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Aquarium Behavioral Genetics

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Abstract:

The relationships between genes, environments, and the stress response, as well as their roles in the development and progression of disease, are largely unclear. Addiction, as well as mood and anxiety disorders, are behavioral diseases that both genetic and environmental factors can influence. It is possible to determine the genetic or epigenetic contribution to polygenic disease with unbiased forward genetic screens. Phenotype analysis is facilitated by the quick distinction between mutant carriers and non-carriers in both larval and adult Zebrafish. Visual sorting is made possible by gene-break transposon mutagenesis techniques or by selectively breeding cloned mutants to fluorescently tagged linkage groups. This crucial step focuses on a single gene's impact rather than a diverse genome's influence on behavioral characteristics. Utilizing mutagenesis in conjunction with trustworthy behavioral assays in both the larval and adult Zebrafish will make it possible to do genome-wide studies on the genes that affect how stress is perceived, how it spreads, and how it is attenuated. Longitudinal screens that look at the stress response as. Its evolution from larvae to adults can be used to identify genetic systems essential for perceiving environmental cues and epigenetic programming of the stress response.

Keywords: genes, environments, stress response, Zebrafish, transposon, mutagenesis

Introduction:

The most often utilized aquatic organism in laboratories right now is the Zebrafish (Danio rerio)[1], a cyprinid fish that is native to India and other adjacent nations[2]

Zebrafish's success is due to various benefits, including minimal breeding costs and a brief lifespan. Cycle, small size, transparent embryos and larvae, and a genome completely sequenced. Therefore, this model species are employed in various biological disciplines, including genetics[3,] Biology of development[4], Sabharwal et al. research in neurosciences[6], biomedicine[7,] and other ecotoxicology[9].

The majority of zebrafish-related scientific publications do not mention strains that were collected in the wild. (native), but rather to zebrafish strains of the so-called "wild-type" (WT) kind. This phrase "wild-type" includes various strains, some of which have unclear histories and are utilized in laboratories. Genetic foundation (purchased from pet shops) for highly tamed strains such as Tübingen (TU), Wild India Kolkata (WIK), and other more recently domesticated species like AB

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TM1, for instance. Additionally, many mutant zebrafish strains, including casper[10], longfin[11], leopard[12], albinos[11], are employed for their unique characteristics, primarily reduced enhancement of transparency by colouring.

It is becoming increasingly clear that these zebrafish strains have unique characteristics. On the levels of genetics, physiology, and behavior Regarding genetic (allelic abundance, In terms of heterozygosity and nucleotide diversity, wild-caught Zebrafish exhibit greater variation than various other Researchers are being prompted by laboratory strains to investigate the consequences of genetic variation in design and interpretation of experiments, particularly for extrapolating results to the population[13,14,15]: mRNA expression patterns and endocrine axis activity at baseline. Additionally, zebrafish strains differ in (cortisol secretion), making investigations in[16]; Zebrafish are a difficult species to study[17]. Additionally, the responses of the casper mutant and wild-type (AB) zebrafish are different, being more AB-like in their resistance to fasting[18].

Articles review:

No behavioral differences have been reported between certain zebrafish strains (WT, mutant, Many research argue in favor of transgenic)[19], significant variations in a variety of behaviors, like color conditioning and inhibitory capacity to swim, avoidance, stress, and anxiety, or social dynamics, either between laboratory strains and wild-caught strains, or between several laboratory strains[20].

A typical response to a genuine or imagined threat is the stress response. However, overworked or unbalanced stress response systems can increase the prevalence and severity of diseases like addiction and mood and anxiety disorders. Identifying the precise genetic and environmental contributions to these behavioral illnesses may be possible by using an animal model with both genetic diversity and large family size. Due to their significance in food production, teleosts have been the subject of substantial research on stress response. A vital model organism with a proven track record for use in developmental biology, genetic testing, and genomic research is the Zebrafish (Danio rerio). Zebrafish larvae and adults' reactions to stress have lately been studied. Automated tracking systems make Behavioral readouts possible with a high throughput of the Zebrafish's reaction to stress. This non-invasive stress response measurement can be used in conjunction with mutagenesis techniques to analyze the genes responsible for complex stress response behaviors in vertebrates. Understanding the genetic and epigenetic underpinnings of the stress response in vertebrates will aid in developing enhanced diagnostic methods and therapeutic approaches for diseases like addiction and mood and anxiety disorders exacerbated by stress.

Stress-aggravated illnesses have a very large clinical impact. An important factor in some of the leading causes of death and disability worldwide is the alteration of brain function brought on by stress, which also contributes to addiction and mood disorders. The two most preventable causes of death in the United States, respectively, are smoking and alcohol use[21]. Each year, about one in every four individuals, experiences a diagnosable anxiety, mood, impulsive, or substance use disorder[22]. Neuropsychiatric illnesses have a disease burden almost as great as the combined disease burden of cancer and cardiovascular disease worldwide[23]. Within 20 years, major depressive disorder is expected to be the largest cause of disability globally[23].

Future efforts to reduce the prevalence and severity of addiction and mood disorders will benefit from understanding stress's key role in developing and maintaining the disease.

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People are more or less sensitive to the crippling effects of stress depending on their ancestry, experiences in life, and other factors. Heritability is the term used to describe the proportion of phenotypic diversity (such as anxiety, mood, or addiction disorders) that can be attributed to genetic variation within the population. The population's environmental variation, on the other hand, accounts for the remaining phenotypic variance. Both major depressive disorder (MDD) and anxiety disorders are expected to have a heritability of at least 30–40%[24].

However, in longitudinal studies that represent accurate disease diagnosis, such percentages rise to ranges of 50–80%[5]. Therefore, both hereditary (genetic) and environmental (epigenetic) factors have a role in the beginning of disease.

Numerous hereditary influences, particularly those linked to coping processes and the stress response, may be common to many neuropsychological problems. According to the Swedish National Twin Samples, males and females share around 74% of the heritable or genetic propensity for MDD and generalized anxiety disorder (GAD)[25]. Given that both MDD and GAD share a high degree of genetic predisposition, environmental factors are predominantly responsible for the beginning of either disease (74% in males and 100% in females).

Some patients have trouble telling the difference between the two disorders[26]. Addiction frequently co-occurs with psychiatric conditions, including MDD and GAD, in the same patient[27]. With heritability scores for alcohol and nicotine dependence of 50 to 60 percent and 72 to 72 percent, respectively, the genetic propensity to addiction in the population is comparable to MDD and GAD[28]. The correlation between addiction and mood and anxiety disorders and the genetic influence on these conditions point to similar causes that may be genetic, environmental, or a combination of the two.

Knowing how the stress response affects the start and development of addiction and mood disorders can help with better disease screening and the creation of novel treatments. Indeed, one of the goals of individualized medicine, in which each patient can receive treatment and therapeutic intervention specific to their own genetic background, is the development of genetic or even epigenetic tests. Epigenetics, heritable genetic variables, and later-life experiences that cause illness onset all influence how the stress response interacts with the environment and how diseases progress[29]. In mammalian models, this covers the prenatal, early childhood, and teenage time periods. Life-priming events take place during these crucial stages because they are particularly malleable and receptive to environmental cues to determine future response thresholds[30].

There are various and different biological tissues and mechanisms that support a productive stress response. It is possible to identify the involvement of genes in both recognised and undiscovered or unanticipated pathways using unbiased forward genomic screens that make no assumptions about which pathways are involved in the process of stress response. These technologies allow for the investigation of the genetic or epigenetic component of multigenic illness. To find minor contributions of individual genes to the overall development of disease, quantitative genetic techniques in animal models with moderate genetic diversity are excellent tools[31]. Therefore, utilizing a low-cost genetic model organism to study the stress response will provide significant insight into how well stress response systems should function and possible sites of dysregulation.

Dysregulation of the stress axis affects how well the hypothalamic-pituitary-adrenal (HPA) axis functions in balance. The hypothalamus releases corticotropin-releasing factor (CRF) after detecting

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a stressor. Adrenocorticotropic hormone (ACTH) is released by the pituitary when CRF stimulates it, and ACTH travels through the bloodstream to the adrenal glands to induce the release of glucocorticoid cortisol. The delicate balance of the stress response and related hormones in the body can be shifted by gene doses and an individual's complement of genetic modifiers and direct mutagenesis to produce genetic predispositions to stress-related disorders. The serotonin transporter gene (5HTT) and the corticotropin-releasing factor receptor one gene (CRHR1) are two examples of genetic influences on stress and disease. The gene dosage, or the quantity of protein generated, is influenced by both genes' alleles, but not the protein itself.

These changes in protein concentration affect the likelihood that a stressor experienced in childhood may cause depression in adulthood[28,] event an alcohol relapse in a rat model[33]. Addiction, major depressive disorder, and generalized anxiety disorder are examples of behavioral illnesses that are complex multi-system diseases that necessitate complete animal models for an accurate assessment[34].

Since more than 20 years ago, researchers have been examining the teleost equivalent of the HPA, the hypothalamic-pituitary-interrenal (HPI) axis, and the stress response in fish with the frequent aim of enhancing aquaculture practises and preventing production losses in these significant food commodities[35]. With one exception, the hypothalamus, pituitary, and adrenal cortex—the three main components of the HPA axis—serve similar functions and have comparable structures in fish that exception is that the adrenal gland is composed of chromaffin cells (adrenal medulla) mixed with interrenal cells (adrenal cortex). These cells have a tenuous connection to the head kidney, which is the front part of the kidney, and the posterior cardinal vein[36]. Beyond anatomy, several fish species exhibit higher-order behaviors, such as aggression[37], shifted aggression[38], and alternative coping mechanisms[39]. These behaviors include dominating and submissive behavior. Teleosts have preserved versions of the key stress response genes[40]. The majority of these "large" fish species, like their mammalian counterparts, have poor genetic tractability for mutagenesis experiments to find genes involved in perception, propagation, appropriate attenuation, or epigenetic regulation modifications of the stress response.

A significant model organism for studying the genetic, physiological, and developmental underpinnings of the stress response is the Zebrafish (Danio rerio). A platform for finding gene mutations that quantitatively influence the stress response in larval and adult fish is provided by the high fecundity and genetic diversity of Zebrafish. Zebrafish longitudinal studies will aid in uncovering the processes through which early experiences influence adult phenotypes. A lot of work has been put into creating the first descriptions of the Zebrafish's stress response over the last four years. Here, we will cover these developments as well as the most recent genetic screening techniques in Zebrafish to increase our knowledge of the complex interactions between genes and environment, with a particular emphasis on behavior, neuroendocrine function, and stress.

Discussion:

The reward system is arguably the most significant area in which the adult zebrafish has contributed to behavioral genetics. Animals' instinctual drive to find resources and reproduce is fueled by reward behavior. However, drugs of addiction like cocaine, amphetamine, or opioids can potentially take over the brain's reward circuit. Thus, rewarding behaviors might represent the start of addiction. The conditioned place preference (CPP) test, which matches a main cue (such a drug) with a secondary stimulus like a colored aquarium compartment, can be used to quantify reward in Zebrafish. The

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persistence of CPP after a period of abstinence can also be used to assess drug dependency.

Adult fish have been shown to respond favorably to ethanol[41], cocaine[42], amphetamine[43], opiates[44], nicotine[45], food[46], and the presence of conspecifics[47], in accordance with research on animals (e.g.[48]). Dopamine (DA) is a key neurotransmitter linked to rewarding behavior. Mammals are motivated to apply the stimulus repeatedly by an increase in DAergic transmission from the ventral tegmental region to the nucleus accumbens (nAC). This important DAergic route in Zebrafish most likely consists of projections from the ventral telencephalon (subpallium, (Vv and Vd), see[49]) to the diencephalic posterior tuberculum. Reward-related behavior has also been linked to a number of other neurotransmitters.

Acetylcholine levels in the brain are increased in heterozygous mutant Zebrafish lacking one copy of the acetylcholinesterase (ache) gene because less of the neurotransmitter is broken down. Ache mutants have higher levels of acetylcholine in their brains, which reduces the amount of CPP that amphetamine may generate[50]. Raphe 5-HTergic neurons[51,] as well as a number of inhibiting factors, including as projections from the habenula, are also a part of mammalian reward pathways. In terms of gene expression and raphe innervation, the zebrafish ventral habenula and the mammalian lateral habenula appear to be similar[52]. Genetic modification of the reward system will be achievable thanks to the recently discovered selective molecular markers for both structures[53].

The reward circuitry in Zebrafish can be functionally examined using a targeted method, which may also reveal parallels and differences between the systems governing monoaminergic [56]

For zebrafish mutant families with altered incentive behavior, numerous screens have been conducted. Despite not disclosing the damaged genes, Darland and Dowling found three groups of mutants that were insensitive to the administration of cocaine[42].

Studies on stressors and the stress response in teleosts have a long history (for a summary, see[50]). Among the most frequent acute stressors in laboratories are physical stressors such handling, capture, net chasing, and other physical disruptions. Additionally, fish confinement and overcrowding are physical stressors that have the potential to be both acute and chronic stressors. Fish social interactions like as dominance and submission are social stressors. Fish of the same species or different species interact closely with shoals of conspecifics and heterospecifics or fish of different species, respectively. Both physical and social pressures, crowdedness, and isolation have an impact on these social connections.

Environmental stressors include heavy metals and xenobiotics like insecticides, herbicides, and medicines as well as water quality measurements including dissolved oxygen, nitrogen cycle, hardness, pH, temperature, and salinity. Infection and pathogens can also function as stressors, although persistent stress can lower immunity and increase infection rates[54].

Zebrafish are indigenous to India's floodplains, where they experience quick variations in water quality and flow during the monsoon season, when most of their reproduction takes place[55]. Endocrine reactions to these stressors play a role in how well fish and larvae adapt to various environmental factors. Cortisol production has been directly linked to a number of stimuli.

By spinning embryos for 30 seconds, Alsop and Vijayan successfully induced a stress response in larvae. This modest physical stress simulates the momentary loss of control of the resting embryo

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due to traffic in the waterway or changes in water currents. Zebrafish are a freshwater species that can acclimatise to brackish water, however Alderman and Bernier utilised a hyperosmotic shock to promote cortisol synthesis in larval zebrafish[57]. The capacity to adapt to diverse salinity levels is vital to Zebrafish. It has been shown that fish handling, tank transfers, and water and shoal disruption cause cortisol responses in adult zebrafish[58]. Adult zebrafish are successfully stressed out by overcrowding[59] and turbulent airflow from a bubbler[60].

Many fish species, including Zebrafish, have a high behavioral reaction to predators and alarm pheromones. In the presence of a predator and while viewing the predator, Barcellos et al. assessed the cortisol response[44]. This is in line with important behavioral studies in Zebrafish employing predators and the alarm pheromone (for a review, see[61]). Zebrafish are shown to be more sensitive to novelty stressors when going through drug withdrawal by measuring cortisol production in response to a novel tank[62]. Antidepressants/anxiolytics like fluoxetine can lower cortisol levels and change the behavior of Zebrafish to indicate less anxiety towards the novel tank[63]. Studies on environmental toxicology in Zebrafish are expanding quickly because these small, lab-friendly fish are thought to be excellent models for both acute and latent toxicology[64]. Toxicants like copper in waterborne form have been shown to strongly increase cortisol production by Craig et al[65]. As a result, a variety of stimuli can consistently cause Zebrafish to exhibit stress reactions in a controlled laboratory environment.

Conclusion:

In order to successfully research complex polygenic behaviors, it is essential to have genetic variety and large familial populations, both of which are present in the zebrafish model system. A number of diseases' onset and severity are influenced by stress. Among them are addiction and mood and anxiety disorders, which are, respectively, the world's top causes of death and disability due to preventable causes. Future screening and medical care must take into account the hereditary factors that either raise or diminish a person's sensitivity to stress and disease. In addition to playing a prominent role in the hobby aquarium, the Zebrafish is well-positioned to resist the risks of stress.

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