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Drosophila and *Caenorhabditis elegans* as Discovery Platforms for Genes Involved in Human Alcohol Use Disorder

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Abstract

Background—Despite the profound clinical significance and strong heritability of alcohol use disorder (AUD), we do not yet have a comprehensive understanding of the naturally occurring genetic variance within the human genome that drives its development. This lack of understanding is likely to be due in part to the large phenotypic and genetic heterogeneities that underlie human AUD. As a complement to genetic studies in humans, many laboratories are using the invertebrate model organisms (iMOs) *Drosophila melanogaster* (fruit fly) and *Caenorhabditis elegans* (nematode worm) to identify genetic mechanisms that influence the effects of alcohol (ethanol) on behavior. While these extremely powerful models have identified many genes that influence the behavioral responses to alcohol, in most cases it has remained unclear whether results from behavioral–genetic studies in iMOs are directly applicable to understanding the genetic basis of human AUD.

Methods—In this review, we critically evaluate the utility of the fly and worm models for identifying genes that influence AUD in humans.

Results—Based on results published through early 2015, studies in flies and worms have identified 91 and 50 genes, respectively, that influence 1 or more aspects of behavioral responses to alcohol. Collectively, these fly and worm genes correspond to 293 orthologous genes in humans. Intriguingly, 51 of these 293 human genes have been implicated in AUD by at least 1 study in human populations.

Conclusions—Our analyses strongly suggest that the *Drosophila* and *C. elegans* models have considerable utility for identifying orthologs of genes that influence human AUD.

Keywords

Sensitivity; Tolerance; Behavior; Genetics; Human

The Invertebrate Model organisms (iMOs) *Drosophila melanogaster* (fruit fly, hereafter *Drosophila* or fly) and *Caenorhabditis elegans* (nematode worm, hereafter *C. elegans* or

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worm) have become major experimental platforms for identifying genes, genetic pathways, and mechanisms related to the effects of alcohol on the nervous system and behavior. The extent to which genetic findings from iMOs are directly relevant to the genetics of human alcohol use disorder (AUD), however, has not been fully resolved. Despite an important but somewhat limited number of individual reports of orthologous genes influencing both alcohol-related behavior in iMOs and AUD in humans (e.g., Lasek et al., 2011b; Mathies et al., 2015; Morozova et al., 2009; Schumann et al., 2011), fundamental differences between invertebrate and human studies raise reasonable questions regarding the overall translational potential of genetic information from worms and flies. In this review, we comprehensively address this key issue.

BRIEF OVERVIEW OF THE GENETICS OF HUMAN AUD

Humans have deliberately produced and consumed ethanol (EtOH, hereafter alcohol) for 10,000 to 12,000 years (Dietrich et al., 2012). The original motivations for producing alcohol were probably quite varied and could have included the need for clean sources of hydration, a mechanism to bring individuals together for cultural festivals, and a form of payment for laborers (Dietrich et al., 2012). Although moderate alcohol consumption is associated with some health benefits (Spanagel, 2009), heavy consumption of alcohol contributes to a number of serious diseases and other societal problems that together lead to >5% of the global burden of disease and almost 6% of all deaths worldwide (WHO, 2014).

Individuals with AUD can exhibit a number of negative behavioral and physiological alcohol-related phenotypes that include alcohol abuse and alcohol dependence (NIAAA, dynamic). A diagnosis of AUD is warranted when an individual meets any 2 of 11 alcohol use-related criteria in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) within a single 12-month period (American Psychiatric Association, 2013). Nearly 11% of all individuals in the United States will meet the criteria for AUD within the previous year (Edenberg and Foroud, 2013) and the lifetime risk for developing AUD approaches 25% (Haeny et al., 2014; Nery et al., 2014), although the lifetime risk of alcohol consumption leading to obvious harmful dysfunction might be much lower (Wakefield and Schmitz, 2014). Regardless of the analysis method, however, it is clear that AUD has an enormous, negative impact on human health across the globe.

The heritability of AUD is ~50% (Verhulst et al., 2014), suggesting that an in-depth understanding of the underlying genetic causes of AUD could greatly facilitate risk diagnosis and possibly successful treatment of affected individuals. Although genetic linkage, association, and other types of studies have generated suggestive evidence implicating a large number of genes in AUD or related disorders, to date, only genes encoding several major enzymes involved in the metabolic disposition of alcohol (*ADH1A*, *ADH1B*, *ADH1C*, and *ALDH2*) have been causally associated with AUD in multiple studies (Edenberg and Foroud, 2013, 2014; Rietschel and Treutlein, 2013). Thus, despite the significant negative health consequences of AUD and its heritability, we do not yet have a detailed understanding of the genes that drive alcohol abuse and other disorders related to problematic alcohol consumption.

INVERTEBRATE MODEL IN ALCOHOL RESEARCH

Flies and worms are the main iMOs currently being used to investigate the genetics of alcohol-related behavior. Fundamental advantages of these 2 iMOs include relatively low costs, high-throughput genetic analyses, and suites of powerful tools to manipulate the functions of individual genes along with a host of molecular and bioinformatic resources that facilitate genomic analyses. Importantly, there is considerable conservation between gene products in the iMOs and humans. In particular, much of the major molecular machinery that supports nervous system function, including several neurotransmitter systems, is structurally and functionally similar in iMOs and humans (Heberlein et al., 2004; Kaletta and Hengartner, 2006; Rodan and Rothenfluh, 2010a; Scholz and Mustard, 2011).

Behavioral responses to acute alcohol exposure in iMOs and humans are also conserved overall (Devineni and Heberlein, 2013; Rothenfluh et al., 2014). Low doses of alcohol elicit locomotor or psychomotor stimulation, while moderate doses of alcohol produce sedation in flies, worms, and humans. Tolerance to alcohol (a blunted effect of the drug after prolonged or repeated exposure) is also observed in both iMOs and humans. A number of assays for measuring the effects of alcohol on behavior have been described for both flies and worms.

In flies, alcohol sedation and/or the effects of alcohol on postural control can be assessed by exposing flies to alcohol vapor (which progressively increases their internal alcohol as occurs in humans when drinking alcohol) and then monitoring the ability of flies to move or remain standing over time (e.g., Bhandari et al., 2009; Lasek et al., 2011a; Maples and Rothenfluh, 2011; Rothenfluh et al., 2006; Sandhu et al., 2015; Schumann et al., 2011; Wen et al., 2005). Additionally, recovery from alcohol sedation is also a useful behavioral end point in flies (e.g., Cowmeadow et al., 2005; Ogueta et al., 2010). The locomotor stimulating effects of alcohol in flies can be assessed by exposing flies to alcohol vapor in conjunction with computer-based data analysis of video recordings of individual fly movement (Wolf et al., 2002). Furthermore, flies will preferentially consume food containing alcohol, allowing measurement of both volume and frequency of alcohol consumption (Devineni and Heberlein, 2009; Ja et al., 2007; Pohl et al., 2012; Shohat-Ophir et al., 2012; Xu et al., 2012), and this preference for alcohol can be modified by experience (Peru Y Colón de Portugal et al., 2014). Alcohol can act as a rewarding substance in flies (Kaun et al., 2011). Fly larvae can develop cognitive dependence on EtOH which can be measured as a decrease in learning ability in alcohol-dependent larvae that are undergoing withdrawal from alcohol (Robinson et al., 2012). Rapid tolerance to alcohol can be measured by assessing the ability of the drug to sedate flies during 2 alcohol exposures separated by a recovery period (flies are more resistant during the second exposure due to adaptations in the nervous system) (e.g., Bhandari et al., 2009; Chan et al., 2014; Cowmeadow et al., 2005; Scholz et al., 2000). Readers are directed to several comprehensive reviews on *Drosophila* as a model for alcohol behavior for additional details and discussion (Devineni and Heberlein, 2013; Kaun et al., 2012; Morozova et al., 2012; Robinson and Atkinson, 2013; Rodan and Rothenfluh, 2010b; Rothenfluh et al., 2014; Scholz and Mustard, 2011).

The behavioral effects of alcohol in worms are most often assessed by exposing the animals to alcohol and then tracking their locomotion either on an agar surface (crawling) or in a

liquid medium (swimming) (e.g., Alaimo et al., 2012; Davies et al., 2003; Morgan and Sedensky, 1995; Speca et al., 2010). Tissue alcohol concentrations, which are substantially lower than exogenous concentrations, continue to rise slowly over the course of at least 50 minutes of exposure (Alaimo et al., 2012). Additional behavioral assays determine the effects of alcohol on egg-laying or hypercontraction of the body wall muscles (Davies et al., 2003; Hawkins et al., 2015). Worms develop acute functional tolerance to alcohol over the course of a 30-minute continuous exposure, which is observed as a decrease in locomotor sedation caused by alcohol despite increasing tissue alcohol concentrations (e.g., Davies et al., 2004; Jee et al., 2013; Mathies et al., 2015; Raabe et al., 2014). In addition, worms can develop chronic tolerance to alcohol, which is observed by withdrawal-induced clumping behavior after 20 hours of exposure (Davies et al., 2004), by withdrawal-induced tremor after 4 hours of exposure (Jee et al., 2013) or by withdrawal-induced increases in omega turns without accompanying reversals after 6 to 48 hours of exposure (Mitchell et al., 2010). Like flies, worms can also express complicated behavioral changes in response to alcohol; they can learn state dependently (Bettinger and McIntire, 2004) and can develop a preference for alcohol when they are exposed to it for 4 hours in the presence of a food source (Lee et al., 2009).

Studies in flies and worms have contributed substantially to our understanding of molecular–genetic mechanisms that influence the effects of alcohol on the nervous system and behavior. To compile all genetic manipulations (and therefore genes) that are important for alcohol-related behavior in flies and worms, we performed extensive searches of PubMed through 2014 (using combinations of the search terms EtOH, alcohol, *Drosophila*, *C. elegans*, names of individual investigators, etc.) and supplemented these searches with lists of genes obtained from several recent reviews (Davies and Bettinger, 2014; Kaun et al., 2012; Morozova et al., 2012; Rodan and Rothenfluh, 2010a; Rothenfluh et al., 2014) in addition to a recent publication from one of the authors (Mathies et al., 2015). Together, studies in flies and worms have identified 91 and 50 genes, respectively, that influence behavioral responses to alcohol (Tables 1 and 2). The 50 worm genes are orthologous to 50 genes in flies (identified by DIOPT scores ≥3 [Hu et al., 2011] and BLASTP searches [Altschul et al., 1997]). Of these 50 genes, only 7 (*Adh*, *Clic*, *Dop1R1*, *iav*, *NPFR*, *Sir2*, and *slo*) have been reported to influence behavioral responses to alcohol in flies. Similarly, the 91 fly genes that influence alcohol-related behavior are orthologous to 92 worm genes and only 8 of these (*exc-4*, *exl-1*, *dop-4*, *npr-1*, *osm-9*, *sir-2.1*, *slo-1*, and *sodh-1*) have been reported to be important for alcohol-related behaviors in worms. Presumably not all genes have been tested in both invertebrate models, and therefore, the overlap between genes in flies and worms described here probably underestimates the true genetic congruence in these 2 species.

The large number of genes influencing alcohol response behaviors uniquely contributed by flies and worms highlights the combined analytical power of these iMOs for further understanding molecular–genetic mechanisms underlying behavioral responses to alcohol. The uniquely contributed genes represent a potentially rich resource for exploring conserved gene function in the context of acute behavioral responses to alcohol. Importantly, it is possible that some molecular–genetic processes may be more amenable for study in one

model versus the other. The overlap of genes that influence alcohol response behaviors in both iMOs is also informative; the genes identified in both flies and worms encode a diverse set of proteins that mediate membrane flux of potassium (*slo* family) and other cations (*iav*/*osm-9* family). Additionally, these gene products participate in histone deacetylation (*Sir2* family), alcohol metabolism (*Adh*/*sodh-1* family), and dopamine signaling *(Dop1R1*/*dop-4* family) or have incompletely characterized functions (*Clic* family). Readers are referred to several excellent recent reviews for additional details on the molecular function of the genes in flies and worms (Davies and Bettinger, 2014; Kaun et al., 2012; Morozova et al., 2012; Rodan and Rothenfluh, 2010a; Rothenfluh et al., 2014).

GENETICS OF ALCOHOL BEHAVIOR IN INVERTEBRATE MODEL ORGANISM AND HUMAN AUD

The large number of genes identified in iMO studies (Tables 1 and 2) highlight the power of the fly and worm model systems for investigating fundamental molecular-genetic mechanisms that influence behavioral responses to alcohol. The utility of the iMOs for identifying orthologs of individual genes or conserved genetic pathways involved in human AUD, however, has not been systematically evaluated. In fact, as counterpoints to the conservation in behavioral responses to alcohol and the molecular underpinnings of nervous system function in humans and iMOs discussed above, there are a number of notable differences between studies in invertebrates and humans that could, in principle, lead to disparate findings across species. For example, studies in humans examine naturally occurring genetic variation that has undergone natural selection during evolution and (typically) determine how that variation is associated with problems related to chronic alcohol exposure that often lasts for years. Studies in iMOs are often just the opposite. Genetic variance in iMOs is usually generated in the laboratory, although naturally occurring genetic variation in EtOH responsiveness in worms and flies has been assessed in some studies (Davies et al., 2004a; Morozova et al., 2009). Most studies in iMOs have used genetic manipulations that are the most severe that still allow the organism to live and perform basic tasks like locomotion, and—since they are maintained in a laboratory setting—these genetic manipulations largely escape the forces of evolution. Alcohol exposure in iMOs is also typically acute (lasting minutes to hours). The alcohol-related behaviors routinely assessed in iMOs (sedation, tolerance, locomotor activation) are fundamentally distinct from and simpler than the phenotypes analyzed in humans (alcohol abuse, alcohol dependence, alcohol craving, etc.) because iMO phenotypic end points are devoid of human social influences and occur in response to forced exposure to alcohol. Consequently, the experimental questions that are addressed in iMOs and humans are substantially different. Studies in humans typically address questions such as: What are the naturally occurring genetic variants that are associated with an AUD, or an endophenotype of an AUD, in response to chronic, voluntary alcohol intake in a defined population? In contrast, studies in iMOs typically investigate questions such as: What are the genes required for normal behavioral responses to forced acute alcohol exposure?

The intrinsic differences between studies in iMOs and humans raise the question of the utility of using flies and worms for identifying individual genes and genetic pathways

relevant for AUD. In this review, we address this issue by assessing the overlap—at the level of individual genes— between genetic results from studies on alcohol-related behaviors in iMOs and studies on AUD in humans. Additionally, we determine whether behavioral–genetic studies on alcohol in iMOs have identified conserved genetic pathways relevant to human AUD.

To assess the overlap between genetic findings in iMOs and humans at the level of individual genes, it was necessary to use common gene symbols for all orthologs, regardless of origin. We therefore identified human orthologs of fly and worm genes that influence alcohol-related behavior using DIOPT (Hu et al., 2011), FlyBase (Wilson et al., 2008), OrthoDB (Kriventseva et al., 2015), BLASTP (Altschul et al., 1997), and g:Profiler (Reimand et al., 2011) in addition to our recognition of well-established biochemical activities of gene products (e.g., the alcohol dehydrogenase [ADH]-encoding genes). Genes predicted to be conserved between iMOs and humans by these approaches were visually inspected and unconvincing orthologs (i.e., genes whose gene products were judged to be poorly conserved between humans and iMOs) were ignored. In practice, orthologs with fairly conservative scores (≥3) in DIOPT (which in turn uses several bioinformatic databases) were considered convincing.

The collection of genes that influence alcohol-related behavior in flies and worms (Tables 1 and 2) correspond to 293 unique orthologous genes in humans (hereafter iMO–human genes or orthologs; Table 3). Twenty-two of the iMO–human genes are derived from studies in both flies and worms, while 182 and 89 of the iMO–human genes are exclusively from studies in flies and worms, respectively. The identification of orthologs in some cases can be somewhat challenging (cf. Hu et al., 2011), and therefore, the list of genes in Table 3 should be viewed as highly representative of the current sum of iMO–human orthologs as opposed to being definitive for the inclusion or exclusion of any single potential iMO–human gene.

Unfortunately, there is no consensus set of human AUD genes that can be used to determine which of the iMO–human genes (Table 3) have been implicated in human AUD. Thus, the 293 iMO–human genes were queried against a set of 732 human genes compiled from (i) several comprehensive reviews on the genetics of AUD (Edenberg and Foroud, 2013, 2014; Palmer et al., 2012; Rietschel and Treutlein, 2013; Schuckit, 2014) and (ii) genes in the HuGe Navigator (Yu et al., 2008) identified by the search terms “alcoholism.” A small number of these 732 human genes have established roles in AUD, whereas the remaining genes have been implicated in AUD by smaller scale studies, single studies only, etc. Although very few of the 732 genes were implicated by studies that observed formal statistical significance of association with AUD, we included all 732 genes in our analyses in an attempt to capture the broad landscape of genetic findings from studies in humans.

Of the 293 iMO–human genes (Table 3), 83 were found among our compiled set of 732 human AUD genes. Based on literature reviews, only 51 of these had been implicated in 1 or more aspects of AUD (Table 4). The remaining 32 genes were among the HuGe Navigator “alcoholism” genes, but had no experimentally supported connection to AUD and were ignored. Hereafter, the 51 genes in Table 4 are referred to as iMO–human-AUD genes because (i) their respective orthologs influence behavioral responses to alcohol in iMOs and

(ii) they have been implicated in human AUD. As expected, *ALK*, *AUTS2*, *GPC5*, *LMO1*, and several SWI/SNF orthologs—genes previously described within single reports as modulators of alcohol behavior in iMOs and human AUD—were among the 51 iMO–human-AUD genes. Seven of the iMO–human-AUD genes were derived from studies in both flies and worms, while 23 and 21 were orthologs of genes identified exclusively in fly and worm studies (Table 4).

Assuming an ideal set of circumstances, a quantitative statistical assessment could be performed to determine whether the 51 iMO–human-AUD gene set is larger than would be expected by chance. For example, given 293 iMO–human genes and 732 human genes in the query sample, and assuming 21,000 total human genes (Harrow et al., 2012), one would expect $293/21{,}000 \times 732 \approx 10$ genes in the iMO–human-AUD set by random chance alone. As the observed iMO–human-AUD set contains 51 genes, this would correspond to an approximately 5-fold overrepresentation. Unfortunately, analyses of this type are not strictly valid for several reasons. First, the sets of 293 iMO–human and 732 human alcoholism-related genes queried for overlap are not independent, which is evidenced by published connections between studies in iMOs and humans for several individual genes (the ADH family, *AUTS2*, *ALK*, *GPC5*, *GABBR1*, *NPY*, etc.). Second, not all of the genes appearing in the HuGe Navigator have been associated with alcoholism, alcohol dependence, or other forms of AUD. Specifically, we found that of 83 genes in the HuGe Navigator evaluated as part of this review, 32 had neither a statistically significant nor a nominally significant association with AUD. Thus, based on our experience, approximately 40% of the "alcoholism" genes in the HuGe Navigator are not associated with AUD, leaving the number of genes with a reported connection to AUD in the navigator closer to approximately 450. Finally, genes tested in iMOs, but found to not have connections to alcohol response behaviors, are typically not reported, adding further uncertainty to statistical analysis of the number of genes in Table 4. These intrinsic features of the published data make a formal statistical analysis of the overlap impossible.

A small number of the 51 iMO–human-AUD genes (Table 4) have well-established roles in 1 or more features of AUD. Human *ADH1A*, *ADH1B*, *ADH1C*, *ALDH2*, *ALD-DH18A1*, and *ALDH4A1*, genes that encode key alcohol-metabolizing enzymes, are associated with alcohol dependence, alcohol intake, and other related phenotypes in numerous human studies (Table 4). The human genes *CHRNA3*, *DRD1*, *GAD1*, *NPY*, and *SLC18A2* have also been implicated in AUD by multiple studies in humans (Table 4). Given that these human genes are the most or among the most widely accepted for having roles in AUD, it is noteworthy that the invertebrate orthologs of all of these genes influence behavioral responses to acute alcohol exposure (Tables 1 and 2). The remaining 40 iMO–human-AUD genes have been implicated in human AUD by smaller scale or single studies (Table 4). Although it is not clear at this time whether these 40 genes have bona fide roles in human AUD given the lack of replication of the associations in independent populations, the results from studies on the invertebrate orthologs of these genes suggest that additional human studies are warranted.

A major potential limitation to the approach used to identify the 51 iMO–human-AUD genes (Table 4) is that it is based on overlap at the level of individual orthologs of iMO and human

genes. This approach almost certainly would miss key signaling or biochemical pathways in which, for example, a gene encoding a ligand was investigated in iMOs and the gene encoding the orthologous receptor for that ligand was found to be associated with human AUD. In such a case, the iMO data would provide strong evidence for a role of the biochemical process in alcohol-related behavior relevant to human AUD, even in the absence of directly implicating the particular orthologous human gene. Thus, as a complement to our analysis of the overlap between individual iMO and human genes, we visually compared the predicted or known biochemical functions of the iMO genes (Tables 1 and 2) with the functions of genes described in several comprehensive reviews on the genetics of AUD (Edenberg and Foroud, 2013, 2014; Palmer et al., 2012; Rietschel and Treutlein, 2013; Schuckit, 2014). As is true for individual genes, the most compelling evidence for a pathway important in iMOs and humans is for the alcohol-metabolizing machinery of ADH and ALDH. In addition, several other cellular processes also have strong support in iMOs and humans including signaling via dopamine, NPY, growth factors, and potassium channels (Tables 1 and 2). Thus, the 51 iMO–human-AUD genes in Table 4 probably under represent the functional overlap of findings from alcohol studies in iMOs and humans.

SUMMARY AND PERSPECTIVES

The large number of genes that influence alcohol-related behaviors identified in iMOs (Tables 1 and 2) demonstrates the analytical power of flies and worms for investigating molecular–genetic mechanisms underlying nervous system responses to alcohol. This analysis provides strong support for the use of iMOs as key experimental platforms for identifying and subsequently investigating novel genes that modulate alcohol-related behavior. Importantly, our analysis also demonstrates that studies in both flies and worms have independently contributed to our understanding of genetic mechanisms that influence behavioral responses to alcohol. Several major open questions remain regarding the function of many iMO genes identified to date: (i) Which of the genes influence developmental versus adult physiological processes relevant to alcohol-related behavior? (ii) Are there interactions between the gene-driven developmental and adult physiological processes that influence alcohol-related behavior? (iii) Do subsets of genes act in an integrated fashion to influence behavioral responses to alcohol? (iv) Do the genes alter alcohol-related behavioral responses via a common set of neuronal or other cellular mechanisms? (v) What are the major areas of the nervous system in which the genes function and what neurotransmitter systems are modulated by the genes? (vi) Do the genes influence alcohol-related behavior by functioning in non-neuronal cells? (vii) Do the genes influence multiple behavioral responses to alcohol similarly? (viii) Are the gene products direct pharmacological targets of alcohol? (ix) What is the complete complement of genes that is required for normal behavioral responses to alcohol? Flies and worms have contributed substantially to the field, yet much work remains to be done in iMOs on the genetics of alcohol-related behavior.

The numerous orthologs of genes that influence both human AUD and alcohol-related behaviors in iMOs support the concept of conservation of gene function in alcohol responses in humans and iMOs. Thus, additional genetic information gleaned from the fly and worm models should have translational utility for understanding AUD in humans. Given the

intrinsic and unavoidable differences between studies in iMOs and humans (see Genetics of Alcohol Behavior in Invertebrate Model Organisms and Human AUD), it is reasonable to expect that not all alcohol behavior genes identified in iMOs will be associated with human AUD. Nevertheless, orthologs of alcohol behavior genes in iMOs (Table 3) might be prime candidates for targeted investigations in studies on human AUD. Conversely, additional orthologs of genes identified in studies on human AUD could be investigated in iMOs to better understand (i) the fundamental alcohol behavioral consequences of altered gene function and (ii) the genetic pathways and gene networks that function in concert with the originally identified human AUD gene. An understanding of these 2 aspects of gene function in iMOs might ultimately provide a more comprehensive appreciation of molecular and cellular mechanisms underlying human AUD. Consequently, the integration of information from behavioral–genetic studies on alcohol in iMOs with genetic findings from humans has the potential to lead to a much deeper understanding of AUD, its diagnosis, and its treatment.

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Table 1

Genes that Influence Alcohol-Related Behavior in Flies

Gene (aka)	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
AcCoAS	Acetyl CoA synthesis	LOF mutant	Booz-o-mat	ACT	Decrease	Kong et al. (2010a)
Adh	Alcohol dehydrogenase	LOF mutants	Booz-o-mat	% Sed	Increase	Wolf et al. (2002)
		LOF mutants	Unnamed	Locomotor activity	Decrease	Grell et al. (1968)
		LOF mutant	Inebriometer	MET, Rap Tol (MET)	Decrease	Cavener (1979)
		LOF mutant	Larval preference	Larvae on alcohol agar	Decrease	Ogueta et al. (2010)
Akt1 (Akt)	Serine/threonine kinase	LOF mutant	Sedation	Time to Sed	Increase	Eddison et al. (2011)
		RNAi	Sedation	Time to Sed	Increase	
		Overexpression	Sedation	Time to Sed	Decrease	
Alk	Receptor tyrosine kinase	LOF mutants	Booz-o-mat	Time to Sed	Increase	Lasek et al. (2011b)
amn	PACAP-like neuropeptide	LOF mutants	Inebriometer	MET	Decrease	Moore et al. (1998)
		LOF mutants	Booz-o-mat	ACT, % Sed	Increase	Wolf et al. (2002)
		LOF mutant	Sedation	Time to Sed	Decrease	Peru Y Colon de Portugal et al. (2012)
apt	Myb/SANT-containing transcription factor	LOF mutants	Sedation	Time to Sed	Increase	McClure and Heberlein (2013)
		RNAi	Sedation	Time to Sed	Increase	
Arf51F (Arf6)	Small G protein	LOF mutants	Sedation	Time to Sed	Decrease	Peru Y Colón de Portugal et al. (2012)
Arfip	Dynactin binding	LOF mutant	Sedation	Time to Sed	Decrease	Peru Y Colón de Portugal et al. (2012)
aru	Epidermal growth factor receptor substrate	LOF mutants	Inebriometer	MET, Time to Sed	Decrease	Eddison et al. (2011)
		LOF mutants	Sedation	MET, Time to Sed	Decrease	
		RNAi	Inebriometer	MET, Time to Sed	Decrease	
		RNAi	Sedation	MET, Time to Sed	Decrease	
Bacc	Ribosomal RNA-binding domain protein	LOF mutants	Sedation	Time to Sed	Increase	Chen et al. (2013)
		RNAi	Sedation	Time to Sed	Increase	
bsk	Serine–threonine kinase	LOF mutant	Booz-o-mat	ACT	Increase	Kapfhamer et al. (2012)
Bx (dLmo)	Zinc-finger protein, LIM-type	LOF mutant	Sedation	Time to Sed	Decrease	Lasek et al. (2011a)
		GOF mutant	Sedation	Time to Sed	Increase	
CASK	Molecular scaffold	LOF mutants	Inebriometer	Rap Tol (MET)	Decrease	Maiya et al. (2012)

Gene (aka)	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
Cdc42	Small G protein	GOF transgenic	Sedation	% Sed	Increase	Rothenfluh et al. (2006)
chico	Insulin receptor substrate	LOF mutant	Inebriometer	MET	Decrease	Corl et al. (2005)
Clic	Numerous proposed	LOF mutants	eRING	Time to Sed	Increase	Bhandari et al. (2012)
		LOF mutants	Sedation	Time to Sed	Increase	Chan et al. (2014)
		RNAi	Sedation	Time to Sed	Increase	
Crz	Neuropeptide	RNAi	Sedation	Time to Sed	Increase	McClure and Heberlein (2013)
		LOF mutant	Sedation recovery	Time to Rec	Increase	Sha et al. (2014)
CrzR	Corazonin receptor	RNAi	Sedation recovery	Time to Rec	Increase	Sha et al. (2014)
cyc	Transcription factor	LOF mutant	Sedation	Rap Tol (Time to Sed)	Decrease	Pohl et al. (2013)
Cyp1	Peptidyl-prolyl cis-trans isomerase activity	RNAi	Inebriometer	MET	Increase	Morozova et al. (2011)
dally	Glypican	LOF mutant	Video	ACT	Decrease	Joslyn et al. (2011)
		LOF mutant	Sedation	Time to Sed	Decrease	
DAT	Dopamine transporter	LOF mutant	Video	ACT	Decrease	Kong et al. (2010b)
		Overexpression	Video	ACT	Increase	
dlg1	Membrane-associated guanylate kinase	LOF mutants	Inebriometer	Rap Tol, Chron Tol (MET)	Decrease	Maiya et al. (2012)
dlp	Glypican	LOF mutant	Video	ACT	Decrease	Joslyn et al. (2011)
		LOF mutant	Sedation	Time to Sed	Decrease	
		LOF mutant	Sedation	Rap Tol	Increase	
Dop1R1	Dopamine receptor	LOF mutant	Video	ACT	Decrease	Bainton et al. (2000)
		LOF mutant	Video	ACT	Decrease	Kong et al. (2010b)
Egfr	Epidermal growth factor receptor	Overexpression	Sedation	Time to Sed	Increase	Corl et al. (2009)
		RNAi, inhibitor	Sedation	Time to Sed	Decrease	
elm	P22 calcineurin B	LOF mutant	Inebriometer	MET	Decrease	LaFerriere et al. (2008)
Fas2	Ig-domain adhesion molecule	LOF mutants	Inebriometer	MET	Decrease	Cheng et al. (2001)
Fng	UDP-glycosyltransferase	RNAi	Inebriometer	Rap Tol (MET)	Increase	Morozova et al. (2011)
FOXO	Transcription factor	Overexpression	Inebriometer	MET	Decrease	Corl et al. (2005)
Fs	Negative regulator of activin receptor signaling	GOF mutant	Inebriometer	MET	Increase	Morozova et al. (2011)
GABA-B-R1	Metabotropic GABA receptor	RNAi	Sedation recovery	Sed Rec Time	Decrease	Dzitoyeva et al. (2003)
		Antagonist	Sedation recovery	Sed Rec Time	Decrease	
		Agonist	Sedation recovery	Rap Tol (Sed Rec Time)	Decrease	
H15	T-box transcription factor	RNAi	Inebriometer	MET	Increase	Morozova et al. (2011)

Gene (aka)	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
hang	Zinc-finger protein	LOF mutant	Inebriometer	Rap Tol (MET)	Decrease	Scholz et al. (2005)
		LOF mutant	eRING	Rap Tol (Time to Sed)	Decrease	Bhandari et al. (2009)
homer	Postsynaptic scaffolding	LOF mutant	Sedation	Time to Sed	Decrease	Urizar et al. (2007)
		LOF mutant	Sedation	Rap Tol (Time to Sed)	Decrease	
hppy	Ste20 kinase	LOF mutants	Video, Sedation	Time to Sed	Increase	Corl et al. (2009)
		LOF mutant	Sedation	Time to Sed	Increase	Eddison et al. (2011)
Hsp26	Heat shock protein	Transposons	Sedation	Rap Tol (Time to Sed)	Decrease	Awofala et al. (2011)
		RNAi	Sedation	Rap Tol (Time to Sed)	Decrease	
		Overexpression	Sedation	Rap Tol (Time to Sed)	Increase	
htl	FGF receptor	LOF mutant	Video	ACT	Decrease	King et al. (2014)
iav	Cation channel	LOF mutant	Inebriometer	MET	Decrease	Scholz (2005)
InR	Insulin receptor	LOF mutants	Inebriometer	MET	Decrease	Corl et al. (2005)
Jwa	Microtubule-binding protein	Antisense RNA	Inebriometer	Rap Tol (MET)	Decrease	Li et al. (2008)
		Overexpression	Sedation recovery	Rap Tol (Sed Rec Time)	Increase	
KCNQ	Voltage-dependent potassium channel	LOF mutant	Sedation	Time to Sed	Decrease	Cavaliere et al. (2012)
		RNAi	Sedation	Time to Sed	Decrease	
		Overexpression	Sedation	Rap Tol (Time to Sed)	Increase	
Men	Malate metabolism	LOF mutant	Inebriometer	MET	Increase	Morozova et al. (2009)
		RNAi	Inebriometer	MET	Increase	Morozova et al. (2011)
Mlc-c	Myosin light chain	RNAi	Inebriometer	MET	Decrease	Morozova et al. (2011)
moody	G protein-coupled receptor	LOF mutant	Inebriometer	MET	Increase	Bainton et al. (2005)
mys	Integrin beta subunit	LOF mutants	eRING	Time to Sed	Decrease	Bhandari et al. (2009)
		LOF mutants	eRING	Rap Tol (Time to Sed)	Increase	
NmdaR1	NMDA receptor	LOF mutant	Inebriometer	Rap Tol, Chron Tol (MET)	Decrease	Kaun et al. (2011)
NPF	Neuropeptide F	Overexpression	Sedation	Time to Sed	Decrease	Wen et al. (2005)
NPFR	Neuropeptide F receptor	RNAi	Sedation	Time to Sed	Increase	Wen et al. (2005)
		RNAi	CAFÉ	Alcohol Preference	Increase	Shohat-Ophir et al. (2012)
Orco	Odorant receptor co-receptor	LOF mutant	Booz-o-mat	ACT	Increase	Kong et al. (2010a)
		LOF mutants	Alcohol trap	Alcohol Odor Preference	Decrease	Schneider et al. (2012)
Osi9	Unknown	GOF mutant	Inebriometer	MET	Increase	Morozova et al. (2011)
par-1	Serine–threonine kinase	LOF mutant	Video	ACT	Suppresses tao LOF	King et al. (2011)

Gene (aka)	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
Pdk1	PIP3-dependent serine/threonine kinase	Overexpression	Sedation	Time to Sed	Decrease	Eddison et al. (2011)
per	CYC/CLK stability	LOF mutant	Sedation	Time to Sed	No circadian effect	van der Linde and Lyons (2011)
		LOF mutant	Sedation	Rap Tol (Time to Sed)	Decrease	
Pi3K21B (p60)	PI3K inhibitory subunit	Overexpression	Inebriometer	MET	Decrease	Corl et al. (2005)
Pi3K92E (p110)	PI3K catalytic subunit	Overexpression	Sedation	Time to Sed	Decrease	Eddison et al. (2011)
		Dominant negative	Sedation	Time to Sed	Increase	
Pka-C1 (DCO)	PKA-catalytic subunit 1	LOF mutants	Inebriometer	MET	Decrease	Moore et al. (1998)
		LOF mutants	Inebriometer	MET	Decrease	Rodan et al. (2002)
Pka-R2	Protein kinase A regulatory subunit	LOF mutant	Sedation	Time to Sed	Increase	Park et al. (2000)
Pkc98E	Protein kinase C calcium independent	RNAi	Sedation	Time to Sed	Increase	Chen et al. (2008)
		RNAi	Sedation	Time to Sed	Increase	Chen et al. (2010)
psq	Helix-loop-helix protein	LOF mutant	Inebriometer	MET	Decrease	Morozova et al. (2009)
		LOF mutant	Inebriometer	MET	Decrease	Morozova et al. (2011)
Pten	Phosphatidylinositol 3,4,5-triphosphate phosphatase	Overexpression	Sedation	Time to Sed	Increase	Eddison et al. (2011)
puc	Tyrosine phosphatase	LOF mutant	Booz-o-mat	ACT	Decrease	Kapfhamer et al. (2012)
Rac1	Small GTPase	GOF transgenic	Sedation	% Sed	Decrease	Rothenfluh et al. (2006)
Rheb	Small GTPase	Overexpression	Sedation	Time to Sed	Decrease	Eddison et al. (2011)
rho	Ligand-activated peptidase	LOF mutant	Sedation	Time to Sed	Decrease	Corl et al. (2009)
Rho1	Small GTPase	GOF transgenic	Sedation	% Sed	Decrease	Rothenfluh et al. (2006)
RhoGAP18B	Rho Gap	LOF mutants	Video	ACT	Increase	Rothenfluh et al. (2006)
			Sedation	% Sed	Decrease	
rl	ERK kinase	Overexpression	Sedation	Time to Sed	Increase	Corl et al. (2009)
rut	Ca^{2+}/calmodulin-sensitive adenylyl cyclase	LOF mutants	Inebriometer	MET	Decrease	Moore et al. (1998)
		LOF mutants	Booz-o-mat	ACT, % Sed	Increase	Wolf et al. (2002)
		LOF mutant	CAFÉ	Alcohol Preference	Decrease	Xu et al. (2012)
S	Chaperone	LOF mutant	Sedation	Time to Sed	Decrease	Corl et al. (2009)
sca	Fibrinogen	LOF mutants	Conditioned preference	Alcohol preference	Decrease	Kaun et al. (2011)
SCAP	Unknown	GOF mutant	Inebriometer	MET	Increase	Morozova et al. (2011)
scb	Integrin alpha subunit	LOF mutants	eRING	Time to Sed	Decrease	Bhandari et al. (2009)
		LOF mutants	eRING	Rap Tol (Time to Sed)	Increase	
sgl	UDP-glucose 6-dehydrogenase	LOF mutant	Inebriometer	MET	Increase	Morozova et al. (2011)

Gene (aka)	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
shi	Dynamin	LOF mutants	Sedation recovery	Rap Tol (Sed Rec Time)	Decrease	Krishnan et al. (2012)
Sip1	Unknown	GOF mutant	Inebriometer	MET	Decrease	Morozova et al. (2011)
Sir2	Histone deacetylase	LOF mutant	Booz-o-mat	ACT	Decrease	Kong et al. (2010a)
		LOF mutant	Booz-o-mat	% Sed	Decrease	
		LOF mutant	Booz-o-mat	Rap Tol (% Sed)	Decrease	
slo	Calcium-activated potassium channel	LOF mutants	Sedation recovery	Rap Tol (Sed Rec Time)	Decrease	Cowmeadow et al. (2005)
		Overexpression	Sedation Recovery	Rap Tol (Sed Rec Time)	Induced Rap Tol	Cowmeadow et al. (2006)
		LOF mutant	Seizure induction	Seizure Threshold (V)	Decrease	Ghezzi et al. (2012)
spi	Epidermal growth factor receptor ligand	Overexpression	Sedation	Time to Sed	Increase	Corl et al. (2009)
Spn27A	Serine-type endopeptidase inhibitor	LOF mutant	Booz-o-mat	ACT	Decrease	Kong et al. (2010a)
Syn	Synapsin	LOF mutant	Inebriometer	Rap Tol (MET)	Increase	Godenschwege et al. (2004)
Syx1A	Syntaxin	LOF mutant	Sedation recovery	Rap Tol (Sed Rec Time)	Decrease	Krishnan et al. (2012)
Tao	Serine–threonine kinase	LOF mutant	Booz-o-mat	ACT	Decrease	King et al. (2011)
tay	AUTS2 ortholog	LOF mutant	Sedation	Time to Sed	Increase	Schumann et al. (2011)
		RNAi	Sedation	Time to Sed	Increase	
Tbh	Tyramine hydroxylase	LOF mutant	Inebriometer	Rap Tol (MET)	Decrease	Scholz et al. (2000)
		LOF mutant	Inebriometer	Rap Tol (MET)	Decrease	Berger et al. (2004)
		LOF mutant	Inebriometer	Rap Tol (MET)	Decrease	Scholz et al. (2005)
		LOF mutant	Sedation	Rap Tol (Time to Sed)	Decrease	Awofala et al. (2011)
		LOF mutants	Alcohol trap	Odor Preference	Decrease	Schneider et al. (2012)
tim	CYC/CLK stability	LOF mutant	Sedation	Rap Tol (Time to Sed)	Decrease	Pohl et al. (2013)
tra	Female-specific mRNA splicing protein	Overexpression (♂)	Sedation	Time to Sed	Decrease	Devineni and Heberlein (2012)
		RNAi (♀)	Sedation	Time to Sed	Increase	
Tre1	G protein-coupled receptor	GOF mutant	Inebriometer	MET	Increase	Morozova et al. (2011)
unc-13	Calmodulin binding; diacylglycerol binding	LOF mutant	CAFÉ	Alcohol Preference	Increase	Das et al. (2013)
tank	EI24/PIG8 ortholog	LOF mutant, RNAi	Booz-o-mat	Time to Sed	Increase	Devineni et al. (2013)
w	ABC transporter	LOF mutant	eRING	Time to Sed	Decrease	Chan et al. (2014)
		RNAi	eRING	Time to Sed	Decrease	Chan et al. (2014)
		LOF mutant	Fly Bar	Time to LORR	Increase	van der Linde et al. (2014)

Columns are the gene name abbreviations, a brief functional description of the gene product, the type of genetic manipulation that was used (LOF, loss of function; RNAi, RNA interference, or overexpression), the name of the assay used to assess alcohol-related behavior, the behavioral end point that was measured in the assay (ACT, alcohol-stimulated locomotor activity or locomotor activity in

the presence of alcohol; % Sed, % of flies sedated after a defined exposure to alcohol; MET, mean elution time; Rap Tol and Chron Tol, rapid tolerance and chronic tolerance, respectively, to the behavioral measure indicated in parentheses; Time to Sed, duration of alcohol exposure required to sedate flies to a defined level; Sed Rec Time, time required for flies to recover from sedation; Alcohol Preference, alcohol drinking preference; Time to LORR, alcohol exposure time required for flies to lose a defined amount of their ability to right themselves; Seizure Threshold (V), voltage of electric shock required to produce seizures in a defined fraction of subjects; Alcohol Odor Preference, fraction of flies captured in a trap with alcohol odor vapor), the effect of the genetic manipulation on the behavioral measure, and the citations for the relevant publications.

Table 2

Genes that Influence Alcohol-Related Behavior in Worms

Gene	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
aex-3	RAB3 GTP exchange factor	LOF mutant	Crawling (400 mM)	Crawling speed at 20 minutes	Resistant	Kapfhamer et al. (2008)
alh-13	Aldehyde dehydrogenase	RNAi	Crawling (400 mM)	Crawling speed at 10 minutes	Sensitive	Alaimo et al. (2012)
alh-6	Aldehyde dehydrogenase	RNAi	Crawling (400 mM)	Crawling speed at 10 minutes	Sensitive	Alaimo et al. (2012)
bbs-1	BBS1	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Increased IS; Enhanced AFT	Bettinger et al. (2012)
cat-1	Vesicular monoamine transporter	LOF mutant	State-dependent learning	SDL	Fails to develop SDL	Bettinger and McIntire (2004)
cat-2	Tyrosine hydroxylase	LOF mutant	State-dependent learning; Alcohol preference	SDL; Alcohol preference	Fails to develop SDL Does not develop Alcohol preference	Bettinger and McIntire (2004), Lee et al. (2009)
cha-1	Cholineacetyltransferase	LOF mutant	Hypercontraction	Hypercontraction and Recovery	Resistant	Hawkins et al. (2015)
ctbp-1	Transcriptional co-repressor	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Increased IS; Decreased AFT	Bettinger et al. (2012)
dgk-1	Diacylglycerol kinase	LOF mutant	Crawling (500 mM) Crawling (400 mM)	Crawling speed at 20 minutes; Crawling speed; initial sensitivity and AFT	Resistant; Decrease in IS	Bettinger et al. (2012), Davies et al. (2003)
dpff-1	Component of SWI/SNF chromatin remodeling complex	RNAi	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS	Mathies et al. (2015)
dop-4	Dopamine receptor (D1-like)	LOF mutant	Alcohol disinhibition of crawling gait in liquid	Body posture in liquid (500 mM)	Resistant to Alcohol disinhibition of crawling gait in liquid	Topper et al. (2014)
eat-6	Alpha subunit Na+/K+-ATPase	LOF mutant	Hypercontraction	Hypercontraction and recovery	No recovery from hypercontraction	Hawkins et al. (2015)
egl-3	Proprotein convertase	LOF mutant	Alcohol withdrawal-induced “unaccompanied” omega turns (350 mM)	Number of omega turns without a preceding reversal at 5 and 40 minutes	No increase in “unaccompanied” omega turns	Mitchell et al. (2010)
exc-4	CLIC; numerous proposed	LOF mutant	Crawling (400 mM), 10, 20, 30, 40, 50 minutes	Crawling speed at 10, 20, 30, 40, 50 minutes	Decrease in IS at 10 minutes; trend toward decrease in AFT	Bhandari et al. (2012)
exl-1	CLIC; numerous proposed	LOF mutant	Crawling (400 mM), 10, 20, 30, 40, 50 minutes	Crawling speed at 10, 20, 30, 40, 50 minutes	Enhanced AFT	Bhandari et al. (2012)

Gene	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
fat-1	Omega-3 fatty acid acyl desaturase	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Increased IS; No AFT	Raabe et al. (2014)
fat-3	Delta-6 fatty acid desaturase	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Raabe et al. (2014)
fat-4	Delta-5 fatty acid desaturase	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Raabe et al. (2014)
let-526	Component of SWI/SNF chromatin remodeling complex	RNAi	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS	Mathies et al. (2015)
lips-7	Triacylglycerol lipase	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS; Enhanced AFT	Bettinger et al. (2012)
nca-1	NALCN-related leak channel	LOF mutant	Swimming (400 mM)	Frequency of body bends at 10 minutes	Sensitive	Speca et al. (2010)
nca-2	NALCN-related leak channel	LOF mutant	Swimming (400 mM)	Frequency of body bends at 10 minutes	Sensitive	Speca et al. (2010)
nhr-49	Nuclear hormone receptor	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Bettinger et al. (2012)
npr-1	Neuropeptide Y-like GPCR	LOF mutants	Crawling (500 mM) Crawling (400 mM)	Crawling speed at 10, 30, 50 minutes; initial sensitivity and AFT Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS; Enhanced AFT; Decreased IS; Enhanced AFT	Bettinger et al. (2012), Davies et al. (2004)
osm-9	TRPV channel	LOF mutant	Crawling (500 mM)	Crawling speed at 10, 30, 50 minutes; initial sensitivity and AFT	Partial suppression of npr-1 enhanced AFT	Davies et al. (2004)
pag-3	Zinc-finger transcription factor	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Bettinger et al. (2012)
pbrm-1	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased AFT	Mathies et al. (2015)
phf-10	Component of SWI/SNF chromatin remodeling complex	RNAi	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Mathies et al. (2015)
rab-3	Small molecular weight GTP-binding protein	LOF mutant	Dispersal assay (200 and 400 mM); Crawling (400 mM)	Movement toward food; Crawling speed at 20 minutes	Fast dispersal; Resistant	Kapfhamer et al. (2008)
sbp-1	Transcription factor	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS; No AFT	Bettinger et al. (2012)
seb-3	CRF receptor-like GPCR	LOF mutant GOF mutant	Crawling (500 mM) Withdrawal induced tremor (400 mM)	Crawling speed at 10, 30, 50 minutes, AFT; Number of animals with tremor after withdrawal from 4-hour exposure	LOF: Decreased AFT, GOF: Increased AFT; LOF: Resistant to tremor	Jee et al. (2013)
sir-2.1	Transcription factor	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS; Enhanced AFT	Bettinger et al. (2012)
slo-1	BK voltage and calcium-sensitive large conductance K+ channel	LOF mutants	Crawling (500 mM) Egg laying (500 mM) Crawling (400 mM)	Crawling speed at 20 minutes; Number of eggs laid on Alcohol; Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Resistant; Resistant; Decreased IS; Decreased AFT	Bettinger et al. (2012), Davies et al.

Gene	Function	Genetic manipulation	Behavioral assay	Measure	Effect	Citation
						(2003), Dillon et al. (2013) Dillon et al. (2013)
sodh-1	Alcohol dehydrogenase	LOF mutants	Crawling (200 mM); Crawling (400 mM)	Crawling speed at 10 and 50 minutes; Crawling speed at 10 and 50 minutes; initial sensitivity and AFT	Resistant; Resistant	Alaimo et al. (2012)
swsn-1	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Mathies et al. (2015)
swsn-2.1	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Mathies et al. (2015)
swsn-2.2	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS; No AFT	Mathies et al. (2015)
swsn-3	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Increased IS; No AFT	Mathies et al. (2015)
swsn-4	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	No AFT	Mathies et al. (2015)
swsn-6	Component of SWI/SNF chromatin remodeling complex	RNAi	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS; No AFT	Mathies et al. (2015)
swsn-7	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; initial sensitivity and AFT	Decreased IS	Mathies et al. (2015)
swsn-9	Component of SWI/SNF chromatin remodeling complex	LOF mutant	Crawling (400 mM)	Crawling speed at 10 and 30 minutes; Initial sensitivity and AFT	No AFT	Mathies et al. (2015)
tph-1	Tryptophan hydroxylase	LOF mutant	Alcohol preference	Alcohol preference	Decrease in preference	Lee et al. (2009)
unc-17	Vesicular acetylcholine transporter	LOF mutant	Hypercontraction	Hypercontraction and Recovery	Resistant to Hypercontraction	Hawkins et al. (2015)
unc-18	SM protein	LOF mutant	Swimming (400 mM)	Number of thrashes at 10 minutes	Resistant	Graham et al. (2009)
unc-25	Glutamic acid decarboxylase	LOF mutant	Hypercontraction	Hypercontraction and Recovery	Resistant to Hypercontraction	Hawkins et al. (2015)
unc-47	GABA vesicular transporter	LOF mutant	Hypercontraction	Hypercontraction and Recovery	Resistant to Hypercontraction	Hawkins et al. (2015)
unc-63	Nicotinic acetylcholine receptor	LOF mutant	Hypercontraction	Hypercontraction and Recovery	Resistant to Hypercontraction	Hawkins et al. (2015)
unc-79	Interacts with voltage insensitive cation leak channels	LOF mutant	Immobility over a dose curve; Swimming (400 mM)	EC_{50} (immobility) at 5 minutes Frequency of body bends at 10 minutes	Resistant; Sensitive	Morgan and Sedensky (1995), Speca et al. (2010)
unc-80	Interacts with voltage insensitive cation leak channels	LOF mutant	Swimming (400 mM)	Frequency of body bends at 10 minutes	Sensitive	Speca et al. (2010)

Columns are the gene name abbreviations, a brief functional description of the gene product, the type of genetic manipulation that was used (LOF, loss of function mutation; GOF, gain of function mutation; RNAi, RNA interference), the name of the assay used to assess alcohol-related behavior, the behavioral end point that was measured in the assay (Crawling speed, locomotion speed on an agar

surface; Swimming, number of body bends or thrashes in a liquid medium; SDL, state-dependent learning; Alcohol preference; Hypercontraction; Alcohol disinhibition of crawling gait in a liquid assay; Alcohol withdrawal-induced "unaccompanied" omega turns, omega turns observed without accompanying reversal; Dispersal assay; Alcohol withdrawal-induced tremor; Egg-laying; Immobility in liquid), the effect of the genetic manipulation on the behavioral measure, and the citations for the relevant publications.

Table 3

Invertebrate Model Organism (iMO)–Human Genes: Human Orthologs of Genes that Influence Alcohol-Related Behaviors in iMOs

Human gene	iMO source	Human gene	iMO source	Human gene	iMO source	Human gene	iMO source	Human gene	iMO source	Human gene	iMO source
ABCG2	Fly	*CLIC1*	Fly, Worm	*FGFR4*	Fly	*LMO1*	Fly	*PIK3CD*	Fly	*SLC6A3*	Fly
ACSS1	Fly	*CLIC2*	Fly, Worm	*FOXO1*	Fly	*LMO2*	Fly	*PIK3CG*	Fly	*SLC9A3R1*	Fly
ACSS2	Fly	*CLIC3*	Fly, Worm	*FOXO3*	Fly	*LMO3*	Fly	*PIK3R1*	Fly	*SLC9A3R2*	Fly
ACTL6A	Worm	*CLIC4*	Fly, Worm	*FOXO4*	Fly	*LTK*	Fly	*PIK3R2*	Fly	*SMARCA2*	Worm
ACTL6B	Worm	*CLIC5*	Fly, Worm	*FOXO6*	Fly	*MADD*	Worm	*PIK3R3*	Fly	*SMARCA4*	Worm
ADCY1	Fly	*CLIC6*	Fly, Worm	*FST*	Fly	*MAP4K1*	Fly	*PPIA*	Fly	*SMARCC1*	Worm
ADH1A	Fly, Worm	*COX6C*	Fly	*FSTL3*	Fly	*MAP4K2*	Fly	*PPIF*	Fly	*SMARCC2*	Worm
ADH1B	Fly, Worm	*CRYAA*	Fly	*GABBR1*	Fly	*MAP4K3*	Fly	*PRAF2*	Fly	*SMARCD1*	Worm
ADH1C	Fly, Worm	*CRYAB*	Fly	*GAD1*	Worm	*MAP4K5*	Fly	*PRKACA*	Fly	*SMARCD2*	Worm
AKT1	Fly	*CSAD*	Worm	*GAD2*	Worm	*MAPK1*	Fly	*PRKACB*	Fly	*SMARCD3*	Worm
AKT2	Fly	*CSNK1A1*	Fly	*GADL1*	Worm	*MAPK10*	Fly	*PRKACG*	Fly	*SMARCE1*	Worm
AKT3	Fly	*CSNK1D*	Fly	*GFI1*	Worm	*MAPK3*	Fly	*PRKAR2A*	Fly	*SREBF1*	Worm
ALDH family (19 genes)	Worm	*CSNK1E*	Fly	*GFI1B*	Worm	*MAPK8*	Fly	*PRKAR2B*	Fly	*SREBF2*	Worm
		CTBP1	Worm	*GPC1*	Fly	*MAPK9*	Fly	*PRKCE*	Fly	*STX1A*	Fly
ALK	Fly	*CTBP2*	Worm	*GPC2*	Fly	*MARK1*	Fly	*PRKCH*	Fly	*STX1B*	Fly
ARF6	Fly	*DBH*	Fly	*GPC3*	Fly	*MARK2*	Fly	*PSMD1*	Fly	*STX2*	Fly
ARFIP1	Fly	*DGKQ*	Worm	*GPC4*	Fly	*MARK3*	Fly	*PTEN*	Fly	*STX3*	Fly
ARFIP2	Fly	*DLG1*	Fly	*GPC5*	Fly	*MARK4*	Fly	*RAB3A*	Worm	*STX4*	Fly
ARID1A	Worm	*DLG2*	Fly	*GPC6*	Fly	*ME1*	Fly	*RAB3B*	Worm	*STXBP1*	Worm
ARID1B	Worm	*DLG3*	Fly	*GPR84*	Fly	*ME2*	Fly	*RAB3C*	Worm	*STXBP2*	Worm
ARID2	Worm	*DLG4*	Fly	*GRIN1*	Fly	*ME3*	Fly	*RAB3D*	Worm	*STXBP3*	Worm
ARL6IP5	Fly	*DNM1*	Fly	*HNF4A*	Worm	*MFNG*	Fly	*RAC1*	Fly	*SYN1*	Fly
ARNTL	Fly	*DNM2*	Fly	*HNF4G*	Worm	*MTNR1A*	Fly	*RAC2*	Fly	*SYN2*	Fly
ARNTL2	Fly	*DNM3*	Fly	*HOMER1*	Fly	*MTNR1B*	Fly	*RAC3*	Fly	*SYN3*	Fly
ATP12A	Worm	*DPF1*	Worm	*HOMER2*	Fly	*MYL1*	Fly	*RFNG*	Fly	*TAF4*	Fly
ATP1A1	Worm	*DPF2*	Worm	*HOMER3*	Fly	*MYL3*	Fly	*RHBDL1*	Fly	*TAF4B*	Fly
ATP1A2	Worm	*DPF3*	Worm	*HPGD*	Fly	*MYL4*	Fly	*RHBDL2*	Fly	*TAOK1*	Fly
ATP1A3	Worm	*DRD1*	Fly, Worm	*IGF1R*	Fly	*MYL6*	Fly	*RHBDL3*	Fly	*TAOK2*	Fly

Human gene	iMO source	Human gene	iMO source	Human gene	iMO source	Human gene	iMO source	Human gene	iMO source	Human gene	iMO source
ATP1A4	Worm	*DRD5*	Fly	*INSR*	Fly	*MYL6B*	Fly	*RHEB*	Fly	*TAOK3*	Fly
ATP4A	Worm	*DUSP10*	Fly	*INSRR*	Fly	*NALCN*	Worm	*RHEBL1*	Fly	*TBX20*	Fly
AUTS2	Fly	*EGFR*	Fly	*IRS1*	Fly	*NAT10*	Fly	*RHOA*	Fly	*TH*	Worm
BBS1	Worm	*EI24*	Fly	*IRS2*	Fly	*NCAM1*	Fly	*RHOB*	Fly	*TIMELESS*	Fly
BRD7	Worm	*EPS8*	Fly	*IRS4*	Fly	*NCAM2*	Fly	*RHOC*	Fly	*TPH1*	Worm
BRD9	Worm	*EPS8L1*	Fly	*ITGB1*	Fly	*NPY*	Fly	*SCAP*	Fly	*TPH2*	Worm
CASK	Fly	*EPS8L2*	Fly	*ITGB2*	Fly	*NPY1R*	Fly, Worm	*SDC1*	Fly	*TRPV1*	Fly, Worm
CDC42	Fly	*EPS8L3*	Fly	*ITGB3*	Fly	*NPY2R*	Fly, Worm	*SDC2*	Fly	*TRPV2*	Fly, Worm
CHAT	Worm	*ERBB2*	Fly	*ITGB5*	Fly	*NPY4R*	Fly, Worm	*SDC3*	Fly	*TRPV3*	Fly, Worm
CHP1	Fly	*ERBB3*	Fly	*ITGB7*	Fly	*PBRM1*	Worm	*SDC4*	Fly	*TRPV4*	Fly, Worm
CHP2	Fly	*ERBB4*	Fly	*KCNMA1*	Fly, Worm	*PCSK2*	Worm	*SGK1*	Fly	*TRPV5*	Fly, Worm
CHRNA1	Worm	*FADS1*	Worm	*KCNQ1*	Fly	*PDPK1*	Fly	*SGK2*	Fly	*TRPV6*	Fly, Worm
CHRNA2	Worm	*FADS2*	Worm	*KCNQ2*	Fly	*PER1*	Fly	*SIRT1*	Fly, Worm	*UGDH*	Fly
CHRNA3	Worm	*FADS3*	Worm	*KCNQ3*	Fly	*PER2*	Fly	*SIRT3*	Worm	*UNC13A*	Fly
CHRNA4	Worm	*FBRSL1*	Fly	*KCNQ4*	Fly	*PER3*	Fly	*SLC18A1*	Worm	*UNC13B*	Fly
CHRNA6	Worm	*FGFR1*	Fly	*KCNQ5*	Fly	*PHF10*	Worm	*SLC18A2*	Worm	*UNC13C*	Fly
CHRNB2	Worm	*FGFR2*	Fly	*KCNU1*	Fly, Worm	*PIK3CA*	Fly	*SLC32A1*	Worm	*UNC79*	Worm
CHRNB4	Worm	*FGFR3*	Fly	*LFNG*	Fly	*PIK3CB*	Fly	*SLC6A2*	Fly	*UNC80*	Worm

Columns are the human orthologs of genes originally identified in the iMO source indicated (fly, Worm, or both).

Table 4

Invertebrate Model Organism (iMO)–Human-Alcohol Use Disorder (AUD) Genes: Orthologs of Genes that Influence Alcohol-Related Behavior in iMOs and also have been Implicated in Human AUD

Human gene	Function	Fly ortholog	Worm ortholog	Human genetics	Human phenotype	Citations
ADH1A	Alcohol dehydrogenase	*Adh*	*sodh-1*	SNP(s) associated (gene cluster)	AD	Birley et al. (2009), Kuo et al. (2008), Luo et al. (2006), Park et al. (2013), Zuo et al. (2013)
ADH1B	Alcohol dehydrogenase	*Adh*	*sodh-1*	SNP(s) associated and suggested associated (gene cluster)	AD, alcohol intake	Birley et al. (2009), Duell et al. (2012), Kuo et al. (2008), Li et al. (2011), Luo et al. (2006), Park et al. (2013), Zuo et al. (2013)
ADH1C	Alcohol dehydrogenase	*Adh*	*sodh-1*	SNP(s) associated (gene cluster)	AD	Birley et al. (2009), Kuo et al. (2008), Li et al. (2012), Zuo et al. (2013)
ALDH2	Aldehyde dehydrogenase		*alh-6, alh-13*	SNP(s) associated with protection	Alcohol drinking, AD	Ayhan et al. (2015), Edenberg (2007), Peng et al. (2014), Thomasson et al. (1991)
ALDH1A1	Aldehyde dehydrogenase		*alh-6, alh-13*	SNP(s) associated	AD	Crawford et al. (2014), Ehlers et al. (2004), Lind et al. (2008)
ALDH1B1	Aldehyde dehydrogenase		*alh-6, alh-13*	SNP associated with protection	AD, alcohol induced hypersensitivity	Bjerregaard et al. (2014), Linneberg et al. (2010)
ALDH5A1	Aldehyde dehydrogenase		*alh-6, alh-13*	“leading edge gene”	SREF, BSA, SHAS	Joslyn et al. (2010)
ALK	Receptor tyrosine kinase, insulin receptor family	*dAlk*		SNP(s) associated	Low LR	Lasek et al. (2011b)
ARL6IP5	Microtubule binding protein	*jwa*		SNP(s) associated	AD	Edenberg et al. (2010)
ARNTL	Helix-loop-helix transcription factor	*cyc*		Suggestive SNP(s) associated	AC	Kovanen et al. (2010)
ARNTL2	Helix-loop-helix transcription factor	*cyc*		Suggestive SNP(s) associated	AA	Kovanen et al. (2010)
AUTS2	Unknown	*tay*		SNP(s) associated	AC, max drinks	Kapoor et al. (2013), Schumann et al. (2011)
BRD7	Component of SWI/SNF chromatin remodeling complex		*swsn-9*	SNP associated	AD	Mathies et al. (2015)
CHRNA1	Acetylcholine receptor		*unc-63*	“leading edge gene”	SREF, BSA, SHAS	Joslyn et al. (2010)
CHRNA2	Acetylcholine receptor		*unc-63*	“leading edge gene”	SREF, BSA, SHAS	Joslyn et al. (2010)
CHRNA3	Acetylcholine receptor		*unc-63*	SNP(s) in the cluster A6 B3 A5 A3 B4 associated “leading edge gene”	AD, SREF, BSA, SHAS	Choquet et al. (2013), Haller et al. (2014), Hallfors et al. (2013),

Human gene	Function	Fly ortholog	Worm ortholog	Human genetics	Human phenotype	Citations
						Joslyn et al. (2010), Schlaepfer et al. (2008)
CHRNA4	Acetylcholine receptor		*unc-63*	"leading edge gene"; SNP(s) associated	SREF, BSA, SHAS Alcohol use	Ehringer et al. (2007), Joslyn et al. (2010)
CHRNB2	Acetylcholine receptor		*unc-63*	SNP associated	Initial response to alcohol	Ehringer et al. (2007)
CHRNB4	Acetylcholine receptor		*unc-63*	SNP(s) in cluster A5 A3 B4 associated	LR	Choquet et al. (2013)
CTBP2	Transcriptional co-repressor		*ctbp-1*	SNP associated	AD	Lind et al. (2010)
DBH	Dopamine beta-hydroxylase	*Tbh*		SNP associated	AD in women, alcoholism	Kohnke et al. (2006), Preuss et al. (2013)
DLG1	Synaptic scaffold	*dlg1*		SNP(s) associated in gene set analysis	LR	Joslyn et al. (2010)
DLG4	Synaptic scaffold	*dlg1*		SNP(s) associated in gene set analysis	LR	Joslyn et al. (2010)
DRD1	Dopamine receptor	*DOP1R1*	*dop-4*	SNP(s) associated	AD, AUD problems	Batel et al. (2008), Kim et al. (2007), Prasad et al. (2013)
DRD5	Dopamine receptor	*DOP1R1*		SNP associated	AD disinhibitory factor score	Hack et al. (2011)
GABBR1	Gamma-aminobutyric acid receptor	*GABA-B-R1*		SNP(s) associated in gene set analysis and other	AD	Kertes et al. (2011), Reimers et al. (2012)
Human gene	Function	*Fly ortholog*	*Worm ortholog*	Human genetics	Human phenotype	Citations
GAD1	Glutamate decarboxylase		*unc-25*	SNP(s) associated	IS, AD age of onset, AD males, AC	Joslyn et al. (2010), Kuo et al. (2009), Loh el et al. (2006), Tabakoff et al. (2009)
GAD2	Glutamate decarboxylase		*unc-25*	SNP(s) associated; "leading edge gene"	AD, SREF, BSA, SHAS	Joslyn et al. (2010), Lappalainen et al. (2007)
GPC5	Cell-surface heparin sulfate proteoglycan	*dlp, dally*		SNP(s) associated	Body-sway	Joslyn et al. (2010)
GRIN1	Glutamate receptor	*NMDAR1*		SNP(s) associated in gene set analysis and other	AD	Karpyak et al. (2012), Wernicke et al. (2003)
IGF1R	Insulin-like growth factor receptor	*InR*		SNP(s) associated in gene set analysis	LR	Joslyn et al. (2010)
ITGB2	Integrin beta subunit	*mys*		SNP(s) associated in gene set analysis	LR	Joslyn et al. (2010)
KCNMA1	Voltage and calcium-sensitive potassium channel	*slo*	*slo-1*	Suggestive SNP(s) associated	AD	Kendler et al. (2011)
KCNQ5	Voltage-gated potassium channel	*KCNQ*		Suggestive SNP(s) associated	AD	Kendler et al. (2011)
LMO1	LIM domain transcriptional regulator	*Bx*		SNP(s) associated	Max drinks	Kapoor et al. (2013)

Human gene	Function	Fly ortholog	Worm ortholog	Human genetics	Human phenotype	Citations
MARK1	Microtubule-associated protein kinase	*par-1*		SNP(s) associated	AD comorbid with nicotine dependence	Lind et al. (2010)
NALCN	Sodium leak channel		*nca-1, nca-2*	SNP associated	AD	Wetherill et al. (2014)
NCAM1	Immunoglobulin family cell adhesion molecule	*Fas2*		SNP(s) associated	AD	Yang et al. (2007, 2008)
NPY	Neuropeptide Y	*NPF*		SNP(s) associated or suggestive associations	AD, alcoholism, AW	Bhaskar et al. (2013), Ilveskoski et al. (2001), Lappalainen et al. (2002), Mottagui-Tabar et al. (2005), Okubo and Harada (2001)
NPY2R	Neuropeptide Y receptor	*NPFr*	*npr-1*	SNP(s) associated	AD, AW, other	Wetherill et al. (2008)
PER2	Transcriptional repressor	*per*		SNP(s) associated	AC with sleep problems	Comasco et al. (2010)
PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	*Pi3K21B*		SNP(s) associated	AC in males, lifetime prevalence of drunkenness, max drinks	Desrivieres et al. (2008)
SLC18A2	Monoamine transporter		*cat-1*	SNP(s) associated	AD	Fehr et al. (2013), Schwab et al. (2005)
SLC6A2	Norepinephrine transporter	*DAT*		SNP(s) associated	Alcoholism	Clarke et al. (2012)
SLC6A3	Dopamine transporter	*DAT*		SNP(s) associated	Alcoholism, AC, withdrawal seizures	Bhaskar et al. (2012), Du et al. (2011), Lind et al. (2009)
SMARCA2	Component of SWI/SNF chromatin remodeling complex		*swsn-4*	SNP(s) associated	AD	Mathies et al. (2015)
TH	Tyrosine hydroxylase		*cat-2*	SNP associated	AD	Dahmen et al. (2005)
TPH1	Tryptophan hydroxylase		*tph-1*	SNP(s) associated	AD	Mokrovic et al. (2008), Sun et al. (2005)
TPH2	Tryptophan hydroxylase		*tph-1*	SNP(s) associated	AC	Agrawal et al. (2011)
TRPV1	Nonselective cation channel; capsaicin receptor	*iav*	*osm-9*	SNP(s) associated	Whole-mouth alcohol intensity	Allen et al. (2014)
UNC79	Unknown		*unc-79*	SNP associated	AD and Nicotine dependence comorbidity	Lind et al. (2010)

Columns are the human gene symbol, a brief description of the function of the gene product, the relevant *Drosophila* or *Caenorhabditis elegans* orthologs, the genetic evidence from human studies implicating the gene in some aspect of AUD, the phenotypes (AD, alcohol dependence; SREF, self report of the effects of alcohol; BSA, body sway anterior/posterior; SHAS, subjective high assessment scale; LR, level of response; AC, alcohol consumption; IS, initial sensitivity; AW, alcohol withdrawal) that were investigated in humans, and the citations for the human studies.