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REVIEW ARTICLE

Genes, Brain and Behavior

The Collaborative Study on the Genetics of Alcoholism: Overview

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Abstract

Alcohol use disorders (AUD) are commonly occurring, heritable and polygenic disorders with etiological origins in the brain and the environment. To outline the causes and consequences of alcohol-related milestones, including AUD, and their related psychiatric comorbidities, the Collaborative Study on the Genetics of Alcoholism (COGA) was launched in 1989 with a gene-brain-behavior framework. COGA is a family based, diverse (~25% self-identified African American, ~52% female) sample, including data on 17,878 individuals, ages 7–97 years, in 2246 families of which a proportion are densely affected for AUD. All participants responded to

questionnaires (e.g., personality) and the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) which gathers information on psychiatric diagnoses, conditions and related behaviors (e.g., parental monitoring). In addition, 9871 individuals have brain function data from electroencephalogram (EEG) recordings while 12,009 individuals have been genotyped on genome-wide association study (GWAS) arrays. A series of functional genomics studies examine the specific cellular and molecular mechanisms underlying AUD. This overview provides the framework for the development of COGA as a scientific resource in the past three decades, with individual reviews providing in-depth descriptions of data on and discoveries from behavioral and clinical, brain function, genetic and functional genomics data. The value of COGA also resides in its data sharing policies, its efforts to communicate scientific findings to the broader community via a project website and its potential to nurture early career investigators and to generate independent research that has broadened the impact of gene-brain-behavior research into AUD.

KEYWORDS
alcohol dependence, alcohol use disorder, AUD, brain, developmental, EEG, ERP, family, genomics, lifespan, longitudinal, psychiatric, SSAGA

1 | INTRODUCTION

The personal and societal costs of alcohol use disorders (AUD) are tremendous. In 2019, it was estimated that approximately 14.1 million US adults, 5.6% of those 18 years or older, and an estimated 414,000 adolescents between 12 and 17 years of age, met criteria for AUD in the past year.[1] Further, there have been alarming increases in problematic drinking in older drinkers.[2] Worldwide, about 5% of both deaths and burden of disease are attributed to alcohol consumption. AUD is heritable (h^2 = 50%–60%) and polygenic, and results from the contributions of many genes and environmental factors.[3–6] This genetic liability manifests, in part, through variability in neurobiology.[7] Due to the etiological complexity underlying the typical fluctuating course of alcohol use and AUD over the lifetime course, research that weaves together genomic, neurobiological, environmental and developmental influences is most likely to provide insights into the mechanisms underlying risk and resilience, and entry points for prevention and treatment.

The goal of this series of reviews is to describe the study design, highlight the multi-modal data available in the Collaborative Study on the Genetics of Alcoholism (COGA), and document the insights that these data have produced in our understanding of the lifecourse of AUD. COGA is an interdisciplinary project with the overarching goal of understanding the contributions and interactions of genetic, neurobiological and environmental factors towards risk and resilience over the developmental course of AUD, including relapse and recovery. COGA is a family-based study[8] and members of large families (Figure 1), a subset of which are densely affected with AUD, have

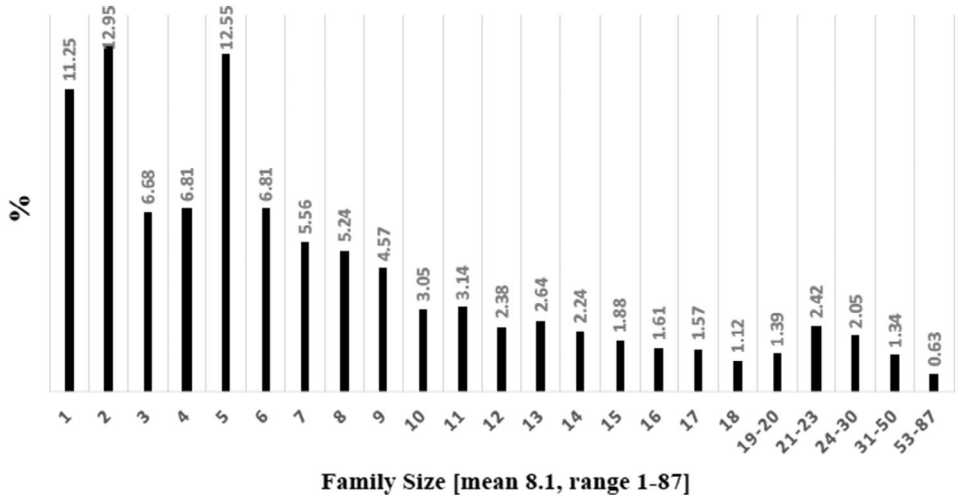

FIGURE 1 Distribution of family sizes (mean 8.1, range 1–87) in COGA families (2246 families; N = 17,878; age range 7–97).

TABLE 1 Overview of COGA participants across data modalities[a] including the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), genome-wide association study (GWAS) and electroencephalography (EEG) data.

	Full sample with SSAGA[c]	GWAS[b] and SSAGA	EEG and SSAGA	SSAGA, GWAS and EEG
N	17,878	12,009	9871	9076
Female %	52.6	52.7	52.1	52.5
Black %	24.4	26.0	27.7	28.1
White %	71.4	69.2	67.0	66.7
Hispanic %	7.4	7.8	8.3	8.2
DSM-IV Alcohol Dependence (lifetime)	27.5	28.9	27.0	28.0

[a]Additional details are available in accompanying reviews.
[b]dbGaP accession numbers: phs000125, phs000763, phs000976 and phs001208.
[c]>95% have SSAGA while the remainder have a child/adolescent version, or c-SSAGA.

been longitudinally characterized[9] in clinical, behavioral, neuropsychological, neurophysiological and socio-environmental domains, yielding a rich multi-modal phenotypic dataset paired with a large repository of biospecimens and genetic data (Table 1 provides sample sizes). In this overview, we outline the motivation behind and design of COGA as a multi-modal project. Accompanying this overview are individual reviews (2. Sample and Clinical Data, 3. Brain Function, 4. Genetics and 5. Functional Genomics) that provide in-depth characterization of our clinical, behavioral, genomic, functional genetic and brain function (electro-encephalograms [EEGs] and event-related potentials [ERPs] and oscillations [EROs]) data and the research that these data have supported to date. Each of these domains has produced novel findings, highlighted in the companion reviews. However, the fundamental strength of COGA has been our ability to integrate across these domains in a cohort of families with whom we have established a robust research relationship for over three decades.

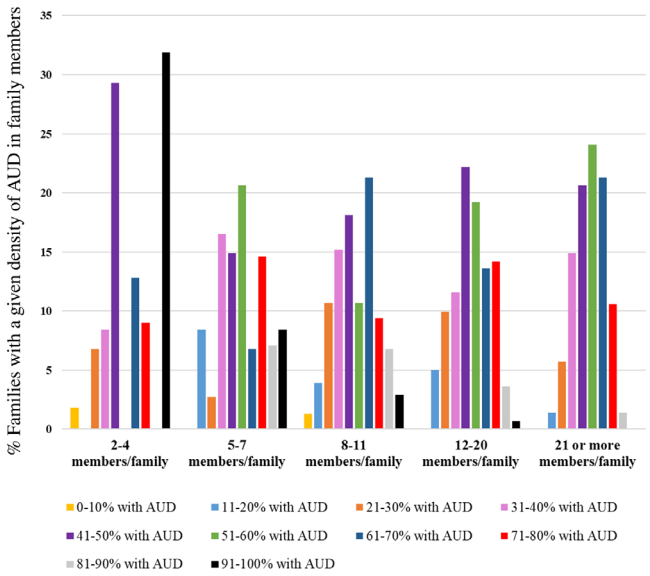

FIGURE 2 Distribution of density of individuals with alcohol use disorders (AUD) as a percentage of family members in families ascertained for AUD, stratified by broad categories of family size. The original COGA probands were ascertained from treatment facilities, based upon DSM-IIIR and Feighner alcohol dependence criteria; with consent, additional family members were interviewed. Diagnostic definitions have changed over the decades; thus the data plotted reflect whether an interviewed family member met criteria for DSM-IIIR *or* DSM-IV alcohol abuse *or* dependence *or* DSM-5 AUD (without requirement of clustering of criteria within a 12 months period). The *X*-axis provides broad percentage groups of interviewed family members with AUD (e.g., 10%–20% with AUD) while the individual bars on the *Y*-axis represent the percentage of families with a given density of interviewed members with AUD. For instance, 29.3% of families with 2–4 individuals interviewed per family (i.e., family size of 2–4) have 41%–50% of their interviewed family members diagnosed with AUD, while nearly 32% of these families ($n = 454$) have 91%–100% diagnosed with AUD. Note that families with 1 individual are not shown.

2 | HISTORICAL CONTEXT

Established in 1989 with NIAAA support, COGA is among the most enduring of psychiatric genetics consortia supported by NIH. Consistent with state-of-the-art genetic discovery methods of the time, COGA was initially designed as a family-based linkage study with deep psychiatric, behavioral and brain function phenotyping. The project initially included data collection across six sites: University of Connecticut (Farmington, CT), SUNY Downstate (Brooklyn, NY), Indiana University (Indianapolis, IN), University of Iowa (Iowa City, IA), Washington University (St Louis, MO), University of California San Diego (CA), with Howard University (Washington, DC) joining the consortium several years after.

3 | RECRUITMENT: A FOCUS ON FAMILIES

COGA ascertained probands in treatment for alcohol dependence, and a smaller number of comparison individuals from the same communities, and then recruited their families. Approximately 75% of the families were ascertained via a proband in treatment for alcohol dependence. Initial recruitment prioritized families with at least three first degree relatives meeting criteria for alcohol dependence (i.e., densely affected) although many families include more than three individuals with AUD, hence the higher than population prevalence of alcohol dependence and AUD (Table 1). As shown in Figure 2, the

proportion of families where more than half of the members met criteria for AUD ranged from 51% to 57%. Both probands and family members were characterized with age-appropriate assessments, including a standardized diagnostic instrument designed by COGA, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA),[10,11] administered by trained interviewers. Additional questionnaires (e.g., personality, family history and home environment) were also administered (see 2. Sample and Clinical Data for details). Given the focus on brain-related phenotypes, COGA collected neurocognitive and neurophysiological measures using EEG and ERP/EROs (Event-Related Potentials/Event-Related Oscillations; see 3. Brain Function for details). Blood samples were obtained for genomic data generation and were also immortalized as cell lines in the NIAAA/COGA Sharing repository (see 4. Genetics for details). This rich database has grown over the past three decades via the phased recruitment of additional families or family members and longitudinal follow-up of participants. For example, the COGA prospective study gathered longitudinal assessments of adolescent and young adult offspring from the families. More recently, recognizing the numerous changes including marriage, divorce, childbirth and career transitions that can significantly impact the course of alcohol use, AUD and remission, COGA has focused on longitudinal data collection of those in mid-life (30–40s). In addition, because heavy drinking can exacerbate age-related physical and neurocognitive problems, interact with medications, and cause falls and accidents, especially in older adults, a longitudinal follow-up of COGA participants aged 50 and older is in progress. A detailed timeline of data collection may be found in 2. Sample and Clinical Data. Of note, assessments, interviewer training and data cleaning are standardized across all sites, with some variations in assessment driven by individual institutional IRB criteria. Taken together, these waves of longitudinal follow-up provide a perspective of AUD risk and resilience across the lifespan.

4 | BEHAVIORAL AND CLINICAL DATA

The vast majority of COGA's clinical and behavioral data are drawn from the comprehensive, reliable, valid and standardized assessment tool, the SSAGA that provides data on symptoms and diagnoses of substance use disorders and related psychiatric history (e.g., major depressive disorder, suicidal thoughts and behaviors, conduct disorder and posttraumatic stress disorder), detailed family history, family environment (e.g., parental discord, divorce, economic status, parental knowledge of their child's activities and friendships and parental supervision) and drinking behavior (e.g., lifetime maximum drinks in a single 24 h period, typical drinking) of each participant. The SSAGA has been updated to reflect changing diagnostic criteria, from DSM-III-R to DSM-IV and DSM-5.[10–12] It is modular in structure (e.g., the SUD section of the assessment is independent of the depression section), freely available (including access to a programmed version in Blaise/RedCap and coding algorithms; cogastudy.org) and has been translated into nine languages. Several U.S. national studies have used the SSAGA (e.g., National Consortium on Alcohol and Neurodevelopment in Adolescence—Adulthood,[13] Human Connectome Projects[14]), and other interview assessments have used the SSAGA as a framework for modifications (e.g., Semi-Structured Assessment for Drug Dependence and Alcoholism, SSADDA[15]; SSAGA-OZ—an Australian version[16]). In addition to the SSAGA, COGA participants are administered a variety of questionnaires that target a broad spectrum of alcohol-related personality traits (e.g., NEO-5,[17] negative urgency[18] and sensation seeking[19]), environmental triggers (e.g., discrimination, COVID), health-related functioning and alcohol sensitivity.[20]

These longitudinal data have been instrumental in COGA's ability to chart the etiology and course of alcohol use and AUD across the lifecourse. For instance, our early family data documented the increased co-aggregation of multiple SUDs in AUD probands and their first degree relatives, relative to comparison families, providing initial support for familial clustering of and potential genetic influences on the comorbidity across AUD and SUDs (e.g., References 21,22). We have since conducted several studies that have disentangled family history into elements of genetic liability, nurture and density of risk (e.g., References 23–25). Our data on adolescent offspring of individuals with AUD documented the role of behavioral precursors, such as externalizing problems, and social environments, such as peers and parents, in trajectories that separated persisting drinking problems from developmentally-delimited heavy alcohol use (e.g., References 26–28). We were also able to examine the risk posed by early initiation of alcohol use on later drinking milestones using several analytic paradigms (e.g., References 29,30). More recently, our longitudinal design has facilitated characterizations of remission and recovery in AUD (e.g., References 31–33). A detailed description of these findings is outlined in the accompanying review (2. Sample and Clinical Data).

5 | BRAIN FUNCTION

From its inception, COGA has focused on the importance of brain function and on developing novel brain intermediary phenotypes of risk for and consequences of alcohol use and AUD. This has been done through the examination of neuropsychological tests and noninvasively recorded brain electrical activity during resting state and cognitive tasks, and more recently, by deriving measures of neural synchrony and connectivity (3. Brain Function). About 80% of those with brain function data have more than one assessment, yielding a relatively large longitudinal cohort with these data.

The collection of brain data in COGA was motivated by early studies that documented alterations in P300 brain activity in offspring of individuals with AUD, prior to the age of alcohol initiation.[34] COGA further reinforced the role of P300 ERPs and pioneered the use of ERO methods as a means to further deconstruct the P300 component in this context, with frontal theta EROs being particularly useful in our genetic and phenotypic studies.[35,36] The intersection of longitudinal data and family structure allowed us to evaluate both predispositional (i.e., differences in brain activity that precede and predict onset of AUD in those with familial risk) and neurotoxic (i.e., heavy alcohol

intake modifications of brain activity) mechanisms operating at the brain-behavior interface.[37] Further, incorporation of genomic data, not only allowed for GWAS of novel phenotypes such as neural synchrony[38] but also polygenic characterization of sex-specific longitudinal trajectories of brain maturation.[39] The addition of social and environmental contributors, such as peer affiliations and trauma exposure[40,41] have contributed to gene–environment interplay analyses within this gene-brain-behavior framework. The accompanying review (3. Brain Function) covers the available brain function data and resulting findings in detail.

6 | GENETICS DATA

COGA was initiated as a linkage study with microsatellite markers, and subsequently genotyped variants in genes encompassed by these linkage regions. With the advent of genome-wide association study (GWAS) arrays, several periods of funding secured GWAS genotyping of a majority of the sample (4. Genetics). Other genomic data in COGA include a small subset of families with whole exome sequence data as well as whole genome methylation data on a subset of youth who transitioned to heavy episodic drinking. However, our analytic focus remains on the fuller GWAS dataset (4. Genetics) which contributed to some of the first GWAS of AUD.[42,43] The contribution of COGA data to meta-analyses ultimately yielded the sample sizes necessary to identify credible loci for AUD and problem drinking,[5,6] however the deep phenotyping of COGA has also allowed us to discover variants associated with individual alcohol dependence criteria, criterion-count based severity,[44] subjective ratings of ethanol,[45] drug dependence,[46] maximum drinks,[47] as well as brain function phenotypes. We have also utilized polygenic scores (PGS, or polygenic risk scores, PRS) extensively in COGA. Integrated with both our behavioral/clinical and brain function data, PGS data in COGA have uncovered the importance of genetic susceptibility in longitudinal pathways of alcohol involvement, internalizing and externalizing phenotypes, as well as novel neural synchrony measures (e.g., References 38,48,49). In addition, the family structure of COGA data have allowed the investigation of social genetic mechanisms, such as assortative mating and cultural transmission,[50–52] which were recently identified as confounds in standard large-scale GWAS.[53,54] COGA has also contributed to a small but steadily increasing number of genetic discoveries in individuals of African ancestry. These data have allowed us to contribute to GWAS meta-analyses, PGS analyses that utilize emerging cross-ancestry methods, and locus discovery using admixture mapping (e.g., References 5,44,55). A detailed outline of these findings is available in the accompanying review (4. Genetics).

7 | GENOMICS AND FUNCTIONAL EXPERIMENTS

In addition to identifying genetic variants associated with AUD and outlining polygenic liability to trajectories of brain and behavioral development, a substantial component of genetic research within COGA relates to the functional characterization of this genetic risk. There are two main components of our functional genomic research (5. Functional Genomics). First, individuals who have been interviewed in COGA and have agreed to deposit samples into the NIAAA/COGA Sharing Repository provides an opportunity for COGA to study the physiology of individuals in the laboratory. EBV-transformed lymphoblastoid cells have been studied to determine differences in gene expression between individuals with and without AUD diagnoses as well as assess the effects of ethanol exposure on gene expression.[56] Further, cells in the NIAAA/COGA Sharing Repository can be induced into pluripotent stem cells and then differentiated into different types of neurons (e.g., glutamate, GABA). This allows COGA to study the effects of specific genetic/polygenic and phenotypic properties of neurons from COGA participants, providing missing links between the genetic, functional, and ultimately, behavioral studies.[57] Studies utilizing human neurons derived from COGA stem cells have identified altered neuronal activity associated with GWAS candidates, diagnostic data and frontal theta ERO endophenotypes.[56] Second, COGA has partnered with brain banks to generate single cell/nucleus RNAseq and ATACseq data on striatal brain regions critical to addiction development. Data generation has accompanied methodological innovation in approaches such as high throughput reporter assays which provide a convenient method for screening specific functional characteristics (e.g., binding site modifications) of large numbers of variants from GWAS (e.g., Reference 58).

In addition to generating functional genomic data, COGA has collaborated with other research groups and used curated gene expression, chromatin architecture and methylation data, from both humans and non-human animals, to tease apart causal variants from the increasing number of genome-wide significant loci emerging from large-scale GWAS meta-analyses of AUD and related traits. For instance, our multi-omic cell-type specific approach to analyzing existing summary statistics of AUD and typical drinking yielded strong associations with genes implicated in neurodegenerative diseases.[59] COGA's multi-pronged functional genomic approach weaves data generation and curation together, and related findings are reviewed in an accompanying article (5. Functional Genomics). These data continue to serve, not only as a platform for characterization of loci discovered in our own GWAS of behavioral and brain data but also for emerging signals from larger scale meta-analytic GWAS of AUD.

8 | IDENTIFYING AN INTEGRATED APPROACH FOR AUD RESEARCH

COGA as a consortium relies on the integrative analyses of these four broad domains of data. The nearly 600 manuscripts generated with COGA data since its inception underscore the importance of ensuring that all COGA scientists (~60), and our external collaborators, as well as those analyzing COGA data that they obtain from NIH-supported resources (see below) have access to the same high quality of harmonized behavioral, clinical, genomic and brain function data that was systematically quality-controlled, not only at the individual level but

also within the large COGA pedigrees so as to maintain the intended study design. From the outset, COGA utilized a single linking variable (record identifier, but without personal identifying information) that was unique to each family, and a sub-variable for individuals within each family indicative of their relationship to the proband. A core harmonized set of gene-brain-behavior data are available to all COGA investigators while additional data are harmonized across the various waves of data collection as the analytic needs of investigators arise—for instance, while some research questions may require the cross-sectional coding of a lifetime measure of suicidal ideation, another may entail the study of repeated assessments of suicidal ideation in past 12 months. However, all data are connected to a specific study participant via this common "id" variable regardless of longitudinal wave or phase of data collection (data are further anonymized prior to sharing with repositories or external collaborators). Further synergy across the diverse expertise of COGA members, which includes epidemiologists, psychologists, clinicians, geneticists, neuroscientists, statisticians, and molecular and cellular biologists, is generated by monthly meetings, both within data modalities and a single meeting of all COGA investigators, which allows for all aspects of COGA to benefit from the collective insights of this community of scientists. These meetings have been critical in empowering investigators to incorporate a data modality into their COGA analyses that they may be typically unfamiliar with, by partnering with a field expert and utilizing shared resources for data harmonization, code and protocol documents. The participation of all COGA investigators at these meetings also ensures that a legacy is in place for onboarding new scientists joining the group.

9 | DATA SHARING WITH THE RESEARCH COMMUNITY

There are numerous mechanisms by which scientists who are not COGA co-investigators can access COGA data (cell lines, derived genotypes and gene expression data, EEG/ERP, behavioral and clinical data). The COGA website provides additional details on how COGA data may be accessed (https://cogastudy.org/resources-for-researchers/) and additional details may also be found in the accompanying reviews on these data modalities (see also footnote of Table 1 for dbGaP accession numbers). While some investigators elect to obtain COGA data from sources such as dbGaP, many collaborate directly with COGA scientists, which is especially the case when an investigator wishes to access a phenotype that requires additional levels of data extraction and coding, or a specific analysis using their preferred method. Such a collaboration requires the submission of a brief proposal that is sponsored by a COGA investigator. A review committee, composed of members representing the various aspects of COGA's research, approves and monitors these proposals. This mechanism is consistent with protocols established by many multi-site consortia that collect sensitive and complex data types. Assigning a COGA sponsor also ensures that the external investigator receives the required data/analysis in a timely manner. COGA data have also contributed to the development of novel methods for genetic analyses of family data, via data sharing (e.g., Psychiatric Genomics Consortium, Genetic Analysis Workshops). To date, 181 scientists have collaborated with COGA investigators, 349 researchers have used COGA data through dbGaP, and 30 investigators have requested COGA data through NIAAA directly—for a total of 560 external scientists using COGA data in their work.

10 | THE COGA WEBSITE AS AN INFORMATIONAL PLATFORM

Alcohol use disorder, and other substance use disorders are often misunderstood and stigmatized. The concept that there are both genetic and environmental contributions to risk for AUD and its outcomes can be difficult to explain. Polygenic risk can also be challenging to communicate, and can lead to unrealistic expectations of what genomic medicine can do for the treatment and prevention of AUD. To provide a community-facing forum for sharing our own research findings and also provide summaries of the state of scientific knowledge in the field of alcohol research, COGA has developed a series of resources for the public to understand how genetic and environmental factors contribute to the development of alcohol use problems. These were developed in collaboration with digital communication specialists and include short videos, text descriptions, interactive graphical elements, and key take-aways, and can be found at cogastudy.org. An accompanying blog provides an overview of new findings with an eye towards public communication.

11 | A VENUE FOR CAREER DEVELOPMENT

As COGA data have served as a springboard for novel, independent research grants, the intellectual and analytic resources, along with these data, have nurtured the development of numerous scientists who have joined the consortium at various career stages. Many of COGA's original investigator team remain fully engaged in the project and provide mentorship to incoming early career scientists. The project has weathered the sometimes, unexpected loss of some of its early leaders, whose memory continues to inspire COGA's mission. Notably, the project has welcomed numerous investigators at early career stages and supported their careers via funding, support for independent grants, publications, leadership opportunities and importantly, the nurturance of an open, safe, egalitarian and collaborative framework for team science. Many of the current COGA investigators have traversed the academic pathway from graduate student or postdoctoral scholar to professorship within this >30 years period. Still others are part of the third and fourth generation of COGA scientists. Investigators at all career stages have leveraged the integrated data collection and analyses of COGA to fuel their independent work that was inspired by COGA discoveries (e.g., References 60–63). This range in our investigator team has ensured that fresh perspectives and novel approaches are being continuously brought to bear on the science against a backdrop of well-organized data collection that

remains consistent with COGA's overall objective of studying the lifecourse of AUD in families.

12 | HIGHLIGHTS

Individual reviews in this issue provide detailed illustrations of the ways in which COGA data have contributed towards advancing our understanding of the etiology, course and consequences of AUD, and pathways from onset to remission and relapse. COGA's intergenerational design has, in addition to identifying genetic risk factors, contributed to our understanding of the role of social genetic mechanisms[50,52,64–66] in the interplay between genetic liability and the socio-environmental milieu (e.g., References 40,48,67,68). Diversity in the data have driven gene discoveries within our dataset (e.g., Reference 44) and in collaboration with others (e.g., References 5,55,69). Our ability to develop iPSCs from individuals with different genetic loading is producing insights into properties of cells derived from persons with archival electrophysiological and behavioral phenotyping, and how the cells differentially respond to ethanol exposure. A notable contribution of COGA's family design has been to disentangle antecedents of, and predisposition to AUD from its sequelae. By characterizing brain and behavior in offspring from families enriched for AUD liability—both genetic and environmental—prior to the onset of maladaptive drinking behaviors, COGA data have shown the importance of precursors of AUD in a neurobehavioral framework (e.g., References 23,34,70–72). COGA data have validated the 3-stage neurobiological model[73] of AUD and added to conceptualizations of related multi-modal assessments (e.g., Reference 74) while also extending them by identifying novel contributors to "exiting" the cycle of AUD towards remission and recovery, amplifying the role of familial liability (e.g., References 23,31,33,75).

13 | LIMITATIONS

The design of COGA as a large, multi-modal, family-based study that was enriched for AUD liability also brings forth certain caveats. Large families that are densely affected may not be representative of the constellation of genetic and socio-environmental risk and resilience factors influencing AUD in the general population. COGA has contributed to large, collaborative studies (e.g., References 5,55,69) that bring together data from many different studies with different ascertainments, and thereby enriched those studies. However, it is worth noting that effect sizes of loci and of polygenic scores may be influenced by our ascertainment strategy. Reassuringly, many COGA findings have been replicated in other samples (e.g., References 76–79).

14 | COGA: PAST, PRESENT AND FUTURE DIRECTIONS

In this collection of reviews (2. Sample and Clinical Data, 3. Brain Function, 4. Genetics and 5. Functional Genomics), the reader will find a deep characterization of the various data that comprise COGA, the motivation and procedures for collection, and snapshots of the scientific insights that COGA has contributed to the field of alcohol research. This reflection represents over three decades of research which began with the simple, important yet unanswered question: how does AUD emerge and manifest in families, and what are the factors that exacerbate or mitigate its progression? Relying on our multimodal data framework within a longitudinal context, we continue to identify new approaches and avenues to answer not only this question but the myriad of questions that arise as our knowledge of risk and resilience to AUD over the lifespan increases. Our data have also begun to produce exciting insights into possible prevention and intervention paradigms through independent studies (e.g., References 60–63). There are numerous priority areas in the field of alcohol research where COGA continues to have scientific impact. For example, while most AUD research, including in our own prospective cohort, has focused on the onset of AUD and its persistence and abatement during middle adulthood, far less is known about the medical and psychosocial sequelae of AUD in later life. Recent epidemiological surveys call attention to notable increases in heavy drinking in older adults,[2,80,81] and quite likely, the factors conferring risk and resilience in this epoch of life might be distinct. In addition to understanding why an individual might continue to engage in problematic drinking as they age, the consequences of AUD—on neurocognitive markers, risk for cardiometabolic disease, liver health, accidents and importantly, shortened life expectancy—is one scientific domain in which COGA's longitudinally characterized, family-based and aging cohort may be of utility. At the other end of the lifecourse, as offspring of COGA members attain child-bearing age, opportunities to address questions related to intergenerational transmission of behavioral, genetic/epigenetic and brain-related liability arise.[7] While current studies of childhood and even neonatal development in the context of familial risk do exist, gathering data on the next generation of COGA bears the advantage of framing questions regarding early development against a wealth of longitudinal familial data, which are one of few data patterns that allow nature to be disentangled from the impact of nurture.

Our functional genomics efforts continue to accelerate the pace at which genetic discoveries can be placed in a biological context. While gene editing in a cell-type specific manner and the observation of the functional effects of these changes in organoids are components of our ongoing work, the NIAAA/COGA Sharing Repository as well as continued contact with participants allowing for additional biospecimen collection, sets the stage for experiments tailored to research questions for specific aspects of AUD (e.g., remission) and to developmental periods (e.g., early vs. later life). Furthermore, whole genome sequencing (WGS) methods, especially as their accessibility increases, would substantively improve COGA's ability to study rarer and structural variants, the role of which continues to emerge for psychiatric disorders. A particularly attractive feature of studying rare variation in COGA is its family design, which aids the identification of both private and disorder-generalized mutations. Similarly, our ability to measure the brain's activity during resting state and during various cognitive tasks with exquisite temporal accuracy, allows us to develop

and implement EEG protocols that uniquely address questions regarding the course of AUD. While COGA has maintained its focus on EEG, a subset of COGA participants have been imaged using brain Magnetic Resonance Imaging (MRI) allowing for comparisons between these data.[82] Moreover, genetic differences in COGA participants are now being translated into changes in neuronal function using advanced molecular and cellular tools, potentially leading to novel therapeutic strategies for treating AUD.

COGA's asset is its family-based longitudinal design that supports an intensive clinical, behavioral, genetic, genomic and brain function data collection. As the project enters its late third decade of scientific exploration, we approach our contributions to the study of AUD with optimism. At the core of COGA's scientific mission is our expectation that through the systematic characterization of the clinical, genetic, environmental and brain-related factors that contribute to alcohol use and misuse, we can begin to identify mechanisms that will eventually truncate the course of AUD, if not substantially deter its onset altogether. Our science aims to identify pathways to enduring remission and processes that can be modified to minimize the deleterious impact of AUD across the lifespan. Through our collaborative gene-brain-behavior paradigm, we aspire to address both the causes and consequences of heavy alcohol use and AUD, which still contributes annually to 3 million preventable deaths globally.

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DATA AVAILABILITY STATEMENT

COGA data are available in dbGaP (phs000125, phs000763, phs000976 and phs001208), or via an application to the National Institute on Alcohol Abuse and Alcoholism (https://www.niaaa.nih.gov/research/major-initiatives/collaborative-studies-genetics-alcoholism-coga-study), or through a COGA investigator-sponsored secondary analysis proposal.

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