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Effects of genetic variants of *ADH1B* and *ALDH2* and social network on continued alcohol drinking among young adolescents in Taiwan☆

Te-Tien Ting[a,b], Shiao-Yun Huang[a], Kuang-Hung Chen[b,c], Ching-Ing Tseng[d], Keh-Ming Lin[b], Chuan-Yu Chen[b,c,e,**], Wei J. Chen[a,d,e,*]

[a] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei 100, Taiwan
[b] Center of Neuropsychiatric Research, National Health Research Institutes, 35 Keyan Road, Zhunan, Miaoli County 350, Taiwan
[c] Institute of Public Health, National Yang-Ming University, No. 155, Sec. 2, Linong Street, Taipei 112, Taiwan
[d] Genetic Epidemiologic Core, Center of Genomic Medicine, National Taiwan University, 7F, 2 Xu-Zhou Road, Taipei 100, Taiwan
[e] Department of Public Health, College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei 100, Taiwan

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ABSTRACT

Background: This study aimed (i) to evaluate the effects of genetic variants of *ADH1B* and *ALDH2* and social network position on continued alcohol use in early adolescence, and (ii) to explore possible moderating role of pubertal development on genetic effects.
Methods: The sample comprised 496 children who ever drank alcohol before the ages of 10–12. Information pertaining to sociodemographic background, pubertal development, parental drinking, alcohol and tobacco use, alcohol-metabolizing genes, and nominated best friends was collected in four waves of assessment. Polymorphisms of *ADH1B* (rs1229984) and *ALDH2* (rs671) were genotyped. The latent class analysis was first used to characterize longitudinal alcohol use pattern, followed by the multinomial logistic regression analyses to assess its association with genes, pubertal development, and social network.
Results: Three distinct classes of alcohol users (i.e. ex-drinkers, sporadic drinkers, and continued drinkers) were derived from alcohol-experienced children. Both alcohol-metabolizing genes appear to have protective effects, yet such relationships were only significant for youngsters in pre-to-early pubertal stage: the adjusted odds ratio (aOR) of *ADH1B* fast-genotype for sporadic drinkers was 0.46 and that of *ALDH2* slow-genotype for both sporadic and continued drinkers was 0.47 and 0.42, respectively. Children having the bridge position in their peer network were more likely to be sporadic drinkers (aOR = 4.15) and continued drinkers (aOR = 3.16).
Conclusions: Our results illustrate a potential moderating effect of pubertal development on the protective influence of alcohol-metabolizing genes on subsequent alcohol use among alcohol-experienced children as well as the independent contribution of early life's social network to their alcohol involvement.

1. Introduction

Over the last two decades, the prevalence of adolescent drinking has been increasing in many parts of the world. In Taiwan, recent national surveys from 2004 to 2006 had indicated that the incidence rate of alcohol consumption increased from 13.97 to 18.08% for middle school students and from 13.51 to 26.08% for high school students (Chen et al., 2009). Alcohol consumption during adolescence may exert not only harmful effects on mental and physical health (Duncan et al., 1997; Hill et al., 2000; Kandel, 1975) but also long-term impact on multiple domains of life in adulthood (Grant et al., 2001; Spear, 2013). To prevent negative consequences

☆ Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

* Corresponding author at: Institute of Public Health, National Yang-Ming University, No. 155, Sec. 2, Linong Street, Taipei 112, Taiwan. Tel.: +886 2 33668010; fax: +886 2 3366 8004.
** Corresponding author at: Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei 100, Taiwan. Tel.: +886 2 28267344; fax: +886 2 28221942.
E-mail addresses: chuanychen@ym.edu.tw (C.-Y. Chen), wjchen@ntu.edu.tw (W.J. Chen).

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associated with underage drinking, it is important to understand the predictors accounting for the occurrence and transition of earliest stages of alcohol drinking (Faden, 2006). With few exceptions (Poelen et al., 2008), prior research on etiological factors for alcohol use problems in adolescence generally supports that alcohol initiation was moderately heritable and largely explained by common environmental factors (Fowler et al., 2007; Kendler et al., 2008; Rose et al., 2001). Meanwhile, in terms of continuation of alcohol consumption, both genetic and socio-environmental factors are shown to play strong role through adolescence (Cheadle and Whitbeck, 2011; Poelen et al., 2008; Rose et al., 2001).

Genetic variants encoding two alcohol-metabolizing enzymes, alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2), are two of the most well-studied genetic factors influencing alcohol use, particularly in Asian adult populations (Edenberg, 2007). After ingestion, ethanol is first oxidized by ADH to acetaldehyde, which is further oxidized by ALDH to acetate. One variant of *ADH1B*, allele *ADH1B*2*, encodes a high-activity enzyme that leads to faster oxidation of ethanol and buildup of acetaldehyde than allele *ADH1B*1*; and one variant of *ALDH2*, allele *ALDH2*2*, encodes an inactive ALDH enzyme that results in slower oxidation of acetaldehyde to acetate than allele *ALDH2*1*. After consumption of alcohol, build-up of acetaldehyde in tissues may lead to flush and several other dysphoric symptoms and hence to reduction of an individual's alcohol drinking (Chen et al., 1998). These variants of *ADH1B* and *ALDH2*, highly prevalent in Asian populations, have been associated with reduced risk of alcohol use disorders (Chen et al., 1996; Hendershot et al., 2009; Li et al., 2012; Luczak et al., 2006; Takeshita and Morimoto, 1996). Notably, in Asian populations the estimated protective effect of *ALDH2*2* is much stronger than that of *ADH1B*2* (Chen et al., 1996; Luczak et al., 2006). Evidence from alcohol-challenge studies has shown that the reduced enzyme activity encoded by *ALDH2*2* was associated with higher level of acetaldehyde in the blood after ingestion of alcohol, whereas the enhanced enzyme activity encoded by *ADH1B*2* was not (Peng and Yin, 2009; Wall et al., 1997). Although a series of studies had reported the association between alcohol-metabolizing genes and alcohol use disorders, few of these samples had involved children. Previous studies comparing adults of different ages had showed that the protective effects of *ALDH2* and *ADH1B* on alcohol use behaviors diminished in younger adults (Hendershot et al., 2005; Higuchi et al., 1994; Kim et al., 2010; Spivak et al., 2007), indicating the possibility that the effect of alcohol-metabolizing genes may be developmental stage dependent.

In adolescence, several unique features surfacing in physical and social development have been linked with alcohol use and related problems, including early onset pubertal development and peer influence (Bauman and Ennett, 1996; Costello et al., 2007; Cruz et al., 2012; Dick et al., 2000; Downing and Bellis, 2009). For some populations, these features might be expected to modify or to compete with the genetic effects (e.g. alcohol-metabolizing genes) in terms of predicting further alcohol involvement (Irons et al., 2012; Rose and Dick, 2004). To illustrate, the prominent physical changes resulting from significant changes in hormone levels lead to a cascade of brain behavior interaction (Peper and Dahl, 2013). Both animal (Sherrill et al., 2011) and human studies (Crone and Dahl, 2012; Luna et al., 2013; Peper and Dahl, 2013) have reported that pubertal hormones may influence the processes of reward, emotional stimuli, and social-cognitive reasoning, and hence sensitize young people to the social-facilitating and rewarding effects of alcohol in the developmental transition (Spear, 2013). Indeed, such brain development may make adolescents become more sensitized to the social connectedness/interaction with important others in their daily environments, e.g. parents and peers (Chen et al., 2011; Somerville, 2013). Small but growing body of literature suggests that, other than behavioral socialization, peers can also exert their influences on adolescent drinking via peer network structure (Ennett et al., 2006; Kreager and Haynie, 2011). For instance, some studies reported that adolescents who occupied the bridge position connecting different subgroups of peer network were more likely to continue alcohol use, indicating that they might have greater opportunities to meet drinkers or to have easier access to alcoholic beverages (Kreager and Haynie, 2011). For the primary school-aged youngsters whose main source of alcohol is often limited to parents (Chen et al., 2011), occupying the bridge position in a peer network may be possibly risky in terms of alcohol drinking since it offers the other way to obtain alcoholic beverages.

To date, the contribution of specific genetic pathways and social structure to early stages of alcohol use remains rarely investigated, probably due to the fact that few prospective studies on specific gene markers and network structural measures included children (Cruz et al., 2012). It is less clear whether genetic contribution to alcohol drinking operates homogeneously through the period transiting from childhood into adolescence (Irons et al., 2012). Given that early adolescence is the peak period when most experimental alcohol use emerges, understanding how alcohol-metabolizing genes and social network may shape further alcohol consumption behaviors after alcohol initiation and whether genetic effects may be development dependent is especially crucial in order to devise age or development-tailored interventions. To address these gaps, we prospectively followed up a cohort of school-aged children who had started alcohol drinking in childhood, and assessed their alcohol drinking behaviors on two consecutive years during early adolescence. This study aimed to investigate the extent to which the genetic variants of *ADH1B* and *ALDH2* and social network position were associated with subsequent continuation of alcohol drinking and examine whether the genetic effects may be different across subgroups defined by pubertal development.

2. Methods

2.1. Participants

Participants of this study were a subsample of a cohort established in a project entitled Alcohol-Related Experiences among Children (AREC) in Taipei. The original sample was composed of 1306 fourth graders (~aged 10) and 1324 sixth graders (~aged 12), with 98% being Han Chinese, recruited via a stratified multistage probability sampling from 28 public schools in Taipei city. In each of the four strata defined by sizes of the school and neighborhood characteristics, four to eight schools were randomly chosen. In each school, three classes were randomly selected at the fourth and sixth grades. All students in the sampled classrooms were eligible and invited to participate in the study. The baseline response rate was 59.1% for the fourth graders and 62.2% for the sixth graders. More detailed sampling procedures have been described elsewhere (Chen et al., 2011). For the longitudinal follow-ups, 17 out of 28 public schools were targeted, since those schools were highly supportive of the survey, with a total of 868 fourth graders and 928 sixth graders being included for the prospective follow-ups. Using the data of these 1796 students recruited from the 17 schools in the first semester of 2006 academic year as baseline (W1), a second-wave (W2) assessment was conducted in the second semester, with a follow-up rate of more than 99% (only two students were not followed up). From the second year on, annual follow-ups were conducted in the 2007 academic year for wave-3 assessment (W3), with a follow-up rate of 86.6%, and in the 2008 academic year for wave-4 assessment (W4), with a follow-up rate of 80.5%.

Among 1796 participants, 1537 (86%) had completed four waves of surveys, and 1165 (65%) agreed to provide a saliva sample for DNA retrieval at the third year upon consent from the children and their parents. Attrition analyses indicated no significant differences between those with saliva specimen and those without in relation to sociodemographic characteristics (e.g. gender, monthly allowance, and living with none or one parent), pubertal development, alcohol drinking, tobacco use, and peer's alcohol drinking, except parental education (56.8% had a college degree or above, vs. 40.1% without a higher degree). Among those providing a saliva specimen, 496 (42.5%) were ever drinkers at the baseline assessment and hence were included in this study. The study was approved by the Institutional Review Board of the National Health Research Institutes (EC0951194).

2.2. Measures

The participants completed a paper-and-pencil self-administered questionnaire in each wave of assessment held during regular class hours. The questionnaire

Table 1
Model fit for tests of two to four class solutions derived from the latent class analysis of participants who had information on alcohol use frequency at all of three consecutively yearly assessments, the Alcohol-Related Experiences among Children (AREC), Taipei, 2006–2008 ($N = 1537$).

No. of classes	Log likelihood	No. of free parameters	BIC	AIC	LRT for 1 less class
2	−3671.4	13	7438.2	7368.8	562.9 ($p < 0.0001$)
3	−3648.4	20	7443.5	7336.8	45.1 ($p = 0.0092$)
4	−3646.3	27	7490.7	7346.6	4.1 ($p = 0.2052$)

Note: BIC = Bayesian information criterion; AIC: Akaike information criterion; LRT = Likelihood ratio test.

consisted of basic information, such as sociodemographic characteristics (W1), family composition (W1), initiation of tobacco smoking (W1), alcohol drinking of parents (W1), pubertal development (W3 and W4), as well as alcohol consumption behaviors (W1, 3, 4). Since actual parental marital status might be unclear to our young participants, we asked whether they were living with both parents rather than whether they were from a single-parent family to assess connectedness with two parents in daily life. At each wave, the questionnaire typically required 30 min to be completed.

Information pertaining to the direct observation of paternal and maternal drinking was collected via two questionnaire items at W1. If the participant reported to have ever observed both parents drink alcohol, the variable of both parental drinking was coded as presence. Peer networks, collected at W2, were constructed via the participants' nominations of their best friends in their class (no more than three nominations).

2.2.1. Peer network. In a peer network, a bridge position is one connecting to other subgroups or peripheral individuals (de Nooy et al., 2005). If a bridge position is removed from the structure of peer networks, certain subgroups become disconnected or isolated. Using Pajek network analysis software (de Nooy et al., 2005), the respondents in the bridge position were coded as "1" and those not in the bridge position were coded as "0".

2.2.2. Pubertal development. Participants' pubertal stage was measured using the self-rating pubertal development scale (PDS) (Petersen et al., 1988) at W3 (i.e. during the fifth or seventh grade). The scale includes items related to height, body hair, skin change, deepening voice (or breast growth for girls), and facial hair (or menarche for girls). The internal consistency alpha of the PDS in this study was 0.76, which is similar to that of the original scale (Petersen et al., 1988). On the basis of the total score, participants could be categorized into five developmental stages: pre-pubertal, early pubertal, mid-pubertal, late pubertal, and post-pubertal. Following the regrouping in our previous study (Ting et al., 2015), individuals in the pre- and early pubertal stages were combined as the reference (pre-to-early pubertal stage), and those in the other three stages were considered as the group with advanced pubertal development (mid-to-post pubertal stage).

2.2.3. Alcohol-use behaviors. Alcohol drinking behaviors were assessed on an annual basis (W1 in 2006, W3 in 2007, and W4 in 2008). At baseline, participants were asked whether they had ever drunk alcohol more than a few sips and, if yes, on how many occasions they had drunk alcohol. Since W3, participants were asked whether they had drunk alcohol in the past year and, if yes, on how many occasions they had drunk alcohol in the past year.

2.3. DNA genotyping

Two SNPs of alcohol-metabolizing genes, rs1229984 for *ADH1B* and rs671 for *ALDH2*, were genotyped for this study. DNA was extracted from saliva specimen (collected in wave 4 with parental consent) using the QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA). Genotyping work was carried out in the National Taiwan University Center of Genomic Medicine using TaqMan probe assays and an ABI PRISM 7900HT Sequence Detector System (Applied Biosystems, Foster City, CA, USA). The quality control was assured by the inclusion of duplicated DNA samples and negative controls.

2.4. Statistical analyses

We identified subgroups of drinking profile of 1537 participants who had information on alcohol use frequency at W1, W3, and W3 using latent class analysis (LCA) with Mplus 7 (Muthén and Muthén, 1998–2012). Following the practice of a previous study (Rose et al., 2007), the optimal number of classes was determined by a combination of parsimony (a likelihood ratio test for the models with one less class), model fit statistics (both Bayesian Information Criterion and Akaike Information Criterion), and meaningfulness/distinctness of each class.

Among the participants having saliva specimen available, 496 with alcohol use experience at baseline were classified according to the latent class membership and used for subsequent analyses. Group comparisons were first conducted using the chi-squared test. The main effects of metabolizing genes, family and peer influence, pubertal development, and structure properties of peer network on subsequent pattern of alcohol consumption were estimated using multinomial logistic regression analysis. Potential interplay between metabolizing genes (i.e. *ADH1B* and *ALDH2*) with pubertal development were evaluated by adding interaction term in the model. These analyses were performed with SAS software version 9.1.3 (SAS Institute and Inc, 2004).

3. Results

The results of LCA indicated that a three-class solution appeared plausible (i.e. lower values of Bayesian Information Criterion and Akaike Information Criterion) and better than a two-class solution ($p = 0.0092$ for the likelihood ratio test) (Table 1). For the three-class solution, the average latent class probabilities for the most likely latent class membership were 0.82, 0.77, and 0.84, for latent classes 1, 2, and 3, respectively, indicating good class membership assignment. Based on the three-class solution, class 1 comprises individuals with three or more drinking occasions at two waves or more; class 3 comprises individuals with rare alcohol use; and class 2 comprises the remaining individuals. Sociodemographic features of members in three latent classes are described in more details in Supplementary Table S1.[1]

According to the three-latent-class membership, 496 children with alcohol-using experience at the baseline and saliva sample available were classified as follows: 93 (19%) into class 1 and named as continued drinkers, with their alcohol use frequency remaining at or advancing to the level of 3 or more during the follow-up; 229 (46%) into class 2 as sporadic drinkers, with their alcohol use frequency fluctuating during the follow-up; and 174 (35%) into class 3 as ex-drinkers, with their alcohol use frequency reduced to none during the follow-up. A cross-tabulation of alcohol drinking experiences at three waves is displayed in Supplementary Table S2[2]. Selective sociodemographic and class-based network characteristics are displayed in Table 2. Compared to ex-drinkers, both sporadic and continued drinkers had higher proportions of sixth graders, being in mid-to-post pubertal stage, tobacco initiation, and occupying the bridge position (i.e. liaison).

3.1. Alcohol-metabolizing genes and alcohol use during the follow-up

The genotype distributions of both *ADH1B* and *ALDH2* did not deviate from Hardy-Weinberg equilibrium, with the allele frequency of *ADH1B*2* (leading to a faster production rate of acetaldehyde) being 0.74 and that of *ALDH2*2* (leading to a slower removal rate of acetaldehyde) being 0.29 (Supplementary Table S3[3]). Due to the sample size with genotype *ADH1B*1*1* ($n = 33$) being small, for subsequent analyses it was pooled with *ADH1B*1*2* ($n = 185$) as the reference group, while participants with *ADH1B*2*2* were classified as the fast-genotype group. Similarly, sample with *ALDH2*2*2* ($n = 37$) was small, so for subsequent analyses it was pooled with *ALDH2*1*2* ($n = 215$) as the slow-genotype group, while

[1] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[2] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[3] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

Table 2
Distributions of sociodemographic characteristics among the alcohol-experienced children, by the latent classes of alcohol profiles, the Alcohol-Related Experiences among Children (AREC), Taipei, 2006–2008.

	Total (N = 496)		Latent class membership[a]						
			Ex-drinkers (N = 174)		Sporadic drinkers (N = 229)		Continued drinkers (N = 93)		Group comparison
Variables	n	%	n	%	n	%	n	%	p-value
Sixth grade (vs. fourth)	249	50.2	75	43.1	113	49.3	61	65.6	0.002
Male gender	268	54.0	96	55.2	112	48.9	60	64.5	0.036
Mid-to-post pubertal stage at W3	245	49.9	74	43.3	120	52.6	51	55.4	0.090
Higher parental education (any parent ≥ college)	286	57.7	105	60.3	131	57.2	50	53.8	0.574
Tobacco initiation	27	5.4	4	2.3	12	5.2	11	11.8	0.005
Both parental drinking	272	54.8	84	48.3	131	57.2	57	61.3	0.078
Living with none or one parent	62	12.5	16	9.2	30	13.1	16	17.2	0.158
Network's bridging at W2	42	8.5	7	4.0	27	11.8	8	8.6	0.021

[a] Based on a three-class solution derived from the latent class analysis on three consecutive assessments of alcohol use frequency of 1537 participants.

participants with *ALDH2*1*1* were declared the reference group. Table 3 displays the distribution of three latent classes of alcohol involvement in relation to dichotomized genotypes of *ADH1B* and *ALDH2*. The results of multinomial logistic regression analyses indicated that the fast-genotype of *ADH1B* and the slow-genotype of *ALDH2* had an odds ratio (OR) of lower than 1, though only that of the *ADH1B* fast-genotype for sporadic drinkers reached statistical significance.

3.2. Stratification analysis by pubertal development

Possible effects of pubertal development on the relationship between alcohol-metabolizing genes and subsequent alcohol consumption profile are summarized in the center and right panels of Table 3. For the youngsters in pre-to-early pubertal stage, the reduced OR of the fast-genotype of *ADH1B* was found for sporadic drinkers and that of the slow-genotype of *ALDH2* was seen for both sporadic and continued drinkers. Meanwhile, for adolescents in mid-to-post pubertal stage, the reduced OR of the fast-genotype of *ADH1B* was found only for sporadic drinkers.

To illustrate potential moderating effects of pubertal development on the relationship between the alcohol-metabolizing genes and subsequent alcohol use, the distributions of ex-drinkers, sporadic drinkers, and continued drinkers were plotted against the combination of the fast-genotype of *ADH1B* and the slow-genotype of *ALDH2* among alcohol-experienced adolescents; this was done separately for those in pre-to-early puberty (Fig. 1a) and mid-to-post puberty (Fig. 1b). It is apparent that the proportion of ex-drinkers increased linearly with the sole presence of the fast-genotype of *ADH1B*, followed by the sole presence of the slow-genotype of *ALDH2*, and reached a peak with the presence of both types of genotypes for adolescents in pre-to-early pubertal stage; but such linear trend was not observed for adolescents in mid-to-post pubertal stage.

3.3. Interactions between pubertal stage and genotypes and independent effects of social network

To examine potential interaction between pubertal stage and alcohol-metabolizing genes and the effects of social network on

Table 3
The distribution of follow-up alcohol use behaviors in the alcohol-experienced children, by genotypes and pubertal development, the AREC study.

	Total					Pre-and-early pubertal stage					Mid-to-post pubertal stage				
	ADH1B					*ADH1B*					*ADH1B*				
	Reference (*1*1 or *1*2)		Fast-genotype (*2*2)			Reference (*1*1 or *1*2)		Fast-genotype (*2*2)			Reference (*1*1 or *1*2)		Fast-genotype (*2*2)		
Latent classes	n	(%)	n	(%)	OR[d]	n	(%)	n	(%)	OR[d]	n	(%)	n	(%)	OR[d]
	218		265			104		135			111		128		
Ex-drinkers[a]	62	(28.4)	106	(40.0)	1	34	(32.7)	59	(43.7)	1	27	(24.3)	45	(35.2)	1
Sporadic drinkers[b]	118	(54.1)	107	(40.4)	0.53**	55	(52.9)	51	(37.8)	0.53 (0.30–0.94)*	62	(55.9)	56	(43.8)	0.54 (0.30–0.99)*
Continued drinkers[c]	38	(17.4)	52	(19.6)	0.80	15	(14.4)	25	(18.5)	0.96 (0.45–2.07)	22	(19.8)	27	(21.1)	0.74 (0.35–1.54)
	ALDH2					*ALDH2*					*ALDH2*				
	Reference (*1*1)		Slow-genotype (*1*2 or *2*2)			Reference (*1*1)		Slow-genotype (*1*2 or *2*2)			Reference (*1*1)		Slow-genotype (*1*2 or *2*2)		
Latent classes	n	(%)	n	(%)	OR[d]	n	(%)	n	(%)	OR[d]	n	(%)	n	(%)	OR[d]
	242		251			123		122			118		125		
Ex-drinkers[a]	79	(32.6)	95	(37.9)	1	38	(30.9)	59	(48.4)	1	40	(33.9)	34	(27.2)	1
Sporadic drinkers[b]	114	(47.1)	113	(45.0)	0.82	60	(48.8)	47	(38.5)	0.51 (0.29–0.88)*	54	(45.8)	65	(52.0)	1.42 (0.79–2.54)
Continued drinkers[c]	49	(20.3)	43	(17.1)	0.73	25	(20.3)	16	(13.1)	0.41 (0.20–0.87)*	24	(20.3)	26	(20.8)	1.28 (0.62–2.62)

*p < 0.05; **p < 0.01; ***p < 0.001.
[a] Being alcohol free in two subsequent follow-up years.
[b] Children whose alcohol use frequency fluctuated during the follow-up.
[c] Children whose alcohol use frequency remained at 3 or escalated to 3 occasions during the follow-up.
[d] Multinomial logistic regression analysis.

subsequent alcohol use, we conducted a multivariable multinomial logistic regression analysis by adding interaction terms between pubertal stage and two alcohol-metabolizing genes, with adjustment for gender, living with none or more parent, both parental drinking, and tobacco initiation (see Table 4).

We started with Model 1 with adjustment for all the covariates except living with none or one parent (Table 4). In this model, which separates the two genetic factors, both alcohol-metabolizing genes appear to have protective effects, though the aOR of *ADH1B* fast-genotype for continued drinkers failed to reach statistical significance. In addition, the interaction terms between the pubertal stage and *ALDH2* were significant. That is, the effect of *ALDH2* became non-significant for individuals in mid-to-post pubertal development, with aOR (95% CI) = 1.33 (0.72, 2.45) for sporadic drinkers and 1.17 (0.54, 2.51) for continued drinkers. Further controlling for living with none or one parent (Model 2: aOR = 3.68 for continued drinkers), the effect of ADH1B and ALDH2 remain similar, though the significance level became borderline for the effect of *ALHD2* on continued drinkers.

Since the effects of the variants of both *ADH1B* and *ALDH2* genes as well as their interaction terms with the pubertal stage were similar, we combined both into an ordinal variable in Model 3. Differential weights for the two genes were adopted in the evaluation of the combined effect of the fast-genotype of *ADH1B* and the slow-genotype of *ALDH2*, with the reference genotype of both *ADH1B* and *ALDH2* coded as 0, the presence of *ADH1B* fast-genotype as 1, the presence of *ALDH2* slow-genotype as 2, and the presence of both *ADH1B* fast-genotype and *ALDH2* slow-genotype as 3. Including this composite variable in Model 3, both the effect of the combined genotype (aOR = 0.65 for sporadic drinkers and 0.71 for continued drinkers) and the interaction terms between the pubertal stage and *ADH1B* plus *ALDH2* (aOR = 1.63 for sporadic drinkers and 1.45 for continued drinkers) were significant. The effect of the combined genotypes became non-significant for individuals in mid-to-post pubertal development, with aOR (95% CI) = 1.06 (0.79, 1.41) for sporadic drinkers and 1.04 (0.72, 1.49) for continued drinkers.

The main effect of the bridge position in the peer network remained significant in three models. For example, in Model 1 (Table 4), after controlling for sociodemographics, the bridge position in the peer network remained significantly associated with subsequent alcohol use. The adjusted OR (aOR) for bridge status was 4.15 for sporadic drinkers and 3.16 for continued drinkers. The main effect of social network on three classes of drinking profile, independent from that of alcohol-metabolizing genes and pubertal stage, is illustrated in Fig. 2. Even when the youngsters carry the fast-genotype of ADH1B and the slow-genotype of ALDH2, those who occupied the bridge position in the peer network tend to be continued or sporadic drinkers.

4. Discussion

By means of the latent class analysis on three waves of assessment on alcohol use frequency in a cohort of alcohol-experienced children, we identified three classes of drinking profile during the transition from late childhood into early adolescence. We found that young people carrying the genotypes that lead to accumulation of acetaldehyde after alcohol consumption were less likely to continue alcohol drinking during the follow-ups. However, the biological protective effects of *ADH1B*2* and *ALDH2*2* appeared moderated by pubertal stage; the observed inverse associations were only significant for those in the pre-to-early pubertal stage. Also, the connectedness with significant others, as manifested by living with none or one parent and having the bridge position in a peer social network, were found to have a differential relationship with continued alcohol use. The influence of family structure

Table 4
Risk estimates linking factors with subsequent alcohol use among the alcohol-experienced children, the AREC study.

Variable	Model				Mode2				Mode3			
	Sporadic drinkers		Continued drinkers		Sporadic drinkers		Continued drinkers		Sporadic drinkers		Continued drinkers	
	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Male gender	0.89	0.57–1.41	1.81	1.00–3.28*	0.90	0.57–1.42	1.85	1.02–3.37*	0.90	0.57–1.42	1.85	1.02–3.37*
Mid-to-post pubertal stage	0.68	0.30–1.58	1.13	0.39–3.34	0.68	0.30–1.59	1.16	0.39–3.43	0.61	0.28–1.34	0.91	0.33–2.48
Higher parental education	0.86	0.56–1.33	0.82	0.47–1.42	0.85	0.55–1.32	0.80	0.46–1.41	0.88	0.57–1.35	0.80	0.46–1.40
Tobacco initiation	2.38	0.73–7.81	5.12	1.51–17.38**	2.32	0.70–7.63	4.98	1.45–17.09*	2.33	0.71–7.62	4.99	1.45–17.11*
Both parental drinking	1.39	0.91–2.13	1.87	1.07–3.26*	1.61	1.02–2.56*	2.76	1.45–5.26**	1.57	0.99–2.47	2.77	1.46–5.26**
Living with none or one parent					1.93	0.91–4.08	3.68	1.46–9.28**	1.78	0.85–3.75	3.60	1.44–9.02**
Bridging position in peer network	4.15	1.63–10.56**	3.16	1.03–9.71*	3.70	1.45–9.48**	2.65	0.86–8.19	3.73	1.46–9.52**	2.63	0.85–8.10
ADH1B (ref: *1*1 & *1*2)	0.46	0.25–0.84*	0.82	0.37–1.82	0.46	0.25–0.84*	0.82	0.37–1.83				
ALDH2 (ref: *1*1)	0.47	0.26–0.84*	0.42	0.19–0.92*	0.49	0.27–0.89*	0.48	0.22–1.05				
Pubertal stage × *ADH1B*	1.27	0.54–3.00	0.87	0.29–2.63	1.24	0.53–2.95	0.82	0.27–2.52				
Pubertal stage × *ALDH2*	2.86	1.22–6.71*	2.76	0.92–8.23	2.81	1.19–6.62*	2.60	0.86–7.83				
ADH1B plus *ALDH2*[a]									0.65	0.49–0.85**	0.71	0.50–1.02
Pubertal stage × (*ADH1B* plus *ALDH2*)									1.63	1.09–2.43*	1.45	0.87–2.43

[a]The reference genotype of both *ADH1B* and *ALDH2* was coded as 0, the presence of *ADH1B* fast-genotype as 1, the presence of *ALDH2* slow-genotype as 2, and the presence of both *ADH1B* fast-genotype and *ALDH2* slow-genotype as 3.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

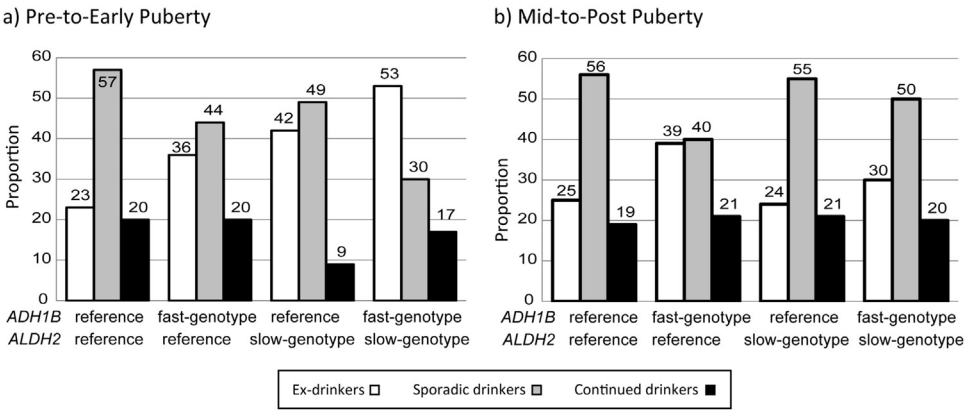

Fig. 1. The distributions of ex-drinkers, sporadic drinkers, and continued drinkers by protective genotypes in *ADH1B* (*2*2) and *ALDH2* (*1*2 or *2*2) among the alcohol-experienced children who were in (a) pre-to-early puberty and (b) mid-to-post puberty.

and peer network was independent of that of alcohol-metabolizing genes and pubertal stage.

One challenging issue in studying alcohol use in young people is that they are undergoing rapid pubertal change and their behaviors may be changing as well. The participants in this study were limited to those who reported having used alcohol at the baseline, which rendered them ideal for investigation into the influence of acetaldehyde-accumulation effect of the alcohol-metabolizing genes after alcohol consumption. Our results were based on several waves of surveys, which might help diminish the ambiguity in temporal sequences. For example, the sociodemographic features, family composition, and the history of parental drinking were based on information at W1, the social network at W2, and pubertal stage at W3. Furthermore, our latent classes of children's alcohol drinking (ex-drinker, sporadic drinker, and continued drinker) are conceptually similar to those derived from latent class analysis on more waves of longitudinal data, i.e. abstainers, sippers/light drinkers, and drinkers with drunkenness (Donovan and Molina, 2013).

The high prevalence of the variants in alcohol-metabolizing genes in this Taiwanese population (74% for *ADH1B*2* and 29% for *ALDH2*2*) provided us an opportunity to explore the complex interplay between alcohol-metabolizing genes and the pubertal development encountered by adolescents. The protection conferred by the two alcohol-metabolizing genes examined in this study appears to be of different magnitudes, with *ADH1B*2* being protective for subsequent sporadic use of alcohol and *ALDH2*2* being consistently protective for subsequent sporadic and continued use of alcohol. In the assessment of the proportion of participants from ex-drinkers to sporadic drinkers to continued drinkers, the reduction in proportion was also greater for the sole presence of *ALDH2*2* than for the sole presence of *ADH1B*2*. This is compatible with the findings from previous alcohol-challenge

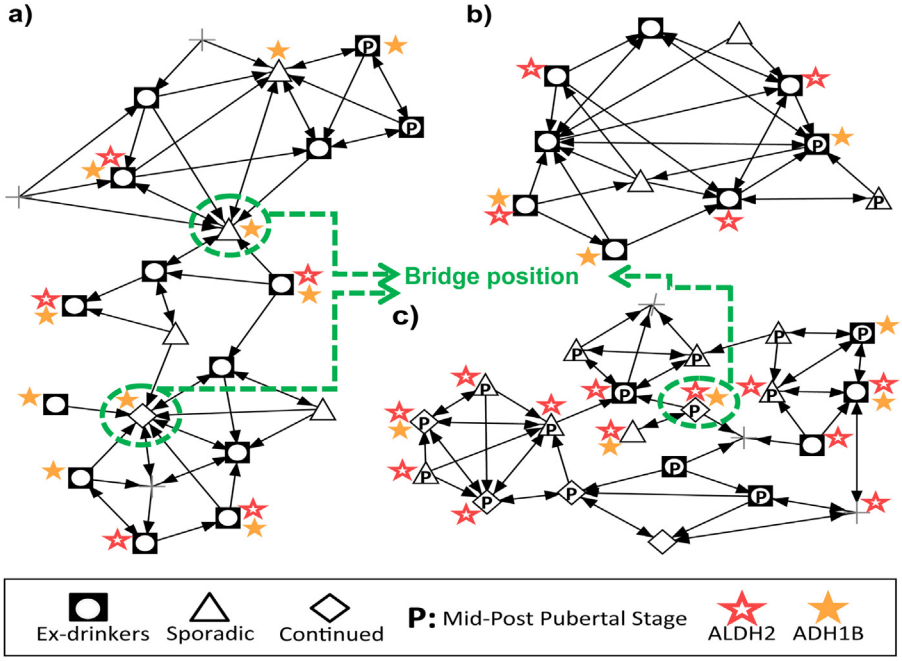

Fig. 2. Three examples of social networks selected from the AREC: (a) a network of 22 members mainly in pre-to-early pubertal stage, in which 14 (64%) were ex-drinkers (57% carrying the fast-genotype of *ADH1B* or the slow-genotype of *ALDH2*), 5 (23%) were sporadic or continued drinkers (60% carrying the fast-genotype of *ADH1B* or the slow-genotype of *ALDH2*, but within the 60%, 40% of them occupying bridge position), and 3 were missing in the information about alcohol use during the follow-ups; (b) a network of 11 members mainly in pre-to-early pubertal stage, in which 8 (73%) were ex-drinkers (75% carrying the fast-genotype of *ADH1B* or the slow-genotype of *ALDH2*) and 3 (27%) were sporadic drinkers (0% carrying the fast-genotype of *ADH1B* or the slow-genotype of *ALDH2*); and (c) a network of 22 members mainly in mid-to-post pubertal stage, in which 6 (27%) were ex-drinkers (67% carrying the fast-genotype of *ADH1B* or the slow-genotype of *ALDH2*), 13 (59%) were sporadic or continued drinkers (62% carrying the fast-genotype of *ADH1B* or the slow-genotype of *ALDH2*), and 3 were missing in the information about alcohol use during the follow-ups.

studies showing a detectable elevation of acetaldehyde in the blood after ingestion of alcohol for *ALDH2*2* but not for *ADH1B*2* (Peng and Yin, 2009; Wall et al., 1997).

One salient finding of this study is that the biological protective effects of *ADH1B*2* and *ALDH2*2* on low-intensity alcohol use were limited to adolescents in the pre-to-early pubertal stage. This indicates that for adolescents with advanced pubertal development, the physiological signs generated by acetaldehyde accumulation after consumption of alcohol might be relatively weak such that they were ignored in the presence of other contributors to alcohol use. Previous studies have shown that the visible signs of maturity are important triggers of alcohol use in adolescents (Costello et al., 2007). Experimental research in rats further indicates the role of gonadal hormones in alcohol-use behavior (Sherrill et al., 2011), and brain-imaging studies have provided growing information about the changes in social and affective processing that emerge approximately at the onset of puberty (Crone and Dahl, 2012; Luna et al., 2013; Peper and Dahl, 2013). Nevertheless, this is not to imply that the protective effect of *ADH1B*2* and *ALDH2*2* on more intensive alcohol use, such as abuse or dependence that may lead to greater intensity of acetaldehyde accumulation, would diminish as well. Adults with these protective genotypes have been associated with reduced risk of alcohol use disorders (Chen et al., 1996; Hendershot et al., 2009; Li et al., 2012; Luczak et al., 2006; Takeshita and Morimoto, 1996). Intriguingly, the diminishing protection by the genetic variants in alcohol-metabolizing genes among adolescents in the face of puberty-initiated changes is in line with a previous finding about the secular trend of the decreasing protection by *ALDH2*2* against developing alcohol-use disorders in Japan as a result of mounting psychosocial stresses (Higuchi et al., 1994).

Equally important, our results also revealed the independent influence of several environmental factors, including living with none or one parent, parental drinking, and social network position. Similar to a prior study (Chen et al., 2011), the observed increased risk associated with "living with none or one parent" may be partially explained by the relatively lower level of parental monitoring/supervision. Since the variable of both parental alcohol drinking was determined by asking the respondents whether they had ever seen both of their parents drink alcohol, our results implied that the behavioral modeling effects of parents in childhood may endure into adolescence. In addition, the observed increased risk of continued drinking associated with having a bridge position in peer network suggests that adolescents in the bridging role may be more likely to have chance to link with friends from different networks, to be exposed to pro-alcohol peers (e.g. drinking peers), to be engaged in social gatherings involving alcoholic beverages, or even to have easier access to alcohol (Kreager and Haynie, 2011). Although the proportion of children who occupied the bridge position was small (less than 10%), indicating that primary school students were highly connected with each other, those individuals are key persons for class-based intervention. The salience of the social network position, relative to parental drinking, reinforced the need to take development into consideration when investigating the social context contributing to alcohol drinking behavior (i.e. peer network).

This study has several limitations. First, the analyses were limited to the participants whose saliva was available. Posthoc analyses found the distribution of parental education were significantly different between the participants with saliva and those without. Selection bias may emerge when parental education was related to children's drinking behaviors or genetic composition. Second, the decline in follow-up rate over successive waves (from 99 to 86.6 to 80.5%) might be vulnerable to selection bias. Further analyses indicated that the loss-to-follow-up was associated with positive drinking status at prior assessment, suggesting the bias direction should be toward the null. Third, due to the limited variables assessed in late childhood, we were unable to take some important variables into account, including mental health, personality traits, and relationship with parents. Finally, our sample represents a primarily metropolitan population in Taipei city. Therefore, the generalizability to adolescents in non-metropolitan regions in Taiwan or other societies may be limited.

Notwithstanding these limitations, this study has several strengths. First, the Taiwanese adolescent sample covers useful information with sufficient variation in alcohol-metabolizing genes, parental drinking, peer network, and their transition of pubertal development. This provides us an opportunity to explore the complex influences of alcohol-metabolizing genes and social environment from the perspective of developmental theory. This theory emphasizes the influence of social context, along with the interplay between alcohol-metabolizing genes and pubertal development, in the transition from late childhood into adolescence. Second, this prospective design allowed us to clarify the temporal sequence of the alcohol-metabolizing gene, pubertal development, and social environment on adolescent alcohol involvement. Finally, the integration of the social network approach extended our research on peer influences from peer behaviors (e.g. peer drinking) to peer structure position.

In conclusion, the influence of alcohol-metabolizing genes on the continuation of alcohol use among alcohol-experienced children in Taiwan appeared to be moderated by pubertal stage. Meanwhile, independent of alcohol-metabolizing genes and pubertal stage, occupying the bridge position in the peer network alone may possibly elevate the risk of continued drinking. Our results highlight the significant contribution of genetic factors and early life's social context in the period transitioning from late childhood into adolescence in the Taiwanese populations.

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Contributors

TTT was responsible for the development of the research theme, the analysis, and the drafting of the manuscript. SYH conducted the genotyping work and preliminary analysis. KHC helped with the field work and data collection. CIT was in charge of specimen management and genotyping. KML supervised the implementation of the project and assisted in the interpretation of the data. CYC originated the study, supervised its progress, and advised on the writing. WJC was responsible for the study concept, the genotyping work, the overseeing of the analysis, and the editing of the manuscript. All authors have critically reviewed the content and approved the final version submitted for publication.

Conflict of Interest

All authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2014.12.014.

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