *shank3b* mRNA was significantly reduced in the mutant zebrafish, whereas the zebrafish expression of *shank3a* mRNA was not affected.	morphological defects, ↓ locomotor activity, ↓ social interactions.	Weinschutz et al., 2023
adult zebrafish	zebrafish with *slc6a3* knockout gene via CRISPR-Cas9 system.	-	↓ locomotor activity, ↑anxiety.	Li et al., 2025
adult zebrafish	knockout of *lrrtm4l1.*	high expression of gene levels in the anterior telencephalon, the inferior lobe, optic tectum, low expression of gene level in cerebellum.	↓ aggressive behaviour, ↑anxiety, = locomotor activity, = social behaviour.	Kim et al., 2017
zebrafish	knockout of *dyrk1aa*.	lower neuronal activity, size reduction of the brain.	↑social impairment in anxiolytic behaviour, ↑social behaviour.	Gemmer et al., 2022
adult zebrafish	*oxtr* and *oxtrl* receptors knock-out.	isotocin leads to significantly reduced *oxt* expression levels, unaffected expression of *oxtr* and *oxtrl*.	↓ social preference, = aggressive behaviour, = anxiety.	Karimi et al.,2023

Abbreviations: ↑, increased effect; ↓, decreased effect; =, no significant change

4.1. The Epigenetics of Aggressive Behaviour in ASD Zebrafish Models

Several studies have documented the possible implication of pesticides, heavy metals, and drugs in modulating epigenetic changes associated with ASD, leading to relevant and measurable behavioural trends in zebrafish models, including some aggressive behavioural patterns (Kalkbrenner et al., 2014; Robea et al., 2024; Robea et al., 2025; Qi et al., 2025). Epigenetic properties of valproic acid over both behaviour and gene expressions were described in the zebrafish ASD model (Figure 2) (Zhang & Zhao, 2018; Dwivedi et al., 2019) by reducing the gene expression of *shank3a, shank3b* and *oxytocin receptor gene* (Rahmati-Holasoo et al., 2023). At the same time, Rahmati-Holasoo et al. (2023) revealed that exogenous oxytocin administered to zebrafish larvae increased the *shank3a, shank3b*, and *oxytocin receptor gene* expression and improved aggressive and social behaviour (Rahmati-Holasoo et al., 2023). Similar neurotoxicity of valproic acid exposure was assessed in an adult zebrafish ASD model by Li et al. (2024). They noted altered gene expression (for the *adsl, mbd5, shank3a*) and ASD-associated behaviour (Li et al., 2024). Moreover, valproic acid also suppresses the gene involved in the developmental processes of zebrafish (Zhang & Zhao, 2018; Dwivedi et al., 2019; Lee et al., 2013). Furthermore, alcohol exposure modulates both molecular processes with behavioural results. The aggressive behaviour in adult zebrafish was triggered after alcohol exposure of adult zebrafish along with reduced expression of *comta*, *bdnf3* and *slc6a3* and increased expression of *slc6a4a* genes (Franco-Restrepo et al., 2021). In zebrafish embryo exposure to alcohol leads to impairments in social behaviour and anxiety associated with decreased mRNA expression of *hrt1aa* and *oxtr*, and transient up-regulation of *slc6a4* (Parker et al., 2014) (Table 3).

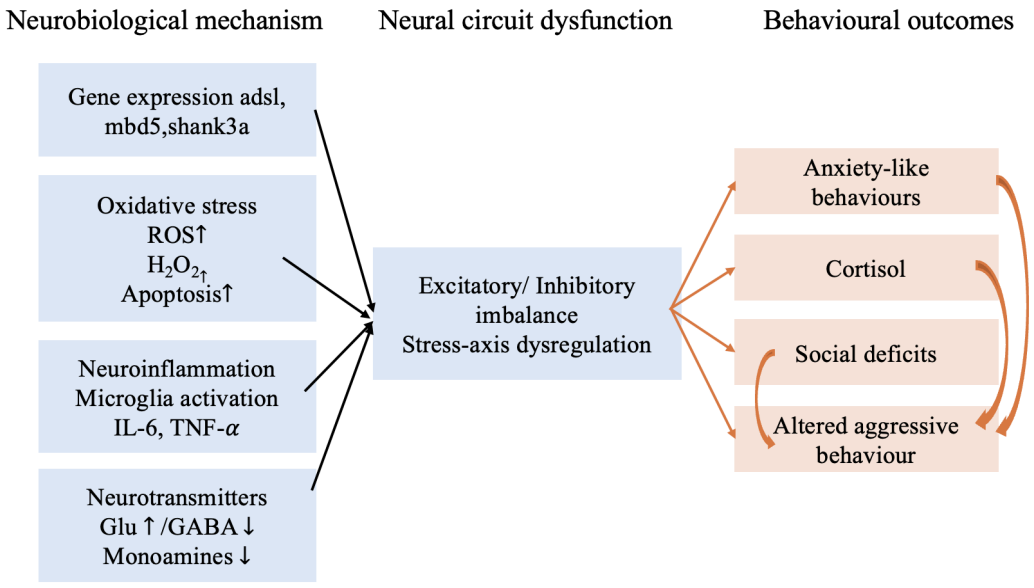

Figure 2. Neurobiological mechanism underlying aggressive behaviour

Figure 2 highlights the main neurobiological effects of valproic acid (VPA) exposure in zebrafish. These effects include altered gene expression, increased oxidative stress, neuroinflammation, and changes in neurotransmitter systems. Together, these changes are associated with a range of behavioural outcomes, including altered aggressive behaviour, anxiety-like behaviour, elevated cortisol levels, and impaired social interaction. Aggressive behaviour may be influenced both directly and indirectly through stress- and anxiety-related pathways.

Moreover, exposure to VPA leads to increased oxidative stress, characterised by elevated ROS production, higher H_2O_2 levels, and enhanced apoptosis. Such alterations have been associated with anxiety-like behaviour and may, in turn, indirectly affect aggressive behaviour (Wang et al., 2024; Camussi et al., 2024) However, alterations in cortisol levels, together with neuroinflammatory

responses, point to a disruption of the stress response system following VPA exposure and are consistent with microglial activation (Camussi et al., 2024; Li et al., 2026). Evidence from zebrafish studies also supports a bidirectional relationship between stress signaling pathways and microglial activity (Yang et al., 2020; Tao et al., 2025)

Early exposure to VPA has been linked to persistent deficits in the social behaviour in zebrafish, including reduced shoaling and a lower preference for conspecifics (Zimmermann et al., 2015; Liu et al., 2016; Sun et al., 2025). These behavioural changes are thought to reflect underlying alterations in neurotransmitter systems, particularly disruptions in the balance between glutamatergic and GABAergic signaling, along with broader monoaminergic involvement (Zimmermann et al., 2015; Baronio et al., 2018; Flores-Prieto et al., 2024). Findings from systematic reviews and meta-analyses further indicate that these social impairments are consistently observed across different experimental settings (Hoffman et al., 2016).

Table 3. Epigenetics pathways and behavioural effects in zebrafish

Animal model	Gene	Genetic alteration	Behavioural effect	Reference
zebrafish larvae	*shank3a*	significantly reduced gene expression (after 48 µM VPA exposure for 48 h); significantly increased gene expression (after 50 µM OT in both exposure times, 24 and 48 h); significantly reduced gene expression (after 25 and 100 µM OT in both exposure times, 24 and 48 h).	OT in specific concentrations and time intervals reduced autistic zebrafish larvae's impaired social communication and aggressive behaviour.	Rahmati-Holasoo et al., 2023
	shank3b	significantly reduced gene expression (in VPA exposure group); significantly increased gene expression (in 50 µM OT exposure group); no significant effect of gene expression (in 25 and 100 µM OT exposure groups).		

	OT receptors genes	significantly reduced gene expression (in VPA group); substantially increase gene expression (in 50 μM OT exposure group); significantly reduced gene expression (in 25 and 100 μM OT exposure groups).		
zebrafish larvae	*adsl, mbd5, shank3a* (after 500 μM VPA exposure for 4 days).	Significantly upregulated gene expression of *adsl, mbd5,* no significant effect of *shank3a* gene expression.	↓social interaction, aggressive behaviour (of time spent near the mirror), ↓number of attacks, ↓total attacks, ↑anxiety	Li et al., 2024
zebrafish larvae	*β-actin, wnt3, β-catenin, lef1, gsk3β* (after 0.2 or 2 mM VPA exposure for 3 h).	unchanged gene expression of *β-actin,* not significantly different gene expression of *wnt3*, reduced gene expression of *β-catenin, lef1*, increased gene expression of *gsk3β*.	learning not altered, avoidance response not altered, preference for the bottom side of the tank not altered.	Lee et al., 2013
zebrafish larvae	*beta-2-microglobulin b2m, chd8, ctnnb, gsk3β, lrp6* (after 1 μM VPA exposure for 120 hours).	increase expression of *chd8, ctnnb, of gsk3β, lrp6 genes*.	↑ anxiety, ↑passive avoidance ↑ learning impairment alter the social behaviour.	Karimi et al., 2023
zebrafish larvae	*shank3a, nrxn 1, nlgn 3,* (after 75μM VPA exposure for 5 days).	significant reduction of gene expression.	impaired social interaction, ↑ anxiety measured by wall-sticking behaviour, cognition deficit (that it didn't recognise the evasive stimulus), ↑cycling.	Zhang & Zhao, 2018
adult zebrafish	*slc6a4a, slc6a3*, comt and *bdnf3* after exposure to alcohol.	reduced expression of *comta*, *bdnf3 and slc6a3,* increased expression of *slc6a4a*.	↓ aggressive responses.	Franco-Restrepo et al., 2021

Abbreviations: VPA, valproic acid; OT, oxytocin; μM, micromolar; ↑, increased effect; ↓, decreased effect.

Despite significant progress in understanding the biological mechanisms underlying aggression in ASD, several limitations should be acknowledged. Current findings included in this review are heterogeneous regarding study design, molecular targets, behavioural assessment, and animal models, which may limit direct comparisons between studies. In particular, differences in species, genetic backgrounds, induction protocols, and behavioural paradigms may affect the reproducibility and comparability of results. In addition, reported associations between genetic, epigenetic, and neurobiological alterations and aggressive behaviour remain predominantly correlational.

Future studies should focus on standardising behavioural protocols, integrating genetic, epigenetic, and environmental factors, and developing more reproducible models that better reflect the heterogeneity observed in individuals with ASD. Advances in multidisciplinary approaches that combine behavioural assessments and molecular analyses may contribute to a better understanding of aggressive behaviour and support the identification of more targeted therapeutic strategies.

Although zebrafish models provide valuable insights regarding neurobiological mechanisms, they cannot fully reproduce the complexity of human ASD manifestations. Moreover, translation of these findings into clinical practice should be approached with caution due to species differences and methodological limitations. Furthermore, the present manuscript represents a narrative review, and the literature selection process was not conducted using a systematic protocol.

5. Conclusions

Aggressive behaviour is a complex behaviour resulting from the interaction of genetic, neurobiological, and environmental factors. The genetic influence of aggressive behaviour involves neurotransmission, synaptic plasticity, and stress regulation, which can modulate susceptibility to aggression through interaction with environmental factors. The altered expression of genes may disrupt the excitatory-inhibitory balance in neural circuits, leading to impaired behavioural regulation, such as increased aggressive behaviour. Understanding these mechanisms provides a foundation for more targeted pharmacological and behavioural interventions. The studies examined in this review indicate that aggressive behaviour in autism spectrum disorder (ASD) is shaped by multiple biological mechanisms. Alterations in serotonin and dopamine signalling, synaptic organisation, and stress-related pathways are frequently associated with aggression and social impairment. Furthermore, several genes, including *SLC6A4*, *DRD4*, *MAOA*, *SHANK1-3*, *CNTNAP2*, and *OXTR*, are consistently implicated in anxiety, repetitive behaviours, and atypical social responses.

Although much of the available data comes from heterogeneous experimental protocols, the findings discussed in this review underline the importance of studying aggression in ASD from an integrative genetic, neurobiological, and environmental perspective. Although the available studies are heterogeneous and largely based on animal models, this review supports an integrative perspective in which aggressive behaviour depends on dysregulation of interconnected neural and molecular systems. In this context, zebrafish models represent a valuable complementary approach for investigating aggression-related phenotypes and the underlying molecular pathways associated with ASD, although their translational relevance should be interpreted with caution and requires further validation across species and clinical settings. Further studies are needed to clarify the causal relationships between genetic, epigenetic, and environmental factors involved in aggression in ASD.

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