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Parental occupational exposure to solvents and autism spectrum disorder: An exploratory look at gene-environment interactions

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1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that includes repetitive behaviors, impairment in reciprocal social interaction, difficulty communicating, and sensory sensitivities (American Psychiatric Association [APA], 2013). Environmental and genetic factors have been implicated in the etiology of ASD (Feinberg et al., 2015; Schmidt et al., 2011; Volk et al., 2014). Given the complex nature of ASD, gene-environment interaction research may further elucidate the etiology of ASD and point towards potential preventive opportunities. Few studies have used SNPs from a broad selection of targeted genes to investigate gene-by-environment contributions to autism risk.

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CRediT author statement

Erin C. McCanlies was involved in study design, statistical analysis plan, interpretation of data, and manuscript preparation. Ja Kook Gu contributed to the data analysis plan, conducted the statistical analysis, and wrote the statistical analysis section of the manuscript. Michael Kashon worked collaboratively with Ja Kook Gu to analyze the genetic data. Berran Yucesoy was involved in proposal preparation, study design, and interpretation of results. Claudia C. Ma was involved in cleaning and preparing the data for analysis, developing the ACCESS database for the workplace exposures, and analysis plan. Wayne T. Sanderson conducted the workplace exposure assessment and contributed to manuscript preparation. Kyoungmi Kim reviewed and cleaned the genetic data prior to NIOSH receiving the data, worked with Ja Kook on analyzing the genetic data, and responded to any questions that we had about the genetic data. Yunin Ludena-Rodriguez reviewed all the paper, electronic, and voice records to determine how many fathers specifically responded to the work history questionnaire, and Irva Hertz-Picciotto contributed to the study design, statistical analysis plan, and preparation of the manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The fetus, neonate and young child are more sensitive to exposures due to their small size, higher absorption rates, rapid growth, and development of cellular structures, but inferior ability to detoxify exogenous chemicals (Bondy and Campbell, 2005; Grandjean and Landrigan, 2006). Several reviews cite replicated findings that environmental factors are associated with ASD (de Cock et al., 2012; Fujiwara et al., 2016; Hertz-Picciotto et al., 2018; Kalkbrenner et al., 2014). In addition, parental occupational exposures have been found to be associated with ASD; in particular, parental occupational exposure to solvents (McCanlies et al., 2012; McCanlies et al., 2019). Solvents may be absorbed through the skin or lungs and are metabolized into toxic secondary substances including methyl-butyl ketone or n-hexane and are associated with abnormal white matter, smaller corpus callosum volume, and cerebellar atrophy (Hurley and Taber, 2015). Infants of mothers with solvent exposure show cognitive delays, attention deficit hyperactivity disorder, delayed speech, and motor functioning (Bemanalizadeh et al., 2022; Grandjean and Landrigan, 2006). Mothers occupationally exposed to solvents were 1.5 times more likely to have a child with ASD compared to a typically developing child further implicating solvents in the risk for ASD (McCanlies et al., 2019). Similarly, decades of genetic studies provide overwhelming evidence of linkage between ASD and multiple genes on virtually every chromosome (Butler et al., 2015; De Rubeis et al., 2014; Gaugler et al., 2014; Wong et al., 2014), which nevertheless, does not explain most cases of ASD.

As with most complex diseases, causal pathways likely involve interactions between inherited genetic variants and several environmental, chemical, and physical agents that influence immune, endocrine, and neuro-developmental processes (Dietert and Dietert, 2008; Doumouchtsis et al., 2009; Hertz-Picciotto et al., 2008; Pessah et al., 2008). Growing evidence also points to the increased risk for neurocognitive or behavioral impairments from epigenetic changes, which themselves are modulated by environmental factors (Cheroni et al., 2020; Mordaunt et al., 2020; Ramaswami et al., 2020). Moreover, the overlap in regulatory pathways disrupted by both gene mutations and environmental factors highlights convergence between genetic susceptibility and toxic substances (Cheroni et al., 2020; Mordaunt et al., 2020; Ramaswami et al., 2020). Whereas research on ASD, until the last decade had primarily focused on clinical aspects and genetics of autism, an emerging body of evidence is uncovering environmental or occupational exposures appearing either as risk or protective factors. Yet, little research has been conducted to evaluate gene-environment interactions (Gaugler et al., 2014; Kalkbrenner et al., 2014; Lyall et al., 2014; McCanlies et al., 2019). Studies that have been done have primarily focused on a single gene (Volk et al., 2014), genes involved in a single metabolic pathway(Schmidt et al., 2011), or genome-wide copy number variant burden (Kim et al., 2017). Other recent emerging work on such interactions in autism has focused on epigenetic markers at the interface of genes and the environment (Feinberg et al., 2015; Mordaunt et al., 2020; Ramaswami et al., 2020; Schmidt et al., 2011; Zhu et al., 2019). Given the relationship between parental occupational exposure and ASD, evaluating potential parental occupational exposure to solvents in conjunction with relevant SNPs may contribute to a better understanding of the etiology of ASD, and indicate promising molecular pathways and avenues for prevention. Thus, the current study investigates associations between ASD and gene-by-occupational solvent exposure interactions.

2. Subjects and methods

2.1 Study population

The CHildhood Autism Risks from Genetics and Environment CHARGE study is a population-based case-control study that has been previously described (Hertz-Picciotto et al., 2006; McCanlies et al., 2012). Briefly, the CHARGE study enrolls children with a previous diagnosis of autism as well as children from the general population, selected from California State Vital Statistics birth files. Eligible children are between the ages of 2 and 5 years old, born in California, living with at least one biologic parent who speaks English or Spanish, and residing in the catchment areas of a specified list of California Regional Centers that coordinate services for persons with developmental disabilities. Children with autism are identified through the California Department of Developmental Services, which administers the Regional Center system, and general population controls from state birth files are frequency-matched to the expected sex distribution, as well as the age, and catchment area of the autism cases. The National Institute for Occupational Safety and Health (NIOSH) received genetic information on the children, diagnosis, parental occupational, and basic demographic data on 976 children and their parents who were enrolled in the CHARGE study. Among those, 423 were typically developing (TD) children serving as controls. After excluding 265 participants who had missing genetic data, the sample for the present study consisted of 711 children: 414 with ASD, 297 with TD, and their parents.

2.2 Diagnostic criteria

All the children were evaluated at the UC Davis MIND Institute and the UCLA Neuropsychiatric Institute. Children with a previous ASD diagnosis were assessed using the Autism Diagnostic Observation Schedule-2 (ADOS-2) (Lord et al., 2000; Lord et al., 2003) and their parents completed the Autism Diagnostic Interview-Revised (ADI-R) (Le Couteur et al., 1996; Lord et al., 1994) to confirm their child's ASD diagnosis. The Mullen Scales of Early Learning (MSEL) (Mullen, 1995) and the Vineland Adaptive Behavior Scales (VABS) (Sparrow et al., 1984) were used to evaluate cognitive and adaptive function. Children from the general population were assessed using the Social Communication Questionnaire (SCQ) (Rutter et al., 2003) screening instrument for ASD. If they scored < 15 on the SCQ and within the normal range on the MSEL and VABS, they were defined as typically developing (TD). Children who scored ≥ 15 were evaluated for ASD on the ADOS-2 as described above and their parents completed the ADI-R (Lord et al., 2000; Lord et al., 2003; Lord et al., 1994; Risi et al., 2006). The algorithm of Risi et al. (2006) was used to assign final diagnosis of ASD or non-ASD (Risi et al., 2006).

2.3 Specimen collection and genotype analysis

Study children provided a blood sample from which genomic DNA was isolated using standard procedures (Gentra Puregene kit: Qiagen). Quality control and data cleaning was performed in Genotyping Console, using the 2-step process recommended in Affymetrix's Best Practices (Affymetrix, 2016). In the first step, 175,000 well-characterized SNPS were and then samples with a call rate below 95% were dropped. Samples that passed the 95% call rate threshold then had genotypes called on the full set of SNPs. Before any quality

control measures were applied, the mean call rate was 0.989871 and the number of SNPs was 675,367. All subsequent data cleaning was performed in R and PLINK (Purcell et al., 2007; Team], 2012). The reported sex of all individuals was compared to their likely sex based on X chromosome heterozygosity. Samples which showed a mismatch between recorded and apparent sex were dropped. Three individuals were dropped for very low genotyping rates and 30,601 SNPs were dropped for low call rates. 12,370 SNPs which violated the assumption of Hardy-Weinberg equilibrium at a p-value of less than 10^{-4} were also removed from analyses. No samples showed unexpectedly high levels of heterozygosity, which may indicate sample contamination. PLINK was used to measure cryptic relatedness (Purcell et al., 2007). Testing indicated high levels of cryptic relatedness between a few individuals and the rest of the cohort (relatedness ≥ 0.125), even when only using variants with high minor allele frequencies. However, this is a multi-ethnic cohort, and this apparent over-sharing may be an artifact of the population structure.

2.4 Demographic and lifestyle characteristics

Information on both mothers and fathers, collected through questionnaires, included their age (years), education level, race/ethnicity, birthplace, smoking history, alcohol use, regional center/geographic location of residence, and payment method used for the child's delivery (public or private). Educational level was categorized into High school/GED or less, some college, Bachelor's degree, and Graduate or professional degree. Birthplace had three categories, USA, Mexico, and outside of USA and Mexico. Alcohol use was grouped as none/low and intermediate/high. Smoking was a dichotomous variable, yes or no. There were five regional centers: 1) Alta, far Northern, and Redwood Coast, 2) North Bay, 3) East Bay, San Andreas, and Golden Gate, 4) Valley Mt, Central Valley, and Kern, and 5) All Los Angeles RCs plus Orange, San Diego Tricounties, and Inland. The variable, total years of education, was calculated by summing the two parents' education level. Mothers' and fathers' age were in years, but parent's age was calculated by taking the average of the two parents' age. Due to small numbers in some racial categories, race/ethnicity was grouped as: white, non-Hispanic; black, non-Hispanic; Hispanic (any); or Other. The "other" category consists of those who reported race as American Indian, Alaska Native, Asian, Pacific Islander/Hawaiian Native, or multi-racial. The percent of solvent exposure for each parent. Child variables were age in years, sex (male or female), date of birth, race/ethnicity, and duration of breastfeeding (months). Race/ethnicity was categorized like the parents' race/ethnicity.

2.5 Workplace exposure assessment

Workplace exposure assessment has been previously described in detail (McCanlies et al., 2019). Mothers were interviewed about their job histories and when possible, the father was interviewed about his job history. Approximately, 37% of fathers responded, otherwise mothers reported the fathers' job history, the remaining 63%. Occupational information included, for each job, the place of employment, months, and years of employment, which month(s) of pregnancy (or the postnatal period) the job was held, and the total hours worked per week. Use of personal protective gear was not collected. Each reported job was assigned a 2002 North American Industry Classification System (NAICS; U.S. Census Bureau, 2007) and 2000 Standard Occupational Classification (SOC; Bureau of Labor Statistics,

2000) code. Using this information, two experienced industrial hygienists (IHs), blinded to children's case status, semi-quantitatively estimated occupational exposure levels to sixteen agents, a priori selected based on previously published evidence indicating potential associations with immunologic, metabolic, neurotoxicity, and cognitive abnormalities (Grandjean and Landrigan, 2006; Wigle et al., 2008). Due to nearly complete overlap in exposure (80% for mothers; 64% fathers) and because the chemicals in paint of greatest concern are solvents, solvent/degreasers and paint chemicals were combined (Centre for Industry Education Collaboration [CFIEC], 2016; Park et al., 2016), we referred to this category as solvents. Solvent X gene interactions were the focus of this manuscript due to the previous association observed between ASD and parental solvent exposure (McCanlies et al., 2019).

Each IH independently assigned an ordinal estimate for both the frequency and intensity of solvent exposure. The estimates were compared, any discrepancies resolved, and a consensus estimate determined. The consensus score was then used to determine a binary solvent exposure variable during the index period - the period spanning three months prior to pregnancy until birth of the study child. The binary variable classifies parents as exposed if the frequency of exposure was ≥ 1 anytime during the index period, or not exposed otherwise. We also created a summary binary, a combined variable for exposure via either the mother or father, set to one if at least one parent was exposed to solvents. Approximately 17.6% of the mothers of children with ASD and 14.8% of mothers of TD children had solvent exposure. Among fathers, these figures were 42.8% and 45.8% respectively.

2.6 Ethics

This study complies with all applicable requirements. The CHARGE study protocol was approved by institutional review boards at the University of California, Davis, and the University of California, Los Angeles, and by the State of California Committee for the Protection of Human Subjects and the NIOSH human subjects review board. Written informed consent was collected from all participants, prior to data collection.

3. Statistical Analysis

Descriptive statistics were used to characterize the study population. The outcome was ASD vs. TD. The solvent exposure, SNP, and SNP x solvent exposure served as the primary predictor variables. We present the analysis of mothers' and fathers' data combined. Potential confounders were selected from the literature with reference to the directed acyclic graph (DAG) (Weng et al., 2009). Based on the DAG, all statistical models were adjusted for parents' age, maternal smoking, length of breastfeeding, mom's birthplace, regional center, alcohol consumption, and total years of education.

3.1 Relative excess risk due to interaction (RERI) and Ratio of Odds Ratio (ROR)

Gene-environment interaction was examined additively and multiplicatively using logistic regression models. We fit a logistic regression model containing the child's SNP data alone, solvent exposure alone as well as a SNP-solvent interaction term, adjusting for potential confounders described above. The following logistic regression model was fit to the data:

$$Logit\,P(D|G,E,C) = \beta_0 + \beta_1 G + \beta_2 E + \beta_3 (G * E) + \beta_4 C$$

where D is binary ASD (0=TD, 1=ASD)

G is binary genotype using a dominant model (SNP: 0=wild type, 1=minor allele),

E is binary parents' solvent exposure (0=no exposure, 1=exposure),

C is a vector of potential confounders, and

β_i for i=1-3 are the corresponding coefficients for G, E, GxE, and $\boldsymbol{\beta_4}$ is the vector of coefficients for the confounders.

We can estimate a measure of additive interactions (RERI) and multiplicative interaction (ROR) using the parameters of logistic regression modeling. $OR_{10} = \exp(\beta_1)$, $OR_{01} = \exp(\beta_2)$, and $OR_{11} = \exp(\beta_1 + \beta_2 + \beta_3)$. Odds ratios (OR) and 95% confidence intervals (CI) for the gene SNP alone, solvent exposure alone, and both were calculated, and the measure of interaction on the multiplicative scale for odds ratio (ROR) was determined. The null hypothesis is ROR=1.

$$ROR = exp(\beta_3) = \frac{OR_{11}}{OR_{10}OR_{01}}$$

We obtained results for the RERI from odds ratios ($RERI_{OR}$) and its 95% confidence interval (CI) using SAS macro codes by VanderWeele and Knol (2014)(VanderWeele and Knol, 2011). Standard errors for $RERI_{OR}$ can be obtained using the delta method (Hosmer and Lemeshow, 1992). The null hypothesis is $RERI_{OR}$=0.

$$\begin{aligned} RERI_{OR} &= OR_{11} - OR_{10} - OR_{01} + 1 \\ &= exp(\beta_1 + \beta_2 + \beta_3) - exp(\beta_1) - exp(\beta_2) + 1 \end{aligned}$$

For ROR, a 95% CI that excludes 1, corresponds to a significant p-value. In contrast, for RERI, a 95% CI that excludes 0, corresponds to a significant p-value. Both unadjusted and false-discovery rate corrected p-values were obtained for the ROR and RERI results.

4. Results

4.1 Participant characteristics

The characteristics of the population are presented in Table 1. Due to frequency matching, the TD and ASD children were similar for sex, race/ethnicity, and gestational age. Mothers and fathers of children with ASD were more likely to be white, non-Hispanic (mothers: 60.4%; fathers: 64.0%) or Hispanic (mothers: 22.2%; fathers: 19.5) and born in the U.S. (mothers: 78.0%; fathers: 76.1%). Like the parents of children with ASD, the parents of TD children were also more likely to be white, non-Hispanic (mothers: 53.2%; fathers: 66.3%)

or Hispanic (mothers: 24.6%; fathers: 19.5%) and born in the U.S. (mothers: 84.5%; fathers 86%).

Most of the mothers of children with ASD (86.5%) and the mothers of TD children (90.8%) reported not smoking. Approximately, 18% of mothers and 43% of fathers of children with ASD had solvent exposure, while approximately 15% of mothers and 46% of fathers of TD children had solvent exposure.

4.2 Additive (RERI) and multiplicative (ROR) interactions

Statistically significant additive interactions based on the RERI and multiplicative interactions based on the ROR are shown in Table 2.

A RERI = 0 indicates that the effect of both exposures combined are exactly equal to the sum of the separate solvent and SNP effects. This indicates that there is no interaction effect. In contrast, synergistic, or super-additive joint interactions ($0 < RERI_{OR} < 1$) were observed for parental occupational solvent exposure and child SNPs in the following genes: *ALDH5A1, CNTNAP2, EGF, GABBR1, GLRX3, HLA-C*HLA-B, HTR1A, HTR1B, HTR2A*, HTR4, *HTR7, IFNG, IL12A, IL1B, IL1RN, NAT1, NAT2, PON1, RELN, RORA, SOD2, ST7*WNT2, TAP2, TGFβ2*. Even larger super-additive joint interactions, where $1 \leq RERI_{OR} < 2$, were found between solvent exposure and SNPs in the *PON1, RORA*, and *TGFβ2* genes. These results indicate that the risk of ASD is higher in individuals with both the gene and solvent exposure than the risk associated with the presence of the gene alone, solvent exposure alone, or neither.

Antagonistic, or sub-additive interactions ($RERI_{OR} < 0$) occur when effects of joint exposure are lower than the sum of the separate solvent and SNP associations. Antagonistic interactions were observed for solvents and SNPS in the following genes: *HCP5, HLA-C*HLA-B, HTR1A, HTR2A, HTR7, IL10, IL12A, IL1B, IL1RN, RORA, SOD2, TGFβ2*, and *VEGFA* and indicates that the presence of both solvent exposure and these genes may be protective against ASD.

Statistically significant multiplicative interactions based on the ROR were also observed between solvent exposure and several gene SNPs (Table 2). The highest significant RORs (> 1; FDR $p < 0.05$) included all the genes with SNPs showing additive synergistic activity with solvents (listed above), along with several additional genes: *HTR1F, PSMB9*, and *TAP1*PSMB9*. These results suggest a positive interaction at the multiplicative level between these genes and solvent exposure increasing the risk of ASD above either the genes or solvent exposure alone.

A ROR < 1 was found between solvent exposure and all the SNPs having antagonistic additive joint associations with solvents, plus several additional SNPS in the following genes: *CNTNAP2, HLA-F, IL1RN, and NAT1* indicating a potential protective affect from ASD with these genes in combination with solvent exposure.

4.3 OR of ASD in the presence of the gene SNP alone, solvent exposure alone, and the joint interaction between the solvent and gene SNP

When ORs were calculated for the gene alone, solvent alone, and joint interaction, a few joint interactions stood out (Table 3). The OR for ASD for the joint effect of *EGF* rs11569014 and solvent exposure was 9.7 (95% CI: 1.2, 78.8; p = 0.03), much higher than the OR of ASD for the gene SNP alone (OR = 0.45; 95% CI: 0.17, 1.17; p = 0.1) or solvent exposure alone (OR = 0.9; 95% CI: 0.7, 1.3; p = 0.7), neither of which were significantly associated with ASD. The corresponding RERI was also not significant (p_c = 0.4; Table 2). However, the ROR indicates a positive interaction on a multiplicative scale (ROR = 23.1; 95% CI: 2.3, 232.5; p_c =0.02). Similarly, the joint interactions between solvents and *HTR1F* rs114838037 and *HTR1F* rs76107227 was significantly associated with ASD (OR = 4.6; 95% CI: 1.3, 17.0; p = 0.02) and (OR = 4.7; 95% C.I. 1.0, 21.3; p = 0.05), respectively, in comparison to either solvent or the gene SNPs alone. The corresponding RERI was not significant, but the ROR indicated a positive interaction on a multiplicative scale. The ROR associated with rs11438037 was 13.1 (95% C.I. 2.1, 83.2) and rs76107227, 16.3 (95% C.I. 2.3, 115.3), respectively.

The OR of ASD for the joint effect of solvents and *RELN* rs56041591 (O.R. = 3.5; 95% CI: 1.3, 9.6; p = 0.02) was significant, in comparison to either solvent exposure alone (O.R. = 0.9, 95% CI: 0.6, 1.3; p = 0.5) or the SNP alone (O.R. = 0.71; 95% CI: 0.4, 1.3, p =0.3), which were not significantly associated with ASD. The corresponding RERI was not significant, while the ROR indicated a positive multiplicative interaction between the gene SNP and solvent exposure (ROR = 5.5; 95% C.I. 1.7,18.1; p_c = 0.01). Similarly, the joint effect of solvent exposure and *RORA* rs75941956 (OR = 2.8; 95% CI: 1.0, 7.7; p = 0.05) was significant, in contrast to the solvent exposure or the gene SNP alone (Table 3).

The OR of ASD for the joint solvents and *TGFβ2* rs41313742 exposure was 2.3 (95% CI: 1.1, 4.8; p = 0.02). This was the third largest among the significant interactions observed for combined exposures to solvents and the minor alleles. Neither solvent exposure alone (OR = 0.9; 95% CI: 0.6, 1.2; p =0.4) nor the SNP alone (OR = 0.7, 95% CI: 0.4, 1.3, p = 0.2) were significantly associated with ASD. The corresponding RERI for this SNP was greater than 1 (RERI = 1.8; 95% CI: 0.13, 3.5; p_c = 0.04) indicating additive synergy between the gene SNP and solvent exposure, while the corresponding ROR indicated multiplicative interaction (ROR = 4.1; 95% CI:1.5; 10.7; p_c = 0.01).

Only two genes showed a protective effect (Table 3). The joint effect of *RELN* rs671372 and solvent exposure (OR = 0.6; 95% C.I. 0.4, 1.0; 0.05), solvent exposure alone (OR = 0.5; 95% C.I. 0.3, 1.0; p_c = 0.05; and the gene alone (OR = 0.4; 95% C.I. 0.3, 0.8; p_c = 0.003) were also significantly protective. The joint effect of *RORA* rs67288758 and solvent exposure was protective (OR = 0.4; 95% CI: 0.2, 0.9; p = 0.02), while neither solvent exposure alone (OR = 1.2; 95% CI: 0.9, 1.7; p = 0.2) nor SNP alone (OR=2.4; 95% CI: 1.0, 5.8; p = 0.06) were associated with ASD.

5. Discussion

Herein, we report the combinatorial influence of parental solvent exposure and SNP data on the risk of ASD. We identified statistically significant multiplicative and additive interactions between 31 genes and parental occupational exposure to solvents in their relationships to confirmed ASD diagnoses. To our knowledge, this is one of the first studies to evaluate gene x solvent interaction in the risk of ASD.

Results of additive interactions can indicate which exposures are associated with the highest risk of disease and therefore, which subgroup is the most appropriate to target for intervention (Lash et al., 2021). Although there were several sub-additive relationships indicating that some gene SNPs in the presence of solvents may be protective of ASD, this also suggests that the wildtype allele may confer higher risk than the minor allele, placing more individuals at risk of ASD given solvent exposure. While it is prudent to prevent parental occupational solvent exposure in all workers, results here indicate that some individuals may be more sensitive to the effects of solvent exposure than others. For these individuals, any solvent exposure may put them at the highest risk of ASD. Further research needs to be done to better understand the gene, solvent relationship, and how best to protect those at greatest risk.

In addition to public health effects, additive interactions may also correspond more closely to mechanistic interaction than statistical interaction (Lash et al., 2021). Our results suggest synergism in the sufficient cause framework, indicating that the risk of ASD is higher in individuals with both the genes observed here and solvent exposure compared to those who have one or none of the risk factors. Super additive interactions indicated that the risk of ASD is even higher in the presence of the *PON1, RORA*, and *TGFβ2* gene SNPs and solvent exposure. It's important to note that all the gene SNPs that showed additive interactions, in addition to *HTR1F, PSMB9*, and *TAP1*PSMB9* also showed positive multiplicative interactions, which can also suggest underlying biological mechanisms or sufficient cause interaction (Lash et al., 2021).

A few of the genes we identified have previously been shown to be associated with ASD (e.g. *CNTNAP2*, *RELN, RORA*) (Bai et al., 2020; Carter and Blizard, 2016; National Center for Biotechnology Information [NCBI], 2017; Shehabeldin et al., 2018; Stamou et al., 2013), but many have not. However, based on their known functional roles, they are plausible candidates in the etiology of ASD (Supplementary Table 1), being involved in neuronal migration or development (*HT, CNTNAP2, ST7*WNT2*) (Gilbert and Man, 2017; Muller et al., 2016; Stamou et al., 2013; Stephan, 2008; Watts, 2008), oxidative stress (*GLRX 3, SOD2*,) (Bowers et al., 2011; Giulivi et al., 2010; Stamova et al., 2013), detoxification (*ALDH, NAT1* and *NAT2, PON1*) (Sabbioni et al., 2006; Vasiliou and Nebert, 2005), or an immune response and inflammation (*IL, TGFβ2, HLA*) (Ashwood et al., 2011a; Ferrante et al., 2003; Krakowiak et al., 2017; Torres et al., 2002; Warren et al., 1996). Furthermore, the functional role of these genes suggests how they may be interacting with solvents in the risk of ASD, which we will further discuss below.

We identified joint interactions with solvents and several serotonin genes (*HTR1A, HTR1B, HTR1F, HTR2A, HTR4, HTR7*), *RELN*, *CNTNAP2*, and ST7*WNT. These genes are associated with neurodevelopment or embryonic development. Serotonin specifically is associated with neuronal differentiation, neurogenesis, synaptogenesis and controls the activity of GABAergic interneurons, which have also been found to be affected in autistic children (Watts, 2008; Zafeiriou et al., 2009). Our results are also consistent with research showing an association between serotonin receptor genes and ASD (Butler et al., 2015; Muhle et al., 2004; Whitaker-Azmitia, 2001). While there is little research specifically evaluating solvents and serotonin genes, alcohol consumption can cause cell apoptosis of neurons particularly serotoninergic neurons and xylene exposure has an inhibitory effect on GABA, a product of serotonin (Boschen and Klintsova, 2017; Niaz et al., 2015; Pruett et al., 2013), suggesting that solvents may interact either with serotonin genes directly or their products such as GABA, interfering with neural development. Further research could elucidate the molecular basis for a solvent-HTR interaction mechanism in ASD (Chen et al., 2004; Lin et al., 2009; Niaz et al., 2015).

The joint interaction between *RELN* rs56041591 and parental occupational exposure to solvents was also associated with ASD. *RELN* encodes for an extracellular matrix protein that controls cell-cell interaction critical for cell positioning and neuronal migration during brain development and plays an important role in synaptic connectivity and plasticity (Shehabeldin et al., 2018) (Gilbert and Man, 2017). Solvent exposure is associated with several neurological effects and changes including interfering with the glial guidance processes which inhibit neuritic outgrowth (Bondy and Campbell, 2005; Hurley and Taber, 2015). Thus, the interaction between *RELN* and parental occupational exposure to solvents may reflect converging or intersecting pathways that interfere with critical aspects of brain development (Gilbert and Man, 2017).

Similarly, *CNTNAP2* is a synaptic protein and a member of the neurexin family that mediates cell-to-cell communication and may be involved in axon differentiation and neuronal migration, while *ST7*WNT2* is in the same region as *RELN* on chromosome 7 (National Center for Biotechnology Information [NCBI], 2019; Rodenas-Cuadrado et al., 2014). It is expressed during development in several tissues including the nervous system (Katoh, 2002; National Center for Biotechnology Information [NCBI], 2019). Solvents may interact directly with *CNTNAP2* or *ST7*WNT2* SNPs, or their protein product interfering with cell-to-cell communication, neural connectivity, or migration, increasing the risk of ASD.

In the presence of solvents, *RORA* rs67288758 was protective of ASD. In contrast, we saw significant odds of ASD in the presence of parental solvent exposure and both *RORA* rs75941956 and *EGF* rs11569014, as well as additive and multiplicative interactions between solvents, *RORA, SOD2*, and *GLRX3* SNPs. These results are consistent with the observation that solvent exposure may result in oxidative stress and the formation of reactive oxygen species (ROS) or reactive nitrogen species (RONS) (Khan and Wang, 2018; Moro et al., 2012). Solvent exposure triggers an inflammatory response and can cause neuronal apoptosis (Fisseler-Eckhoff et al., 2011; Pruett et al., 2013). *RORA*, on the other hand, protects neurons from inflammation and oxidative stress (Hu, 2012). Our results suggest

that in the presence of solvents, *RORA* rs67288758 may be able to protect neurons from oxidative stress while the rs75941956 SNP can't (Hu, 2012). It's unclear how solvents may interact with *RORA* SNPs in the risk of ASD, perhaps it directly interacts with the *RORA* SNP triggering an inflammatory response causing neuronal apoptosis, or inflammation that the SNP is unable to mitigate, or solvents may interfere directly with *RORAs* ability to protect neurons from inflammation and oxidative stress (Fisseler-Eckhoff et al., 2011; Pruett et al., 2013).

Like *RORA, EGF, SOD2* and *GLRX3* are associated with buffering oxidative stress(Esparham et al., 2015; Maher, 2006; Stamova et al., 2013). *EGF* is involved in redox regulation and signaling and promotes cell differentiation and proliferation in neural progenitor cells and has been shown to be associated with ASD (Behring et al., 2020; Galvez-Contreras et al., 2017) (National Institutes of Health [NIH], July 16, 2019). Similarly, *SOD2* and *GLRX3* have been shown to offset or reduce oxidative stress (Stamova et al., 2013) (Bowers et al., 2011; Maher, 2006). GLRX3 is thought to be important in maintaining nerve cell function, which may also partially explain its association with ASD (Bowers et al., 2011). Solvent exposure may interfere with either the genes or the gene products, reducing their ability to buffer oxidative stress, increasing the risk of ASD.

PON1 has a multitude of functions including altering the expression of numerous genes associated with oxidative stress, but also plays a role in detoxification, specifically, it detoxifies organophosphate pesticides (OP) (Carter and Blizard, 2016; Mackness and Mackness, 2015). *PON1* variants interact with OPs in the risk of autism (D'Amelio et al., 2005). Whether *PON1* SNPs interact with solvents like OPs, or results in oxidative stress increasing the risk of ASD is unclear, further research is necessary to clarify this relationship and how solvent exposure may be interacting with *PON1* SNPs to increase the risk of ASD.

ALDH5A1, NAT1, NAT2 are involved in detoxification and drug metabolism (National Center for Biotechnology Information [NCBI], 2017; National Center for Biotechnology Information [NCBI], 2019; Vasiliou and Nebert, 2005). Variations in *ALDH5A1* are associated with developmental delays and other neurological complications (National Center for Biotechnology Information [NCBI], 2019; Vasiliou and Nebert, 2005). Our results may indicate that *ALDH5A1* variants are involved in the metabolism of solvents and poor metabolism may be associated with ASD (National Center for Biotechnology Information [NCBI], 2019). *NAT* encodes for enzymes that help metabolize xenobiotics and drugs (National Center for Biotechnology Information [NCBI], 2017). *NAT2* fast acetylation was associated with neuropsychological impairment in solvent exposed dock workers (Dick et al., 2002). Our results indicate that *NAT1* and *NAT2* may be involved in the biotransformation of solvents influencing the risk of ASD.

Several studies suggest that neuroinflammation may be involved in pathogenesis of ASD (Ashwood et al., 2008; Ashwood et al., 2011a; Ashwood et al., 2011b; Ashwood et al., 2011c; Kelder et al., 1998; Krakowiak et al., 2017; Matta et al., 2019; Pardo et al., 2005). In the presence of solvents, several inflammatory gene SNPS in the IL, *TGFβ2, HLA* class I and class I MHC genes, including SNPs in *GABBR1, PSMB9, TAP1*PSMB9*, and *TAP2* SNPs were associated with ASD. Inflammatory cytokines are expressed in the

developing brain, affecting the function and development of neuronal and glial cells, and a large literature implicates maternal immune activation in ASD (Zawadzka et al., 2021). Similarly, *TGFβ2* is important in embryonic development and regulates the immune system (National Institutes of Health [NIH], July 16, 2019). The joint interaction between *IL* or *TGFβ2* gene SNPs and solvents may trigger an immune response, interfere with the glial guidance process in infants, interfere with the genes resulting in inflammation, or cause cell apoptosis, increasing the risk of ASD (Barragan-Martinez et al., 2012; Bondy and Campbell, 2005; Hurley and Taber, 2015; Pruett et al., 2013).

Lastly, class I *HLA* proteins are important in synaptic plasticity and neuronal connections (Boulanger and Shatz, 2004). Independent of the inflammatory response, HLA-class II is expressed in human neurons and microglia and may be important in embryonic neural development (Vagaska et al., 2016). Immune challenges may change levels of MHC-I proteins in the brain, indicating an important link between immune activation and brain wiring. Solvents may affect immune responses or increase auto-immune tendencies(Barragan-Martinez et al., 2012; Gerhardsson et al., 2021; Khan and Wang, 2019), suggesting ASD risk could be influenced by *HLA* genes interacting with solvents in an immunologic cascade affecting brain development, wiring, or neuronal cell death or in the case of antagonistic relationships, be protective against damage (Barker et al., 2001; Kahn et al., 1964).

Solvent exposure is associated with several neurological effects and changes including oxidative stress, inflammation, and cell apoptosis of neurons (Hurley and Taber, 2015; Pruett et al., 2013). For example, in infants, solvent exposure interferes with the glial guidance process which inhibits neuritic outgrowth (Bondy and Campbell, 2005). It has an inhibitory effect on GABA and has been found to bind directly to the $GABA_A$ receptor (Boschen and Klintsova, 2017; Niaz et al., 2015). The mechanisms linking solvent exposure to ASD suggests that the interaction between solvents and the genes identified in this study may trigger inflammation, oxidative stress, or possibly interfere with neuronal development. However, further functional research needs to be conducted to confirm these findings and to help elucidate the causal pathway between gene, solvent exposure, and ASD.

This study has both strengths and limitations. Strengths include: use of gold standard diagnostic instruments for confirmation of case status and research reliable psychometricians, resulting in accurate, consistent developmental classification(Hertz-Picciotto et al., 2006). We employed an efficient strategy to enhance power of gene-environment analyses by selection of candidate gene SNPs based on established or likely role in the etiology of ASD. The analytic methods were designed to reduce confounding through screening and control of many unknown and suspected risk factors for ASD. Additionally, population-based recruitment of participants reduced selection bias, enhancing the representativeness of the target population and thus, increasing the generalizability of the results. Despite the sample size being larger than most gene-environment interaction studies in ASD, it may still have been too small to see potential SNP or solvent associations with ASD, and even more so to identify interactions between occupational solvent exposures and some candidate SNPs in relation to ASD risk. However, after correcting for multiple testing, several interaction p-values remained significant. An additional limitation of the study

may be that the selection of genes discovered originates from primarily European ancestry populations, while our cohort has a substantial proportion of individuals of other ancestries. However, it is also true that most of the studies on autism (and most other disorders, as recognized by the NIH) have been in European-derived populations (National Institutes of Health [NIH], 2019). Therefore, any candidate gene analysis based on the literature would face the same limitations. There have been several instances of cross-population associations in autism and other disorders, so we feel that our choice of candidate genes is reasonable (Keys et al., 2020). Additional analyses that consider genes found in other populations are warranted, though further genetic research in non-European populations would need to be conducted. The proportion of the CHARGE cohort with non-European ancestry, including non-white race and Hispanic ethnicity is about 45%.

Obtaining accurate exposure data can be challenging. Here we used IH-assessment based on parent reported job title, tasks, and responsibilities; a methodology that is less affected by recall bias than asking parents to report their specific workplace exposures (Teschke et al., 2002). Factors that may affect the accuracy of estimating exposure include, the industrial hygienists' familiarity with specific jobs, variability in solvent exposure within each job, the use of personal protective equipment, and in some instances, access to accurate job information. Nonetheless, while IH generated exposure assessment is less sensitive, the specificity is generally more stable, resulting in less misclassification bias and attenuation of the odds ratios (Benke et al., 2001b). Misclassification bias can be further reduced if information such as responsibilities, task, and duties is also available as it was in this study (Benke et al., 2001a; Teschke et al., 2002). However, father's job histories completed by the mother may be less accurate than those completed by the father, which could have led to misclassification of exposure and decreased precision in ORs. Lastly, although we did not have three or more IHs to assess occupational exposure, use of two IHs (as we did) generally improves reliability and validity over a single IH (Fritschi et al., 2003; Siemiatycki et al., 1997).

5.1 Conclusions

Our results suggest that additive and multiplicative interactions between solvents and gene SNPs in several serotonin, inflammatory, major histocompatibility complex, antioxidant metabolism, and extracellular matrix genes may be associated with ASD. These interactions may reflect numerous mechanisms affecting brain development, wiring, oxidative stress, and inflammation. In contrast, some SNPs potentially protect neurons from inflammation and oxidative stress. Overall, this investigation extends the scant extant knowledge about prenatal parental solvent exposures and neurodevelopment. It is one of the first studies to interrogate a relatively large array of SNPs for gene-environment interactions in ASD, a field still in its infancy. Future research is needed on specific gene SNPs, solvents (or other environmental exposures), and their potential convergent or intersecting pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Few studies have evaluated gene-environment interaction in the risk of autism spectrum disorder (ASD).
- Single nucleotide polymorphism (SNPs) in immune, inflammatory, antioxidant metabolism, hormone, extracellular matrix and serotonin genes were analyzed.
- Two experienced industrial hygienists estimated parental occupational exposure to solvents.
- Potential additive and multiplicative gene-environment interactions between SNPs and parental occupational exposure to solvents were evaluated.
- The joint presence of certain gene SNPs and parental occupational exposure to solvents is associated with higher rates of ASD above the risk associated with having the gene SNP alone or solvent exposure alone.

Table 1.

Characteristics of the children and parents by child's ASD status (N=711).

Variable		ASD[a] (n=414)		TD[b] (n=297)	
		n	Mean (SD) or %	n	Mean (SD) or %
Child	Sex				
	Male	352	85.0	249	83.8
	Female	62	15.0	48	16.2
	Race/ethnicity				
	White, non-Hispanic	213	51.4	158	53.2
	Black, non-Hispanic	13	3.1	6	2.0
	Hispanic (any)	107	25.9	73	24.6
	All Others[c]	81	19.6	60	20.2
	Gestational age	408	39.1 (2.2)	295	39.3 (1.8)
	Duration of breast feeding (month)	410	7.8 (7.4)	291	9.3 (8.1)
Mothers	Age at delivery	414	31.0 (5.5)	297	31.1(5.5)
	Educational level				
	High school/GED[d] or less	53	12.8	43	14.5
	Some college	165	39.9	95	32.0
	Bachelor's degree	130	31.4	116	39.0
	Graduate or professional	66	15.9	43	14.5
	Ethnicity/Race				
	White, non-Hispanic	250	60.4	193	65.0
	Black, non-Hispanic	18	4.4	9	3.0
	Hispanic (any)	92	22.2	60	20.2
	All others	54	13.0	35	11.8
	Birthplace				
	USA	323	78.0	251	84.5
	Mexico	30	7.3	15	5.1
	Outside of USA and Mexico	61	14.7	31	10.4
	Smoking before or during pregnancy				
	Yes	55	13.5	27	9.2
	No	352	86.5	265	90.8
	Alcohol consumption				
	None/Low[e]	224	55.3	149	50.9
	Intermediate/High[f]	181	44.7	137	48.1
	Solvent Exposure	73	17.6	44	14.8
Fathers	Age at delivery	414	33.7 (6.4)	295	33.8 (7.0)
	Educational level				

Variable		ASD[a] (n=414)		TD[b] (n=297)	
		n	Mean (SD) or %	n	Mean (SD) or %
	High school/GED or less	91	22.0	74	24.9
	Some College	124	30.0	89	30.0
	Bachelor's degree	124	30.0	89	30.0
	Graduate or professional	74	17.9	45	15.1
	Ethnicity/Race				
	White, non-Hispanic	265	64.0	197	66.3
	Black, non-Hispanic	21	5.1	16	5.4
	Hispanic (any)	80	19.3	58	19.5
	All others	48	11.6	26	8.8
	Birthplace				
	USA	312	76.1	253	86.0
	Mexico	37	9.0	19	6.5
	Outside of USA and Mexico	61	14.9	22	7.5
	Solvent Exposure	177	42.8	136	45.8
Mother/ Father	Regional Center (RC)				
	Alta, far Northern, and Redwood Coast	150	36.2	132	44.5
	North Bay	63	15.2	46	15.5
	East Bay, San Andreas, and Golden Gate	73	17.6	61	20.5
	Valley Mt, Central Valley, and Kern	79	19.1	49	16.5
	All Los Angeles RCs plus Orange, San Diego, Tricounties, and Inland	49	11.9	9	3.0
	Solvent Exposure	215	51.9	154	51.9
	Total Years of Education	414	29.3 (4.2)	297	29.4 (3.8)

a. ASD = autism spectrum disorder

b. TD = typically developing

c. Other = American Indian, Alaskan native, Asian, Pacific Islander/Hawaiian native, or multi-racial

d. General Educational Development

e. 0-8 drinks per month during 3 months before pregnancy though delivery/3-6 drinks per week during 3 months before pregnancy

f. 8+ drinks per month during 3 months before pregnancy though delivery/6+ drinks per week during 3 months before pregnancy

Table 2:

Additive (RERI[a]) and Multiplicative (ROR[b]) Interactions between Single-Nucleotide Polymorphisms and Parental Occupational Solvent Exposures and the Risk of Autism Spectrum Disorders.

CHR[c]	GENE	SNPs[d]	Minor allele	MAF	RERI	95% LL[e]	95% UL[f]	P value	FDR[g] RERI		ROR	95% LL	95% UL	P value	FDR ROR
6	ALDH5A1	rs3765311	G	0.48	0.62	0.17	1.06	0.0071	0.0154		2.13	1.05	4.33	0.0366	0.0401
7	CNTNAP2	rs11771882	T	0.04	−2.70	−5.77	0.37	0.0848	0.0937		0.17	0.04	0.64	0.0092	0.0147
		rs12703756	G	0.05	1.44	0.00	2.88	0.0508	0.0614		4.40	1.46	13.23	0.0083	0.0147
		rs700316	A	0.21	0.86	0.30	1.41	0.0024	0.0089		2.69	1.38	5.21	0.0035	0.0140
		rs75454072	T	0.07	−1.95	−3.86	−0.05	0.0444	0.0542		0.27	0.11	0.70	0.0067	0.0145
4	EGF	rs11569014	A	0.02	9.27	−10.97	29.50	0.3695	0.3695		23.07	2.29	232.53	0.0078	0.0146
		rs2298991	G	0.47	0.59	0.15	1.03	0.0092	0.0169		2.08	1.03	4.17	0.0400	0.0427
		rs6533489	G	0.43	0.69	0.30	1.08	0.0005	0.0031		2.47	1.27	4.80	0.0075	0.0145
		rs6845765	T	0.26	0.79	0.28	1.31	0.0025	0.0089		2.40	1.27	4.53	0.0067	0.0145
		rs9030	G	0.36	0.71	0.25	1.17	0.0026	0.0089		2.27	1.20	4.31	0.0119	0.0177
		rs9990430	T	0.41	0.74	0.35	1.13	0.0002	0.0015		2.64	1.37	5.09	0.0037	0.0140
6	GABBR1	rs28359976	G	0.10	0.88	0.14	1.63	0.0201	0.0307		2.99	1.30	6.85	0.0097	0.0148
		rs29262	G	0.09	0.90	0.13	1.67	0.0214	0.0319		3.07	1.32	7.13	0.0091	0.0147
		rs3025626	A	0.10	0.90	0.14	1.67	0.0204	0.0307		3.06	1.32	7.06	0.0088	0.0147
10	GLRX3	rs650161	A	0.40	0.62	0.27	0.97	0.0005	0.0031		2.44	1.25	4.74	0.0088	0.0147
		rs7085125	C	0.38	0.63	0.20	1.05	0.0041	0.0112		2.17	1.13	4.15	0.0202	0.0254
		rs7904125	C	0.43	0.68	0.18	1.19	0.0081	0.0160		2.13	1.07	4.25	0.0314	0.0361
6	HCP5	rs3094604	G	0.14	−1.22	−2.34	−0.09	0.0345	0.0449		0.38	0.19	0.79	0.0096	0.0148
6	HLA-C * HLA-B	rs2442727	A	0.12	−1.13	−2.14	−0.13	0.0266	0.0385		0.35	0.17	0.73	0.0054	0.0140
		rs2524067	G	0.15	−1.12	−2.11	−0.14	0.0253	0.0371		0.36	0.18	0.74	0.0050	0.0140
		rs4469339	A	0.41	0.64	0.23	1.05	0.0022	0.0089		2.29	1.16	4.49	0.0165	0.0217
		rs4992474	T	0.35	−1.36	−2.58	−0.14	0.0283	0.0400		0.38	0.20	0.71	0.0028	0.0134
		rs73728881	C	0.35	−1.17	−2.29	−0.05	0.0415	0.0512		0.42	0.22	0.79	0.0073	0.0145
6	HLA-F	rs3116807	A	0.44	−1.27	−2.58	0.05	0.0589	0.0677		0.41	0.21	0.81	0.0098	0.0148
5	HTR1A	rs1402912	A	0.25	0.72	0.26	1.17	0.0021	0.0089		2.39	1.26	4.53	0.0074	0.0145

CHR[c]	GENE	SNPs[d]	Minor allele	MAF	RERI	95% LL[e]	95% UL[f]	P value	FDR[g] RERI		ROR	95% LL	95% UL	P value	FDR ROR
		rs173689	T	0.49	0.66	0.20	1.13	0.0052	0.0131		2.22	1.07	4.62	0.0323	0.0364
		rs347664	G	0.47	0.71	0.25	1.18	0.0025	0.0089		2.33	1.13	4.78	0.0215	0.0269
		rs6861297	G	0.10	−1.42	−2.72	−0.12	0.0319	0.0436		0.31	0.14	0.71	0.0057	0.0140
		rs72758792	G	0.19	−1.26	−2.31	−0.21	0.0185	0.0293		0.35	0.18	0.69	0.0023	0.0128
6	HTR1B	rs10943542	T	0.14	0.97	0.28	1.66	0.0056	0.0136		3.09	1.47	6.49	0.0029	0.0134
		rs1335430	G	0.24	0.59	0.22	0.95	0.0017	0.0086		2.39	1.26	4.53	0.0075	0.0145
		rs236852	A	0.50	0.60	0.21	1.00	0.0029	0.0096		2.24	1.08	4.65	0.0297	0.0352
		rs3004002	A	0.41	0.81	0.47	1.16	0.0000	0.0001		3.17	1.61	6.24	0.0009	0.0128
		rs4075570	G	0.37	0.72	0.24	1.20	0.0033	0.0105		2.25	1.17	4.33	0.0149	0.0208
		rs4708281	G	0.31	0.49	0.12	0.87	0.0102	0.0175		1.99	1.05	3.77	0.0356	0.0393
		rs58693007	T	0.20	0.70	0.24	1.15	0.0026	0.0089		2.53	1.30	4.92	0.0060	0.0142
		rs62426461	G	0.13	0.85	0.23	1.47	0.0073	0.0155		2.85	1.35	6.00	0.0060	0.0142
		rs62433374	A	0.39	0.70	0.33	1.06	0.0002	0.0015		2.57	1.33	4.96	0.0048	0.0140
		rs75278569	G	0.16	0.94	0.39	1.49	0.0008	0.0046		3.37	1.66	6.85	0.0008	0.0128
		rs7764654	C	0.38	0.60	0.15	1.06	0.0096	0.0169		2.04	1.06	3.90	0.0317	0.0361
		rs7771755	T	0.48	0.59	0.15	1.02	0.0079	0.0159		2.11	1.02	4.39	0.0448	0.0460
		rs77723474	C	0.03	2.28	−0.39	4.94	0.0938	0.0980		7.63	1.84	31.63	0.0051	0.0140
3	HTR1F	rs114838037	G	0.02	4.32	−1.66	10.31	0.1568	0.1596		13.05	2.05	83.24	0.0066	0.0145
		rs76107227	C	0.02	4.44	−2.62	11.49	0.2178	0.2197		16.31	2.31	115.28	0.0051	0.0140
13	HTR2A	rs1172402	C	0.18	−1.16	−2.22	−0.09	0.0331	0.0436		0.38	0.19	0.77	0.0069	0.0145
		rs1928045	C	0.46	0.59	0.17	1.01	0.0061	0.0144		2.11	1.05	4.22	0.0348	0.0389
		rs2149436	C	0.42	0.67	0.24	1.09	0.0020	0.0089		2.31	1.17	4.55	0.0162	0.0216
		rs4942590	C	0.34	0.68	0.22	1.14	0.0035	0.0108		2.23	1.18	4.22	0.0139	0.0199
		rs6311	T	0.41	0.56	0.17	0.96	0.0053	0.0131		2.10	1.07	4.12	0.0315	0.0361
		rs73193067	A	0.14	−1.59	−3.05	−0.13	0.0324	0.0436		0.35	0.16	0.73	0.0056	0.0140
		rs9526307	A	0.50	0.61	0.16	1.05	0.0074	0.0155		2.15	1.04	4.47	0.0396	0.0427
5	HTR4	rs11956922	A	0.47	0.58	0.13	1.03	0.0115	0.0191		2.03	1.00	4.11	0.0498	0.0502
		rs6580550	T	0.47	0.54	0.11	0.98	0.0143	0.0234						
10	HTR7	rs1001064	G	0.38	0.75	0.34	1.17	0.0004	0.0030		2.56	1.33	4.90	0.0048	0.0140

CHR[c]	GENE	SNPs[d]	Minor allele	MAF	RERI	95% LL[e]	95% UL[f]	P value	FDR[g] RERI		ROR	95% LL	95% UL	P value	FDR ROR
		rs1326843	G	0.20	0.80	0.29	1.31	0.0021	0.0089		2.61	1.34	5.06	0.0047	0.0140
		rs17092874	C	0.15	−1.39	−2.57	−0.22	0.0197	0.0305		0.32	0.16	0.67	0.0022	0.0128
12	IFNG	rs10784678	C	0.38	0.62	0.19	1.06	0.0052	0.0131		2.13	1.11	4.05	0.0220	0.0272
1	IL10	rs79707006	G	0.07	−1.69	−3.26	−0.12	0.0353	0.0450		0.24	0.09	0.62	0.0033	0.0140
3	IL12A	rs12491474	G	0.07	−1.95	−3.73	−0.16	0.0323	0.0436		0.22	0.08	0.59	0.0028	0.0134
		rs2647929	T	0.42	0.58	0.16	0.99	0.0064	0.0146		2.08	1.07	4.06	0.0315	0.0361
2	IL1B	rs10169916	T	0.39	0.76	0.40	1.12	0.0000	0.0005		2.86	1.48	5.53	0.0017	0.0128
		rs1143623	G	0.31	0.66	0.21	1.10	0.0039	0.0112		2.21	1.17	4.16	0.0142	0.0201
		rs1143633	T	0.34	−1.38	−2.65	−0.11	0.0327	0.0436		0.40	0.21	0.75	0.0046	0.0140
		rs115821385	A	0.06	−1.67	−3.37	0.03	0.0538	0.0631		0.23	0.08	0.64	0.0046	0.0140
		rs11690539	A	0.35	0.78	0.40	1.17	0.0001	0.0008		2.81	1.49	5.33	0.0015	0.0128
		rs16944	A	0.39	0.73	0.38	1.09	0.0001	0.0007		2.77	1.43	5.36	0.0026	0.0134
		rs2466446	C	0.39	0.74	0.40	1.09	0.0000	0.0005		2.86	1.47	5.53	0.0019	0.0128
		rs2723152	T	0.32	0.70	0.30	1.11	0.0007	0.0041		2.47	1.31	4.65	0.0052	0.0140
2	IL1RN	rs17669228	T	0.18	−1.26	−2.37	−0.14	0.0270	0.0386		0.37	0.19	0.73	0.0044	0.0140
		rs2592346	G	0.44	0.61	0.27	0.95	0.0005	0.0031		2.44	1.21	4.90	0.0125	0.0184
8	NAT1	rs1024363	T	0.27	0.71	0.19	1.24	0.0075	0.0155		2.19	1.16	4.14	0.0160	0.0215
		rs60962775	T	0.10	−1.58	−3.19	0.02	0.0532	0.0629		0.32	0.14	0.76	0.0090	0.0147
		rs6586711	C	0.31	0.66	0.20	1.12	0.0046	0.0121		2.19	1.16	4.13	0.0156	0.0214
8	NAT2	rs6998188	C	0.49	0.62	0.16	1.09	0.0085	0.0165		2.12	1.03	4.34	0.0408	0.0431
7	PON1	rs1157745	T	0.38	0.80	0.47	1.14	0.0000	0.0001		3.20	1.66	6.18	0.0005	0.0128
		rs2074351	A	0.30	0.83	0.41	1.26	0.0001	0.0011		2.82	1.49	5.31	0.0014	0.0128
		rs2237580	G	0.13	1.01	0.34	1.67	0.0031	0.0100		3.14	1.50	6.57	0.0023	0.0128
		rs2299256	A	0.27	0.85	0.45	1.26	0.0000	0.0006		3.11	1.63	5.93	0.0006	0.0128
		rs2299257	C	0.44	0.83	0.46	1.20	0.0000	0.0003		3.12	1.56	6.24	0.0012	0.0128
		rs35339934	A	0.13	0.71	0.25	1.18	0.0025	0.0089		3.00	1.43	6.28	0.0035	0.0140
		rs3917498	T	0.41	0.81	0.45	1.18	0.0000	0.0003		3.07	1.54	6.11	0.0014	0.0128
		rs3917577	C	0.13	0.99	0.32	1.67	0.0040	0.0112		3.03	1.45	6.31	0.0031	0.0140
		rs662	C	0.38	0.81	0.48	1.14	0.0000	0.0001		3.24	1.68	6.26	0.0004	0.0128

CHR[c]	GENE	SNPs[d]	Minor allele	MAF	RERI	95% LL[e]	95% UL[f]	P value	FDR[g] RERI		ROR	95% LL	95% UL	P value	FDR ROR
		rs854555	A	0.39	0.61	0.22	0.99	0.0021	0.0089		2.23	1.16	4.31	0.0166	0.0217
6	PSMB9	rs10214759	T	0.03	1.77	−0.11	3.65	0.0652	0.0741		8.47	1.80	39.80	0.0068	0.0145
		rs17220241	T	0.03	2.05	−0.32	4.43	0.0897	0.0973		8.64	1.73	43.26	0.0087	0.0147
		rs56672687	T	0.03	1.96	−0.14	4.06	0.0669	0.0753		8.32	1.75	39.58	0.0078	0.0146
		rs73412927	A	0.03	1.88	−0.14	3.90	0.0683	0.0761		7.99	1.68	37.96	0.0090	0.0147
7	RELN	rs34566446	G	0.46	0.54	0.13	0.94	0.0089	0.0169		2.05	1.02	4.12	0.0447	0.0460
		rs56041591	T	0.06	2.90	−0.60	6.40	0.1046	0.1084		5.52	1.68	18.13	0.0049	0.0140
		rs671372	T	0.46	0.61	0.27	0.95	0.0005	0.0031		2.47	1.21	5.05	0.0129	0.0187
		rs6954835	G	0.47	0.56	0.18	0.94	0.0038	0.0112		2.21	1.04	4.73	0.0401	0.0427
15	RORA	rs1523526	C	0.48	0.53	0.14	0.92	0.0077	0.0156		2.09	1.02	4.29	0.0452	0.0460
		rs16944364	G	0.08	1.18	0.29	2.07	0.0096	0.0169		4.00	1.65	9.73	0.0022	0.0128
		rs2143	A	0.50	−2.05	−3.99	−0.12	0.0377	0.0473		0.28	0.13	0.60	0.0010	0.0128
		rs2414708	G	0.24	−1.25	−2.37	−0.12	0.0297	0.0415		0.40	0.21	0.77	0.0055	0.0140
		rs4775287	C	0.34	0.60	0.15	1.05	0.0094	0.0169		2.03	1.07	3.85	0.0297	0.0352
		rs58306294	T	0.25	0.69	0.17	1.22	0.0093	0.0169		2.14	1.13	4.06	0.0197	0.0252
		rs67288758	G	0.05	−2.17	−4.40	0.06	0.0568	0.0659		0.14	0.04	0.46	0.0011	0.0128
		rs7168305	A	0.08	1.03	0.24	1.82	0.0107	0.0180		4.22	1.67	10.68	0.0023	0.0128
		rs72750685	T	0.05	−2.06	−4.46	0.34	0.0929	0.0980		0.21	0.07	0.68	0.0092	0.0147
		rs75885569	T	0.03	2.11	−0.61	4.84	0.1287	0.1322		8.14	1.72	38.63	0.0083	0.0147
		rs75941956	C	0.04	2.46	−0.36	5.28	0.0870	0.0952		7.62	1.90	30.54	0.0041	0.0140
6	SOD2	rs117664822	A	0.04	−1.99	−4.31	0.32	0.0912	0.0980		0.17	0.05	0.64	0.0083	0.0147
		rs4632918	A	0.34	−1.22	−2.37	−0.07	0.0380	0.0473		0.42	0.22	0.79	0.0074	0.0145
		rs6919792	G	0.33	0.64	0.20	1.08	0.0046	0.0121		2.16	1.15	4.07	0.0173	0.0224
7	ST7 * WNT2	rs38911	A	0.46	0.68	0.34	1.02	0.0001	0.0011		2.67	1.32	5.38	0.0061	0.0142
6	TAP1 * PSMB9	rs17213826	T	0.04	1.51	−0.02	3.03	0.0524	0.0627		5.90	1.53	22.66	0.0098	0.0148
6	TAP2	rs3819721	A	0.24	0.60	0.17	1.02	0.0062	0.0144		2.20	1.16	4.19	0.0157	0.0214
		rs73410785	C	0.03	2.63	−0.44	5.69	0.0933	0.0980		14.01	2.77	70.82	0.0014	0.0128
1	TGFB2	rs12119526	T	0.14	−1.42	−2.61	−0.24	0.0188	0.0295		0.32	0.15	0.66	0.0020	0.0128
		rs1473527	A	0.36	0.58	0.16	1.00	0.0071	0.0154		2.06	1.08	3.93	0.0283	0.0342

CHR[c]	GENE	SNPs[d]	Minor allele	MAF	RERI	95% LL[e]	95% UL[f]	P value	FDR[g] RERI		ROR	95% LL	95% UL	P value	FDR ROR
		rs41313742	T	0.07	1.80	0.13	3.47	0.0348	0.0449		4.05	1.53	10.72	0.0048	0.0140
		rs682483	A	0.48	0.54	0.13	0.95	0.0100	0.0174		2.03	1.02	4.06	0.0450	0.0460
		rs878394	A	0.48	0.61	0.24	0.99	0.0015	0.0077		2.34	1.12	4.86	0.0229	0.0279
6	VEGFA	rs62401175	G	0.16	−1.97	−3.57	−0.36	0.0161	0.0260		0.29	0.14	0.60	0.0008	0.0128

[a] RERI = relative excess risk for interaction

[b] ROR= ratio odds ratio

[c] CHR-= chromosome

[d] SNPs=single nucleotide polymorphisms

[e] 95% LL – 95% confidence interval lower limit

[f] 95% UL = 95% confidence interval upper limit

[g] FDR= false discovery rate corrected p-value

Table 3:

Odds ratios associated with gene only, solvents only, and gene – solvent and ASD

CHR[a]	GENE	SNPs[b]	Minor allele	Solvent Only	95% LL[c]	95% UL[d]	p-value	SNP[e] Only	95% LL	95% UL	p-value	Solvent * SNP	95% LL	95% UL	p-value
6	ALDH5A1	rs3765311	G	0.60	0.33	1.11	0.102	0.77	0.46	1.28	0.315	0.99	0.59	1.65	0.964
7	CNTNAP2	rs11771882	T	1.19	0.85	1.66	0.314	3.14	1.22	8.08	0.018	0.63	0.24	1.64	0.341
		rs12703756	G	0.89	0.63	1.25	0.489	0.46	0.22	0.95	0.037	1.78	0.79	4.02	0.167
		rs700316	A	0.71	0.48	1.07	0.099	0.62	0.39	1.00	0.048	1.19	0.73	1.96	0.484
		rs75454072	T	1.26	0.89	1.78	0.197	2.59	1.31	5.13	0.006	0.89	0.47	1.70	0.726
4	EGF	rs11569014	A	0.94	0.67	1.30	0.694	0.45	0.17	1.17	0.102	9.65	1.18	78.84	0.034
		rs2298991	G	0.62	0.35	1.12	0.114	0.72	0.44	1.19	0.204	0.94	0.58	1.53	0.803
		rs6533489	G	0.57	0.34	0.98	0.043	0.64	0.40	1.03	0.065	0.90	0.56	1.45	0.679
		rs6845765	T	0.69	0.45	1.07	0.098	0.73	0.46	1.16	0.181	1.22	0.78	1.91	0.388
		rs9030	G	0.64	0.39	1.06	0.081	0.76	0.48	1.20	0.233	1.11	0.70	1.76	0.667
		rs9990430	T	0.56	0.33	0.95	0.030	0.63	0.39	1.02	0.058	0.94	0.59	1.50	0.785
6	GABBR1	rs28359976	G	0.83	0.58	1.19	0.306	0.48	0.28	0.84	0.010	1.20	0.64	2.23	0.575
		rs29262	G	0.84	0.59	1.20	0.329	0.47	0.27	0.82	0.009	1.21	0.64	2.29	0.559
		rs3025626	A	0.83	0.58	1.18	0.297	0.48	0.27	0.84	0.010	1.21	0.64	2.28	0.556
10	GLRX3	rs650161	A	0.58	0.34	0.99	0.047	0.49	0.30	0.80	0.005	0.70	0.43	1.13	0.142
		rs7085125	C	0.66	0.39	1.09	0.106	0.67	0.42	1.09	0.106	0.96	0.59	1.55	0.855
		rs7904125	C	0.62	0.35	1.10	0.103	0.94	0.58	1.54	0.816	1.24	0.76	2.02	0.386
6	HCP5	rs3094604	G	1.34	0.92	1.95	0.123	1.81	1.08	3.03	0.025	0.93	0.55	1.57	0.792
6		rs2442727	A	1.33	0.92	1.93	0.132	1.49	0.88	2.54	0.137	0.69	0.40	1.18	0.177
		rs2524067	G	1.34	0.92	1.96	0.129	1.53	0.92	2.52	0.100	0.74	0.45	1.24	0.254
	HLA-C *	rs4469339	A	0.60	0.34	1.03	0.064	0.66	0.40	1.07	0.094	0.90	0.56	1.45	0.660
	HLA-B	rs4992474	T	1.82	1.11	3.00	0.018	1.71	1.06	2.73	0.027	1.17	0.73	1.87	0.521
		rs73728881	C	1.72	1.05	2.82	0.032	1.58	0.99	2.53	0.055	1.13	0.71	1.81	0.601
6	HLA-F	rs3116807	A	1.92	1.08	3.40	0.026	1.58	0.96	2.59	0.069	1.23	0.76	2.01	0.396
		rs1402912	A	0.71	0.46	1.08	0.111	0.61	0.39	0.98	0.041	1.04	0.66	1.63	0.878
		rs173689	T	0.57	0.30	1.08	0.084	0.86	0.50	1.48	0.594	1.10	0.64	1.88	0.728

CHR[a]	GENE	SNPs[b]	Minor allele	Solvent Only	95% LL[c]	95% UL[d]	p-value	SNP[e] Only	95% LL	95% UL	p-value	Solvent * SNP	95% LL	95% UL	p-value
5	HTR1A	rs347664	G	0.57	0.31	1.06	0.077	0.87	0.50	1.50	0.615	1.15	0.66	2.02	0.614
		rs6861297	G	1.28	0.90	1.84	0.170	1.89	1.04	3.44	0.036	0.76	0.42	1.35	0.343
		rs72758792	G	1.45	0.98	2.15	0.063	1.64	0.99	2.69	0.052	0.83	0.52	1.33	0.434
		rs10943542	T	0.77	0.53	1.12	0.172	0.54	0.32	0.89	0.016	1.28	0.73	2.24	0.396
		rs1335430	G	0.70	0.46	1.09	0.113	0.42	0.27	0.68	0.000	0.71	0.45	1.13	0.147
		rs236852	A	0.57	0.30	1.07	0.080	0.62	0.36	1.08	0.095	0.80	0.46	1.39	0.42
		rs3004002	A	0.48	0.28	0.83	0.009	0.57	0.34	0.93	0.026	0.86	0.52	1.42	0.550
6	HTR1B	rs4075570	G	0.63	0.38	1.05	0.078	0.83	0.52	1.34	0.444	1.18	0.73	1.90	0.503
		rs4708281	G	0.68	0.42	1.11	0.122	0.50	0.31	0.80	0.004	0.67	0.41	1.10	0.112
		rs58693007	T	0.73	0.49	1.10	0.131	0.50	0.31	0.81	0.005	0.94	0.58	1.51	0.788
		rs62426461	G	0.78	0.54	1.13	0.183	0.52	0.31	0.87	0.013	1.15	0.66	1.99	0.631
		rs62433374	A	0.56	0.33	0.96	0.034	0.58	0.36	0.94	0.028	0.84	0.52	1.37	0.485
		rs75278569	G	0.73	0.50	1.07	0.102	0.46	0.28	0.77	0.003	1.13	0.68	1.88	0.642
		rs7764654	C	0.66	0.40	1.10	0.114	0.76	0.47	1.22	0.248	1.02	0.63	1.65	0.932
		rs7771755	T	0.60	0.32	1.12	0.11	0.71	0.41	1.22	0.213	0.89	0.52	1.54	0.687
		rs77723474	C	0.91	0.65	1.27	0.583	0.37	0.14	0.97	0.043	2.56	0.89	7.33	0.080
3	HTR1F	rs114838037	G	0.93	0.67	1.29	0.660	0.38	0.10	1.43	0.154	4.63	1.27	16.95	0.021
		rs76107227	C	0.93	0.67	1.29	0.656	0.31	0.09	1.07	0.063	4.67	1.03	21.27	0.046
		rs1172402	C	1.36	0.92	2.00	0.122	1.68	1.00	2.82	0.051	0.88	0.55	1.39	0.577
		rs1928045	C	0.61	0.34	1.09	0.094	0.71	0.42	1.18	0.187	0.90	0.54	1.51	0.699
		rs2149436	C	0.57	0.33	1.01	0.053	0.75	0.45	1.23	0.252	0.98	0.59	1.63	0.947
13	HTR2A	rs4942590	C	0.66	0.41	1.06	0.086	0.73	0.46	1.17	0.189	1.07	0.68	1.71	0.762
		rs6311	T	0.62	0.35	1.09	0.096	0.61	0.37	1.02	0.057	0.80	0.48	1.33	0.383
		rs73193067	A	1.34	0.92	1.95	0.124	2.34	1.34	4.09	0.003	1.09	0.65	1.82	0.755
		rs9526307	A	0.58	0.31	1.08	0.088	0.77	0.45	1.29	0.316	0.95	0.57	1.60	0.851
5	HTR4	rs11956922	A	0.62	0.34	1.14	0.124	0.78	0.46	1.32	0.356	0.98	0.58	1.67	0.950
		rs6580550	T	0.60	0.32	1.11	0.103	0.72	0.42	1.22	0.222	0.85	0.50	1.46	0.564
		rs1001064	G	0.58	0.35	0.97	0.039	0.68	0.42	1.10	0.121	1.02	0.64	1.64	0.93
10	HTR7	rs1326843	G	0.73	0.49	1.09	0.123	0.59	0.36	0.95	0.032	1.12	0.70	1.79	0.640

CHR[a]	GENE	SNPs[b]	Minor allele	Solvent Only	95% LL[c]	95% UL[d]	p-value	SNP[e] Only	95% LL	95% UL	p-value	Solvent * SNP	95% LL	95% UL	p-value
		rs17092874	C	1.41	0.96	2.05	0.078	1.80	1.05	3.09	0.032	0.81	0.50	1.32	0.408
12	IFNG	rs10784678	C	0.66	0.40	1.09	0.103	0.71	0.44	1.13	0.151	0.99	0.63	1.57	0.968
1	IL10	rs79707006	G	1.24	0.88	1.75	0.220	2.06	1.02	4.15	0.043	0.61	0.32	1.18	0.144
3	IL12A	rs12491474	G	1.25	0.89	1.77	0.199	2.34	1.16	4.73	0.018	0.65	0.32	1.31	0.228
		rs2647929	T	0.63	0.36	1.09	0.098	0.67	0.41	1.08	0.103	0.87	0.54	1.41	0.582
		rs10169916	T	0.55	0.33	0.93	0.025	0.54	0.33	0.88	0.014	0.85	0.52	1.39	0.526
		rs1143623	G	0.69	0.43	1.09	0.109	0.67	0.42	1.06	0.088	1.01	0.63	1.62	0.963
		rs1143633	T	1.75	1.08	2.83	0.023	2.07	1.30	3.31	0.002	1.44	0.90	2.30	0.125
2	IL1B	rs115821385	A	1.26	0.89	1.79	0.192	1.99	0.90	4.39	0.091	0.58	0.31	1.09	0.089
		rs11690539	A	0.58	0.36	0.94	0.026	0.58	0.36	0.92	0.022	0.94	0.59	1.51	0.798
		rs16944	A	0.54	0.32	0.92	0.023	0.55	0.34	0.90	0.018	0.83	0.51	1.36	0.456
		rs2466446	C	0.53	0.31	0.89	0.017	0.54	0.33	0.88	0.013	0.80	0.49	1.32	0.386
		rs2723152	T	0.64	0.40	1.02	0.060	0.59	0.37	0.95	0.028	0.94	0.58	1.50	0.789
2	IL1RN	rs17669228	T	1.41	0.95	2.09	0.084	1.76	1.05	2.96	0.033	0.92	0.58	1.44	0.708
		rs2592346	G	0.55	0.30	0.99	0.046	0.46	0.27	0.78	0.004	0.62	0.37	1.05	0.074
		rs1024363	T	0.73	0.48	1.12	0.151	0.74	0.47	1.17	0.201	1.19	0.75	1.87	0.458
8	NAT1	rs60962775	T	1.26	0.88	1.80	0.207	2.24	1.15	4.34	0.017	0.91	0.54	1.55	0.74
		rs6586711	C	0.68	0.43	1.08	0.100	0.70	0.44	1.10	0.122	1.04	0.66	1.63	0.871
8	NAT2	rs6998188	C	0.60	0.33	1.12	0.110	0.82	0.49	1.37	0.445	1.05	0.63	1.74	0.861
7	PON1	rs1157745	T	0.50	0.29	0.84	0.009	0.51	0.32	0.82	0.005	0.81	0.51	1.29	0.377
		rs2074351	A	0.58	0.37	0.93	0.025	0.65	0.41	1.03	0.064	1.07	0.69	1.66	0.773
		rs2237580	G	0.78	0.54	1.13	0.183	0.54	0.32	0.93	0.025	1.33	0.79	2.23	0.288
		rs2299256	A	0.63	0.40	0.99	0.044	0.51	0.32	0.81	0.005	0.99	0.63	1.56	0.96
		rs2299257	C	0.46	0.26	0.83	0.009	0.67	0.41	1.09	0.106	0.96	0.59	1.56	0.867
		rs35339934	A	0.78	0.54	1.14	0.199	0.56	0.33	0.96	0.034	1.15	0.66	2.02	0.614
		rs3917498	T	0.48	0.27	0.86	0.013	0.61	0.37	1.00	0.049	0.91	0.56	1.47	0.692
		rs3917577	C	0.78	0.54	1.13	0.196	0.57	0.33	0.96	0.035	1.34	0.80	2.25	0.273
		rs662	C	0.50	0.29	0.84	0.009	0.50	0.31	0.81	0.004	0.81	0.51	1.29	0.377
		rs854555	A	0.61	0.36	1.04	0.069	0.59	0.37	0.96	0.032	0.81	0.51	1.29	0.379

CHR[a]	GENE	SNPs[b]	Minor allele	Solvent Only	95% LL[c]	95% UL[d]	p-value	SNP[e] Only	95% LL	95% UL	p-value	Solvent * SNP	95% LL	95% UL	p-value
		rs10214759	T	0.93	0.67	1.30	0.672	0.25	0.07	0.83	0.023	1.95	0.73	5.16	0.181
6	PSMB9	rs17220241	T	0.95	0.68	1.31	0.736	0.28	0.08	0.95	0.041	2.28	0.80	6.51	0.124
		rs56672687	T	0.94	0.68	1.31	0.716	0.28	0.08	0.95	0.041	2.18	0.83	5.75	0.115
		rs73412927	A	0.94	0.68	1.31	0.718	0.28	0.08	0.95	0.042	2.10	0.80	5.54	0.133
		rs34566446	G	0.62	0.34	1.13	0.117	0.58	0.34	0.98	0.040	0.74	0.43	1.24	0.251
7	RELN	rs56041591	T	0.89	0.64	1.26	0.521	0.71	0.38	1.34	0.287	3.50	1.27	9.64	0.015
		rs671372	T	0.54	0.29	0.99	0.047	0.44	0.26	0.75	0.003	0.59	0.35	1.00	0.052
		rs6954835	G	0.54	0.28	1.05	0.07	0.51	0.28	0.92	0.024	0.61	0.34	1.10	0.103
		rs1523526	C	0.60	0.32	1.12	0.107	0.51	0.30	0.89	0.017	0.64	0.37	1.11	0.11
		rs16944364	G	0.84	0.59	1.19	0.326	0.43	0.23	0.82	0.010	1.45	0.77	2.73	0.244
15	RORA	rs2143	A	2.68	1.39	5.18	0.003	1.55	0.94	2.58	0.089	1.18	0.72	1.95	0.51
		rs2414708	G	1.59	1.03	2.45	0.036	1.82	1.14	2.92	0.013	1.17	0.74	1.84	0.505
		rs4775287	C	0.68	0.42	1.11	0.127	0.73	0.46	1.16	0.189	1.02	0.64	1.61	0.942
		rs58306294	T	0.74	0.48	1.14	0.169	0.75	0.47	1.18	0.211	1.18	0.74	1.86	0.486
		rs67288758	G	1.23	0.88	1.72	0.228	2.35	0.95	5.82	0.064	0.42	0.20	0.87	0.02
		rs7168305	A	0.84	0.59	1.19	0.321	0.34	0.18	0.66	0.001	1.21	0.62	2.35	0.573
		rs72750685	T	1.18	0.84	1.65	0.338	2.50	1.00	6.29	0.051	0.63	0.30	1.29	0.202
		rs75885569	T	0.92	0.66	1.28	0.626	0.31	0.11	0.88	0.029	2.35	0.73	7.56	0.153
		rs75941956	C	0.91	0.65	1.27	0.591	0.40	0.15	1.03	0.057	2.77	0.99	7.74	0.052
6	SOD2	rs117664822	A	1.17	0.84	1.63	0.356	2.29	0.87	6.03	0.094	0.47	0.19	1.12	0.087
		rs4632918	A	1.63	1.01	2.63	0.044	1.83	1.15	2.91	0.011	1.24	0.80	1.92	0.329
		rs6919792	G	0.68	0.42	1.09	0.109	0.68	0.43	1.09	0.11	1.00	0.62	1.61	0.991
7	ST7 * WNT2	rs38911	A	0.52	0.28	0.93	0.029	0.52	0.31	0.87	0.013	0.72	0.43	1.20	0.205
6	TAP1 * PSMB9	rs17213826	T	0.93	0.67	1.30	0.674	0.32	0.11	0.90	0.030	1.76	0.74	4.20	0.203
6	TAP2	rs3819721	A	0.74	0.49	1.13	0.163	0.53	0.33	0.84	0.008	0.87	0.54	1.38	0.552
		rs73410785	C	0.92	0.66	1.28	0.606	0.21	0.07	0.69	0.010	2.76	0.90	8.48	0.077
1	TGFB2	rs12119526	T	1.38	0.95	2.00	0.091	1.86	1.08	3.19	0.0242 \	0.81	0.49	1.34	0.416

CHR[a]	GENE	SNPs[b]	Minor allele	Solvent Only	95% LL[c]	95% UL[d]	p-value	SNP[e] Only	95% LL	95% UL	p-value	Solvent * SNP	95% LL	95% UL	p-value
		rs1473527	A	0.67	0.40	1.11	0.116	0.67	0.41	1.07	0.094	0.91	0.56	1.47	0.708
		rs41313742	T	0.86	0.61	1.21	0.388	0.67	0.35	1.28	0.225	2.33	1.12	4.84	0.024
		rs682483	A	0.63	0.35	1.12	0.116	0.60	0.36	1.00	0.048	0.76	0.46	1.26	0.293
		rs878394	A	0.54	0.29	1.02	0.056	0.58	0.33	1.01	0.055	0.73	0.42	1.28	0.275
6	VEGFA	rs62401175	G	1.42	0.97	2.07	0.072	2.64	1.52	4.59	0.001	1.09	0.68	1.74	0.715

a. CHR-= chromosome

b. SNPs= single nucleotide polymorphisms

c. 95% LL – 95% confidence interval lower limit

d. 95% UL = 95% confidence interval upper limit