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# Clinically relevant genetic biomarkers from the brain in alcoholism with representation on high resolution chromosome ideograms

Ann M. Manzardo [a,*], Austen McGuire [a], Merlin G. Butler [a,b]

[a] Department of Psychiatry & Behavioral Sciences, University of Kansas Medical Center, Kansas City, KS 66160, USA
[b] Department of Pediatrics, University of Kansas Medical Center, Kansas City, KS 66160, USA

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ABSTRACT

*Objective:* Alcoholism arises from combined effects of multiple biological factors including genetic and non-genetic causes with gene/environmental interaction. Intensive research and advanced genetic technology has generated a long list of genes and biomarkers involved in alcoholism neuropathology. These markers reflect complex overlapping and competing effects of possibly hundreds of genes which impact brain structure, function, biochemical alcohol processing, sensitivity and risk for dependence.
*Method:* We compiled a tabular list of clinically relevant genetic biomarkers for alcoholism targeting expression disturbances in the human brain through an extensive search of keywords related to alcoholism, alcohol abuse, and genetics from peer reviewed medical research articles and related nationally sponsored websites. Gene symbols were then placed on high resolution human chromosome ideograms with gene descriptions in tabular form.
*Results:* We identified 337 clinically relevant genetic biomarkers and candidate genes for alcoholism and alcohol-responsiveness from human brain research. Genetic biomarkers included neurotransmitter pathways associated with brain reward processes for dopaminergic (e.g., *DRD2*, *MAOA*, and *COMT*), serotoninergic (e.g., *HTR3A*, *HTR1B*, *HTR3B*, and *SLC6A4*), GABAergic (e.g., *GABRA1*, *GABRA2*, and *GABRG1*), glutaminergic (*GAD1*, *GRIK3*, and *GRIN2C*) and opioid (e.g., *OPRM1*, *OPRD1*, and *OPRK1*) pathways which presumably impact reinforcing properties of alcohol. Gene level disturbances in cellular and molecular networks impacted by alcohol and alcoholism pathology include transketolase (TKT), transferrin (TF), and myelin (e.g., MBP, MOBP, and MOG).
*Conclusions:* High resolution chromosome ideograms provide investigators, physicians, geneticists and counselors a convenient visual image of the distribution of alcoholism genetic biomarkers from brain research with alphabetical listing of genes in tabular form allowing comparison between alcoholism-related phenotypes, and clinically-relevant alcoholism gene(s) at the chromosome band level to guide research, diagnosis, and treatment. Chromosome ideograms may facilitate gene-based personalized counseling of alcohol dependent individuals and their families.



## 1. Introduction

Alcoholism arises from the combined effects of multiple biological factors including a wide range of possible genetic variations and/or abnormalities, as well as non-genetic causes including interpersonal and psychosocial relationships, neuroadaptive responses, and gene/environmental interaction (epigenetics)( Enoch, 2013; Koob, 2013; Mayfield et al., 2008; Morozova et al., 2014; Rietschel and Treutlein, 2013). The risk to develop alcoholism is strongly related to the family history, childhood environment particularly the number of life stressors and presence or absence of co-occurring mental disorders (Bierut et al., 1998; Brady and Back, 2012; Brady and Sinha, 2005; Enoch, 2013; Keyes et al., 2012; Schepis et al., 2011). The interface of these relationships are complex and involve overlapping and competing effects of many genes impacting brain development, structure, and function, as well as, alcohol processing and sensitivity (Enoch, 2013; Koob, 2013).

### 1.1. Candidate gene strategies

Alcohol-responsive brain networks have been reported and identified by case–control, population and family-based studies incorporating

*Abbreviations:* COGA, collaborative study on the genetics of alcoholism; DNA, deoxyribonucleic acid; FDA, Food and Drug Administration; GWAS, genome-wide association studies; mRNA, messenger ribonucleic acid; SAGE, study of addiction: genetics and environment; SNPs, single nucleotide polymorphisms.

* Corresponding author at: University of Kansas Medical Center, Department of Psychiatry & Behavioral Sciences, 3901 Rainbow Boulevard, MS 4015, Kansas City, Kansas 66160, USA.
*E-mail address:* amanzardo@kumc.edu (A.M. Manzardo).

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candidate gene approach with whole-genome methodology in individuals with and without alcoholism (Edenberg, 2012; Edenberg and Foroud, 2006, 2013; Enoch, 2013; Morozova et al., 2014; Yan et al., 2014). Candidate gene strategies have considered neurobiological and neurodevelopmental pathways which are key to brain function by emphasizing emotion and reward pathways as well as biochemical processes associated with the physiologic effects and molecular targets of alcohol itself particularly those impacting alcohol metabolism (Blum et al., 1990; Bolos et al., 1990; Chai et al., 2005; Edenberg et al., 2006, 2008; Enoch, 2013; Feinn et al., 2005; Kapoor et al., 2014; Luo et al., 2005; Macgregor et al., 2009; Radel et al., 2005; Tolstrup et al., 2008; Wetherill et al., 2014; Zhang et al., 2008). Further, genetic biomarkers including chromosome regions have been identified by overlapping genetic linkage and functional data with alcoholism-related phenotypes of interest and refined to develop a molecular signature of alcoholism phenotype (Ehlers et al., 2004; Enoch, 2013; Kapoor et al., 2014; Wetherill et al., 2014). A representative example of a candidate gene/biomarker analysis is the alcohol dehydrogenase enzyme (ADH) which is responsible for alcohol metabolism and linked to the ADH gene family located in the 4q23 chromosome band (Chai et al., 2005; Edenberg et al., 2006; Macgregor et al., 2009; Tolstrup et al., 2008). The 4q23 chromosome band has been strongly associated with alcoholism vulnerability in several genome-wide linkage studies (Long et al., 1998; Reich et al., 1998). The activity of alcohol metabolizing enzymes (e.g., ADH) influences sensitivity to alcohol, its effects on the body and the accumulation of metabolites (e.g., acetaldehyde) which may be toxic. Genetic variants that increase production or slow the processing of alcohol intermediates (e.g., *ADH1B*, *ADH1C*, *ALDH2*) influence the likelihood of developing a drinking problem (Chai et al., 2005; Edenberg et al., 2006; Macgregor et al., 2009; Tolstrup et al., 2008). Human genetic studies have similarly identified alcoholism candidate genes involving neurotransmitter pathways associated with brain reward processes including the dopaminergic (e.g., *DRD2*, *MAOA*, *COMT*), serotoninergic (e.g., *HTR3A*, *HTR1B*, *HTR3B*), GABAergic (e.g., *GABRA1*, *GABRA2*), glutaminergic (*GAD1*, *GRIK3*, *GRIN2C*) and opioid (e.g., *OPRM1*, *OPRD1*; Blum et al., 1990; Bolos et al., 1990; Edenberg, 2012; Edenberg and Foroud, 2013; Edenberg et al., 2008; Feinn et al., 2005; Luo et al., 2005; Radel et al., 2005; Zhang et al., 2008). These genes presumably directly impact the reinforcing properties of alcohol driving the motivation to seek and use alcohol to excess. Whole-genome studies have shown abnormalities of chromosomes and identified specific regions (e.g., 4p12, 7q31.32, 13q14.2) where known or candidate genes for alcoholism are located and for alcoholism-related phenotypes such as age of drinking onset (3q26.1, 5q11.2, and 12q32.2; Edenberg, 2012; Edenberg and Foroud, 2013; Enoch, 2013; Kapoor et al., 2014; Morozova et al., 2014; Radel et al., 2005; Yan et al., 2014).

### 1.2. Whole genome investigation

Advances in genetic technology beyond linkage or cytogenetic analysis of affected families with alcoholism or other complex disorders using COGA, SAGE, and other resources have led to genome-wide association studies (GWAS) involving hundreds of affected and control individuals analyzing the distribution and clustering of hundreds and thousands of SNPs to search for candidate genes (Edenberg, 2012; Edenberg and Foroud, 2013; Enoch, 2013; Morozova et al., 2014; Rietschel and Treutlein, 2013; Yan et al., 2014). GWAS studies have identified genetic linkage to primary disease risk, alcoholism-related phenotypes and responsiveness such as consumption, level of response to alcohol's effects and event-related potential. Examples of candidate genes identified by GWAS studies include functional roles in cell adhesion important for brain development and implicated in Autism Spectrum Disorder (e.g., *AUTS2*, *CDH13*, *EFNA5*), molecular transporters (e.g., *SLC1A3*, *SLC5A11*, *SLC6A4*), and growth factors (e.g., *BDNF*) (Edenberg, 2012; Edenberg and Foroud, 2006, 2013; Enoch, 2013; Morozova et al., 2014; Rietschel and Treutlein, 2013; Yan et al., 2014).

### 1.3. Functional genomic biomarkers from brain

Additional functional genomic biomarker studies using high resolution microarrays have identified regionally distinct gene and exon level expression disturbances in post-mortem brain impacting neuronal growth and function which may influence alcoholism onset and progression (Flatscher-Bader et al., 2005, 2006, 2010; Lewohl et al., 2000; Liu et al., 2004, 2006; Manzardo et al., 2014; Mayfield et al., 2002; Sokolov et al., 2003). Functional gene expression profiling has identified disturbances in selected brain regions associated with reward processing and prefrontal inhibitory control mechanisms relevant to the development and propagation of abuse behaviors (Flatscher-Bader et al., 2005, 2006, 2010; Lewohl et al., 2000; Liu et al., 2004, 2006; Manzardo et al., 2014; Mayfield et al., 2002; Sokolov et al., 2003). An overrepresentation of down-regulated vs up-regulated genes at the mRNA level have been reported in addiction-related brain regions and functional disturbances impacting myelination, cellular signaling and energy production influencing brain structure, function, growth and development (Lewohl et al., 2000; Liu et al., 2004, 2006; Manzardo et al., 2014; Mayfield et al., 2002; Sokolov et al., 2003). These effects have been correlated with medical and psychiatric co-morbidities such as cirrhotic liver disease, smoking status and/or nutritional deficiency (Liu et al., 2007) and become potential genetic biomarkers for considerations in assessment and treatment development.

Advanced genetic platforms incorporating sophisticated bioinformatics techniques have enhanced our ability to identify SNPs and biomarkers involved in the genetics of alcoholism including risk factors for the development and progression of illness and have provided invaluable insight into the molecular and cellular mechanisms underlying the pathophysiology of alcoholism and the addictions. This insight has contributed to the development of the first targeted, clinically-validated and FDA approved drug treatments for alcoholism. The field will continue to advance through the use of next generation sequencing (whole genome or exome) which will yield additional valuable information on the location and description of genes contributing to alcoholism, enabling the identification of specific and recurring mutations of single genes impacting upon alcoholism-related phenotypes such as tolerance, withdrawal sensitivity, and craving which may provide novel therapeutic targets for future interventions. A current list of clinically relevant genetic biomarkers from brain in alcoholism are summarized and incorporated into high resolution chromosome ideograms (850 band level) to facilitate research, diagnostic testing and genetic counseling options for families in the clinical setting. The location of the 337 genes now recognized by searching literature and website information as playing a role in alcoholism are also presented in tabular form listing the individual gene symbol, name and chromosome location.

## 2. Materials and methods

We searched key words such as genetics, genes, alcoholism, alcohol abuse and alcohol dependence, mutations or gene variants and gene expression related to molecular disturbances in humans and alcoholism using computer-based internet sources including peer-reviewed medical literature (e.g., PubMed), federally sponsored (e.g., National Center for Biotechnology Information) and other informative websites (e.g., Online Mendelian Inheritance in Man; Ethanol-Related Gene Resource) (Guo et al., 2009) to compile a list of genetic biomarkers. The research articles ascertained were examined for evidence of gene or genetic biomarker involvement in alcoholism causation or pathology. These searches included whole-genome microarray and sequencing data and results from genome-wide association studies (GWAS) of alcoholism and families with and without a history of alcoholism as well as functional gene expression profiles using human brain. This