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The Genetics of Amygdaloid Disorders

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ABSTRACT

The amygdala, a major constituent of limbic region, is recognized for playing a pivotal role in emotion, behavior, memory, autonomic integration, and motivation. Genome instability and multifactorial inheritance are plausible agents to cause dysfunctional amygdala. Some examples of genetic amygdaloid disorders: Williams syndrome (WS), Urbach-Wiethe disease, anxiety disorders, major depressive disorder (MDD), intermittent explosive disorder, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Although prenatal maternal depression and hypochondriasis are correlated with larger amygdala volume, distinctively, schizophrenia, posttraumatic stress disorder, and inhibitory control deficits have low volumetric abnormalities of amygdala. Subtle disruption of amygdala is an ordinary integrant of pediatric neurodevelopmental diseases (e.g., autism spectrum disorder (ASD), pediatric bipolar disorder, etc.). A significant percentage, i.e., 4.5%-9% of progressive amygdala enlargement has been shown in very young children with ASD. Regardless of the individuals with more common genetic amygdaloid disorders, WS has historically been estimated to affect 1 per 7,500-20,000 births. Importantly, recent genome-wide association studies (GWAS) have identified few SNPs within UCN, BDNF, 5-HT, Tacr3, and NPSR1 loci that induced hyperresponsive amygdala. It is noteworthy that increased MAOA-uVNTR expression in prefrontal cortex but not in amygdala of peripubertally stressed animals may lead to aggressive behavior and orbito-frontal reactivity. Interestingly, anxiety candidate genes, including 5-HTTLPR, TMEM132D, and MAD1L1 influence the susceptibility to dependent risk factors for loneliness and incident depression across the lifespan in intact depression-psychological vulnerability spectrum. Mutated genes of shift work sleep disorder (i.e., CLOCK, Rev-erbβ, and BMAL1) confer robust players for MDD morbidity and mortality. NR3C1 and FKBP5 expression were markedly decreased in amygdala of completed suicide male victims without manifestations of diagnosable psychiatric disorders like suicidality, paranoid personality disorder, substance abuse, manic depression, etc. The presented paper is the first, to the best of my knowledge, in its approach to scrutinize the genetics of amygdaloid disorders. Moreover, it is novel in exhibiting that neurological disorders-associated genetic variants can potentially trigger multisystem diseases. Lastly, many rare but important amygdaloid disorders and monogenic mutations implicated in the phylogenetic etiology of several neuropsychiatric diseases are intensively analyzed in this review article.

Keywords
Amygdala, Amygdaloid disorders, Anxiety disorders, Intermittent explosive disorder (IED), Depression, Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS).

Introduction

The amygdala, a major constituent of limbic region, is recognized for playing a pivotal role in emotion, behavior, memory, autonomic integration, and motivation. In 1822, Karl Friedrich Burdach first introduced the term "amygdala" (Greek origin: amygdale−almond) that was a set of nuclei in medial portion of mammalian temporal lobe and later extensively described by Meynert (1876). Generally known as "emotional center", amygdala functionally coordinates with hippocampus that generates a complex hippocampal-amygdalar circuit. Thus, it forms synergistically long term memory consolidation of remarkable life events and stores contextual fear memory of perceived insecurity.

Genetic disorders of amygdala can range from minuscule to crucial. Elementally, a permanent alteration in the DNA sequence either by point mutation, deletion, or insertion of nucleotides results in amygdala dysfunctions. Genome instability and multifactorial inheritance are plausible agents to cause hyperfunctional amygdala. Some examples of genetic amygdaloid disorders: Williams syndrome (WS), Urbach-Wiethe disease, frontotemporal dementia, anxiety disorders, somatization disorder, depression, intermittent explosive disorder, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Likewise, accumulating evidence suggests that the amygdala volume is highly inheritable. Although prenatal maternal depression and hypochondriasis (newly termed as illness anxiety disorder) are correlated with larger amygdala volume, distinctively, schizophrenia, posttraumatic stress disorder, nonverbal social impairment, and inhibitory control deficits have low volumetric abnormalities of amygdala.

Subtle disruption of amygdala is an ordinary integrant of pediatric neurodevelopmental diseases (e.g., autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), pediatric bipolar disorder (PBD), and Tourette's syndrome). A significant percentage, i.e., 4.5%-9% of progressive amygdala enlargement has been shown in very young children with ASD [118]. However, current neuroscience studies have established that the right whole amygdala volume and its paralaminar nucleus, accessory basal nucleus, and cortico-amygdaloid traditional area reduced 7.6% in manic PBD [119]. Early childhood adversity (e.g., physical and emotional abuse, incest, chronic neglect, household dysfunction, etc.) persistently sensitize the amygdala, which activates prolonged toxic stress and vulnerability to psychiatric disorders later in life, in particular, anxiety and mood disorders [120].

The amygdala has a central role in fear and anxiety responses to psychological stress, physical danger, emotional threat, and arousal events. Anxiety is a term often used to encompass feelings of unease, apprehension, worry, dread, vigilance, sustained arousal, muscle tension, insomnia, and anticipation of future threat. Nevertheless, fear is characterized by negative valence, present focused, brief phasic, initiates in a specific threat, escape behavior, and blunt pain perception. While anxiety and fear are interrelated alerting signals, other similar terms (e.g., agitation, nervousness, panic, vexation, stress, tension, upset, discomfort, phobia, etc.) can be differentiated from them both neurobiologically and psycho-emotionally.

Regardless of the individuals with more common genetic amygdaloid disorders, WS has historically been estimated to affect 1 per 7,500-20,000 live births. It is an autosomal dominant condition caused by hemizygous deletion of chromosome 7q11.23, that specific region contains approximately 27 genes. Given that WS is a multisystem disorder, frequently people with WS have distinctive facial features (e.g., broad forehead, elfin nose, micrognathia, etc.), supravalvular aortic stenosis, hypercalcemia, intellectual disability, stellate iris, puffy eye, soft skin, and osteomalacia. Interestingly, hypersociability (e.g., interact with strangers, indiscriminate sociability, extreme outgoing, and engaging personalities) in WS has linked to abnormal structural/pathological disturbances of lateral amygdala [121].

Anxiety disorders

Anxiety disorders are a group of psychiatric problems whose key features include recurring or unexpected anxiety attack, uncontrollable worrying, hypervigilance, sweating and flushing, fear of an impending medical emergency or public scrutiny, avoidance, obsessive thoughts resulting in compulsive rituals, and depersonalization, with current world wide prevalence rates as high as 31.7% [1]. Different anxiety disorders (e.g., generalized anxiety disorder (GAD), agoraphobia, selective mutism, obsessive compulsive disorder (OCD), panic disorder, social phobia, and posttraumatic stress disorder (PTSD)) have their own sets of signs and symptoms.

Of these, GAD is the most frequent both in community and clinical settings. Also, the high prevalence of GAD in primary care (21.5%) compared to that reported in the general population (12-month prevalence rate of 3.9%) suggests that GAD patients are high users of primary care resources [2, 3]. K. Kroenke et al. applied GAD-7 scale, diagnostic and statistical manual of mental disorders fourth edition (DSM-IV), structured clinical interview for DSM (SCID), patient health questionnaire (PHQ), Hopkins symptom checklist (SCL), social phobia inventory (mini-SPIN), global anxiety, depression and pain severity scores, and composite international diagnostic interview (CIDI) in 965 random patients to determine the current prevalence, impairment, and comorbidity of anxiety disorders in primary care. According to this study, PTSD is the second most common anxiety disorder with a prevalence of 8.8% followed by panic disorder (6.9%) and social phobia (6.3%) [4]. Globally, it is a consistent finding that women (33.6%) are more than twice as likely to be diagnosed with an anxiety disorder than men (19.2%) [5].

Most individuals with anxiety disorders are present with other mental illnesses (e.g., depression, substance abuse, anorexia nervosa, bipolar disorder, narcissistic personality disorder, somatic symptom disorder, autism spectrum disorder, dysthymic disorder, oppositional defiant disorder, etc.). Researchers have identified a number of risk factors and socio-psychiatric variables for these disorders (e.g., interpersonal trauma (physical or sexual abuse, domestic violence, torture and forcible confinement, poverty,

pandemic disease, death threats, witness or victim of a crime, homicide, war, natural disasters, etc.), complex trauma, stress, behavioral inhibition, inherit genetic vulnerability, overactive amygdala or underactive prefrontal cortex, neuroticism, decreased function of GABA (gamma aminobutyric acid) and serotonin, high glutamate, judgements of perceived threat, and inadequate ego defense mechanism).

Relying on the current literature based on humans and animals suggested that functional and morphological abnormalities of amygdala (e.g., hyperactive and/or reactive amygdala, reduced amygdala-hippocampal volume, enhanced basolateral-medial-central neural circuit excitation, monoaminergic neurotransmitters (dopamine, epinephrine, norepinephrine, serotonin) dysfunctional receptors in central amygdaloid nuclei, increased total volume of amygdala, deficits in amygdala-bed nucleus stria terminalis (BNST), direct connection from amygdala to hippocampus, entorhinal cortex, dorsomedial thalamus or brainstem interruption, suppression of GABAergic modulation, etc.) are the principle reasons for the anxiety disorders.

It is important to note that genetic predisposition plays a critical role in anxiety disorders. Genes related to amygdala have been identified as maximum contributors to potential anxiogenic and anxiolylic effects. Recent genome-wide association studies (GWAS) have identified few single nucleotide polymorphisms (SNPs) within UCN, BDNF, 5-HT, Tacr3, and NPSR1 loci that induced hyperresponsive amygdala.

UCN gene

Urocortin (UCN) gene, also known as prepro-urocortin, is a member of the sauvagine/corticotropin-releasing factor (CRF)/urotensin I/corticoliberin family located on chromosome 2p23.3. UCN is broadly expressed in hippocampus, Edinger-Westphal nucleus, sphenoid nucleus, supraoptic nucleus, thymus, heart, colonic lamina propria, endometrium, pituitary glands, adrenal glands, sweat glands, hair follicles, erector pili muscle, cutaneous nerve/blood vessels, and dermal mononuclear cells. Structurally related to the CRF (central driver of the hypothalamic-pituitary-adrenal (HPA) axis under basal and stress conditions), it is responsible for the effects of stress on appetite by reducing food intake and regulating ghrelin levels in gastric body and plasma. Further, it increases heart rate and cAMP accumulation, stimulates the secretion of adrenocorticotropic hormone (ACTH) which binds with high affinity to CRF receptor types (1, 2-alpha, 2-beta), and may play a cardinal role in the establishment of normal hearing thresholds.

Conversely, a concatenation of findings from preclinical and clinical tests exhibited dozens of disorders are linked to UCN variants in the pathophysiology of gastrointestinal tract, cardiac system, skeletal, and otolaryngology disorders (e.g., Crohn's disease, ulcerative colitis, colitis, gravidic intrahepatic cholestasis of pregnancy, systolic heart failure, coronary heart disease, left ventricular hypertrabeculation/non-compaction (LVHT), sporadic mitochondrial myopathy, muscle pain, lactic acidemia, and nonsyndromic deafnes). Progressive neurodegeneration and psychiatric disorder have been associated with the mutation in UCN gene, such as ataxia, dysarthria, myoclonus epilepsy MERRF/MELAS overlap syndrome (MERRF: myoclonic epilepsy with ragged-red fibers and MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), monomelic amyotrophy, anxiety, depression, stress, alcoholism, and panic disorder.

Of note, D. E. Vetter et al. generated mice carrying a null mutation of the urocortin gene and demonstrated the interplay between UCN gene deficient mice and amplified anxiety episodes, although they had normal stress induced behavior, basal feeding, or autonomic responses [6]. Unlike UCN, which equally has affinity for both corticotropin-releasing factor receptors (CRFR) 1 and 2, UCN2 [Cytogenetic band: 3p21.31] is likely to selective for CRFR-2. Besides, widely localized in medial amygdala nucleus, CRFR-2 is activated by other structurally similar biochemical peptides, UCN3 and CRF. Stresscopin, or UCN3 gene [Cytogenetic band: 10p15.1], is expressed in thalamus, hypothalamus, medial amygdala, striatum, pancreas (α and β cells), medulla oblongata, and pons, which modulates the social discrimination abilities, depression vulnerability, anxiety, plasma glucose levels, and energy homeostasis. Lacking all three urocortin genes (UCN, UCN2, UCN3), Adi Neufeld-Cohen's triple urocortin knockout (tKO) mouse model reveals increased anxiety related behaviors following to post stress exposure [7].

BDNF gene

In 1982, Yves-Alain Barde and Hans Thoenen first discovered BDNF (Brain-Derived Neurotrophic Factor) gene [Cytogenetic Location: 11p14.1]. BDNF, like the other members of the neurotrophin family, promotes trophic (i.e., survival, growth, maturation/differentiation, and maintenance) effects on sensory and sympathetic nerves, also, helps to regulate synaptic plasticity, axonal and dendritic growth, drinking, eating, learning, body weight, and neuronal apoptosis. It is the second member of the "classic neurotrophins family", namely, NGF: Nerve Growth Factor and NT: neurotrophin 3 & 4 of neurotrophic factors (ligands of glial derived neurotrophic factors (GDNF: Glial cell/astrocyte Derived Neurotrophic Factor, NRTN: neurturin, ARTN: artemin/neublastin/enovin, and PSPN: persephin) and neuroprotective cytokines (EGF: Epidermal Growth Factor, IGF: Insulin-like Growth Factor 1 and 2, FGF: Fibroblast Growth Factor 2 and 19, HGF: Hepatocyte Growth Factor, EPO: erythropoietin, VEGF gene: Vascular Endothelial Growth Factor, CNTF: ciliary neurotrophic factor, IL: interleukin-27, TNF: Tumor Necrosis Factor-α, and OSM: oncostatin M).

Abrineurin (or neurotrophin/BDNF) gene contains total 11 exons (i.e., I–IX, Vh, and VIIIh) and its encoded protein activates signaling cascades downstream of NTRK-2 (Neurotrophic Tyrosine Kinase Receptor Type-2) via the heterodimeric receptor TrkB (tyrosine kinase B) formed by NGFR (Nerve Growth Factor Receptor) and SORCS-2 (Sortilin related VPS10 domain Containing Receptor-2).

NGFR and SORCS-2 are coupled to the Ras, CDC42 (Cell division control protein 42)/Rac (Related Family Small GTPase cell)/RhoG (Ras Homolog Family Member G), MAPK-ERK (Mitogen/Wortmannin Activated Protein Kinase Extracellular-Regulated Kinase), PI3K (Phosphatidyl Inositol-3 Kinase), and PLC gamma (phospholipase C-γ) signaling pathways. As a signaling molecule, it is secreted from forebrain white matter: fibrous astrocytes, spinal cord white matter: fibrous astrocytes, VA 1 & 2 (velate astrocyte) fibrous cells during embryonic neural development, etc., which affects pre-myelinating oligodendrocyte of forebrain & spinal cord white matter as well as immature Schwann cells (SWs). Subsequently, SWs induce TrkB ligand receptor dimerization and autophosphorylation of tyrosine residues.

Findings in human and nonhuman primates demonstrated that BDNF gene expression is profound in medial prefrontal cortex, dorsal hippopotamus, ventral hippopotamus, inferior temporal cortex, basolateral amygdala (BLA), medial amygdala (MeA), and caudate putamen. Systemic diseases and neuropsychiatric disorders are associated with reduced serum BDNF levels, such as systemic lupus erythematosus (SLE), mastocytosis, pulmonary sarcoidosis, WAGR syndrome (Wilms' tumor, aniridia, genito-urinary abnormalities, and mental retardation), central hypoventilation syndrome, affective personality disorder, Pick disease, Alzheimer's disease, bipolar disorder, PTSD, eating disorders, anxiety disorders, substance dependence, schizophrenia, OCD, major depressive disorder (MDD), Parkinson's disease, and Huntington disease, indicating that if it is too low, it might paradoxically menacing, as it might affect several organs and systems in the body.

Val66Met, also called Rs6265, or G196A, a common SNP in BDNF resulting genetic predisposition in a valine (Val) to methionine (Met) amino acid at codon 66, could have contributed to the result of negative memory bias in women with PTSD. Moreover, F. P. Moreira et al. studied 816 participants from a population-based study who were genotyped by qPCR for the BDNF functional variant Val66Met, and concluded that Val66Met perhaps involved in increasing the vulnerability to GAD [8]. However, H. J. Lee et al. suggested that the BDNF G196A polymorphism does not play a major role in PTSD after analyzed two different groups (106 PTSD patients and 161 unrelated healthy patients) using a case control design in Korean population [9]. In a follow up study, E. Shimizu et al. investigated 109 patients diagnosed with panic disorder. The authors summarized that the same polymorphism is not significantly associated with panic disorder and agoraphobia, still, it may play a pathological biomarker in eating disorder and MDD [10]. In contrast to neuropsychiatric diseases, Val66Met has been found to be interlinked with systemic illnesses, such as metabolic syndrome, psoriasis, fibromyalgia, etc. Strikingly, others have demonstrated that the Met66 allele of the functional Val66Met is likely to protect against the decline of motor and psychomotor cognitive functions in patients with longstanding SLE.

5-HT receptor gene

Serotonin receptors, or 5-hydroxytryptamine receptors (5-HT), is a unique autacoid, monoamine neurotransmitter, and cysteine loop ligand gated ion channel (CYS-LGIC; cation selective) whose effects are regulated by minimum 13 distinct G protein-coupled receptors (GPCRs). In humans, it is synthesized from L-tryptophan (converted into L-5OH-tryptophan by enzymes called tryptophan hydroxylase (TPH) and aromatic L-amino acid decarboxylase (AADC)) in serotonergic neurons and enterochromaffin cells of the gastrointestinal tract. The subdivision of 5-HT receptors into 18 genes designed: 5-HT_{1A}(gene: HTR1A), 5-HT_{1B}(HTR1B), 5-HT_{1D}(HTR1D), 5-HT_{1E}(HTR1E), 5-HT_{1F}(HTR1F), 5-HT_{2A}(HTR2A), 5-HT_{2B}(HTR2B), 5-HT_{2C}(HTR2C), 5-HT_{3}(HTR3A, HTR3B, HTR3C, HTR3D, HTR3E), 5-HT_{4}(HTR4), 5-HT_{5A}(HTR5A), 5-HT_{5B}(HTR5BP), 5-HT_{6}(HTR6), and 5-HT_{7}(HTR7), has been based on radioligand studies and experiments in isolated tissues.

The HTR1A gene [Cytogenetic band: 5q12.3], E. Fakra et al. hypothesized that it blocks gene specific transcriptional repression, leading to an increased 5-HT_{1A} autoreceptor expression that was associated with the decreased amygdala reactivity and anxiety traits [11]. Reciprocally, J. M. Hettema et al. using multiple sources (i.e., multivariate structural equation modeling, twin pairs from the population-based Virginia Adult Twin Study of Psychiatric and Substance scoring, imaging genetics in participants from an archival database, resulting sample of 589 cases and 539 controls, and four SNPs spanning the HTR1A locus) suggested that the HTR1A gene may not play a major role in the genetic susceptibility underlying anxiety-related phenotypes [12].

5-HT_{1B} receptor (encoded by HTR1B) can be detected in brain cortex, basal ganglia, limbic system (amygdala, hippocampus), striatum, medulla, caudate nucleus, and putamen, plays an integral role in thermoregulation, respiration, vasoconstriction of cerebral arteries, appetite control, ejaculation latency time, ovarian tumor suppression, aggression, neural activity, mood, nociceptive processing, and pain perception. J. Lappalainen et al. implied that without HTR1B gene people may manifest impulsive aggression (provocation rather than proactive aggression which is purposive and plotted) and tranquility both of which are correlated with psychopathy, including antisocial, alcohol dependence, egotistical, self-reported anger autism spectrum disorder, and hostility in young women [13].

K. Mekli et al. proposed that 5-HT_{1A} receptor genes (HTR1A, HTR1B) influence stress related information processing and convey vulnerability to anxiety disorders [14]. Most notably, A. Milatovich et al. have mapped the HTR1C locus to the human Xq24 chromosome by using somatic cell hybridization in cytogenetic analysis (SCHCA) and Fluorescence in situ hybridization (FISH), offering new insights into the gene expression in paleomammalian cortex and dysfunctional properties implicated in OCD, mood disorder, and social phobia [15].

Anorexia nervosa (AN), simply referred as anorexia (Greek origin: an−without, orexis−appetite), is a life threatening eating disorder and psychological illness, and is marked by intense self-starvation,

emaciation, hypophagia, low body weight, high lifetime mortality, extreme fear of gaining weight, and a distorted perception of body weight. AN, mostly seen in teen girls and young women, has an estimated standardized mortality ratios (SMRs) of 6.1%. Bulimia (Greek origin: bous−ox, limos−hunger), or bulimarexia (BR), is defined as an emotional disorder characterized by a distorted body image and an obsessive desire to lose weight, in which bouts of extreme overeating are followed by self-induced throwing up (purging), fasting, abuse laxatives, and eluding to washroom. "The brain 5-HT system" is believed to be the key to control of food intake. In eating disorders, it has an inhibitory effect on homeostatic and hedonic feeding behavior. Physiological and pharmacological studies support the possibility that a disturbance of serotonin neuronal pathways may contribute to the pathogenesis of AN, BR, and obesity.

Tacr3 gene

Tachykinin receptor 3 (Tacr3) is a receptor for the tachykinin neuropeptide neuromedin-K (neurokinin B/neurokinin 3). Associated with G proteins and 7 hydrophobic transmembrane regions, it activates a phosphatidylinositol-calcium second messenger system. It is worth noting that couple of disorders, i.e., idiopathic hypogonadotropic hypogonadism a.k.a. Kallmann syndrome and congenital gonadotrophin deficiency are interlinked with Tacr3 gene mutation.

Most recently, W. Q. Cui et al. have discovered that the Tacr3 gene in lateral habenula can induce allodynia and anxiety like behaviors in a mouse model of trigeminal neuralgia (Tn) [16]. A broad cohort study of total 127 patients (MDD 63.8% & anxiety 19.8%) with idiopathic Tn who underwent Jannetta microvascular decompression neurosurgery ensured significant pain relief [116]. Beyond their contribution in activation of gonadotropin releasing hormone, Tacr3 and its product neurokininin 3 (Nk3) receptors were discerned retrospective to schizophrenic patients in Japanese population [117].

NPSR1 gene

Neuropeptide S receptor 1 (NPSR1) gene encodes a member of the arginine vasopressin/oxytocin subfamily of G protein-coupled receptors. Neuropeptide S is a neurotransmitter that acts to suppress anxiety, fear, appetite etc., and operates as a neuromodulator in the onset of arousal and hyperactivity. Despite NPSR1 gene was first identified as an asthma candidate gene, an increased expression of this gene has found in fear conditioning circuit (i.e., amygdala, hypothalamus, and prefrontal cortex).

In panic disorder and agoraphobia (AG), NPSR1rs324981 polymorphism has been investigated in 122 patients who underwent functional magnetic resonance imaging (fMRI) using disorder specified Westphal-Paradigm. This study demonstrates for the first time that the association of NPSR1 gene variation in panic disorder and AG might drive malfunctioning in "fronto-limbic fear network" [17]. Subsequently, L. Lennertz et al. exhibited that the functional coding variant Asn107Ile of NPSR1 influences OCD and schizophrenia [18]. Specific NPSR1 alleles might act as genetic risk factors for neuroendocrine tumors, anxiety, primary insomnia, depression, PTSD, atopic eczema, recurrent abdominal pain, GAD, impulsivity/hyperactivity, systemic anaphylaxis, rheumatoid arthritis, and inflammatory bowel disease.

Intermittent explosive disorder

Intermittent explosive disorder (IED) first appears in childhood or adolescence and is typified by episodes of violent, aggressive, or impulsive behavior, explosive outbursts of verbal tirades, intense arguments, and disproportionate rage control. It is a lesser known mental illness falls in the category of impulse control disorders (ICD) (e.g., oppositional defiant disorder, conduct disorder, kleptomania, pyromania, pathological gambling, and trichotillomania). While anger is designed to promote survival, pathological anger is thought to underlie normal mood, various stress, and self-destructive behavior disorders, including IED, which has a lifetime prevalence of 7.2% in adults [19].

DSM criteria for IED were mediocre in terms of upgraded edition and research implementation. Recent work has shown that IED can co-occur with other psychiatric disorders like ADHD, antisocial personality disorder, bipolar disorder, MDD, psychotic disorder, conduct disorder, anxiety disorders, or PTSD. Cognitive reconstruction therapy, behavioral therapy, coping skill training, and certain medications, such as antidepressants: selective serotonin reuptake inhibitors−SSRIs (escitalopram, sertraline, fluvoxamine); serotonin-norepinephrine reuptake inhibitors−SNRIs (duloxetine, levomilnacipran, venlafaxine); monoamine oxidase inhibitors−MAOIs (phenelzine, isocarboxazid, selegiline); tricyclics (nortriptyline, doxepin, imipramine) and tranquilizers (chlorazepate, midazolam, lorazepam) are recommended treatment options for IED.

Due to the high hostile aggression, racing thoughts, and serious assaultive acts or destruction of property characteristics of IED, a series of studies were carried out which focused on the legal consequences of IED. They found a prominent linkage between IED and criminality. For instance, clients with IED were more likely to be habitual offenders and accumulate chronic arrests for murder, attempted murder, interference with law enforcement officers, arson, and aggravated sexual assault. In Bangladesh, it was found that the IED prevalence rate was 19.3% among a nationwide random sample of 1706 prisoners. The correspondence between IED and aggression reflects the need to develop and implement specific and individually tailored intervention approaches to correct IED offenders' behavior in order to avert new crime.

Scientists have discovered that aggression is regulated and inhibited by amygdala, the same region of limbic system that processes fear, triggers anger, controls behavior and emotion, and motivates us to act. M. S. McCloskey et al. concluded that hyperactive amygdala and relatively reduced orbital medial prefrontal cortex (OMPFC) potentially lead to IED [20]. In addition, IED patients showed less coordination between amygdala and OMPFC activation to angry facial expression while performing an explicit emotion information processing task during fMRI. Despite this is an overview of IED

associated genes, its generic trait, aggression is principally focused and explored to provide a comprehensive outlook on genetics of IED.

LRRC7 gene

Densin, or leucine rich repeat containing 7 (LRRC7), is a major component of post-synaptic density, has a biased expression in brain (i.e., amygdala, hippocampus, nucleus accumbens, putamen, and anterior cingulate cortex), and is a candidate gene for juvenile emotional dysregulation, aggressive and anxious behavior, and hypersociability. An essential paralog of this gene is ERBIN (Erbb2 Interacting Protein) that binds to unphosphorylated Erbb2 protein, may inhibit NOD2-dependent NF-kappa-B signaling.

New large-scale genome-wide association studies (GWASs) revealed that LRRC7 gene is linked to neurodevelopmental disorders, such as ASD, personality difficulties, Fragile X syndrome, global development delay, specific language impairment, and mood disorder, affording sufficient statistical power to elucidate LRRC7 variants associated intellectual disabilities. A rare neonatal disorder, chromosome 3q29 microdeletion syndrome (C3q29MS) is shown to be associated with DEL3Q29 and LRRC7. As children with C3q29MS get older, they may develop myeloid leukemia, patent ductus arteriosus, microcephaly, chronic ear infections, hypotonia, PBD, ASD, and schizophrenia.

Metabotropic glutamate receptor 5 (mGluR5) at striatonigral synapses releases calcium from intacellular stores, can be reduced by deletion of LRRC7 in 'C57 black 6' mice, thus, induces long term depression. LRRC7 is suggested to enhance mGluR5-mediated neurite development in embryonic neurons. However, to date, the molecular interaction between mGluR5 and LRRC7 in neurite morphogenesis remains unexplored. H. J. Carlisle et al. proposed that the mutant LRRC7 affects the localization of mGluR5 through reducing the amount of alpha actinin which promotes emotional dysregulation and persistent psychiatric difficulties [21]. In a separate study, the mutations in the WNT (Wingless-related integration site) pathway, including ROR2 (receptor tyrosine kinase-like orphan receptor 2) and LRRC7, involve both β-catenin-dependent (LRRC7) and β-catenin-independent (ROR2) pathways, suggesting that mutated LRRC7 play a predominant role in developing tracheomalacia and complete tracheal ring deformity in scleroderma associated interstitial lung disease.

MAOA gene

Monoamine oxidase A (MAOA) gene encodes MAOA enzyme that catalyzes oxidative deamination of amines, such neurotransmitters are dopamine, serotonin, adrenaline, and noradrenaline. It has earned the nickname "warrior gene" because people with defective MAOA exhibit increased level of violence and aggression in evidence and survey based studies. C. Marquez et al. showed that increased MAOA gene expression in prefrontal cortex but not in amygdala of peripubertally stressed animals led to aggressive behavior, altered amygdala, and orbito-frontal reactivity [22]. Others have demonstrated that the low expression of MAOA-uVNTR (upstream variable number tandem repeat) increases the risk of hyperactive amygdala and reduces corticolimbic volume, medial prefrontal cortex-rostral cingulate circuit abnormality, and insular cortical thickness.

Located on the X chromosome (Xp11.23), MAOA-uVNTR polymorphism has been documented to impact on the MAOA gene at the transcriptional level, and it is commonly found in 57.6% of Black males, 53.1% of Asian males, and 35% Caucasian males [24]. Assessed through DARTEL voxel based morphometry genotype technique, C. R. Rebollar et al. demonstrated that the violent-low activity MAOA-uVNTR carriers had decrease of gray matter concentration in right superior temporal pole [23]. The second domain of MAOA gene, i.e., MAOA-dVNTR seems to have a weak involvement in disorder, whereas MAOA-uVNTR is associated with several psychogenic traits, for example nicotine dependence, suicide attempts, chronic alcoholism, impulsivity, antisocial personality disorder, criminality, and callous unemotional.

MAOA gene deletion causes Brunner syndrome (BS), which is an X linked recessive disorder characterized by impulsive aggressiveness, lower than average IQ, mild mental retardation, limited friendships, hypersexuality, mood swings, and sleep disorders. E. E. Palmer et al. investigated two families with BS and summarized the different protein truncating variants of MAOA (p.S251KfsX2 and p.R45W), further found biochemical abnormalities, such as high serum serotonin, urinary metadrenaline, and low urinary 5-hydroxyindoleacetic acid (5-HIAA) [25]. Additionally, MAOA mutations in BS patients has an increased Nmethyl-D-aspartate (NMDA) receptor mRNA expression that results remarkable network bursts on microelectrode arrays (MEAs) [26].

ABCG1 gene

ATP-Binding Cassette (ABC) transporter gene is considered as one of the largest and oldest gene families in human biology. The human genome contains potentially or transcriptionally 49 active ABC transporter genes, are divided into 7 subfamilies (A to G) and facilitates ATP-dependent substrates across the cellular membranes (e.g., amino acid, cholesterols, bile acid, lipopolysaccharide, Na^{+}, NO_3^{-}, Mg^{2+}, proteins, glucose, and endobiotics). ABC gene has been gaining research interests due to its role in genetic disorders.

According to the genetic data, ABCG superfamily further classified into 5 categories: ABCG1, ABCG2, ABCG4, ABCG5, and ABCG8. Among these, ABCG1 has possibilities to influence the cellular lipid homeostasis; hence, aggression related traits (e.g., violence, hostility, suicidal behavior, irritability, and substance abuse) have observed high in state-trait anger expression inventory (STAXI) and questionnaire for measuring factors of aggression (FAF) scoring system.

ABCG1 plays a pivotal role in biosynthesis, efflux, and relocation of phospholipids, including phosphatidylethanolamine (PE), sphingomyelin, low density lipoprotein (LDL) and its oxygenated derivatives like cholestanetriol, cholesterol-beta-epoxide,

25-hydroxycholesterol, etc. In line with considerable research, PE (or lecithin) is documented to regulate osteoclastogenesis, in which ABCG1 and ABCB4 contribute to its translocations (A. Irie et al. 2017) [27].

As ignited be anticipated, ABCG1 gene is expressed in cholesterol-laden macrophage, liver X receptor (LXR), retinoid X receptor (RXR), duodenum, hippopotamus, central nucleus of amygdala, substantia nigra of basal ganglia, pancreatic beta cells, adopocytes, bone marrow, and lungs. Mutated ABCG1 gene is responsible for life threatening diseases, for example Tangier disease, sitosterolemia, diabetes mellitus, gout, atherosclerosis, ischemic heart disease, cholangiocarcinoma, breast cancer, non-small cell lung cancer, etc.

Suicidal ideation is one of the principle causes of death worldwide, mortality from it being 3%. In line with Carolin Donath's theoretical-epidemiologic model, there is an elevated risk for suicidal self injuries with a migration background (male lifetime prevalence 4.6%, female lifetime prevalence 15.7%). For instance, data on the epidemiology of suicidal ideation, suicide attempts, and direct self-injurious behavior in adolescents with a migration background in Germany suggested that the 12-month prevalence of direct self harm tendency was 17.6% and 7.9% had a lifetime history of suicide attempts [29]. Furthermore, the incidence of completed suicide is vastly higher in migrant men than native men (4.8% vs. 3.2%). Seemingly rare, five variants of ABCG1 in a sample study of 570 suicide attempters, spontaneous aggression and reactive aggression were clearly identified [28].

PPP1R1B gene

Phosphoprotein Phosphatase 1 Regulatory Inhibitor Subunit 1B (PPP1R1B) gene encodes dopamine and cAMP-regulated neuronal phosphoprotein-32 kDa (DARPP-32) that was initially discovered as an enzyme substrate of dopamine-activated protein kinase A (PKA) in dopaminoceptive neurons in the neostriatum. Dopaminergic and glutamatergic receptors regulate its phosphorylation profile, which, in turn, modulates protein phosphatase 1 activity, notwithstanding, they can be dysregulated by cAMP transducers in brain.

T-DARPP, a truncated version of dual kinase/phosphatase inhibitor DARPP-32, lacks the threonine containing 34 sequence at the N-terminus, and is overexpressed in tumor cells of breast, colon, prostate, esophagus, and lung. Notably, de novo trastuzumab resistance [a humanized monoclonal antibody targeting ERBB2 (Human epidermal growth factor 2: Her2 receptor)] has been occurred by the expression of both isoforms, t-DARPP and DARPP-32 in metastasis breast cancer, non-small cell lung cancer, and gastroesophageal cancers [30-32].

DARPP-32 is a key regulatory molecule in the dopaminergic signaling pathway for dopamine related phenotypes like extraversion, neuroticism, drug addiction, and schizophrenia. Numerous data have suggested that DARPP-32 plays a cardinal role in the regulation of ion channels activity by controlling directly or indirectly their phosphorylation state through inhibition of protein phosphatase 1 (PP1). In Huntington's chorea, altered DARPP-32 expression and protein levels in the striate nucleus are observed in both human and mouse models. A genetic and epigenetic study on 838 healthy German Caucasians revealed that DARPP-32 (SNP: rs907094) is associated with anger [33]. Moreover, these findings detected a negative association between anger scores and the volume of the left amygdala. As mentioned above, DARPP-32 is a robust integrator of dopamine and glutamate signals and is thought to play critical roles in the actions of multiple drugs of abuse, such as nicotine, Lysergic acid diethylamide (LSD), Phencyclidine (PCP), cocaine, ethanol, morphine, and 3,4-Methylenedioxymethamphetamine (MDMA). Genome-wide linkage scan and postmortem brain comparative study on Japanese population (subjects with schizophrenia=383, subjects with bipolar disorder=317, control subjects=384) suggested that PPP1R1B polymorphisms (i.e., rs907094, rs12601930, rs879606, and rs3764352) have significant involvement in bipolar disorder but are unlikely be the risk factor of schizophrenia [34]. Surprisingly, young males with lower volume of amygdala demonstrated longstanding history of persistent aggression, committing future violence, and development of early psychopathic features from childhood to adulthood [35].

CYP19 gene

The human CYP19 (Cytochrome P450, Family 19) gene is located on chromosome 15q21.2 region, contains ten exons and nine introns, spans approximately 123 kb of genomic DNA (93 kb regulatory region; 30 kb coding region), is regulated by four different microRNAs: miR-98, miR-181a, miR-378, and let-7f, and codifies aromatase, or estrogen synthetase. In general, aromatase is monooxygenase, mediates the final steps of androgens to estrogens by three successive 19-oxoandrostenedione oxidation of carbon at position 19 (C19) of the androgens; therefore, converts androstenedione to estrogen and testosterone to estradiol, estrone, and estradiol through a process called steroidogenesis. The CYP19 is predominantly expressed in gonads (ovary, uterus, prostate, placenta, testis), nervous system (brain, cortex, cerebellum, hypothalamus, amygdala), secretory organs (adrenal, skin, breast, thyroid, pancreas), and internal organ tissues (adipocyte, colon, lung, liver, spleen, bladder). N. Tabatadze et al. have found that the maximum expression of aromatase mRNA is present in the amygdala, bed nucleus of stria terminalis (BNST), and preoptic area of hypothalamus in male Sprague-Dawley rats [36].

Externalizing behaviors are maladaptive problematic actions directed toward an individual's environment, such as violates societal norms or basic rights of others, ignores teachers' reprimands, uses obscene gestures, cheating, physical aggression, vandalism, and stealing. Remarkably, the CYP19 variant allele was observed in association with problem behaviors (i.e., ADHD, externalizing behaviors, irritability, and poor adaptability) in male offspring of mothers who carried functional sex steroid polymorphisms known to affect estrogenic and androgenic compounds during pregnancy [37]. Also, lacking the same gene causes complete loss of reactive aggression in males, which is reinstated by 17β-estradiol supplementation [38].

Depression

Depression, a serious medical illness affecting more than 265 million people worldwide, is characterized by injured self esteem, persistent pessimism, polyphagia, hypothymia, abandoning hobbies (anhedonia), and sleep disturbances. The amygdala, best known for sympathetic responses (fear & stress), may play a determiner to store and interpret intense emotional memories like love, heartache, distress, humiliation, rejoice, etc.

A more recent research has shown that the amygdala-prefrontal cortex (especially subgenual cingulate cortex, lateral orbitofrontal cortex, and dorsolateral prefrontal cortex areas) connectivity was weakest in depressed MAOA-uVNTR carriers [39]. In a subsequent study, whole-brain analysis revealed significantly larger gray matter volume in the bilateral amygdala in first degree relatives of patients with depression [40]. Yet, compelling studies demonstrated that increased amygdala activation in adolescents is accompanied with MDD. By contrast, preservation of hyperactive amygdala reactions in early life stress has lowered effects on depressive symptoms.

Traumatic brain injury (TBI) and MDD share many somatic symptoms. A case controlled, prospective, and surveillance study conducted by R. E. Jorge et al. suggested that the prevalence of MDD in 32.7% individuals across the first year of post TBI [41]. As noted, several epidemiological studies on depression-pain syndrome (DPS) convey a clear message that the lifetime prevalence of overlapping symptoms (e.g., cluster headache, extremity pain, chronic lumbago, chest pain, pelvic pain, and abdominal pain) ranges from 23% to 36%, while the prevalence for concurrent MDD in patients of 65.3% identified as leading reason that they seek mental health care. Middle aged and elderly people diagnosed with depression have poor long-term prognosis, and remitting rates to tricyclic antidepressants, including amoxapine, nortriptyline, desipramine, etc., are almost identical among them. Older patients with late onset depression are, nevertheless, at higher risk of medical comorbidity. Indeed, depression is frequently known as one of the common comorbidities accompanied with somatic and chronic organic diseases, for example stroke, AIDS, inflammatory bowel disease, arthritis, cancer, anxiety disorders, and cardiovascular diseases.

A growing body of systematic methodology has established that young women (aged 15-25) greater than men experience unipolar depression, and the depressive symptomatology number is ranging as high as 41.6% [42]. Gradually developing postpartum depression affects new moms during or after pregnancy that may happen 1 in every 10 women within the first year of childbirth. It is well established that dysthymia is relatively more frequent in females (1.2% of males and 1.9% of females) that can lead to major lethality and suicide attempts in early onset of the disorder.

Genome-wide scan conduction by applying microsatellite markers in approximately two thousands people with a strong history of clinical depression revealed that chromosome loci 6p21, 12q22-q23.2, 18p11, and 18q11-23 as well as suggestive linkage regions on chromosome 2, 8, and 17 harboring genes are involved in the development of lifetime MDD [43, 44]. The presence of apolipoprotein E epsilon 2 & 4 (APOE ε[2, 4]) alleles are identified in adults along with geriatric populations (B. Richard et al. 2020) [45]. Astonishingly, anxiety candidate genes, including 5-HTTLPR, TMEM132D, and MAD1L1 may influence the susceptibility to dependent risk factors for loneliness and incident depression across the lifespan in intact depressionpsychological vulnerability spectrum.

LMO3 gene

MDD is a highly inheritable psychiatric issue in modern health care settings; nonetheless, only a handful causal genes (e.g., LMO3 (LIM Domain Only 3), or Rhombotin-3) provide new insights into its biochemical mechanisms. LIM is an idiosyncratic double-zinc fingers domain, coordinates three proteins (i.e., Mechanosensory protein 3 (MEC-3), Caenorhabditis elegans/Abnormal cell lineage protein 11 (LIN-11), and Insulin gene enhancer protein 1 (ISL-1)), and mediates “interactome” in the context of the protein-protein interactions. Inversely, LMO homeodomain (LMO-HD) comprises two exclusive cysteine-LIM domains and dearth of a DNA-binding sequence motif.

LMO3 promotes lung adenocarcinoma, neuroblastoma, gastric cancer cell invasion, renal cell carcinoma, Ewing sarcoma, B-cell lymphoma, T-cell leukemia, meningioma, anaplastic thyroid carcinoma, colorectal cancer, etc., in terms of carcinogenicity and genetic predisposition. To investigate the role of LMO3 in hepatic malignancy, Y. Cheng et al. selected HCCLM3, MHCC-97H, HepG-2SMMC-7721, SKHep-1, SNU-449, and HUH-7 samples to convey a research and its results suggested that the LMO3 is abundant in SMMC-7721 and MHCC-97H cells, on the other side, Salvador-Warts-Hippo pathway’s (SWH) phosphorylation of LATS1/YAP signaling was drastically increased by knockdown of the same gene [46].

LMO3 mRNA is preferentially expressed in basolateral nucleus of amygdala, accumbens nucleus septi, midbrain A10 dopaminergic nuclei, retina, anterior cingulate cortex, and uterus. There is a unique comprehensive hypothesis proposed by R. Remedios et al. that demonstrated the LMO-HD and LIM domains may play a crucial role in developing and patterning amygdaloid nuclei throughout life, mutant LHX2 (LIM Homeobox 2) embryo however, died with a disrupted lateral olfactory tract nucleus at mid gestation [47]. Importantly, network perspective on genetic generation and regulation of emotional hub, LMO3 depletion was associated with depression-related phenotypes and impaired innate fear-memory [48].

The 17-item Hamilton Depression Rating Scale (HAM-D) is used to predict the healthy-adolescents’ first degree relatives of patients with MDD are likely to have increased cerebral blood flow (CBF) in right amygdala [49]. In support of this, C. J. Bench et al. have reported that focal abnormalities regional CBF (rCBF) in the anterior cingulate cortex, left dorsolateral prefrontal cortex, and angular gyrus in patients with MDD [50]. The authors

also suggested that recovery from depression is associated with increases in rCBF in the same areas in which focal decreases in rCBF are described in the depressed state. In a follow up study, specifically the late onset monopolar major depressed patients had materially lower uptake of tracer Tc-99m HMPAO (Technetium-99m Hexamethylpropylene amine Oxime) in the left anterior frontal region when radio-imaged with single photon emission computed tomography (SPECT) [51].

CLOCK gene

Circadian rhythmicity (CR) (Latin origin: circa−around, diem−day) are the chronobiological phenomena and the physical, emotional, and internal environmental fluctuations that optimized at any points of a cycle of roughly 24-hour in physiological processes of living organisms, including animals, plants, fungi, cyanobacteria, and many microscopic organelles. Circadian locomoter output cycles protein kaput (CLOCK) genes encode the transcriptional activators which are considered as the fundamental components of CR maintenance.

Understanding the current post-translation regulation of autonomous oscillation model in human behavior control, CLOCK genes are two types: 1) central/master neural CLOCK resides in suprachiasmatic nucleus (SCN) of hypothalamus; 2) peripheral/secondary CLOCK is ubiquitous (e.g., liver, esophagus, pancreas, etc.) and integral. The disturbance of circadian rhythms contributes to somnipathic abnormalities, for example reduced total rapid eye movement (REM) sleep time, excessive daytime sleepiness (EDS) in narcolepsy, restless legs syndrome (RLS), shift work sleep disorder (SWSD), and delayed sleep phase syndrome (DSPS).

Distinctly, sleep disorders are regarded as the key etiological agent in developing MDD morbidity and mortality; therefore, conspicuously have drawn research attention. A study on 600 night shift working women in Bangladesh's garment factories−a single export division of international exchange for last 30 years reported the interlink between workers and the depression (23.4%) [52]. Accordingly, these workers had depression associated issues, such as traumatic life events, dysuria, part time employment, and chronic pain in multivariate regression model.

Mounting evidence has shown that autonomous circadian clock desynchrony (ACCD) may promotes coronary heart disease [53], dilated cardiomyopathy [54], ventricular arrhythmia [55], diabetes mellitus [56], obesity [57], breast cancer [58], hepatic carcinoma [59], lung cancer [60], schizophrenia [61], bipolar disorder [62], and GAD [63]. In ophthalmology, it has been demonstrated that retinal-specific KO of BMAL1 affects retinal development, induces myopia, and accelerates cone photoreceptor degeneration, providing new frontiers for ocular disease.

MDD-CR relation was previously been hypothesized. In contrast to this idea, P. H. Desan et al. explored that there is no association between CLOCK gene allele (SNP: T3111C) and MDD [64]. They demonstrated that none of the groups (European American 280, African American 58, history of MDD 143, and controlled 137) were significantly deviated from Hardy-Weinberg equilibrium. It is worth noting that CLOCK, cryptochrome 2 (CRY2), and period 1, 3 (PER1, PER3) expression in basolateral amygdala was significantly involved in pathophysiology of chronic mild stress (CMS)-induced anhedonia−oftentimes a symptom of depression [65]. In a sample of 219 healthy Italians, PER2 C111G polymorphism showed no influence on circadian phenotypes [66]. F. Calabrese et al. elegantly demonstrated that CLOCK and BMAL1 protein levels were significantly reduced in the nuclear compartment of the prefrontal cortex of CMS rodents [67]. Further, prolonged lurasidone treatment was able to normalize the molecular alterations induced by CMS exposure in prefrontal cortex, and was also able to regulate Rev-erbβ, PER1, and BMAL1 genes within the hippocampus.

MTHFR gene

Homocysteine (HCY) [a thiol-containing amino acid] and its remethylation to methionine (Met) process are governed by the MTHFR (5,10-Methylenetetrahydrofolate reductase) enzyme (encoded by MTHFR gene) that catalyzes the conversion of 5,10-methylene THF → 5-methyl THF and binds S-adenosyl-L-methione (SAMet) compound which, in turn, assists in hormonal activities together with one-carbon (1C) metabolism. The stratification of patients based on gender, ethnicity, age, and geography revealed that the MTHFR mutation leads to depression and anxiety [68], dementia and Alzheimer's disease [69], ASD [72], schizophrenia [70], and bipolar disorder [71]. Schizophrenia and depression are the most frequently reported in associated with MTHFR gene polymorphism, particularly C667T [73]. A. Gales et al. studied MTHFR deficit two adult siblings who had experienced focal onset epilepsy and pinpointed a polymorphism in exon 5; c.665C > T, p.(Ala222Val) as well a stop loss mutation in exon 12; c.1970G > C [74].

Total blood HCY is a predictor of depression, confirmatory data from a sample of 3751 patients aged ≥ 70 years implied that the total HCY lowering therapy (0.19mg/L) could be effective in treating the odds of mood affective disorders [75]. Despite B6, B12, and adjunctive folic acid treatment lowered the total HCY by 29.1%, on VITACOG trial, vitamin B-complex supplements reversed the accelerated cerebral atrophy rate and appeared to have an effect on mild cognitive impairment (MCI) to develope dementia like Alzheimer's disease [76]. Although people with C677T variants can process all types of folate, including folic acid, 5-MTHF, etc., another common polymorphism of MTHFR, A1298C was identified in patients who were more susceptible to early-and late-onset unipolar depressive disorder, OCD [77], papillophlebitis [78], chronic glaucoma [79], cerebral sinovenous thrombosis [80], arterial thrombophilia [81], idiopathic male infertility [82], migraine [83], ischemic stroke [84], renal insufficiency & cancer [85], primary varicose vein disease [86], and esophageal adenocarcinoma & Barrett esophagus [87].

FKBP5 gene

Newly discovered 51 KDa FK506-binding protein (FKBP5) is a peptidylprolyl cis-trans isomerase (or rotamase) whose methylated

status presumably predicts the individual response to integrated eye movement desensitization & reprocessing-dialectical behavior therapy (EMDR-DBT) in subjects with emotionally unstable personality disorder: borderline type (EUPD: bt) and PTSD (A. Snoek et al. 2020) [88]. While a retrospective case control study was performed in 101 Dutch individuals (57 intravitreal triamcinolone acetonide responders and 44 non responders) to investigate the corticosteroid induced intraocular hypertension, haplotypes of the FKBP5 demonstrated nil associations. Nonetheless, myocilin trabecular meshwork inducible glucocorticoid response (MYOC) gene was detected in two individuals of control group [89].

Controversial melancholia (literally meaning a mental condition characterized by great depression of spirits and gloomy forebodings; the dictionary.com, a feeling of deep sadness; Oxford dictionary) is a specifier for MDD and depressive patients with melancholic features have reduced probability of remission from MDD compared to those with non-melancholic depression. Evidence exists that FKBP5 may not be associated with melancholia, bipolar patients with suicidality however, have weak association with the haplotypes of FKBP5 [90]. Curiously, FKBP4 gene elevated in human immunodeficiency virus (HIV) infection, but was either silenced or downregulated in the pathogenicity of HIV-infected patients' depression [91].

Playing a relevant contribution to the hypothalamic pituitary adrenal (HPA) axis, FKBP5 and its product have been shown to lead persistent depressive episodes among end-stage gastric cancer sufferers and renal transplantation recipients [92, 93]. A pioneer work on amygdala exhibited that following a chronic stress induced FKBP5 mRNA expression is highly unregulated in the central amygdala and hypothalamic paraventricular nucleus [94]. Glucocorticoid receptor gene NR3C1 (Nuclear Receptor Subfamily 3 Group C Member 1) and FKBP5 expression were markedly decreased in amygdala of completed suicide male victims without manifestations of diagnosable psychiatric disorders like suicidality, paranoid personality disorder, substance abuse, anxiety, and manic depression [95].

EIEE79 gene

Epileptic encephalopathy, early infantile, 79 (EIEE79), or commonly known as GABRA5 (Gammaaminobutyric acid receptor-A subunit alpha 5), is related to GABAergic neurotransmission that has been implicated in the pathogenesis of affective disorders (i.e., bipolar disorder, manic depression, cyclothymia, and schizoaffective disorder) [96, 97]. The point prevalence of juvenile myoclonal epilepsy (JME)/Janz syndrome in large cohorts has been estimated at 5.3/10,000 and constituted 9.2% of all epilepsies. Compelling studies have demonstrated that JME may not associate with dinucleotide repeat polymorphisms of EIEE79 and GABRB3 genes [98, 99].

GABRA5 receptors are more confined in their expression with the highest levels prominent in distinct sets of neurons in the frontal cortex, amygdala, hippocampus, olfactory bulb, and cerebellum. Of note, performing massively parallel high-throughput sequencing (HTS) technology on 1695 epileptic patients, de novo mutations of GABRA5 (c.880G>T, p.V294F) and GABRA1 (c.343A>G, p.N115D) were identified as the attractive candidate for the early onset of epileptic encephalopathy [100].

L. Kallay et al. proposed that positive allosteric modulator KRM-II-08 (a new potent, innocuous benzodiazepine derivative binds to the GABRA-alpha5 subunit) induces apoptosis in pediatric medulloblastoma (MB) group 3 cells [101]. Mounting evidence pointed to a correlation between modest GABA receptor-A deficits and altered neuroendocrine transmission that was encountered in mechanistic heritability of depressed phenotypic populations [102]. The nucleus accumbens, an indispensable core of ventral striatum that receives dense innervation from limbic system (i.e., basolateral amygdaloid complex and anterior hippocampus), and its GABA network dysregulation displayed chronic unpredictable mild stress (CUMS) induced addiction and depression-like traits [103]. Notably, hippocampal downregulated TAC1 (tachykinin precursor 1), CALB1 (calbindin 1), and GABRA5 paradigms were confirmed in integrated datasets analysis of impaired memory and learning new tasks in Alzheimer's disease [104].

Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis

Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are all potentially debilitating neurological conditions. Statistical studies have been described that AD has the highest estimation, i.e., approximately 51 millions people age 65 or older globally and in middle-income developing countries this will be projected increase to 67% in prevalence rates by 2050. Albania has the fastest growing PD prevalence in the world, demographic figures for Parkinsonism were demonstrated to be 900 per 100,000. Furthermore, a result of swelling geriatric PD deaths exceeded 0.21% of total deaths in Bangladesh.

Remarkably, C9ORF72 [cytogenetic location: 9p21.2] is implicated in the phylogenetic etiology of AD, PD, and ALS patients [105-107], yet, the signature volume reduction of three areas: the accessory basal nucleus, cortico-amygdalar tradition region, and medial prefrontal cortex during Pavlovian fear conditioning (dorsolateral part) found in progressive degenerative neuromuscular diseases, such as primary lateral sclerosis (PLS) and frontotemporal dementia-motor neuron disease (FTD-NMD) are associated with C9ORF72 gene mutation [108]. SNCA (synuclein non-A-beta component of amyloid precursor) gene encodes alpha-synuclein (αS) which seems to have a high affinity for amygdala in vitro PET employing radiotracer PIB (Pittsburgh compound B) targeted amyloid-β peptide lesions in AD [109]. αS-pathic fibrillization in amygdala is dynamic, rather than simply Lewy bodies (LBs) formation, and is one of the major drivers of neurodegeneration through disruption of cellular functions seen in AD and PD and indicating mitochondrial damage and deficits (A. L. Mellier et al. 2020) [110].

Keratoconus (KC), a progressive thinning and corneal dome shaped tissue into a conical ventral bulging, is an ophthalmic

disorder that results in extreme myopia, glare or halos around lights, distorted diplopia, blurred and/or hazy vision, and in severe cases ruptured cornea. [Cu-Zn] superoxide dismutase 1 (SOD1) mutations, such as 7 base deletion in intron 2 and lacking entire exon 3 variant on chromosome 21 are recognized rare candidate for familial KC [111]. However, apparently 65 different mutations of SOD1 (e.g., defect in TATA box, leu144phe, D76V, etc.) [112-114] were confirmed in 22% of patients with sporadic ALS and familial ALS.

Lytico-bodig disease, or Parkinsonism-ALS-dementia complex (PALSD), is an endemic neurodegenerative disorder with high incidence described on island of pacific Guam' Chamorro community residents. A recent research has suggested that the amygdala may be selectively vulnerable to developing both αS and tau pathology [115]. αS was detected in 36.4% PALSD patients but not detected in Guamanians without primary α-syncleinopathies (e.g., dementia with LBs, AD, multiple system atrophy, etc.). Genetically, αS appears to enhance tau phosphorylation; however, in PALSD, taupathy occurs independent of β-amyloid deposition in amygdala, indicating the dissociation of intraneural communication−a hallmark of neurodegeneration frequently observed in this location.

Conclusion

The presented paper is the first, to the best of my knowledge, in its approach to scrutinize the genetics of amygdaloid disorders. Moreover, it is novel in exhibiting that neurological disorders-associated genetic variants can potentially trigger multisystem diseases. Lastly, many rare but important amygdaloid disorders and monogenic mutations implicated in the phylogenetic etiology of several neuropsychiatric diseases are intensively analyzed in this review article.

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