Genetics' Influence on Drug Abuse & Addiction; Interactions of Endophenotypes & Genotypes

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ABSTRACT

"Addiction" is a multifaceted complicated disorder with many interrelated causes, as well as environmental and genetic features. Several hereditary variables that have an effect on these features might work in together to influence vulnerability and the extent of being an addict. Molecular re-sequencing of the latest and formerly researched genes holds a crucial place with regards to the breakthrough of hereditary alternates of possible interest. This report presents a brief review of this complicated disorder through genotyping and phenotyping aspects, and examines their correlation in creating and driving this disease.

Introduction

The development of a person's vulnerability towards the addiction to drugs is not only genetically influenced but there is a strong contribution of the environment. These reasons along with the effects of drugs directly leads to a progressive influence from irregular to habitual drug usage, in other words it's a shift from misuse to habit, and the tendency for recurring setbacks even after the person reaches a "drug-free state" (Kreek, LaForge & Butelman, 2002;Kreek, Bart, Lilly, LaForge & Nielsen, 2005).

Continual contact with commonly abused drugs leads to continual adjustments of the brain. This means variation in gene expression as well as in expression of their protein products, in protein-protein interactions, in neural networks and in neurogenesis and synaptogenesis. Eventually all of these have an effect on patients' actions.

As the levels of strains differ they tend to show different results with respect to the molecular and cellular reaction to drugs (Kosten, Miserendino, Haile, DeCaprio, Jatlow & Nestler, 1997). Factors which are hereditary are somewhat involved in the effects of drugs that are induced directly, which include modification of "pharmacodynamics" or "pharmacokinetics" of a misused drug or even a treatment chemical. For almost all of the studied diseases, mostly different cancers, the precise contributions that are hereditary and the varying factors of the genes have not only been recognized but also verified by various studies. on the other hand, the variants that were identified, as a whole, make up a small part of the probable hereditary contribution. The study of genes related to the multifaceted disorders of "psychiat-

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ric or behavioral" nature, like addiction, presents a challenge. They have particular "phenotypic" classification of people and the categorization of racial/cultural base. Similar challenges have to be faced during the research of additional also must be faced in the study of other complex genetic disorders.

Until now the medical health cost related to addiction is at the to as compared to other medical disorders. The foreboding disorders such as hepatitis C, lung cancer and HIV/AIDS are also featured in these disorders. As a result, it is important that all contributing components towards addiction that include the hereditary factors should be looked into, aiming at the improvement of primary prevention, early intervention and long term treatment.

Studies carried out in the domain of family and twin epidemiologies reveal the connection of addictive disease with genes, displaying the role of genes in increasing a person's susceptibility to addictive disease, with estimates of heritability of 30-60%. The first demonstration of addiction heritability was related with alcoholism, which is resulted by distinctive genetic factors such as the aldehyde dehydrogenase genotype (Kreek et al., 2005). Vulnerability towards addiction can possibly be caused by both genetic alternates, common to all addictions as well as to those specific to a particular addiction. However, some genetic variance is peculiar to drug class, as in the case of opiate addiction (Tsuang et al., 1998).

In addition, there are several environmental impacts as opposed to genetic factors causing the shift from early not consistent drug use to regular intake of drugs, and eventually to drug addiction/ dependence that might potentially lead to relapse (Tsuang et al., 1999).

Addiction's Endophenotyping

In genetic studies, we can consider addiction as a single pathology or phenotype or divide it to some underlying pathologies or endophenotypes that could results in, or manifest as addiction. Endophenotypes are defined as "measurable components unseen by the unaided eye" and may be neuropsychological, endocrinological, cognitive, neuroanatomical or biochemical in nature (Gottesman and Gould, 2003). Endophenotypic approach to addiction can provide insight into the etiology of addiction syndrome and such information can provide possibilities for categorizations of its underlying pathologies and its subtypes. Impulsivity, risk taking, stress responsivity, or components thereof may represent important endophenotypes for substance addictions and other impulse control

Clinical Phenotypes	Cognitive/ Personality Endophenotypes
- Stage of Abuse/ Dependence - Type of Drug/ s - Age of Onset & Duration - Severity of Addiction - Comorbidities - Other Risky Behaviors	- Reward vs Punishment / Time / Probability • Varieties of Impulsivity • Risk Taking Tendencies • Novelty / Experience Seeking - Stress Responsivity - Emotional Learning
Biological Endophenotypes	**Neurotransmitters & Their Receptors**
- Hormonal Reactivity • HPA Axis • Sympatomimetic Hormones • Oxytocin/ Prolactin - Cell Interactions & Signaling Pathways - Plasticity & Synaptic Learning	- Dopamine - Serotonine - GABA - Adrenergic/ Cholinergic - Opioids - Glutamate

Table 1. Different Participating Factors in Working on Genetic Basis of Drug Abuse and Addiction NEUROSCIENCE

disorders such as intermittent expulsive disorder or pathological gambling (Brewer and Potenza, 2008). This approach could help differentiate subclasses of addictive disorders (genetically based and otherwise), providing possibilities for clustering, diagnosis, medical approaching and individualized treatment (Brewer and Potenza, 2008). In this approach, We can address some main cognitive processing involved in addictive behaviors such as impulsivity, risk taking or more detailed cognitive characteristics such as novelty seeking, reward dependence, harm avoidance, varieties of impulsivity and etc (Ekhtiari et al., 2008a). Variation in these dimensions, may contribute to the initiation of drug use as well as the transitions from initial drug use to regular use to addiction. Each of these endophenotypes may have, in part, its own genetic basis (Table- 1).

Some of these endophenotypes could be assessed by self reported personality questionnaires or by indirect cognitive assessment tasks. Different self report instruments often used in genetics research to quantify personality dimensions such as the Tridimensional Personality Questionnaire (TPQ) or the more complete version, the Temperament and Character Inventory (TCI; which measures novelty seeking, harm avoidance, reward dependence and persistence), the NEO Personality Inventory-Revised (NEO-PI-R; which measures neuroticism, extroversion, openness, agreeableness and conscientiousness) and the Barratt Impulsiveness Scale (BIS) (Ekhtiari et al., 2008b); which measure cognitive and motor impulsivities Some of these questionnaires and variables are based on the concept of factor analysis, in which a large number of individual questions contribute to a smaller number of underlying traits. In addition, addiction can be defined with scales such as the KMSK, which measure duration and magnitude of drug use. The TPQ, TCI, and NEO-PI-R provide a broader and more timeintensive characterization of endophenotypes. By contrast, the Barratt and KMSK (Kreek–McHugh–Schluger–Kellogg) scales provide a relatively rapid evaluation of a particular phenotype (impulsiveness and degree of exposure to a drug of abuse, respectively).

There are some cognitive tasks for indirect quantification of addiction endophenotypes, but few genetic studies have been used them till now. Iowa Gambling Task (IGT) (Bechara et al., 1995; Ekhtiari et al., 2002a), Balloon Analogue Risk Task (BART) (Lejuez et al., 2003; Ekhtiari et al., 2004a), Go/No Go Tasks, Delayed Discounting Tasks (Ekhtiari et al., 2002b; 2003) are well-known tasks in this field (Ekhtiari et al., 2008a).

These cognitive-behavioral tasks evaluate underlying cognitive processing in prefrontal cortex and other related areas (Ekhtiari & Behzadi, 2001) that are directly participate to addiction vulnerability and addictive behaviors such as reward-punishment evaluation (Ekhtiari et al., 2005; 2009), temporal discounting (Ekhtiari et al., 2004b) and risk taking tendencies.

Classifying Heritable Aspects in Endophenotypes & Addiction

Studies related to the link of family were most extensively used, until recently. These studies explored the spread of heritable indicators of precise "genomic regions" of importance and "phenotypes" in family history of at least two or more generations preferably, that include the study of pairs of siblings that may have been affected even more dominant when the parents as well as the siblings are included. An alternate is the study through association like, whether a specific "DNA allele" is more common in patients in comparison with "control subjects", rather than expecting it to be by chance.

Studies related to association most likely distinguish connected variables that may be concerned with some malady (1) if they fall between forty to eighty thousand "nucleotides of genotyped variants", (2) if the balance of association is comparatively high which often happens when there is "a non-random distribution of allele combinations; for example, in a haplotype" and (3) if size of the consequences is between "moderate to high". It is a slightly lesser distance in comparison to the possibly "family-based linkage studies". Even though these studies may be possible for "endophenotypes" like impulsiveness, response to anxiety and risk taking, "family studies" in illegal drug usage are hard to carry out for the simple reason of massive disgrace of addiction, the disturbance of concerned families and the complexity in determining the members of the family.

A study in the area of alcohol addiction was undertaken with the help of these family studies called the "Collaborative Study on the Genetics of Alcoholism" which was funded by "United States National Institute on Alcoholism and Alcohol Abuse" (Foroud et al., 2000). There was strong evidence provided with the help of these researches relating to the association of several DNA, including "GABA receptor subunit A2 (GABRA2) and muscarinic acetylcholine receptor M2 (CHRM2)", about the dependence on alcohol (Edenberg et al., 2004; Wang et al., 2004). "Hypothesis-oriented selection" is another basic approach used to identify precise involvement of genes in a disease.

Initially one may think while making a study of addiction to drugs, that the heritable factors leading "direct and downstream" particle proceedings changed by persistent exposure to the misuse of drugs. For instance, cocaine hastens extracellular dopamine through jamming the dopamine transporter's action. Furthermore it raises the expression of gene and encourages the discharge of opioid ligand dynorphin in the striatum". Similarly the variants of the "preprodynorphin gene (PDYN)" are known to be connected with susceptibility to develop "cocaine addiction" (Kreek et al., 2005).

An additional method is to utilize the "positional approach", this is done by carrying out "genome-wide scans" to recognize "chromosomal" points that possibly will be connected with a particular "disorder or addiction". More over there is a requirement of 'fine mapping' in the recognized "chromosomal regions". Previously different ways that used the "single nucleotide polymorphism (SNP) arrays" or additional "panels of single SNPs" permitted the classification of more distinct areas for 'fine mapping' in a much easier way, much advanced system than "microsatellite marker panels". As "SNP panels" turn out to be more comprehensive regarding the general differences in the "human genome", the examination of these variants linked with a "phenotype" can be done faster.

Alternatives in the area of coding DNAs may alter the 'protein product', as in 'A118G' alternatives of the "μ opioid receptor gene (OPRMl)". Some might change the quantity of 'gene expression' like "prodynorphin promoter region variants", and some might change the speed of "mRNA degradation" like the "dopamine receptor D2 variant, DRD2", all can be contributional towards the functionality (Kreek et al., 2005; Nielsen et al., 1998). These factors in turn affect not only the "normal physiology" and but also the particular features of "addiction pathophysiology".

Finally, though, the thorough "phenotypic" evaluation seems crucial in case of these studies of "addiction genetics" as insufficient or poor "phenotypic assessments" direct towards false outcomes. This type of evaluation involves the use of a varied series of devices in order to assess "endophenotypes, comorbid disorders, detailed histories of initiation of drug use, and progression to addiction". Particular "phenotyping" not only takes time but also requires personnel that are well trained. Furthermore, due to the expense and time, there may be a fewer number of subjects to study.

There are other factors that may be influencing the inheritance in population --like, there are major racial/cultural dissimilarities in "allelic frequencies" of alternatives of many precise genes. To use the recently designed techniques basically involving a mixture of SNPs or other variants they need to be analyzed and controlled. Various techniques have been evolved regarding the methods used for statistical genetics like the "statistically determining inferred haplotypes".

The study at hand looks into only some of the previously conducted research which was considered to hold possible meaning; mostly they are taken from reputed studies that made use of suitable or best possible designs, "phenotypic assessments, molecular techniques and statistical genetics analyses". Furthermore, emphasis must be laid on the proof of improved hereditary susceptibility to becoming an addict does not mean that it will happen to be. Various things including the influence of the environment or the drug availability are a strong force for the progress towards abuse of drugs or its addiction.

Endophenotypes & Addiction: Impulsivity

One of the endophenotypes is impulsivity which is distinguished by "behavioral disinhibition", explained as sudden act totally unplanned in order to satisfy a want. Some of the things that show are "aggression, violence and suicide". Nevertheless, "impulsivity", as a characteristic, happens on a range; therefore, it is not a marker of pathology. Earlier studies indicated "low serotonin levels" and its "metabolites" in dissimilar "bio-liquids" in a variety of forms of "impulsivity" (Ekhtiari et al., 2008a). Reduced amounts of 5-hydroxylindolacetic acid (5-HIAA), which is cerebrospinal fluid considered as the most important metabolite of serotonin as well as an indicator of serotonin metabolism, are associated with severe despair, impulsivity, hostile and violent behavior as well as early-onset alcoholism. (Kreek et al., 2004; Nielsen et al., 1998). Furthermore , the discharge of Prolactin as a result of Fenfluramine challenge test, a biomarker of serotonin metabolism, displays that low serotonin metabolism and impulsive behavior (Coccaro et al., 1994), are somewhat related to each other. This is also associated with an increased risk for impulsive endophenotypes in close relatives (Coccaro et al., 1994).

The lack of control over impulses can be because of "impaired inhibitory control" resulting in "drug-induced" modifications in the "frontal cortex". It is a general behaviour found in the adolescents that they will experiment with drugs and hit off on usage of drugs, however there are a few cases that have been reported about al-

cohol use and "prescription opiate addiction", normally at a later stage even in the elderly. Another factor of the adolescents to move into the drug addiction category may be the hormonal changes they are undergoing or the "Neurodevelopmental" processes that may bring changes in the level of impulsiveness.

Attitudes generally set apart by shortfalls in "impulse control" have been considered for linkage and association with contender DNAs within "serotonergic system (for example, tryptophan hydroxylase 1 and 2 [TPH1 and TPH2] and serotonin transporter [SERT]), the dopaminergic system (tyrosine hydroxylase [TH], dopamine receptor, and dopamine transporter [DAT]), the monoamine metabolism pathway (monoamine oxidase A [MAOA] and catechol-O-methyltransferase [COMT]), and the noradrenergic system (dopamine β-hydroxylase [DBH], inhibitory system, GABAergic and nitric oxide systems, as well as other genes)" (Kreek et al., 2004; Nielsen et al., 1994; Limosin et al., 2005). All of them are allegedly connected with either addiction or alcoholism. Additionally, the "neurotransmitter systems" as coded by the DNA play an active part in the "acute and chronic" results of highest abuse and, so bring about addiction along with beginning the drug usage.

In rash aggressive reprobatea, a "TPH1 gene variant was associated with reduced CSF 5-HIAA and suicidal behavior" (Nielsen et al., 1998; Nielsen et al., 1994).These differences are also linked to impulsivity, violent behavior and a variety of suicidality.

The rest of the genes like DRD3, SERT, 5-HT2A, MAOA, and dopamine receptors D3 and D4 (DRD3 and DRD4) are associated with impulsiveness (Kreek et al., 2004; Nielsen et al., 1994). It is on the whole connected with precise diseases related to addiction. More work done on the position of this impulsiveness and its hereditary alternatives at particular levels of addiction might be able to through some light on "neurobiological mechanisms" which primarily defines clinically the levels in the course of addiction, reversion and healing.

Endophenotypes & Addiction: Risk Taking

The behaviors associated with ambiguity, possibly accompanied by natural unconstructive penalty, any potential harm, or without any strong emergency planning can be termed as Risk taking. The phenomenon can be measured as responsibilities that involve an assessment of some associated risk and reward.

Signs of taking risk are seen in patients who are "pathological" gamblers or addicted patients that may be evaluated with the help of particular "clinical questionnaires" like the "South Oaks Gambling Screen" or measures of behaviours like "Balloon Analogue Risk-taking Task" (Lejuez et al ., 2003; Khodadadi et al., 2009; Zuckermann et al., 1995) stated that "Novelty or Experience seeking, frequently considered as one of the dimensions of risk taking, characterized by considerably high reactivity to novel stimuli, can alternatively be considered an endophenotype, detected in certain psychometric instruments (such as the Temperament and Character Inventory or Sensation Seeking Scale)" (Ekhtiari et al., 2008 a).

Seeking originality can be interrelated with the progress from the single time use to complete habitual usage in many drugs. "DRD4 receptors" are components of the 'D2-like' family of "Gi-coupled dopamine receptors". Several researches describe a link between the quest for innovation with "DRD4 receptor" alternatives, like, among high "Tridimentional Personality Questionnaire" these scores and a particular "allelic variant" (Lusher, Chandler & Ball, 2001; Schinka, Letsch & Crawford, 2002). DRD4 binding is located in the brain areas in the tissue, that consist of the "prefrontal and entorhinal cortex, hippocampus, dorsomedial thalamus, lateral septal nucleus and hypothalamus" (Primus et al., 1997). Particularly, no obvious "DRDR4 binding" is notices in the "nucleus accumbens, caudate or putame", that is the main spot of "D2 receptor binding" and arbitrate the straight "psychostimulant and reinforcing effects" of drugs of abuse. In disparity, the 'DRD4' allocation guide proposes roles in motivational, intentional, mnemonic and emotional functioning, on the foundation of some main tasks which are considered to be arbitrated by these areas of the brain.

Even though many researches recognized the link between the various "DRD4 polymorphisms" with the search for novelty, the results were not able to be duplicated time after time (Lusher, Chandler & Ball, 2001; Schinka, Letsch & Crawford, 2002). These varied results may be the outcome from differences in the subjects age, phenotyping tools employed and racial fusion of patient populations, along with other issues, in various studies (Lusher et al., 2001).

Further 'molecular' aims drawn in "monoaminergic" task have been associated to "novelty seeking and drug abuse". The "DRD2 Taq1A polymorphism" is broadly researched and reported in the text and famous press for its connection with not only alcohol addiction but also diverse disorders. Nevertheless, this relationship needs effective documentation, through contradictory "meta-analyses" of various groups of people (Uhl et al., 1993; Gelernter et al., 1993).

Comorbid Disorders

The abuse of substance in many addicts does not become a disorder that is isolated. There are 4 conditions of psychiatry like anxiety, unsociable behavioral mayhem, dejection, and attention deficit/hyperactivity disorder that are usually found in the "psychopathology or physiology" of addiction to "opiates and alcohol" (Rounsaville, Weissman, Crits-Christoph, Wilber, & Kleber, 1982). Commonly known conditions related to being comorbid are sadness and unease, with repeatedly found "unipolar" despair. In "epidemiological studies", twenty to fifty percent people having addiction problems like cocaine, alcoholism, and other kinds like "opiate addiction" encounter anxiety or depression disorders (Rounsaville et al., 1982). On the other hand, the occurrence of "comorbidity" when people initially start on the use of drugs has not been properly defined. It is for certain that people already using illicit drugs or being addicted can be termed as being non-social as far as their personalities are concerned as they are into criminal activities. The disorder of "attention deficit/hyperactivity" in the early days or mature shape is frequent, particularly in people who are reliant on stimulants like cocaine (Levin, & Kleber, 1995).

Another thing that was established was the psychiatric disorders and that involvement of genetics in each of these, similar to the addictive diseases talked about in this paper. While the presence of "comorbidity" makes it complicated to decide which of the DNA alternatives add not only to the addictive disease but also the psychiatric one, or to both. A major area where controversy exists is the part that "comorbidity" holds in the heredity of addiction remains a point of argument.

Response to Stress

The main part of the "stress-responsive system" is the "hypothalamic-pituitary-adrenal" (HPA) axis. "HPA axis" commencement or repression influences obsession. (Kreek, 1972; O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002) A question can be thus posed: "Does a heritable connection among HPA axis function and addiction exist?" Furthermore the typical feedback rule of the hypothalamic-pituitary-adrenal axis by "corticosteroids", scientific researches with "opioid antagonists" show that the "endogenous opioid system", by means of "both μ and k opioid receptors, also tonically inhibits the HPA axis." Another point presented herewith is the out of character response to "stress and stressors", keeping a strict focus on the "HPA axis", adds to the persistence of precise addictions, in addition to the chance of relapse even after the brain undergoes "plasticity" because of addiction. (Kreek et al., 2002; Kreek, 1972; Kreek, 1996). Research has identified that "active heroin addicts have a hypo-responsive HPA system and that patients with cocaine dependence, including former heroin addicts in methadone maintenance treatment (MMT) with ongoing dependence on cocaine, show a hyper-responsive HPA axis." (Kreek et al., 2002; Schluger, Borg, Ho & Kreek, 2001).

In models of animals the accustomed place choice and administering the drugs , chronic and acute affects of stress on the HPA axis, along with additional parts of anxiety response in the brain, and may augment the strengthening effects of drugs of abuse. The properties for reward are influenced by stressors for drugs at the different levels of self-administration studies of laboratory animal that include "initiation, maintenance, extinction and reinstatement". These rae also considered to be representative states in humans of "initiation and maintenance of addiction, withdrawal and relapse".

Generally, it can augment attainment, add to resistance to annihilation, and bring on restoration of self-administration. The studies of animals show that there is a corresponding alteration of the molecules in the HPA axis that come to be because of "acute chronic administration" of drugs of abuse.

Some studies show that when specifically prepared scripts for evoking drug-cue related was raed to the fresh recently cocaoin-abstinent cocaine-dependent subjects were read individually tailored scripts designed to provoke stressful, drug-cue related or neutral, relaxing experiences." It was found seen that the scripts usingemploying stressful and drug-cue brought to mind an increased longing, unease and cardiovascular measures, along with the augmented "plasma levels of ACTH, cortisol, prolactin and norepinephrine," not only demonstrating association of the hypothalamic-pituitary-adrenal axis, but also signifying that the "sympatho-adreno-medullary" method is concerned in cocaine craving during self-restraint (Sinha et al., 2003).

Particularly the μ and k "opioid" receptors also known as "endogenous opioid system", reveal inhibitory control over the said axis. Apparently it is the inhibition of the tonic rather than criticism and inhibition of circadian, just like the "glucocorticoid regulation" of axis. The main purpose of addictive opioid drugs is "μ opioid" receiver. The deficiency of Mice lacking the μ opioid receptor gene (OPRM1) in mice show considerably less or extinct analgesia, reward, physical dependence, and respiratory depression as a result of opiates such as morphine" (Kreek et al., 2005).

In studies of *"in vitro"*, it was found that the "endogenous opioid peptide β-endorphin bound the 118G (Asp40) receptor variant with threefold greater affinity than the prototype 118A (Asn40) receptor30. Also, β-endorphin binding to the Asp40 receptors displayed three times greater effectiveness in triggering the G protein-coupled inwardly rectifying potassium (GIRK) channels, an essential intracellular signaling system of this receptor" (Bond et al., 1998). None of the other tested agonist demonstrated dissimilarities in binding to, or GIRK commencement of, the alternative receptors (Kreek et al., 2002; Bond et al., 1998; Schluger et al., 2001).

However the results of the alteration in reply of the "118G variant μ opioid receptor" leading to the forecasting "HPA-mediated" strain responsivity was changed in people articulating the alternative. (Bond et al., 1998; LaForge et al., 2000). Though the "molecular or cellular" devices still need to be completely made clear, these guess works are borne out in scientific studies in which people who are healthy were managed "a μ opioid receptor antagonist, naloxone or naltrexone", causing instant commencement of the "HPA axis" by jamming the "μ opioid receptor"; that is, by disinhibition. "Subjects heterozygous for the 118G allele showed a greater HPA response to opioid antagonist than did subjects with only the prototype receptor, as measured by serum ACTH and cortisol level" (Kreek et al., 2005; Kreek et al., 2004). In addition to this the people with the "118G" alternative receivers had an additional positive medical response to treat the "alcoholism with the opioid antagonist naltrexone" (Kreek et al., 2005; Kreek et al., 2004).

The differentiation in reaction to the cure may be arbitrated by dissimilarities in "HPA axis" commencement due to "receptor genotype", as modest start of this axis is preferred in any case by some alcoholics (O'Malley et al., 2002). This variation in "HPA axis" responsivity might be a feature in the probable participation of this alternative to the threat for generating addiction and alcoholism as studies have reported. (Bart et al., 2004; Bart et al., 2005).

The next genetic material is COMT which "connects the HPA axis, reacts towards stress and addiction, releases an enzyme which acts as a catalyst in the degradative metabolism of the catecholamine neurotransmitters dopamine, norepinephrine and epinephrine, and dydroxylated estrogens" (Kreek et al., 2002; Schluger et al., 2001). An ordinary "guanine-to-adenine transition" 34 in axon 4 causes the replacement of "methionine for valine at residue 158". The "methionine" type has better thermo capability and a 3 – 4 fold lower "enzymatic activity" than the valine form (Kreek et al., 1998). Hereditary connection and linkage studies propose the "polymorphism" may be concerned in quite a few dissimilar "psychiatric disorders". The low-activity methionine form is connected with greater than before threat for alcoholism in quite a lot of studies.

HPA axis function is influenced by the genotype of this polymorphism. Subsequent to the management of "naloxone", people with the "homozygous Met/Met genotype" have improved augmentation in "plasma ACTH and cortisol" than do individuals with either one or more "high-activity valine alleles (Val/Met or Val/Val)" (Oswald et al., 2004). In this paper, "all subjects were A/A homozygous for the OPRM1 A118G SNP, as this polymorphism also affects HPA response to opiate antagonist challenge".

On the whole, the goings-on of the "HPA axis" seems to experience all-embracing plasticity as a consequence of contact with abuse of drugs. In addition to this "HPA" responsivity is pretentious by heritable alternative. Also with the result that strain is an impulsive issue in deterioration, these consequences find out the requirement for more wide spread studies of inherent alternatives in the "HPA axis" and addiction to drug.

Genetic Factors Directly Associated with Addiction

Previously noted facts that heritable features count to approximately thirty to sixty percent of the general inconsistency involving the threat, are responsible for the progress of drug addictions. However at different stages the influence of environment or genes are different (Tsuang et al., 1998; 1999). The possible influence of the "endophenotypes of impulsivity and risk-taking, of stress responsivity, and of comorbid psychiatric conditions", as well as the possible gene alternates concerned with all of these issues, have already been included. The study will further emphasize direct hereditary studies of "addiction to alcohol, opiates and cocaine and other stimulants". The focus of these studies is on hereditary alternatives and diseases of addiction with no analysis of the "endophenotypes" mentioned previously. Studies of linkages were carried out to classify hereditary determinants of "addictive diseases" (Kreek et al., 2005; Kreek et al., 2004; Gelernter et al., 2005; Uhl, 2004). An early project started as an effort to recognize the involvement of genes in alcoholism was "Collaborative Study on the Genetics of Alcoholism (COGA)".

A "multiple pooling method with a 1,497-SNP microarray identified (Yuferov, 2004) chromosomal regions" that might be concerned in susceptibility to the use of drugs

in "African-Americans and European-Americans". All the subjects affected had "polysubstance abuse", together with "nicotine and alcohol" usage or craving, so the areas recognized may enclose genes that are concerned in "addictions to multiple substances"(Uhl, 2004). Polysubstance abuse studied herewith indicated that a minimum of fifteen large "chromosomal regions" were related with areas recognized in more than one study associated with the addiction of alcoholism and nicotine which suggested that genetic factors were at play (Uhl, 2002).

Genetic variants may also add to opiate habit. One hopeful contender is the μ opioid receptor gene (OPRM1). a number of individual variants and haplotypes at the OPRM1 locus are linked with opiate dependence (Kreek et al., 2005; 2004; LaForge, Yuferov & Kreek, 2000). A number of studies of the A118G SNP, together with other polymorphisms in this gene, have failed to recognize connection of an addiction and this locus, maybe due to variations in the genetic structure of the studied population, distinctions in population substructure or the application of different evaluation standards.

Another connection of the OPRM1118G allele with alcohol dependence has been reported in Swedish individuals from central Sweden, further representing the significance of ethnic/cultural background (Bart et al., 2005). There has been an connection between a single SNP and also a specific haplotype of variants of k opioid receptor gene (OPRK1) and opiate addiction (Yuferov et al., 2004).

Prodynorphin is the antecedent of dynorphin peptides, the endogenous ligands of the k opioid receptor that can keep a check on cocaine-induced increases in perisynaptic dopamine levels in reward-related areas of the brain (Kreek et al., 2002). It has been established that a 68-base replicate polymorphism in the supporter of the dynorphine gene was linked with cocaine exploitation or reliance, as well as with cocaine-alcohol dependence (Kreek et al., 2005). The definite relationship of the addictive position with μ and k opioid receptor systems can be seen in the light of the significance of these two systems in the neurobiology of strengthening and reward by different drugs of cruelty (including opiates and psychostimulants (Kreek et al., 2002). Alleles of the DRD2 gene are associated with alcoholism, cocaine dependence, psychostimulant abuse or polysubstance abuse (Kreek et al., 2005).

The high-activity Val158 allele of the COMT gene V158M polymorphism is related with polysubstance abuse (Vandenbergh, Rodriguez, Miller, Uhl, & Lachman, 1997), with alcoholism (Kreek et al., 2004) and, in family-based haplotype relative-risk study, with heroin addiction (Horowitz et al., 2000). Functional attractive resonance imaging shows that individuals with the high action valine/valine genotype of the COMT gene have improved prefrontal cortex purpose by providing amphetamine through a working memory job, while amphetamine caused weakening of cortical efficiency in persons with the methionine/methionine genotype (kreek et al., 2004). Alleles of the DRD4 and COMT genes also collaborate with methamphetamine abuse (Li et al., 2004).

Cocaine-induced hang-up is connected with a potentially practical variable nucleotide tandem replicate in the (Kosten, Miserendino & Haile, DeCaprio, Jatlow, Nestler, 1997). untranslated region of DAT (kreek et al., 2005). Variants of this gene have also been associated with amphetamine-induced psychosis (kreek et al., 2005) and with alcoholism (kreek et al., 2004). A functional polymorphism in the promoter district of DBH that causes lesser plasma dopamine β-hydroxylase movement is related with cocaine-induced paranoia (Cubells et al., 2000).

Two studies show an connection of heroin addiction with polymorphism in SERT but this discovery was not simulated on other studies (kreek et al., 2005). Variants in SERT, TPH2 and MAO-A and genes programming serotonin receptor 5-HT $_{1b}$ and 5-HT $_{2A}$ have all been linked with alcoholism (kreek et al., 2004). Alcohol dependence is associated with variants of the GABRA2 gene, which codes for the α2 subunit of GABAa; this gene is situated in a area of chromosome 4p, which is linked and connected with alcoholism (Edenberg et al., 2004).

The endogenous cannabinoid structure is also concerned in genetic studies of addictions. A trinucleotide repeat polymorphism in the 3' closest section of the cannabinoid receptor 1 (CNR1) gene is linked with intravenous drug abuse (heroin, cocaine, or amphetamine) (Schmidt et al., 2002).

A study of polymorphisms in CNR1 (Rounsaville, Weissman, Crits-Christoph, Wilber & Kleber, 1982) identified a haplotype in an intronic 5' region of the gene that is associated with matter (cocaine, opiate, alcohol or other drug) abuse (Zhang et al., 2004). Fatty amide acid hydrolase, prearranged by the FAAH gene, is an enzyme that metabolizes endogenous ligands of the cannabinoid receptors.

As thorough already, variants of genes involved in specific neurotransmitter systems are implicated in weakness to alcoholism; genes caught up in biotransformation or degradation of alcohol are also implicated (kreek et al., 1998). The alcohol-metabolizing enzymes alcohol dehydrogenase (ADH1B and ADH1C) and aldehyde dehydrogenase (ALDH) genes have variants that are defensive against alcoholism (kreek et al., 1998). The

information of relations of these alcohol-metabolizing gene variants with shield from alcoholism are various, strong and thoroughly reviewed in another place (kreek et al., 1998).

Environmental Factors

The phrase of a genetic predisposition toward substance abuse may be, in part, provisional on exposure to ecological determinants. In twine studies, environmental factors, including families influence the increase of alcohol dependence in folks with a comparatively high genetic risk. The influence non-family environmental factors also contributes (Kendler, Jacobson, Prescott & Neale, 2003). Among ill-treated children, those with the MAO-A variant that directs high expression levels were not as likely to develop inconsiderate problems in maturity as children with the low-expression variants (Caspi et al., 2002). MAO-A metabolizes a variety of neurotransmitters, including serotonin, norepinephrine and dopamine; defects in the MAO-A gene have been connected to hostility. Although the surroundings contributes to the development of antisocial traits, in these children the resulting antisocial deeds was moderated by hereditary factors.

Another association study investigated why demanding occasions may lead to dejection in some individuals but not in others (Caspi, Sugden & Moffitt, 2003). SERT has a repeat polymorphism in the promoter region, with the extended form of the repeat polymorphism expressing advanced level of SERT mRNA. People at the age of twenty-six years, having long or short form of the SERT promoter polymorphism had comparable depressive indicators and experiences, and desperate ideations, if they missed 'life events' such as service, affiliation or fitness stressors starting at the age 21 and extending to 25. On the other hand, in people who spent a hectic life and underwent traumatic events along with two copies of the short SERT alleles, despair and suicidal ideation augmented at a much higher rate. On the other hand, a middle increase was displayed in heterozygous subjects. These results propose that ordinary hereditary variants maintained at an elevated frequency in people, promote confrontation to environmental stressors.

Two precise variants (the MAOA and SERT promoter polymorphism) are each related with alcoholism. Childhood cruelty also contributes towards the possibility of giving birth to alcoholism or some other drug addictions. These studies indicated the critical communication between precise genetic variants and the environment as primary to association with addiction.

Role of Genetic Findings in Treatment of Addiction

A good and reliable peripheral biomarker is an important problem in CNS disease and psychology disorder like addiction. There is a hypothesis that the expression of neurotransmitter receptors in peripheral blood lymphocytes (PBLs) parallels and may reflect their expression in the brain. Some studies showed that expression of hMOR-1A and hMOR-1O variants and dopamine receptors measured by a suggested peripheral marker can serve to identify people at risk for opioid addiction and also to evaluate the successfulness of methadone therapy (Goodarzi, Vousooghi, Sedaghati, Mokri, & Zarrindast, 2009; Vousooghi, Goodarzi, Roushanzamir, Sedaghati, Zarrindast, & Noori-Daloii, 2009). Although many parameters can interfere in finding a peripheral biomarker for addiction but researcher think that we need such a marker to reduce failures of addiction therapy.

Recent progress in molecular genetic and biotechnology has changed many respects of psychology and open new hopes for understanding and treatment of disease in this subject. Manipulation of gene and expression of genes can help to cure of many diseases such as addiction, mood disorder, pain and so on.

In a study, researcher used specific RNA interference (RNAi) to decrease levels of MOR messenger RNA in the VTA of mice which consummate ethanol. They use a viral vector to infect mice and after one week and one month they examine mice for ethanol consumption.

They found a significant reduction in ethanol consumption which was resulted from expression of mu opioid receptor RNAi in VTA. This study shows that lentiviral delivery and MOR in the VTA can be supposed as a strategy for treatment of addiction (Lasek, Janak, He, Whistler, He & berlein, 2007).

Dopaminergic system has a significant role in addiction, and then it is expectable to use it as target for treatment of addiction. Cocaine, for example, can inhibit dopamine reuptake via blockade of DAT, increasing the synaptic availability of dopamine, prolonging its activity and producing the rewarding and addictive properties of the drug. There are two subtype of dopaminergic receptors: D2-like receptors (include D2, D3 and D4) and D1- like receptors (include D1 and D5). Expression of D2 receptor in the nucleus accumbens (NAc) can be modifed by drug abuse. Several studies indicated lower express of D2 receptor in the nucleus accumbens (NAc) of cocaine addicts. A new study showed increase of the

levels of D2R in the nucleus accumbens (NAc) can treat cocaine-addicted rats. They ruled that gene therapy in order to up-regulating of D2R in the NAc was correlated with a decrease in lever pressing for i.v. infusions of cocaine. They suggested it as a possible therapeutic strategy in the treatment of addiction (Panayotis, Thanos, Michael Michaelides, Umegaki, & Volkow, 2008).

Summary & Conclusions

It can be concluded that addiction is a multifaceted chaos with some consistent aspect, like impacts of environment, neurobiological changes associated with drug-induction, comorbidity, endophenotypes or just a response to stress. Evidently, numerous genetic variants causing such factors can contribute further, leading to helplessness and maximization of addiction. As a concrete example, a functional SNP in the OPRM1 gene (A118G) influences the μ opioid receptor, as defined by molecular and cellular studies and in being studies, and results in clinically visible changes in stress responsivity, vulnerability to opiate addiction and alcoholism in distinct populations, as well as in response to a specific addiction pharmacotherapy.

Molecular re-sequencing of both recent and formerly studied genes, is of grave importance in the detection of genetic variants of possible interest. A relative regularity across laboratories in phenotyping and statistical approaches (and the sharing of these data) is wanted to assess more directly replicability and generality across different populations. Without such comparative homogeny, meta-analyses of studies using highly dissimilar methodologies are difficult. Meta-analyses is based upon particular issues (for example a relationship of a genetic variant and an endophenotype or an addiction) and unite consequences from several studies to form a sound synopsis. These analyses are founded on individual or combined patient statistics, with the earlier being the favored kind, but the latter is more recurrently used. Precise universally-accepted endophenotypic assessments and ethnic/cultural cluster studies must be similar in order to reduce heterogeneity in the shared databases and data gathering platforms; hence, the results of meta-analyses of similar studies may not be openly compared, and meta-analyses of dissimilar studies may be deceptive. Genetic Laboratory in Iranian National Center for Addiction Studies in collaboration with clinical and neurocognitive departments is planning to provide such a multi aspect data gathering platform with different genotypic and endophenotypic aspects and invite all other active colleagues and research centers, nationally and internationally to collaborate on this frame work.

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