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Relationship of family history conditions and early signs of autism spectrum disorder in low and high-risk infants

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ABSTRACT

Background: Early identification and understanding of Autism Spectrum Disorder (ASD) could be facilitated by knowledge of family history of medical, developmental and psychiatric conditions associated with showing early signs of ASD.
Method: The current study used nonparametric analysis of covariance to compare the number of family history conditions n 69 high-risk (biological sibling with ASD) and 108 low-risk (no family history of ASD) infants. Spearman correlation was used to assess the relationship between family history of various conditions and early ASD signs as measured by an early screener, the Parent Observation of Early Markers Scale (POEMS).
Results: There were significantly more family history conditions in the families of the high-risk infants, and significant positive relationships between the number of family history problems and early markers of ASD in both groups.
Conclusions: The results suggest that family history conditions may play an important role in screening infants not yet diagnosed with ASD and reveal etiological pathways.

1. Introduction

Autism spectrum disorders (ASD) are highly inheritable. Monozygotic twins have up to 95% diagnostic concordance (Colvert et al., 2015). Infants who have an older affected biological sibling have about a 17% risk of developing ASD or the broader phenotype (Bolton et al., 1994; Ozonoff et al., 2011; Palmer et al., 2017), compared to about 1.5% in the general population (Christensen et al., 2016). Infants at risk for ASD are being increasingly studied to understand possible etiological mechanisms and early developmental pathways, as well as to screen for early signs (Feldman et al., 2012; Jones, Gliga, Bedford, Charman, & Johnson, 2014; Ozonoff et al., 2011). High-risk infants may experience delays in receptive language by 12 months, and display early impairments in imitation, eye contact, responding to name and gestures, language, temperament, tolerance to waiting, empathy, and motor control (Feldman et al., 2012; Jones et al., 2014).

1.1. Etiology

Accumulating evidence supports a complex, interactive, threshold epigenetic/genetic etiological model for ASD (Loke, Hannan, &

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Craig, 2015). Recent genetic research indicates that both rare and common genetic variants play important roles in ASD etiology (Connolly & Hakonarson, 2014; Grove et al., 2019; Losh et al., 2017). With major technological advances and rapid development in the field of molecular genetics, several hundred ASD-susceptible loci and genes have been identified, suggesting a highly heterogeneous underlying genetic architecture that is consistent with phenotypic variations seen in ASD (Yin & Schaaf, 2017). Besides the small genetic variants such as traditional single-nucleotide variants in these loci/genes, structural variants including copy number variants (CNVs), are also involved in ASD. Affected individuals carry a three to five-fold higher burden of *de novo* CNVs compared to unaffected family members and controls (Connolly & Hakonarson, 2014; Marshall et al., 2008; Moreira et al., 2016; Sebat et al., 2007; Weiss et al., 2008). *De novo* CNV rates have been found to be consistently higher in sporadic ASD (simplex = 5.8%–10.2%) versus familial ASD (multiplex = 2–3%) (Autism Genome Project Consortium, 2008; Marshall et al., 2008; Qiao et al., 2009; Sebat et al., 2007).

Many of the genes associated with ASD are involved in epigenetic pathways (Loke et al., 2015) so it is no surprise that epigenetic dysregulation, including aberrant DNA methylation, chromatin remodeling, and altered miRNA expression, has been implicated in the etiology of ASD and other neurodevelopmental disorders (Celetti, 2013; Gropman & Batshaw, 2010; Loke et al., 2015; Yao et al., 2016). Epigenetic dysregulation involves changes in DNA configuration and accessibility without altering DNA sequence (Hall & Kelley, 2014; Loke et al., 2015). Epigenetic changes often result from intrauterine and environmental conditions and experiences (Hall & Kelley, 2014) and have important consequences for biological processes including imprinting, genome reprogramming, cell differentiation, and maintenance of cell lineages as well as developmental processes including learning and memory (Gropman & Batshaw, 2010). Many adverse conditions have been associated with epigenetic dysregulation related to ASD including maternal infections and accompanying immune system activation (Estes & McAllister, 2016; Jiang et al., 2016), use of oral contraceptives (Strifert, 2015), family history of alcohol-abuse (Sundquist, Sundquist, & Ji, 2014), paternal alcohol-use that alters methylation of paternal sperm cells (Govorko, Bekdash, Zhang, & Sarkar, 2012), prenatal exposure to environmental toxins including organochlorine compounds found in pesticides (Lyall et al., 2017) and vehicular traffic and industrial air pollutants (von Ehrenstein, Aralis, Cockburn, & Ritz, 2014).

1.2. Family history

Identifying family history disorders may help unmask previously undiscovered etiological connections between conditions and aid in assessing the likelihood of inheriting a disorder (Eriksson, Westerlund, Anderlid, Gillberg, & Fernell, 2012; Yoon et al., 2002). Family history of ASD increases the prospect of subsequent children inheriting ASD (Losh et al., 2017; Palmer et al., 2017). Similarly, a family history of non-ASD developmental/learning disorders such as intellectual disabilities, speech-language problems, academic problems and attention deficit hyperactivity disorder (ADHD) is associated with increased prevalence of ASD (Brimacombe, Ming, & Parikh, 2007; Losh et al., 2017). Maternal history of epilepsy is related to ASD in their children (Sundelin et al., 2016) as is the severity of maternal depression, regardless of antidepressant use in pregnancy (Hagberg, Robijn, & Jick, 2018). Many genes implicated in autoimmune disorders (e.g., Type 1 diabetes, rheumatoid arthritis, lupus) cluster within families with ASD (Edmiston, Ashwood, & Van de Water, 2017), and a family history of autoimmune disorders is related to ASD in offspring (Brimacombe et al., 2007; Chen et al., 2016; Mostafa & Shehab, 2010; Patel et al., 2018; Wu et al., 2015). Several neuropsychiatric conditions such as schizophrenia and bipolar disorder may share common etiological factors with ASD (Gregory et al., 2009), and a family history of these conditions has been linked to ASD in offspring (Brimacombe et al., 2007; Ghaziuddin, 2005; Jokiranta et al., 2013; Larsson et al., 2005; Sullivan et al., 2012). Taken together, these family history studies suggest that certain familial medical, developmental and neuropsychiatric conditions share common genetic mechanisms and/or other etiologic factors with ASD (Brimacombe et al., 2007; Cukier et al., 2014; Larsson et al., 2005).

Family history studies have yet to examine the relationship of family history factors in pre-diagnosed infants who have a high risk of ASD (because they have an older sibling with ASD) and compare family histories of conditions associated with ASD to low-risk infants (no family history of ASD). This study goes beyond previous studies that have examined the connection of different family history problems and ASD occurrence. First, the focus on the relationship between the number and type of family history conditions and scores on an ASD screener may reveal family history conditions related not only to ASD in the family, but also the likelihood of future ASD diagnosis. Infants with more family history concerns related to ASD and higher screener scores may be more likely to be diagnosed than infants scoring lower in one or both measures. Second, knowing the family history conditions of the infant and their behavioral developmental profile based on elevated screener items may reveal shared mechanisms that may impact on not only ASD itself but the broader phenotype (Yoon et al., 2002). Different family history conditions may reveal different developmental profiles – i.e., different longitudinal patterns of screener elevated items. For instance, Patel et al. (2018) found that a maternal history of immune system disorders (particularly, asthma and allergies) was associated with increased social impairment in their offspring with ASD. It is possible that a maternal history of immune conditions may be related to higher scores on social items on an infant screener. Third, we include a low-risk group and it is not clear what the associations between family history and screener scores would be in this group. Perhaps, the fact that this group does not have a family history of ASD would lead to no or different relationships between family history and screener scores than the high-risk group.

1.3. Research questions and hypotheses

This study was guided by three central research questions. First, did the frequency of family history problems differ between low-risk (no reported family history of ASD) and high-risk infants (with an older biological sibling with ASD)? We hypothesized that given

the genetic loading seen in ASD (Bolton et al., 1994), families that already have a child with ASD would show more family history problems that may be associated with ASD. Second, was the number of family history problems correlated with early signs of ASD in low and high-risk infants as measured by an ASD screener? We hypothesized a positive correlation between the number of family history problems and scores on the ASD screener. Third, which family history condition categories – medical, developmental and psychiatric – were correlated with ASD screener scores and which specific conditions (e.g., language disorders, depression) within the categories were associated with ASD screener scores? We also examined possible differences in maternal and paternal family history condition frequencies and correlations with ASD screener scores.

2. Methods

2.1. Participants

This study received ethics clearance from the Brock University Research Ethics Board in accordance with the 2014 Canadian Tri-council Policy Statement of Ethical Conduct for Research Involving Humans and the 2000 Declaration of Helsinki; informed consent was obtained from the parent participants. A convenience sample of 112 second born or later low-risk infants from 112 families initially were recruited through word of mouth, online advertisements and posted flyers at physician offices and developmental clinics. Eligibility for inclusion in the low-risk group included: no known family history of ASD, a typically developing second-born (or later) child that was under 37 months of age with no known medical conditions that could impinge on typical development (Feldman, Hendry, Ward, Hudson, & Liu, 2015). The recruited low-risk sample was reduced by four children for all analyses because their parents subsequently self-identified on the Family History Questionnaire as having a family history of ASD that violated the inclusion criteria for this group. The high-risk infant group consisted of 73 high-risk infants from 69 families recruited across North America. High-risk participants had no known medical conditions that could affect development and had an older biological sibling already diagnosed with ASD, confirmed in a previous study (Feldman et al., 2012). Four families had two infant siblings who had POEMS data. For the statistical analyses, each family's demographic and history data should only be included once. Therefore, one sibling from each for the four families with two potential infant participants was chosen at random to be excluded from the analyses, leaving a final high-risk total of 69 infants. Table 1 presents information regarding key child, parent and family characteristics for both groups.

2.2. Measures

2.2.1. Family information questionnaire

The Family Information Questionnaire (FIQ) collected sociodemographic and health information regarding the family, parents and children (Feldman, Hancock, Rielly, Minnes, & Cairns, 2000).

2.2.2. Family history questionnaire (FHQ)

This locally-developed questionnaire asked parents to indicate family history conditions from both the maternal and paternal sides of each family. The multidisciplinary research team consisting of autism experts in genetics and psychology generated the list of conditions based on available research (e.g., Brimacombe et al., 2007) and proposed common etiological mechanisms (Gregory et al., 2009). The original list was given to low-risk participants and consisted of 13 conditions plus space to write in other conditions. To capture more conditions in the high-risk group, the list was expanded to include 29 additional conditions, plus write in space. In the expanded questionnaire two conditions that overlapped in the shorter questionnaire were combined (autism and pervasive developmental disorder, and phobias and anxiety), leaving group overlap on 10 nominal conditions, plus write in space for "other"

Table 1
Parent and family characteristics.

Variable	High-risk (n = 69)	Low-risk (n = 108)
Mean (*SD*) child age (months)**	23.61 (7.13)	18.32 (9.36)
Percentage male children	67%	54%
Mean (*SD*) mothers age in years*	36.29 (4.24)	33.62 (4.44)
Percentage of mothers with college/university education	85%	91%
Percentage of mothers employed, other than or in addition to, homemaker*	62%	82%
Mean (*SD*) fathers age in years*	38.79 (5.01)	35.33 (4.76)
Percentage of fathers with college/university education	72%	67%
Percentages of fathers employed, other than or in addition to, homemaker	100%	96%
Mean (*SD*) annual family income (CDN$)*	$72178 (22465)	$84175 (21886)
Mean POEMS[a] total scores (*SD*)*	73.38 (19.84)	68.87 (9.36)
Mean POEMS no. elevated items (*SD*)*	2.66 (5.36)	1.03 (2.29)

* $p < .05$.
** $p < .001$, based on t -tests, Mann-Whitney (POEMS measures) and chi-square tests.
[a] Parent Observation of Early Markers Scale.

Table 2
Listed conditions in both versions of the FHQ and other conditions specified by parents under the three family history categories.

Medical		Developmental	Psychiatric
10 Common Listed Conditions			
• Epilepsy/seizures		• Attention deficit hyperactive disorder (ADHD)/attention deficit disorder (ADD) • Autism/Autism spectrum disorders • Developmental disabilities/Intellectual disabilities • Language disorders • Learning disabilities/Academic problems	• Anxiety disorder • Bipolar disorder ("manic depression") • Depression • Schizophrenia
Other Conditions Specified by Parents			
• Allergies • Alzheimer disease/early-onset dementia • Anemia • Arthritis • Asthma • Cancer (early onset - less than 50 years old) • Cerebral palsy • Diabetes (Type 1) • Eating disorders (Anorexia/ Bulimia) • Ehlers Danlos syndrome • Fibromyalgia • Gastrointestinal/bowel problems	• Hearing impairment • Lupus • Miscarriages (recurrent, spontaneous) • Multiple sclerosis (MS) • Neurofibromatosis • Phenylketonuria (PKU) • Skin disorders (e.g., eczema, psoriasis) • Thyroid problems • Tourette syndrome/tic disorder • Tuberous sclerosis • Vision Impairment	• Developmental coordination disorder • Down syndrome • Fragile X syndrome • Social problems (e.g., awkward, cold, withdrawn)	• Addiction/Substance abuse • Obsessive-compulsive disorder • Personality disorders • Phobias

conditions. Table 2 presents the list of the 10 conditions common to both questionnaires and other conditions that parents selected from the remaining conditions listed on the long-form version of the questionnaire or wrote in. Both formats asked parents about family history of all indicated conditions going back up to three generations from the child (i.e., great-grandparents). The family history conditions subsequently were organized into three categories – medical, developmental and psychiatric conditions (Brimacombe et al., 2007). Parents were instructed to complete the questionnaire based upon biological family members only, and each parent was encouraged to report the history of their side of the family. The FHQ included a question asking the respondent whether they were very knowledgeable, somewhat knowledgeable or not at all knowledgeable with the family history of the side(s) they were completing. FHQ scoring details are found in Section 3.2.

2.2.3. Parent observations of early markers scale

The Parent Observation of Early Markers Scale (POEMS) is a validated parent-report early screener that monitors the behavioral development of infants at risk for ASD (Feldman et al., 2012). The POEMS consists of 61 items for parents to score, using a 4-point response scale (with ½ scores allowed). The items cover core and subsidiary problem areas related to ASD for children 1–36 months of age. Core problems include social-communicative development, restricted interests and repetitive behaviors. Subsidiary problems include behaviors like sleeping, eating and tolerance often seen in young children with ASD. Total scores can range from 61 to 244 and a score of 3, 3.5 or 4 is considered an elevated item. The POEMS showed acceptable psychometric properties (Feldman et al., 2012). In a prospective study of 108 high-risk infant siblings, the POEMS had acceptable sensitivity (.74) and specificity (.73), and it was able to differentiate high-risk infants starting at age nine months who were independently diagnosed with ASD at 36 months of age, from those who were not (Feldman et al., 2012). A cross sectional study showed that high-risk infants demonstrated significantly more elevated POEMS items than age and gender-matched low-risk infants (Feldman et al., 2015).

2.3. Procedure

The parents completed the three questionnaires through email, mail, or telephone interviews. The POEMS was referred to as the generic name, Parent Observation Checklist (POC), for all participants. Parents were told that the study was about the development of second born or later children with different family histories. While mothers were asked to complete the maternal portion of the FHQ and fathers to complete the paternal portion, 93% and 94% of the full questionnaires were completed by the low- and high-risk group mothers, respectively (not significantly different). However, 90% of respondents said they were very knowledgeable of the history of both sides of the family.

3. Results

3.1. Analyses accommodations

To reduce group selection bias that potentially increased the number of family history conditions in the high-risk group, we

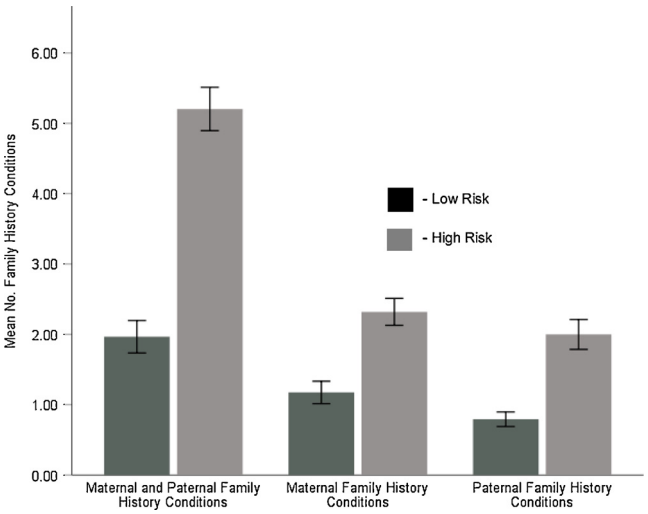

Fig. 1. Mean total number of family history problem comparisons (minus sibling and ASD history data) for low-risk (n = 108) and high-risk (n = 69) infants. Vertical lines in each bar are $\pm$ 1 Standard Error of the Mean.

removed sibling conditions from the family history data from both groups and ASD history from the high-risk group in the between-group comparisons and most of the correlations. We first tested normality of the distributions based on these exclusions. The Shapiro-Wilk test of normality indicated non-normal distributions for the POEMS total score, $SW = .65$, $df = 177$, $p < .001$; total POEMS elevated items, $SW = .48$, $df = 177$, $p < .001$; total number of family history problems, $SW = .92$, $df = 177$, $p < .001$; total number of family history problems on the maternal side, $SW = .87$, $df = 161$, $p < .001$; and the total number of family history problems on the paternal side, $SW = .82$, $df = 161$, $p < .001$. Due to the non-normal distributions, we used nonparametric analyses that do not require normal distributions.

3.2. Between group comparisons of the frequency of family history problems

FHQ items were categorized as belonging to the 10 common conditions or "extra" conditions (the "other" write in category in the short form and the additional items and write in's in the long form). To determine a family history frequency score for the 10 common conditions, if on the FHQ the parents indicated the same condition occurred on both sides of the family, then a frequency score of 2 was given. If the condition was only on one side of the child's family, then a score of 1 was given. The extra category was treated as the 11th condition, regardless of how many extra conditions were listed. For the extra conditions, any number of extra conditions indicated was only counted as one for each maternal and paternal side. When any extra conditions were reported for both maternal and paternal sides, a score of 2 was given, regardless of whether the extra conditions were the same or not on both sides of the family. If only one side had one or more extra conditions, then the extra score was 1. For example, if a family checked off or wrote in a history of allergies in the mother's family and a history of addiction in the father's family, then the extra score would be 2, regardless of how many more extra conditions were listed. Using this scoring system, family history condition total frequency scores could range from zero to 22. The actual range was zero to 14.

As seen in Fig. 1, consistent with the first hypothesis, the mean frequency of family history conditions was greater for high-risk infants than low-risk infants. Note that the displayed frequencies possibly under-estimate total family history conditions because they do not include the infants' siblings' conditions, family ASD history and multiple extra conditions. As the groups differed in child age (see Table 1), we used a simplified variation of Quade's (1967) distribution-free alternative to the parametric analysis of covariance (as cited in Olejnik & Algina, 1985, p. 56). The steps of this analysis involved (1) ranking the child age and number of family history variables; (2) creating a 0/1 group dummy variable; and (3) running a regression with the family history ranks as the dependent variable and ranked age and the group dummy variables as predictors. However, we also included a test for homogeneity of regression that is missing from Quade's approach by including the product of the ranked age and number of family history problems in the last step in the regression. This model yielded an Adjusted $R^2 = .29$. Only the group variable was significant, $t = 8.09$, $p < .001$, showing that a significant difference between the groups on the number of family history problems upheld despite group age differences. The lack of significance of the product indicated that the homogeneity of the regression assumption was not violated. Comparing groups on maternal number of family history problems (see Fig. 1) yielded an Adjusted $R^2 = .14$, with only the group variable being significant, $t = 4.99$, $p < .001$. Group comparison of paternal number of family history problems resulted in an Adjusted $R^2 = .13$, with only the group variable being significant, $t = 4.93$, $p < .001$.

Excluding sibling conditions and ASD history, whereas 64% of the low-risk group reported at least one problem, all but four (94%) of the high-risk group did so, χ^2 (11) = 57.54, $p < .001$. A significantly higher percentage of families in the high-risk group than the low-risk group reported medical: 77% versus 28%, χ^2 (1) = 37.19, $p < .001$; developmental: 61% versus 29%, χ^2 (1) = 16.00, $p < .001$; and psychiatric problems: 64% versus 49%, χ^2(1) = 3.52, $p < .05$, on at least one side of the family.

Table 3
Spearman correlations between number of family history problems and POEMS scores (sibling and ASD histories removed).

Measure	Total Number of Family History Problems	Number of Maternal Family History Problems	Number of Paternal Family History Problems
Both Groups Combined (N = 177)			
Total POEMS Score	.24**	.20**	.10
Total POEMS Elevated Items	.32**	.31**	.14*
Low-risk Group (n = 108)			
Total POEMS Score	.25**	.18*	.12
Total POEMS Elevated Items	.19*	.21*	.04
High-risk Group (n = 69)			
Total POEMS Score	.26*	.27*	.05
Total POEMS Elevated Items	.26*	.27*	.06

** p .01.
* $p < .05$.

3.3. Relationships between family history conditions and POEMS scores

As seen in Table 3, there was support of the second hypothesis using the 10 common and one extra condition scores. Significant positive Spearman correlations in the total sample as well as the separated low-risk and high-risk groups obtained on the number of family history problems (maternal and paternal sides combined and maternal only) and POEMS total scores and number of elevated items. Table 4 shows various significant Spearman correlations in the combined, low- and high-risk groups across the three history categories and POEMS scores.

3.4. Relationships between all family history conditions and POEMS scores

We examined total sample correlations with POEMS scores using all conditions indicated in Table 2. No significant relationships emerged in the Medical category. In the Developmental category, a combined maternal and paternal history of ASD was related to the number of elevated items, $\rho = .27$, $p < .001$. A combined history of language disorders was significantly correlated with POEMS total scores and number of elevated items, $\rho = .14$, $p < .05$, and $\rho = .20$, $p < .01$, respectively. Maternal history of language disorders and ADHD was significantly correlated with number of elevated items, $\rho = .18$, $p = .01$, $\rho = .14$, $p = .05$, respectively. In the Psychiatric category, a combined history of depression was related to POEMS total scores and number of elevated items, $\rho = .23$, $p < .01$, and $\rho = .25$, $p = .001$, respectively. Maternal history of depression was correlated with POEMS total scores and number of elevated items, $\rho = .26$, $p = .001$, and $\rho = .23$, $p = .001$, respectively. Combined history of bipolar disorder was related to POEMS total scores and number of elevated items, $\rho = .20$, $p < .01$, and $\rho = .25$, $p = .001$, respectively. Maternal history of bipolar disorder was correlated with POEMS total scores and number of elevated items, $\rho = .29$, $p < .001$, and $\rho = .29$, $p < .001$, respectively. A combined history of anxiety disorders was associated with the number of elevated items, $\rho = .15$, $p < .05$.

4. Discussion

As all the high-risk infants had older siblings with ASD, the finding that the high-risk group had more family history issues than the low-risk group (controlling for family history of ASD in the high-risk group) is consistent with previous research showing that

Table 4
Spearman correlations between number of family history medical, developmental and psychiatric problems and POEMS scores.

Measure	Medical			Developmental			Psychiatric		
	Combined	Maternal	Paternal	Combined	Maternal	Paternal	Combined	Maternal	Paternal
Both Groups Combined (N = 177)									
Total POEMS Score	.16*	.17*	.15*	.07	.09	.09	.18*	.18*	.05
Total POEMS Elevated Items	.31**	.30**	.26**	.11	.20**	.07	.22**	.21**	.05
Low-risk Group (n = 108)									
Total POEMS Score	.19*	.21*	.24*	.01	.06	−.002	.17	.10	.13
Total POEMS Elevated Items	.27**	.26**	.27**	−.09	.05	−.09	.19*	.14	.12
High-risk Group (n = 69)									
Total POEMS Score	.10	.11	.06	.10	.09	.16	.17	.27*	−.05
Total POEMS Elevated Items	.11	.11	.06	.17	.21*	.13	.18	.23*	−.10

** $p < .01$.
* $p < .05$.

various medical, developmental and neuropsychiatric conditions appear more frequently in families that have children with ASD (Brimacombe et al., 2007; Mostafa & Shehab, 2010). To the best of our knowledge, this is the first study to relate family history conditions to ASD screener scores in pre-diagnosed infants. The findings of positive relationships between the number of family history problems and both the total POEMS scores and the number of elevated items support research suggesting that there may be multiple susceptibility genes or an interaction of multiple genes and epigenetic mechanisms in the developmental pathway of ASD (Kozlowski, Matson, & Worley, 2012). As the developmental pathway of ASD does not follow a simple Mendelian form of genetic transmission and has not been linked to one single gene (Hall & Kelley, 2014), assessing the influence and genetic contributions of multiple family history conditions present in families may serve as a valuable tool to determining familial factors associated with the development of ASD. The interpretation of this prediction is nuanced by the findings of significant correlations between family history conditions and POEMS scores in the low-risk group (no family history of ASD). As the POEMS contains 61 items reflective of core features of ASD as well as subsidiary behaviors often seen in young children with ASD that are rated on severity, low-risk group correlations suggest that the POEMS may be sensitive to detecting small effects of family history on ASD markers in the general population that may predict susceptibility to ASD diagnosis or the broader autism phenotype.

Several specific family history conditions that were significantly correlated with POEMS scores – ASD, ADHD, language disorders, depression, bipolar disorder and anxiety - have been shown in previous research to be associated with current ASD and/or proposed similar underlying mechanisms (Brimacombe et al., 2007; Eriksson et al., 2012; Estes & McAllister, 2016; Gregory et al., 2009; Rai et al., 2013; Sullivan et al., 2012; van der Meer et al., 2012). It is possible that the mothers who had psychiatric conditions were more likely to score their infants higher on the POEMS. However, *post hoc* analyses found no significant differences in POEMS total scores and number of elevated items between mothers with and without psychiatric conditions.

There are several limitations to our study. Given the relatively small high-risk sample, we did not apply correction for multiple tests to reduce Type II error threat. Although low versus high-risk group demographic and POEMS scores differences were expected (Feldman et al., 2015), their influence on the family history measures and analyses is not clear. Whereas this study (as well as other family history studies) suggests certain promising mechanisms, this study did not include genetic testing and epigenetic evidence of family members to trace possible etiologic pathways to explain the relationships between a history of certain conditions and the POEMS scores. The fact that families in the high-risk group already had a child with ASD and the longer list of items in the high-risk FHQ could have elicited more research and recollection of family conditions than in the low-risk group. Conditions that sometimes are comorbid (e.g., depression and anxiety) or tend to occur more often in one sex than the other (e.g., depression, multiple sclerosis, fibromyalgia) may have influenced the relationships found; future research should explore these conditions and their relationship to POEMS scores. Finally, most of the analyses used only 11 conditions common to both the low and high-risk versions of the FHQ. However, many more conditions (as seen in Table 2) were captured in the high-risk Spearman correlations reported in Section 3.4.

5. Implications

This study provides further evidence of the relationship of family history conditions and ASD, including possible early signs in infants. Both early screening practice and research could relatively easily gather family history information that may increase risk prediction and uncover etiological factors. Future research could include expanding the sample size and list of family history conditions, and genetic and epigenetic testing to trace possible etiologic pathways to ASD.

Conflict of interest

The authors declare that they have no conflict of interests.

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