REVIEW

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The relative contributions of genetic and non-genetic factors to the risk of neuroblastoma

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ABSTRACT

Previous literature has well-established genetic factors as being associated with neuroblastoma (NB). About 1%–2% of NB cases are familial, with 85% of these cases predisposed to mutations in the *PHOX2B* and *ALK* genes. The genetic basis of sporadic NB has been studied through genome-wide association studies and next-generation sequencing approaches. Particularly, germline variants, as well as copy number variations, confer increased risks of NB, often with effect estimates ≥1.5, underscoring the strong genetic contributions to NB. However, the strength of the association varied in non-genetic factors. Some risk factors, such as birth defects, maternal illicit drug use, and early infections, had relatively stronger associations (effect estimates ≥1.5 or ≤0.67), while some other factors remain inconclusive. This suggests that certain non-genetic factors may play a more prominent role in NB risk, while further research is needed to clarify the impact of others. We synthesized and critically evaluated existing literature on the risk factors of NB to provide an overview, analyze the current state of knowledge, and outline a research path to address the relative contributions of genetic and non-genetic factors in NB. Future epidemiologic studies should incorporate novel methods for measuring genetic and non-genetic factors to comprehensively assess the full extent of factors contributing to NB. Furthermore, the utilization of dried blood spots holds promise to overcome technical and recruitment challenges for future studies. These strategies will contribute to a more holistic understanding of NB etiology and potentially lead to improved prevention strategies.

KEYWORDS
Environment, Epidemiology, Etiology, Genetics, Neuroblastoma, Non-Genetics

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INTRODUCTION

Neuroblastoma (NB) is the most frequently diagnosed extracranial cancer among infants, accounting for approximately 5% of all cancers in patients under the age of 19 years.[1] Because NB contributes to 15% of pediatric cancer deaths,[2] growing research has been conducted to understand the etiology of NB over the last few decades. However, mainly due to the rarity of NB incidence, our understanding of its etiology remains limited. One particularly critical aspect that necessitates exploration is the extent of genetic and non-genetic contributions to NB development. NB epidemiology research has traditionally relied on case-control studies that examined non-genetic factors.[3] With the advancement in genetic analysis in recent years, researchers have increasingly incorporated genetic factors into their investigations, enhancing our understanding of the molecular causes contributing to NB etiology. However, there have been few studies that assessed both non-genetic and genetic factors associated with NB. A study published in 2008 reviewed epidemiologic studies associated with NB,[3] while other studies focused on genetic aspects without reviewing non-genetic factors.[4–7] Thus, the aim of this study was to provide an updated narrative review of the relative contributions of both genetic and non-genetic factors in NB and outline a research path to address these complex issues.

DESCRIPTIVE EPIDEMIOLOGY

Incidence

About 90% of NB cases are diagnosed in children under 5 years of age.[8] The incidence rates widely vary among countries, with less than five new patients per year in Abidjan, Lubumbashi, Lomé, and Ouagadougou,[9] compared to 700–800 new patients per year in the United States.[10] Hubbard et al.[11] analyzed the international cancer incidence data from 1988 to 2012 and found increasing trends, particularly in high-income countries. However, low- and middle-income countries may face underestimation of NB cases due to underdiagnoses,[12] highlighting the need for etiologic research to establish prevention strategies.

Staging and survival

To address the heterogeneity in clinical outcomes in NB patients, substantial efforts have been made to establish international consensus on staging systems and risk stratification. The International NB Risk Group Staging System employed image-defined risk factors to classify pre-treatment patients into stages L1, L2, M, or MS.[13] Localized tumors were classified into either stages L1 or L2, in consideration of image-defined risk factors.[13] In contrast, metastatic tumors were classified into stage M, except for stage MS, which can regress spontaneously.[13] In addition to the International NB Risk Group Staging System staging, several prognostic factors, including age at diagnosis, tumor histology, grade of tumor differentiation, DNA index (ploidy), *MYCN* amplification status, and chromosome aberrations at 1p and 11q were integrated to categorize patients into low-, intermediate-, and high-risk groups.[13] The risk classification system was validated, using event-free survival and overall survival rates.[13]

As expected, survival rates vary depending on the risk groups. According to the Children's Oncology Group risk classification system, the event-free survival for low-risk NB was nearly 98%, while the event-free survival for intermediate-risk NB was over 85%. High-risk NB presented a considerably lower event-free survival, at approximately 50%.[13] In fact, high-risk NB remains one of the deadliest types of childhood cancer. Approximately 50% of new cases are diagnosed with high-risk NB.[14]

PRENATAL ORIGIN OF NB

Previous studies have suggested that neural crest cells, which can develop into sympathetic ganglion cells and adrenal catecholamine-secreting chromaffin cells, serve as the cell of origin for NB.[15] Neural crest cells arise around the fourth week of gestation and begin to migrate to form diverse types of differentiated cells, including primitive cells of the peripheral nervous system, around the fifth week of gestation.[15] Thus, NB can develop anywhere along the sympathetic nervous system but most commonly develops in the adrenal medulla.[4]

The prenatal diagnosis of NB substantiates the hypothesis that NB originates *in utero*. NB can be diagnosed prenatally via sonograph; when this occurs most diagnoses happen in the third trimester.[16] Additionally, congenital NB, diagnosed within the first month of age, accounts for 5% of total annual NB cases.[17] The short latency between birth and diagnosis strongly suggests that congenital NB originates *in utero*.

Case reports of twins with concordant NB provide further support for the prenatal origin of NB. Six reports documented that one twin manifested an identifiable primary tumor, while the other manifested metastatic NB without a recognizable primary tumor.[18,19] This suggests that metastatic NB cases may have arisen due to fetoplacental metastasis.[18,19] Furthermore, three cases out of the six cases presented molecular and genetic markers that support the prenatal origin of NB. The first study demonstrated similar histology and genetics in twins, thereby indicating the metastasis of NB between twins during gestation.[18] Another study illustrated twins who shared similar histology but had different genetic markers.[19] Yet, the authors proposed the prenatal origin of NB, suggesting that precancerous cells from a twin with primary NB metastasized

via the placenta during fetal development to the other twin. Subsequently, a second genetic event occurred postnatally in the other twin, leading to the development of histologically similar but genetically different NB.[19]

GENETIC CONTRIBUTION

Since NB initiates *in utero*, etiologic research on NB has mainly focused on inherited genetics or perinatal exposures. Current evidence strongly supports significant genetic contributions to NB development. It is well-studied that germline variants contribute to the development of NB, as pediatric cancers, including NB, are characterized by low somatic mutation frequencies.[20,21] Furthermore, recent studies have identified that germline copy number variations (CNVs) can increase the risk of NB. Therefore, our focus is on germline variants and CNVs in understanding the etiology of NB.

Cancer predisposition genes and syndromes associated with NB

Germline whole genome sequencing and whole exome sequencing have implicated that approximately 14% of NB patients had germline pathogenic and likely pathogenic variants in cancer predisposition genes.[22] Those genes include *ALK*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *EZH2*, *NF1*, *PALB2*, *PHOX2B*, *PTPN11*, *SDHA*, *SDHB*, *SMARCA4*, *and TP53*.[20–28]

Additional rare variants, which possibly confer increased risks of NB, have been identified in association with various genetic syndromes.[29–34] For instance, an epidemiologic study estimated a standardized incidence ratio for NB in children with Noonan syndrome who harbored *PTPN11* variants to be 10.8 (95% confidence interval [CI]: 0.3–59.9). Generally, the estimated relative risk of NB for carriers of rare germline variants has ranged from approximately over 50.[35]

Familial NB

Familial NB displays different patterns compared to sporadic NB concerning age at diagnosis and the extent of the tumor. Familial NB patients are likely to be diagnosed at a younger age and tend to have multifocal tumors.[36] Studies of NB pedigrees have revealed an autosomal dominant inheritance pattern with incomplete penetrance,[36,37] underlining the heritability of NB.

The first gene discovered for familial NB was the paired-like homeobox 2B (*PHOX2B*) gene[29,38] and the second gene discovered for familial NB was the anaplastic lymphoma kinase (*ALK*) gene.[36,39,40] Combined, mutations in the *PHOX2B* and *ALK* genes account for about 85% of familial NB cases.

Studies have also suggested the involvement of other genes, including *KIF1Bβ* and *GALNT14* genes,[41,42] envisaging the potential existence of additional genes that could contribute to the increased risk of NB within families. These findings further underscored the significant role of genetic factors in the development of familial NB. However, it is essential to note that familial NB only accounts for 1%–2% of all NB cases,[4–7] indicating that the root causes of the majority of NB cases are still not fully understood.

Sporadic NB

To address this gap in knowledge, genome-wide association studies (GWAS) have identified several germline single nucleotide polymorphisms (SNPs) in patients without a family history of NB.[5–7] Maris et al.[43] published the first GWAS on NB with 720 cases and 2128 controls in 2008. Additional samples were collected from predominantly European patients to validate the previously identified loci and discover novel ones. To date, common germline variants in genes such as *CASC15*, *BARD1*, *LMO1*, *MMP20*, *HSD17B12*, *DUSP12*, *IL31RA*, *DDX4*, *HACE1*, *LIN28B*, *NEFL*, *CDKN1B*, *MLF1/RSRC1*, *KIF15*, and *CPZ* have been associated with NB in European populations.[43–57] Among them, variants in genes including *CASC15*, *BARD1*, *LMO1*, *MMP20*, and *KIF15* were associated with high-risk group.[43,45–51,56] Additionally, studies focusing on African American populations found associations with *BARD1*, *SPAG16*, *CRIM1*, and *TMEM72-AS1*.[58–60] Taken together, GWAS have reported that most of the effect sizes of SNPs in NB were larger than 1.5, even when using relatively small sample sizes, underscoring the strong genetic contributions to NB.[5–7]

In addition to common germline variants, CNVs have been suggested in association with NB susceptibility. A genome-wide study found a common deletion at 1q21.1 in a discovery set of 846 Caucasian NB patients and 803 healthy Caucasian controls, and this deletion was shown to be transmissible in an independent set of 713 cancer-free trios.[61] Within the CNV, a novel transcript highly similar to NB breakpoint family genes was identified.[61] Furthermore, a rare deletion at 16p11.2 was found to predispose individuals to NB in multi-ethnic cohorts including 5585 children with NB and 23 505 cancer-free control children.[62] The odds ratio (OR) for this association was 13.9 (95% CI: 5.8–33.4).[62] Finally, in a study that included 40 pediatric cancer patients recruited between 2016 and 2018, *SLFN11* deletion, *SOX4* duplication, and *PARK2* partial deletion were observed in three NB patients.[63]

Despite these findings, it remains possible that additional germline variants and CNVs play a role in influencing the risk of NB, emphasizing the need for further research to better define the genetic architecture of NB.

TABLE 1 Summary of findings for non-genetic factors associated with neuroblastoma

Suggestive evidence of risk factors	Suggestive evidence of protective factors	Inconclusive factors
Strong association:	Strong association:	Fertility treatment
Maternal medication use	Early infection to chickenpox, mumps, German measles, and red measles	Supplement use
Hyperemesis gravidarum	Daycare attendance & breastfeeding	Maternal hypertension
Birth defects	Weak association:	Pre-eclampsia
Maternal illicit drug use	Birth order	Maternal migraine
Weak association:		Maternal exposure to second-hand smoke
Male sex		Parental occupational exposure to electromagnetic fields
Advanced maternal age		
Advanced paternal age		
Higher maternal education		
Maternal (nutritional) anemia		
High birth weight		
Pre-term birth		
Maternal smoking		
Maternal alcohol use		
Paternal occupational exposure to pesticides		
Maternal exposure to pollutants		

A weak association is indicated when the effect estimate is either between 1 and 1.5 or between 0.67 and 1.
A strong association is indicated when the effect estimate is either greater than or equal to 1.5 or less than 0.67.

NON-GENETIC CONTRIBUTION

Given that sporadic NB cases are predominant, it supports that non-genetic factors play a role in modifying the risk of malignant transformation in NB, in addition to genetics. However, the evidence supporting the association between non-genetic factors and the risk of NB is less robust compared to genetic factors. It is essential to acknowledge that most epidemiologic studies utilized case-control study designs and were conducted predominantly in high-income countries.[3] Additionally, these studies mainly relied on questionnaires or interviews to gather information about risk factors. Thus, self-reporting bias, recall bias, and social desirability bias could have influenced the findings. To overcome the limitations inherent in single epidemiologic studies, we have included meta-analysis studies where possible. Table 1 presents a summary of the findings between non-genetic factors and the risk of NB, based on the literature reviewed.

Demographic factors

Sex

A study that utilized data from the Surveillance, Epidemiology, and End Results Program demonstrated an elevated incidence rate ratio for males (1.13, 95% CI: 1.07–1.19) compared to females.[64] The disparity in incidence can derive from sex-specific gene expressions and genetic variations linked to the X chromosome.[65,66] Furthermore, sex differences in innate and adaptive immune responses due to sex chromosome genes, sex hormones, and environmental mediators may contribute to the disparity.[67]

Interestingly, a US population-based study estimated that 35% of the association between sex and the risk of NB was mediated through birth defects.[68] Birth defects, specifically congenital heart defects, are thought to share a developmental origin and genetic predisposition with NB.[57,69] Considering that males were at a higher relative risk for congenital heart defects,[70] the genetic pleiotropy between NB and congenital heart defects warrants further investigations.

Parental age

Advanced maternal age was associated with an increased risk of NB. A meta-analysis, including 18 studies, reported a suggestive association between maternal age and the risk of NB in children (OR: 1.05, 95% CI: 0.99–1.12).[71]

There has been less research examining the association between paternal age and the risk of NB in children. The pooled analysis that identified the positive linear trend between maternal age and the risk of NB reported an OR of 1.06 (95% CI: 1.01–1.11) for each 5-year increment in paternal age.[72] However, the association became non-significant after adjusting for maternal age.[72] The authors of the study[72] concluded that, despite the lack of an independent association between paternal age and the risk of NB when maternal age was taken into account, maternal age was unlikely to be an isolated risk factor for NB, primarily due to the high correlation between maternal and paternal ages (Pearson's correlation coefficient 0.74). The positive associations between parental age and the risk of NB may be linked to the increased risk of *de novo* chromosomal abnormalities and germline variants associated with advanced parental age.[73]

Socio-economic status

A meta-analysis of six studies generally revealed decreased odds of NB among children born to women with lower levels of education (OR for maternal education less than high school: 0.66, 95% CI: 0.43–1.01; OR for maternal education with high school: 0.74, 95% CI: 0.31–1.75; OR for maternal education more than high school: 0.78, 95% CI: 0.33–1.85).[74] Another study reported that higher maternal education may increase the risk of NB (OR: 1.09, 95% CI: 0.94–1.26).[75] However, the same study found that a higher neighborhood socio-economic status (SES) did not elevate the risk of NB (OR: 0.93, 95% CI: 0.81–1.08).[75] These findings imply that higher maternal education may be associated with a risk of NB. However, because SES can be measured in various ways, further investigations are warranted to explore these associations more comprehensively.

Perinatal factors

Fertility treatment

A meta-analysis of three studies using a random-effects model observed an elevated relative risk for the association between medically assisted reproduction and the risk of NB (OR: 1.45, 95% CI: 0.69–3.05).[76] A pooled analysis conducted in France also reported no significant but positive association between stimulation and the risk of NB (OR: 1.2, 95% CI: 0.6–2.3).[77] Given studies that have investigated medically assisted reproduction and the risk of NB relied on questionnaires or interviews to gather information about the history of medication use for infertility treatment,[76] further study is warranted to draw a conclusion.

ORs for *in vitro* fertilization in the pooled analysis conducted in France were also not significant.[77] Furthermore, a study that evaluated the association between *in vitro* fertilization and the risk of NB in the US, involving 47 cases resulting from *in vitro* fertilization and 260 cases not associated with *in vitro* fertilization, reported a non-statistically significant hazard ratio of 1.10 (95% CI: 0.74–1.65).[78]

Supplement use

In many high-income countries, it is recommended that pregnant women take multivitamins with folic acid during the perinatal period to prevent neural tube defects in offspring. Because folic acid deficiency can interfere with the differentiation and development of neural crest cells, folic acid intake may help prevent NB development.[79] In fact, NB incidence in Ontario decreased from 1.57 cases per 10 000 to 0.62 cases per 10 000 following the fortification of cereals with folic acid.[80] A meta-analysis encompassing two studies demonstrated that the use of prenatal multivitamins during pregnancy could be a protective factor for the risk of NB (OR: 0.53, 95% CI: 0.42–0.68).[81] Furthermore, a pooled analysis conducted in France found an association between maternal use of any supplement containing folic acid, vitamins, or minerals in the three months before conception and a reduced risk of NB (OR: 0.5, 95% CI: 0.3–0.9).[77]

Against expectations, a registry-based study in Norway reported no significant association between periconceptional folic acid levels and the risk of NB, with a hazard ratio of 1.05 (95% CI: 0.53–2.06).[82] Furthermore, no significant association was observed between folate transport or metabolism-related maternal and offspring SNPs and the risk of NB.[83] Given that nearly 97% of pregnant women reported taking prenatal vitamins,[84] of which typically include folic acid, the combinations of various vitamins and minerals can complicate the associations, making them inconclusive.

Maternal medication use

Two studies reported a significant increase in the risk of NB in children whose mothers used diuretics or other antihypertensives during pregnancy.[85,86] Additionally, the use of nervous system medications, categorized as "other analgesics and antipyretics" according to the World Health Organization Anatomical Therapeutic Chemical code, was associated with an increased risk of NB in children (OR: 1.99, 95% CI: 1.07–3.69).[87] Furthermore, the use of nitrosatable prescription medications during pregnancy was associated with an increased risk of NB (OR: 1.96, 95% CI: 1.34–2.85).[88] Consistent reporting of medication groups according to the Anatomical Therapeutic Chemical code, if possible, would facilitate a more targeted investigation into the potential associations between specific medication groups and NB, shedding light on their specific mechanisms on NB etiology.

Maternal health conditions

Previous studies hypothesized that hypoxia could play a role in NB development.[89] Thus, maternal health conditions that are known to cause fetal hypoxia, including hypertension, preeclampsia, and anemia, can be associated with NB development. Epidemiologic studies have investigated the association between these health conditions and the risk of NB.

For maternal hypertension, an increased risk for NB was suggested.[90] Studies have also suggested that preeclampsia was associated with an increased risk of NB.[91] However, there is a possibility of reverse causation for patients diagnosed at a younger age (i.e. less than 6 months old) where undiagnosed NB could manifest

maternal hypertension.[91] Thus, sensitivity analyses for older age groups are warranted.

An increased risk was observed in children born to mothers with anemia.[92,93] When the analysis was stratified by non-nutritional anemia and nutritional anemia, it became evident that nutritional anemia significantly increased the risk of childhood cancer in children.[92,93] These findings underscore the importance of distinguishing between the types of anemia in research to gain a more comprehensive understanding of underlying factors in NB etiology.

For other maternal health conditions, morning sickness and maternal migraine have been examined in relation to the risk of NB in children. A study found an increased risk for NB with hyperemesis gravidarum (OR: 2.52, 95% CI: 1.00–6.36),[94] One study also associated NB with maternal migraine (OR: 1.75, 95% CI: 1.00–3.08).[95]

Birthweight and gestational weeks

Multiple studies have assessed the associations between birth characteristics and the risk of NB. In a meta-analysis that examined the association between birthweight and the risk of NB, it was found that children born with high birthweight (>4000 g) had an OR of 1.19 (95% CI: 1.04–1.36).[96] Furthermore, a linear trend emerged in a sensitivity analysis, showing that for each 1000 g increase in birthweight for children born above 2500 g, the risk of NB increased by 13% (95% CI: 3–25).[96]

Preterm birth (born <37 weeks of gestation) displayed a non-significant and weak association with the risk of NB (OR: 1.09; 95% CI: 0.90–1.32) according to a meta-analysis of five studies.[97] This finding aligns with previous studies associated high birth weight with a higher risk of NB.

Early life infections and immunity

Several factors related to early-life infections and immune system development have been associated with the risk of NB. Birth order, which influences early-life exposure to infectious agents, was associated with a decreased risk of NB for the 4th or higher birth order in a pooled analysis (OR: 0.68, 95% CI: 0.55–0.84).[98] Daycare attendance has been associated with increased infection exposure. Moreover, breastfeeding has been known for building a strong immune system. In comparison to non/occasional breastfeeding, breastfed children had a lower risk of NB (OR: 0.59, 95% CI: 0.44–0.81), and the duration of breastfeeding was associated with a reduced risk of NB (OR for longest vs. shortest breastfeeding: 0.61, 95% CI: 0.44–0.83).[99] Taken together, children who attended daycare ≥6 months and were breastfed over 6 months had a decreased risk for NB (OR: 0.36, 95% CI: 0.16–0.81).[100] Lastly, a history of early-life infectious diseases (chickenpox, mumps, German measles, and red measles) also reduced the risk of NB (OR: 0.60, 95% CI: 0.39–0.93).[100] These findings suggest that the risk of NB may be influenced by the activation of the child's immune response, as shown in the excess risk in males for NB.

Birth defects

As stated earlier, birth defects have shown a strong association with the risk of NB. A study involving over 10 million live births from 1992 to 2013 supported these findings, showing that birth defects in multiple organ systems increased the risk of NB.[101] Specifically, the risk of NB substantially increased when individuals had cardiac and genitourinary defects (OR for left ventricular outflow tract defects: 7.8, 95% CI: 3.5–17.3; OR for atrial septal defect: 3.6, 95% CI: 2.6–5.1; OR for patent ductus arteriosus: 3.9, 95% CI: 2.5–6.2; OR for obstructive genitourinary defects: 4.6, 95% CI: 2.8–7.4).[101] Because NB was associated with non-chromosomal structural birth defects, it is important to examine the pathway through which genetic and non-genetic factors during pregnancy can jointly contribute to the risks of birth defects and NB. As NB and congenital cardiac anomalies both involve the improper migration of neural crest cells[102] and possibly share common genetic susceptibility,[57] they could result from genetic or epigenetic factors during embryonal and fetal development.

Environmental factors

Parental occupational exposures

Numerous parental occupational exposures were evaluated for the association with the risk of NB. One of the well-studied risk factors was pesticides. The finding of a meta-analysis did not support that paternal occupational exposure to pesticides was a significant risk factor for NB (OR: 1.07, 95% CI: 0.79–1.45).[103] However, the analysis did not specify the type of pesticides, and more detail is necessary to investigate potential associations between specific pesticide types and the risk of NB.

Even though radiation is a known risk factor for many types of childhood cancer, studies did not find an association between parental exposure to either high-frequency (ionizing) or low-frequency (non-ionizing) electromagnetic fields and the risk of NB in children.[104] These findings were consistent with prior evidence suggesting a low probability of genotoxicity from electric and magnetic field exposure.[105]

Exposure to tobacco, alcohol, illicit drug use, and pollution

A meta-analysis, which included 17 studies, suggested a non-significant but positive association between tobacco use during pregnancy and the risk of NB (OR: 1.08, 95% CI: 0.96–1.22).[106]

Paternal smoking has received less attention in research compared to maternal smoking. A pooled analysis conducted in France reported that paternal smoking a year before a child's birth was not significantly associated with the risk of NB (OR: 1.1, 95% CI: 0.9–1.4).[107]

Regarding maternal alcohol consumption, a meta-analysis, which included eight studies, showed a non-significant but positive association between maternal alcohol consumption during pregnancy and the risk of NB (OR: 1.01, 95% CI: 0.82–1.18).[106]

Although parental smoking and maternal alcohol consumption did not show a significant increase in the risk of NB, factors, such as recall bias, selection bias, social desirability bias, and varying response rates, could have contributed to lower estimates.[108] In addition, survivor bias may have further led to an underestimation in the analyses.[109,110]

A study in North America demonstrated that the use of any illicit drugs one month before pregnancy, including marijuana, cocaine or crack, heroin, hallucinogens, and simulants, was associated with an elevated risk of NB in children (OR: 1.82, 95% CI: 1.13–3.00).[111] Another study conducted in Minnesota also supported the association between the use of any illicit drugs during pregnancy and an increased risk of NB (hazard ratio: 5.72, 95% CI: 2.32–14.1).[112] Interestingly, another study also reported that opioid agonist intake was related to NB (OR: 2.4, 95% CI: 1.3–4.3).[113]

Emerging evidence suggests an association between exposure to environmental pollutants and the risk of NB. A California-based study included children who lived within specific radii around an air pollutant monitor. The findings indicated that the odds of being diagnosed with NB increased with each interquartile increment in prenatal exposure to total polycyclic aromatic hydrocarbons (OR: 1.39, 95% CI: 1.01–1.91).[114] Among other air pollutants, carbon tetrachloride exposure was associated with an elevated risk of NB (OR: 7.87, 95% CI: 1.37–45.34).[114]

The prenatal period is particularly susceptible to epigenetic modifications as DNA methylation undergoes reprogramming during this phase.[115] For instance, hyper- and hypomethylation can lead to chromosomal instability and aberrant gene expression, including the silencing of tumor suppressor genes and the overexpression of oncogenes.[116] Thus, exposure to environmental hazards including smoking, second-hand smoking, alcohol, illicit drugs, and pollutants during the prenatal period can induce epigenetic changes associated with an increased risk of NB.

FUTURE RESEARCH AGENDA

While ideal research would involve conducting a cohort study with first-degree relatives of NB cases to evaluate the relative contributions between genetics and shared environment, the rarity of NB makes this approach impractical. Thus, genomic and metabolomic data embedded within an epidemiologic study is necessary to maximize the risk assessment. For instance, a case-parent trio study that investigates maternal/paternal exposures to non-genetic risk factors for germline *de novo* mutations can be conducted to elucidate NB etiology.

An alternative source for a case-parent trio study is newborn dried blood spots (DBS). DBS are routinely collected among newborns within 24–48 hours of birth across many states to screen for various genetic diseases.[117] Some states offer residual DBS for research purposes. Utilizing DBS provides several advantages for epidemiologic studies because DBS is less susceptible to storage conditions than urine or blood samples, allows population-based studies, and can be linked to data from many state registries to account for potential confounding factors. In addition, as demonstrated in childhood leukemia studies, DBS is a valuable resource to investigate genetic and non-genetic risk factors around the perinatal period.[118] The information derived from DBS can be used to assess the relative contributions of genetic and non-genetic factors in NB etiology.

In particular, the information derived from DBS can be used to quantify the relative contributions of genetic and non-genetic risk factors to high-risk NB patients. For instance, the integration of metabolomics and genomics has the potential to allow us to evaluate the relative contributions of genetic and non-genetic factors for the development of high-risk NB. Similarly, genetic instruments can be used to explore the causal relationship between non-genetic risk factors (i.e., birthweight) and the risk of high-risk NB. The findings can provide actionable risk factors that benefit at-risk populations and reduce NB-related mortality through early surveillance and detection.

CONCLUSION

Although many studies have examined the effects of genetic and non-genetic factors on the risk of NB, the relative contributions of genetic and non-genetic risk factors to the risk of NB remain obscure. Genomic and metabolomic data embedded in epidemiologic studies are warranted for more

robust risk assessment. In particular, newborn DBS can provide a rich resource to perform a population-based study for identifying the relative contributions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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