Published in final edited form as:

Ann Epidemiol. 2018 August ; 28(8): 521–528. doi:10.1016/j.annepidem.2018.04.005.

The Role of Parental and Perinatal Characteristics on Langerhans Cell Histiocytosis: Characterizing Increased Risk among Hispanics

Erin C. Peckham-Gregory, PhD^{a,b}, Kenneth L. McClain, MD, PhD^{a,b}, Carl E. Allen, MD, PhD^{a,b,c}, Michael E. Scheurer, PhD^{a,b}, and Philip J. Lupo, PhD^{a,b}

^aDepartment of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, One Baylor Plaza, MS: BCM305, Houston, Texas 77030, USA

^bTexas Children's Cancer Center, Texas Children's Hospital, Feigin Center, 1102 Bates St, Houston, Texas 77030, USA

^cProgram in Translational Biology and Molecular Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA

Abstract

Purpose—Potential roles of inherited and environmental risk factors in pathogenesis of Langerhans cell histiocytosis (LCH), a myeloid neoplastic disorder, are undefined. We therefore evaluated the role of parental and perinatal factors on the risk of this childhood cancer.

Methods—Information on LCH cases (n=162) for the period 1995–2011 was obtained from the Texas Cancer Registry. Birth certificate controls were frequency-matched on year of birth at a ratio of 10:1 for the same period. Variables evaluated included parental age, race/ethnicity, size for gestational age, and birth order. Logistic regression was used to generate an adjusted odds ratio (aOR) and 95% confidence interval (CI) testing the association between each factor and LCH.

Results—Few perinatal or parental factors were associated with LCH risk, with the exception of race/ethnicity. Mothers of Hispanic ethnicity were more likely to have children who developed LCH compared to non-Hispanic whites (aOR: 1.51; 95% CI: 1.02–2.25). This risk increased when both parents were Hispanic (aOR: 1.80; 95% CI: 1.13–2.87). Non-Hispanic black mothers were suggested as less likely to give birth to offspring who developed LCH compared to non-Hispanic whites (aOR: 0.50; 95% CI: 0.24–1.02).

Correspondence should be addressed to: Philip J. Lupo, Ph.D., M.P.H., Baylor College of Medicine, Department of Pediatrics, Section of Hematology-Oncology, One Baylor Plaza, MS: BCM305, Houston, Texas 77030, Phone: 1-713-798-2960, Fax: 1-713-798-8711, Philip.Lupo@bcm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest

The authors have no conflicts of interest to disclose.

Conclusions—LCH is characterized by somatic mutations in MAPK pathway genes in myeloid precursors. Increased risk for LCH in children of Hispanic parents suggests potential impact of inherited factors on LCH pathogenesis.

Keywords

Epidemiology; Langerhans Cell Histiocytosis; Race/ethnicity; Risk Factors; Texas Cancer Registry

Introduction

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia and the most common of all the histiocytic disorders.¹ While LCH may occur at any age, the median age at diagnosis is 30 months with an estimated incidence of 5 cases per 1,000,000 children ages 0–14.² Incidence is highest in infants less than one year, and decreases steadily with increasing age.³ Despite a relatively high 5-year survival rate of ~85% for patients with hematopoietic organ involvement and ~99% for multisystem patients without risk organ involvement,^{4, 5} upfront chemotherapy fails in over 50% of cases. Higher risk of long-term sequelae associated with treatment failure includes potential for progressive LCH-associated neurodegenerative disease.^{5, 6} In addition to challenges associated with treatment, children with LCH experience high relapse rates, nearing 50% within the first two years and over 40% of those experience a second relapse event.⁷ These characteristics underscore the need to identify risk predictors for the prevention of pediatric LCH and improved understanding of mechanisms of pathogenesis.

As with many pediatric cancers, few well-established risk factors for LCH exist. In LCH, mutually exclusive *MAPK* pathway activating somatic mutations have been identified in approximately 85% of cases, and ERK activation is universal in LCH dendritic cells.^{8, 9} However, random acquisition of cell-specific somatic mutations may not completely explain LCH pathogenesis. As in other pediatric cancers (e.g. B-cell acute lymphoblastic leukemia)¹⁰ the incidence of LCH appears to vary by race/ethnicity, which suggests a role for inherited genetic factors in LCH susceptibility.^{11–13} Additionally, maternal and neonatal infections^{13, 14} and lack of childhood vaccinations¹⁴ are suspected to increase LCH risk. Notably, there have been several studies evaluating the role of maternal and perinatal characteristics on other pediatric hematologic malignancies to determine the impact of inborn variation on disease risk.^{15–17} However, there have been few population-based efforts to determine the role of these factors on the risk of LCH. Therefore, we leveraged one of the world's largest population-based cancer registries to evaluate the role of parental and perinatal characteristics on the risk of developing pediatric LCH in a state characterized by a growing and diverse population.

Material and methods

Study design and participant ascertainment

We performed a case-control study to investigate the role of parental and perinatal characteristics on LCH susceptibility. Our case eligibility criteria included being born in

Texas between the years 1995–2011 and being diagnosed with LCH during the same time period. The Texas Cancer Registry (TCR) provided information on the cases ($n = 162$) who fulfilled these criteria. Based on this, our case population included children and adolescents up to 16 years of age, which captured the most at-risk age groups in terms of those who present with LCH.^{2, 3} The TCR is one of the world's largest, statewide population-based cancer registries and during the study period was "Gold Certified" by the North American Association of Central Cancer Registries.¹⁸ The selection of LCH histologic subtypes in this study was based on the most recent version of ICD-O3 histologic codes (ICD-O3) with malignant behavior and included Langerhans cell histiocytosis, not otherwise specified (9751/3) and Langerhans cell histiocytosis, disseminated (9754/3). Given a previous debate as to whether LCH was an inflammatory disorder or myeloid neoplasia, LCH cases reported to the Surveillance Epidemiology and End Results (SEER) registry prior to 2009 would most likely include those with high-risk organ involvement sites (spleen, liver, and bone marrow).

Data on case, parental, and perinatal characteristics were obtained from Texas birth certificates that were probabilistically-linked and provided by the Center for Health Statistics (CHS), Texas Department of State Health Services. Approximately 87% of LCH cases registered in the TCR for children and adolescents born and diagnosed in the period of 1995–2011 were successfully linked to Texas birth records by the CHS. Eligibility criteria for controls included being born in Texas during 1995–2011 without a history of cancer during that same time period. Parental and perinatal characteristic data for all children born in Texas who fulfilled these criteria served as the eligibility pool from which controls were selected. As with cases, eligible controls were between the ages of 0–16. We randomly selected 10 non-cancer controls per case matched on year of birth using a random-number generator ($n = 1,620$). The Institutional Review Boards at Baylor College of Medicine and the Texas Department of State Health Services approved this study.

Parental and perinatal variables

Data obtained from birth records for cases and controls included: infant sex; date of birth; birthweight in grams; plurality (singleton and 2); maternal and paternal age (<20, 20–24, 25–29, 30–35, and 35 years); maternal and paternal race/ethnicity (non-Hispanic White [NHW], Hispanic [Hisp], non-Hispanic Black [NHB], and non-Hispanic other [NHO]); maternal education (<high school, high school, and >high school); maternal nativity (United States [US], Mexico, and other foreign country); residence at time of delivery in a county on the US-Mexico border (vs. not); urban or rural residence at delivery identified by 2000 census tract data; history of other live births (1, 2, and 3); maternal smoking history during pregnancy (yes or no); mode of delivery (vaginal spontaneous, vaginal forceps or vacuum, and cesarean); history of infant Hepatitis B vaccination prior to hospital discharge (yes or no); and term of birth (pre- and early-term defined as <39 weeks, full term defined as 39–41 weeks, and late-term defined as 41 weeks). Season of birth was based on birthdate and classified as spring, summer, fall, or winter based on solstice and equinox dates. Birth records for cases and controls also provided the date last normal menses began (LMP) and clinical estimate of gestation in weeks. LMP was used to determine the gestational age for most births.^{19, 20} However, if the LMP date was missing or there was an absolute difference

greater than 2 weeks between the LMP date and clinical estimate of gestational age, the clinical estimate was used per established guidelines.^{19, 21} If both LMP date and clinical estimate of gestational age were missing, that birth was excluded from the gestational age-specific analyses. Births were classified as small-for gestational-age (SGA) if the birthweight was <10th percentile for their gestational age, or large-for-gestational-age (LGA) if the birthweight was >90th percentile for their gestational age. These estimates were based on 2009–2010 US live birth data stratified by infant sex.²²

Maternal pre-pregnancy body-mass index (BMI) was calculated from 2005–2011 birth records since maternal height and weight was only collected from 2005 onward. A subgroup analysis tested for an association between maternal BMI and pediatric LCH. History of the infant being breastfed prior to hospital discharge was also only available in birth records from 2005 onward (yes or no). To generate a combined parental race/ethnicity variable representative of both maternal and paternal race/ethnicity, we used maternal and paternal race (white, black, other) and ethnicity (e.g., of Hispanic origin, yes or no) data to categorize each parent as non-Hispanic white (NHW), non-Hispanic black (NHB), non-Hispanic other (NHO), and Hispanic (regardless of race; Hisp). We then combined maternal race/ethnicity and paternal race/ethnicity to generate a parental race/ethnicity variable for each possible parental combination. Due to sparse data concerns regarding some of the possible combinations (e.g., NHW/NHO parental race/ethnicity $n = 2$), we opted to evaluate those categories with an adequate number of subjects, including: NHW/NHW, NHW/NHB, NHB/NHB, NHW/Hisp, and Hisp/Hisp parental race/ethnicity combinations.

Statistical Analysis

Unconditional logistic regression was used to evaluate the association between various parental and perinatal characteristics obtained from vital records and the risk of the LCH. Each parental or perinatal characteristic of interest served as the exposure in each analysis. First, we generated odds ratios (OR) and 95% confidence intervals (CI) to evaluate the association between each characteristic and LCH, adjusting only for the matching variable: year of birth. We then calculated an adjusted OR (aOR) including other independent variables if they were: a) differentially distributed between cases and controls at $P < 0.05$; and b) identified as important predictors of LCH in the literature. These covariates included: maternal race/ethnicity (reference = non-Hispanic white), infant sex (reference = male), and the matching variable birth year. To control for acculturation effects when evaluating the associations between maternal, paternal, and parental race/ethnicity and LCH, we opted to adjust for maternal nativity (reference = US), residence in one of 14 counties along the US-Mexico border (reference = no), in addition to infant sex (reference = male), and birth year. When estimating the association between paternal race/ethnicity and LCH risk, we adjusted for those variables included in the maternal and parental race/ethnicity estimations, and additionally adjusted for maternal race/ethnicity (reference = non-Hispanic white). All analyses were conducted in Stata 13.1 (StataCorp LP, College Station, Texas).

Results

Some parental characteristics were associated with pediatric LCH in this study population (Table 1). While not statistically significant, mothers who were less than 20 years of age at delivery were more likely to have offspring who developed LCH compared to mothers who were 20–24 years of age (aOR: 1.65; 95% CI: 0.98–2.77). In terms of maternal race/ethnicity, non-Hispanic black mothers were less likely to give birth to offspring who developed LCH compared to non-Hispanic white mothers (aOR: 0.50; 95% CI: 0.24–1.02). Similarly, non-Hispanic black fathers were significantly less likely to have offspring who developed LCH (aOR: 0.23; 95% CI: 0.05–0.98). Conversely, Hispanic mothers were at significantly increased risk of giving birth to offspring who developed LCH compared to non-Hispanic white mothers (aOR: 1.51; 95% CI: 1.02–2.25). No association was observed between Hispanic fathers and LCH risk among offspring. Mothers who were born in Mexico compared to the US were marginally suggested as less likely to give birth to offspring who developed LCH after adjusting for maternal race/ethnicity (aOR: 0.69; 95% CI: 0.43–1.11). Further, mothers who resided in one of 14 Texas counties along the US-Mexico border at time of infant birth were suggested as less likely to give birth to offspring who developed LCH (aOR: 0.56; 95% CI: 0.31–1.03).

The association between selected combined parental race/ethnicity categories and pediatric LCH risk in Texas is displayed in Figure 1. Notably, parental race/ethnicity was strongly associated with pediatric LCH. Children born of two Hispanic parents were at a significantly increased risk of developing LCH compared to children born of two non-Hispanic white parents (aOR: 1.80; 95% CI: 1.13–2.87; *P*-for-trend = 0.01).

In this study population, perinatal characteristics were not strongly associated with LCH risk (Table 2). Females were suggested as being less likely to develop LCH (aOR: 0.81; 95% CI: 0.59–1.13). Those children pre- or early-term were suggested as more likely to develop LCH in unadjusted analyses (OR: 1.28; 95% CI: 0.90–1.81), however this association was attenuated when adjusting for maternal race/ethnicity, infant sex, and birth year (aOR: 1.24; 95% CI: 0.88–1.76). No other associations between perinatal characteristics and LCH risk were identified.

Discussion

Maternal and parental race/ethnicity were highly associated with LCH risk in this population-based assessment. No perinatal characteristics were identified that strongly influenced LCH risk, although females were marginally suggested as less likely to develop LCH. This aligns with previous studies that have reported a slight predominance of male LCH cases.^{3, 23}

There have been a handful of US-based epidemiologic studies of LCH, few of which have focused on LCH risk or outcome differences by race/ethnicity (Table 3). Solvent exposure, family history of benign tumors, maternal urinary tract infections during index pregnancy, and feeding problems or blood transfusions during infancy were associated with increased LCH risk in one study of 177 LCH cases.²⁴ Another assessment among 459 LCH cases

found that thyroid disease in a case or a family history of thyroid disease were highly associated with LCH, as were postnatal exposures including infections, diarrhea and vomiting.¹⁴ Infection during infancy was also associated with an increased risk of LCH in a smaller study comprised of 60 LCH cases, as were having a family history of cancer, or parental occupational exposure to metal, granite, or wood dust.¹³ Lack of childhood immunizations was associated with increased LCH risk in a few studies.^{13, 14} In a recent SEER study of 145 cases, LCH risk was higher in areas with low educational levels and in counties with a high proportion of overcrowded households. Specifically, LCH incidence according to crowding level was higher among Hispanics compared to non-Hispanics.¹²

According to the same SEER study, Hispanics experience higher age-standardized LCH incidence rates compared to non-Hispanics among those ages 0–19 (RR = 1.63, 95% CI: 1.15–2.29). For Hispanic LCH cases who were diagnosed under 1 year of age, an increased risk compared to non-Hispanics was also observed (RR = 1.83, 95% CI: 1.03–3.24). This SEER study also reported that blacks experience lower age-standardized LCH incidence rates compared to whites (RR = 0.41, 95% CI: 0.18–0.81), a result that was also more pronounced among those diagnosed less than 1 year of age: (RR = 0.24, 95% CI: 0.03–0.91).¹² An additional study conducted at Children’s Hospital Los Angeles (CHLA) reported a higher proportion of Hispanic cases compared to white cases in their study population (53% versus 18%, respectively), and a lower proportion of black cases compared to white cases (0% versus 18%, respectively).¹³ In another SEER study that assessed all pediatric Histiocytic disorders in unison, white children had a higher incidence compared with blacks, $P < 0.05$. In this same study, asian and/or Pacific Islander or Native American descent had the highest rates of LCH.¹¹ While no comment regarding disparities in risk by race/ethnicity were noted in a study by Bhatia, et al., 96.5% of their 459 LCH cases were white versus 92.0% of community controls, while 1.6% of cases were black versus 4.6% of community controls.¹⁴

The findings of this study along with previous reports^{11–13} repeatedly identify Hispanic ethnicity as a risk factor for developing LCH. Hispanics also experience higher rates of other *MAPK* pathway driven malignancies including papillary thyroid carcinoma²⁷ and melanoma²⁸ compared to other minority groups. In this study, we noted that Hispanic mothers were at significantly increased risk of giving birth to offspring who developed LCH compared to NHW mothers. Additionally, NHB mothers and fathers were less likely to give birth to offspring who developed LCH compared to NHW counterparts. When we assessed combined parental race/ethnicity, those children born from two Hispanic parents were at a substantially increased risk of developing LCH compared to those children born from two NHW parents, consistent with previous studies.^{12, 13} Risks of several pediatric cancers are documented to differ across racial/ethnic backgrounds, including that children of mixed ancestry tend to have risks that align more closely with those of racial/ethnic minority children than NHW children.²⁹

The etiology of LCH is unclear, and historically LCH was attributed to immune dysregulation from environmental or other early life exposures (e.g., infection). It is possible that early life exposures may explain the emerging differences in risk observed across racial/ethnic groups. As noted in Venkatramani et al., infection during infancy and lack of

childhood vaccines increased LCH risk in a predominately Hispanic population.¹³ However, these findings were also noted in the study by Bhatia, et al., that had a study population of mostly white cases.¹⁴ Another early life exposure, household crowding, has been described to increase LCH risk, and this association was more pronounced among Hispanics.¹² However, these early life and environmental exposures may not completely explain the incidence differences across all racial/ethnic groups. Like Hispanics, blacks are at higher risk of adverse early life and environmental exposures and yet are at decreased risk of LCH. Differences in genetic substructure across racial/ethnic groups may therefore be another contributing risk factor.

Risks of other pediatric hematologic malignancies differ across racial/ethnic group; differences attributed, at least in part, to the underlying genetic risk factors of each population. As example, Hispanics have a 10%–30% higher acute lymphoblastic leukemia (ALL) incidence than do NHWs, and a rate twice higher than NHBs.^{30, 31} Hispanics also experience a lower 5-year survival rate and are at a higher risk of relapse than NHWs.^{32, 33} ALL risk differences across racial/ethnic groups may be due to differences in underlying genetic risk factors, as exemplified by the finding that Amerindian ancestry could account for increased incidence and decreased survival among Hispanics.³³ Genome-wide association studies (GWAS) have identified genetic risk variants that increase ALL risk and occur with a higher frequency in Hispanics compared to NHWs.^{34, 35} To evaluate the role of underlying genetic risk factors on LCH susceptibility, our research group recently completed a GWAS of LCH and identified a variant within the gene *SMAD6* associated with increased LCH risk (*SMAD6*rs12438941 summary OR = 3.72; 95% CI: 2.54–5.44; P = 1.29×10^{-11}).³⁶ Notably, in 1000 Genomes Phase 3 data³⁷ the *SMAD6*rs12438941 (A) risk allele is more common in Mexican ancestral (0.25) and Peruvian (0.36) populations compared to those of African ancestry [Americans of African Ancestry in Southwest US (0.04); Gambian (0.00); and Nigerian (0.00)], which supports the differences in LCH risk across racial/ethnic groups observed in the current study.

In this study, children born to mothers who resided along the US-Mexico border at time of infant birth were suggested as less likely to develop LCH. There is evidence that cancer diagnoses are oftentimes underreported and made at later stages in the rural US or along the US-Mexico border.^{38, 39} Along the border, there is also a regional shortage of cancer specialists.^{39, 40} As LCH oftentimes presents as a skin rash similar to cradle cap, it is possible that only the most severe cases would have been captured as having a tumorigenic source. However, as children born to mothers of Mexican nativity were also suggested as less likely to develop LCH compared to children born to US-born mothers, it is possible that the observed association is truly a reflection of differences in risk factors (i.e., genetic substructure or environmental exposures), or perhaps another example of the Hispanic paradox, where infants born to Hispanic immigrants often have better outcomes compared to non-Hispanic whites or Hispanics born in the US.^{41, 42}

The findings reported in this study should be considered in light of certain limitations. Provided these data are based on birth records, we were limited in regards to the information available for assessment. Specifically, we were unable to investigate how observed associations would be influenced if other suspected risk predictors of LCH, like maternal

infections during pregnancy, were taken into account. Also, we were limited in our assessment of paternal race/ethnicity in particular as this data was missing on 14.8% of birth certificates. Additionally, there is the potential for underreporting of LCH cases in earlier registry years as only disseminated LCH cases were considered reportable to cancer registries prior to 2009, and these were more likely to include cases with higher-risk organ site involvement (spleen, liver, bone marrow). These factors may limit the generalizability to less severe cases of LCH. Further, if controls were more likely to move due to known/suspected (i.e., socioeconomic factors¹²) or unknown risk predictors of LCH compared to cases, our control population may not have truly reflected the underlying source population of Texas. However, recent studies exploring the impact of residential mobility on exposure assessment indicate most individuals who move often stay in the same region or county.^{43–45} Finally, parental and perinatal data for this assessment were obtained from birth certificates rather than questionnaires. However, data from Texas birth certificates have been used in several previous assessments^{46–49} and have been demonstrated to be relatively complete and accurate compared to data obtained from questionnaires and medical records.^{50, 51} As result of these limitations, these study findings would benefit from validation in a larger assessment to further delineate the role of parental and perinatal risk factors on pediatric LCH risk.

This study does have several strengths. A gap in the literature regarding LCH descriptive epidemiologic studies has been noted in LCH publications over the years.^{3, 13, 24} Not only does this study help to fill that gap, this study also represents one of the largest population-based linkage studies to investigate epidemiologic risk factors for the prevention of pediatric LCH. Further, only a limited number of studies have investigated risk factors related to parental and perinatal characteristics and pediatric LCH. Moreover, this study is one of few evaluations among an ethnically and racially diverse population;^{12, 13, 26} a unique study asset as exemplified by the lack of such studies in Table 3. The majority of previous studies have reported associations among relatively homogenous groups (i.e., French, English, Nordic or East Asian cohorts).^{2–4, 23, 52} Thus, the ability to investigate a diverse population may have allowed for specific high-risk subgroups to be identified that would have remained unobserved in a homogenous population. The potential for selection bias was also limited given the record-based, randomized control selection. Finally, utilizing registry-based data helped evade misclassification bias due to self-reported estimates.

In this population-based evaluation, maternal and parental race/ethnicity were associated with LCH risk. These results add to growing evidence that LCH risk is higher among Hispanics, and suggest specific subgroups that may be more susceptible to pediatric LCH in the US. As LCH is characterized by somatic mutations in MAPK pathway genes in myeloid precursors,^{53, 54} the increased risk for LCH in children of Hispanic parents observed here suggests the potential impact of inherited factors on LCH pathogenesis.

Acknowledgments

Cancer data have been provided by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, 1100 West 49th Street, Austin, TX 78756, <http://www.dshs.state.tx.us/tcr/default.shtm>, or (512) 776–3080.

Role of the funding source

The funding sponsors had no involvement in any portion of the study design, data collection, analysis, interpretation of data, writing of the report, or decision to publish this study. The corresponding authors confirm that they had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Funding sources

This work was supported by the National Institutes of Health Training Program in Pediatric Cancer Epidemiology and Control [R25 CA160078 awarded to MES]; Alex's Lemonade Stand Foundation Epidemiology Grant [awarded to PJJ]; American Society of Hematology Scholar Award in Clinical Research [awarded to EPG]; and the Thrasher Research Fund Early Career Award Program Grant [awarded to EPG].

List of abbreviations

LCH	Langerhans cell histiocytosis
aOR	adjusted odds ratio
CI	confidence interval
TCR	Texas Cancer Registry
SEER	Surveillance Epidemiology and End Results program
NHW	non-Hispanic white
Hisp	Hispanic
NHB	non-Hispanic black
NHO	non-Hispanic other
US	United States
LMP	date last normal menses began
SGA	small for gestational age
LGA	large for gestational age
BMI	body-mass index
OR	odds ratio
CHLA	Children's Hospital Los Angeles
ALL	acute lymphoblastic leukemia
GWAS	genome-wide association study

References

- 1 Berres ML, Merad M, Allen CE. Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X? *Br J Haematol*. 2015; 169:3–13. [PubMed: 25430560]
- 2 Alston RD, Tatevossian RG, McNally RJ, Kelsey A, Birch JM, Eden TO. Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1998. *Pediatr Blood Cancer*. 2007; 48:555–60. [PubMed: 16652350]

- 3Guyot-Goubin A, Donadieu J, Barkaoui M, Bellec S, Thomas C, Clavel J. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000–2004. *Pediatr Blood Cancer*. 2008; 51:71–5. [PubMed: 18260117]
- 4Chow TW, Leung WK, Cheng FWT, Kumta SM, Chu WCW, Lee V, Shing MMK, Li CK. Late outcomes in children with Langerhans cell histiocytosis. *Arch Dis Child*. 2017; 102:830–5. [PubMed: 28442470]
- 5Gadner H, Minkov M, Grois N, Pötschger U, Thiem E, Aricò M, Astigarraga I, Braier J, Donadieu J, Henter J-I, Janka-Schaub G, McClain KL, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. *Blood*. 2013; 121:5006–14. [PubMed: 23589673]
- 6Haupt R, Nanduri V, Calevo MG, Bernstrand C, Braier JL, Broadbent V, Rey G, McClain KL, Janka-Schaub G, Egeler RM. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society-Late Effects Study Group. *Pediatr Blood Cancer*. 2004; 42:438–44. [PubMed: 15049016]
- 7Minkov M, Steiner M, Pötschger U, Aricò M, Braier J, Donadieu J, Grois N, Henter J-I, Janka G, McClain K, Weitzman S, Windebank K, et al. Reactivations in Multisystem Langerhans Cell Histiocytosis: Data of the International LCH Registry. *The Journal of Pediatrics*. 2008; 153:700–5.e2. [PubMed: 18589441]
- 8Chakraborty R, Burke TM, Hampton OA, Zinn DJ, Lim KP, Abhyankar H, Scull B, Kumar V, Kakkar N, Wheeler DA, Roy A, Poulikakos PI, et al. Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis. *Blood*. 2016; 128:2533–7. [PubMed: 27729324]
- 9Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, Kuo FC, Ligon AH, Stevenson KE, Kehoe SM, Garraway LA, Hahn WC, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood*. 2010; 116:1919–23. [PubMed: 20519626]
- 10Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Vergara X, Kheifets L. Race/ethnicity and the risk childhood leukemia: a case-control study in California. *J Epidemiol Community Health*. 2015; 69:795–802. [PubMed: 25792752]
- 11Golpanian S, Tashiro J, Gerth DJ, Thaller SR. Pediatric histiocytoses in the United States: incidence and outcomes. *J Surg Res*. 2014; 190:221–9. [PubMed: 24766726]
- 12Ribeiro KB, Degar B, Antoneli CB, Rollins B, Rodriguez-Galindo C. Ethnicity, race, and socioeconomic status influence incidence of Langerhans cell histiocytosis. *Pediatr Blood Cancer*. 2015; 62:982–7. [PubMed: 25586293]
- 13Venkatramani R, Rosenberg S, Indramohan G, Jeng M, Jubran R. An exploratory epidemiological study of Langerhans cell histiocytosis. *Pediatr Blood Cancer*. 2012; 59:1324–6. [PubMed: 22434707]
- 14Bhatia S, Nesbit ME Jr, Egeler RM, Buckley JD, Mertens A, Robison LL. Epidemiologic study of Langerhans cell histiocytosis in children. *J Pediatr*. 1997; 130:774–84. [PubMed: 9152288]
- 15Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and Family Risk Factors for Non-Hodgkin Lymphoma in Early Life: A Swedish National Cohort Study. *J Natl Cancer Inst*. 2012; 104:923–30. [PubMed: 22623506]
- 16Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and Family Risk Factors for Hodgkin Lymphoma in Childhood Through Young Adulthood. *Am J Epidemiol*. 2012; 176:1147–58. [PubMed: 23171883]
- 17Oksuzyan S, Crespi CM, Cockburn M, Mezei G, Kheifets L. Birth weight and other perinatal characteristics and childhood leukemia in California. *Cancer Epidemiol*. 2012; 36:e359–e65. [PubMed: 22926338]
- 18Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. [Accessed May 5, 2015] The source of cancer data in Texas <http://www.dshs.state.tx.us/tcr/default.shtm>. Published 2015
- 19Wier ML, Pearl M, Kharrazi M. Gestational age estimation on United States livebirth certificates: a historical overview. *Paediatr Perinat Epidemiol*. 2007; 21:4–12.
- 20Sprehe MR, Barahmani N, Cao Y, Wang T, Forman MR, Bondy M, Okcu MF. Comparison of Birth Weight Corrected for Gestational Age and Birth Weight Alone in Prediction of Development of Childhood Leukemia and Central Nervous System Tumors. *Pediatr Blood Cancer*. 2010; 54:242–9. [PubMed: 19813253]

- 21Hoffman CS, Messer LC, Mendola P, Savitz DA, Herring AH, Hartmann KE. Comparison of gestational age at birth based on last menstrual period and ultrasound during the first trimester. *Paediatr Perinat Epidemiol*. 2008; 22:587–96. [PubMed: 19000297]
- 22Talge NM, Mudd LM, Sikorskii A, Basso O. United States Birth Weight Reference Corrected For Implausible Gestational Age Estimates. *Pediatrics*. 2014; 133:844–53. [PubMed: 24777216]
- 23Stålemark H, Laurencikas E, Karis J, Gavhed D, Fadeel B, Henter J-I. Incidence of Langerhans cell histiocytosis in children: A population-based study. *Pediatr Blood Cancer*. 2008; 51:76–81. [PubMed: 18266220]
- 24Hamre M, Hedberg J, Buckley J, Bhatia S, Finlay J, Meadows A, Nesbit M, Smithson A, Robison L. Langerhans cell histiocytosis: an exploratory epidemiologic study of 177 cases. *Med Pediatr Oncol*. 1997; 28:92–7. [PubMed: 8986144]
- 25Glass AG, Miller RW. U.S. mortality from Letterer-Siwe disease, 1960–1964. *Pediatrics*. 1968; 42:364–7. [PubMed: 5663744]
- 26Jubran RF, Marachelian A, Dorey F, Malogolowkin M. Predictors of outcome in children with Langerhans cell histiocytosis. *Pediatr Blood Cancer*. 2005; 45:37–42. [PubMed: 15768381]
- 27Weeks KS, Kahl AR, Lynch CF, Charlton ME. Racial/ethnic differences in thyroid cancer incidence in the United States, 2007–2014. *Cancer*. 2018; 0
- 28Wu X-C, Eide MJ, King J, Saraiya M, Huang Y, Wiggins C, Barnholtz-Sloan JS, Martin N, Cokkinides V, Miller J, Patel P, Ekwueme DU, et al. Racial and ethnic variations in incidence and survival of cutaneous melanoma in the United States, 1999–2006. *J Am Acad Dermatol*. 2011; 65:S26.e1–S.e13. [PubMed: 22018064]
- 29Chow EJ, Puumala SE, Mueller BA, Carozza SE, Fox EE, Horel S, Johnson KJ, McLaughlin CC, Reynolds P, Von Behren J, Spector LG. Childhood cancer in relation to parental race and ethnicity: a five-state pooled analysis. *Cancer*. 2010; 116:3045–53. [PubMed: 20564410]
- 30Walsh KM, de Smith AJ, Welch TC, Smirnov I, Cunningham MJ, Ma X, Chokkalingam AP, Dahl GV, Roberts W, Barcellos LF, Buffler PA, Metayer C, et al. Genomic ancestry and somatic alterations correlate with age at diagnosis in Hispanic children with B-cell ALL. *Am J Hematol*. 2014; 89:721–5. [PubMed: 24753091]
- 31Yamamoto JF, Goodman MT. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997–2002. *Cancer Causes Control*. 2008; 19:379–90. [PubMed: 18064533]
- 32Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA*. 2003; 290:2008–14. [PubMed: 14559954]
- 33Yang JJ, Cheng C, Devidas M, Cao X, Fan Y, Campana D, Yang W, Neale G, Cox NJ, Scheet P, Borowitz MJ, Winick NJ, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. *Nat Genet*. 2011; 43:237. [PubMed: 21297632]
- 34Perez-Andreu V, Roberts KG, Harvey RC, Yang W, Cheng C, Pei D, Xu H, Gastier-Foster J, E S, Lim JY, Chen IM, Fan Y, et al. Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse. *Nat Genet*. 2013; 45:1494–8. [PubMed: 24141364]
- 35Archer NP, Perez-Andreu V, Stoltze U, Scheurer ME, Wilkinson AV, Lin T-N, Qian M, Goodings C, Swartz MD, Ranjit N, Rabin KR, Peckham-Gregory EC, et al. Family-based exome-wide association study of childhood acute lymphoblastic leukemia among Hispanics confirms role of ARID5B in susceptibility. *PLoS One*. 2017; 12:e0180488. [PubMed: 28817678]
- 36Peckham-Gregory EC, Chakraborty R, Scheurer ME, Belmont JW, Abhyankar H, Sengal AG, Scull BP, Eckstein O, Zinn DJ, Mayer L, Shih A, Merad M, et al. A genome-wide association study of LCH identifies a variant in SMAD6 associated with susceptibility. *Blood*. 2017; 130:2229–32. [PubMed: 28935696]
- 37NCBI 1000 Genomes Browser, Phase 3 May 2013 call set, 2013:Ancestral Population Data for *SMAD6*rs12438941.
- 38Ko E, Zuniga ML, Palomino H, Peacher D, Watson M. Qualitative Study of Latino Cancer Patient Perspectives on Care Access and Continuity in a Rural, U.S.-Mexico Border Region. *J Immigr Minor Health*. 2017

- 39 Monroe AC, Ricketts TC, Savitz LA. Cancer in Rural Versus Urban Populations: A Review. *The Journal of Rural Health*. 1992; 8:212–20. [PubMed: 10121550]
- 40 Palomino H, Peacher D, Ko E, Woodruff SI, Watson M. Barriers and Challenges of Cancer Patients and Their Experience with Patient Navigators in the Rural US/Mexico Border Region. *J Cancer Educ*. 2017; 32:112–8. [PubMed: 26362872]
- 41 Camacho-Rivera M, Kawachi I, Bennett GG, Subramanian SV. Revisiting the Hispanic Health Paradox: The Relative Contributions of Nativity, Country of Origin, and Race/Ethnicity to Childhood Asthma. *Journal of Immigrant and Minority Health*. 2014; 17:826–33.
- 42 Page RL. Positive Pregnancy Outcomes in Mexican Immigrants: What Can We Learn? *Journal of Obstetric, Gynecologic & Neonatal Nursing*. 2004; 33:783–90.
- 43 Urayama KY, Von Behren J, Reynolds P, Hertz A, Does M, Buffler PA. Factors Associated With Residential Mobility in Children With Leukemia: Implications For Assigning Exposures. *Ann Epidemiol*. 2009; 19:834–40. [PubMed: 19364662]
- 44 Lupo PJ, Symanski E, Chan W, Mitchell LE, Waller DK, Canfield MA, Langlois PH. Differences in exposure assignment between conception and delivery: the impact of maternal mobility. *Paediatr Perinat Epidemiol*. 2010; 24:200–8. [PubMed: 20415777]
- 45 Canfield MA, Ramadhani TA, Langlois PH, Waller DK. Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. *J Expos Sci Environ Epidemiol*. 2006; 16:538–43.
- 46 Danysh HE, Zhang K, Mitchell LE, Scheurer ME, Lupo PJ. Maternal residential proximity to major roadways at delivery and childhood central nervous system tumors. *Environ Res*. 2016; 146:315–22. [PubMed: 26802618]
- 47 Kumar S, Lupo P, Pompeii L, Danysh H. Maternal Residential Proximity to Major Roadways and Pediatric Embryonal Tumors in Offspring. *Int J Environ Res Public Health*. 2018; 15:505.
- 48 Marengo L, Farag NH, Canfield M. Body Mass Index and Birth Defects: Texas, 2005–2008. *Maternal and Child Health Journal*. 2013; 17:1898–907. [PubMed: 23371247]
- 49 Peckham-Gregory EC, Danysh HE, Brown AL, Eckstein O, Grimes A, Chakraborty R, Lubega J, McClain KL, Allen CE, Scheurer ME, Lupo PJ. Evaluation of maternal and perinatal characteristics on childhood lymphoma risk: A population-based case-control study. *Pediatr Blood Cancer*. 2016 n/a-n/a.
- 50 Tinker SC, Carmichael SL, Anderka M, Browne ML, Conway KMC, Meyer RE, Nembhard WN, Olney RS, Reefhuis J. Next steps for birth defects research and prevention: The birth defects study to evaluate pregnancy exposures (BD-STEPS). *Birth Defects Research Part. A: Clinical and Molecular Teratology*. 2015; 103:733–40. [PubMed: 25846741]
- 51 Tinker SC, Gibbs C, Strickland MJ, Devine OJ, Crider KS, Werler MM, Anderka MT, Reefhuis J. Impact of Time to Maternal Interview on Interview Responses in the National Birth Defects Prevention Study. *Am J Epidemiol*. 2013; 177:1225–35. [PubMed: 23645625]
- 52 Morimoto A, Ishida Y, Suzuki N, Ohga S, Shioda Y, Okimoto Y, Kudo K, Ishii E. Nationwide survey of single-system single site Langerhans cell histiocytosis in Japan. *Pediatr Blood Cancer*. 2010; 54:98–102. [PubMed: 19728332]
- 53 Chakraborty R, Hampton OA, Shen X, Simko SJ, Shih A, Abhyankar H, Lim KP, Covington KR, Trevino L, Dewal N, Muzny DM, Doddapaneni H, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood*. 2014; 124:3007–15. [PubMed: 25202140]
- 54 Nelson DS, van Halteren A, Quispel WT, van den Bos C, Bovee JV, Patel B, Badalian-Very G, van Hummelen P, Ducar M, Lin L, MacConaill LE, Egeler RM, et al. MAP2K1 and MAP3K1 mutations in Langerhans cell histiocytosis. *Genes Chromosomes Cancer*. 2015; 54:361–8. [PubMed: 25899310]

Highlights

- In this population-based study, parental race/ethnicity was associated with LCH.
- These results add to evidence that LCH risk is higher among Hispanics in the US.
- LCH is characterized by somatic mutations in *MAPK* genes in myeloid precursors.
- This increased risk among Hispanic children suggests impact of inherited factors.

Figure 1. Association between parental race/ethnicity and risk of LCH

Odds ratios adjusted for birth year, child's sex, maternal nativity, and residence on Mexican border.

Odds ratio (OR); confidence interval (CI); Non-Hispanic white (NHW); Hispanic (Hisp); and non-Hispanic black (NHB).

Table 1

Associations between parental characteristics and risk of pediatric LCH in Texas, 1995–2011

Parental Characteristics and LCH	Cases (<i>n</i>)	Controls (<i>n</i>)	OR (95% CI) ^a	aOR (95% CI) ^b
Maternal Age				
Less than 20 years of age	30	243	1.69 (1.01–2.83)	1.65 (0.98–2.77)
20–24	34	465	Reference (1.00)	Reference (1.00)
25–29	47	430	1.50 (0.94–2.37)	1.45 (0.91–2.31)
30–35	34	319	1.46 (0.89–2.40)	1.38 (0.83–2.29)
35 and above	17	163	1.43 (0.78–2.63)	1.37 (0.74–2.54)
Paternal Age				
Less than 20 years of age	9	101	1.03 (0.48–2.22)	0.80 (0.32–1.99) ^c
20–24	32	269	1.37 (0.83–2.28)	1.48 (0.84–2.62)
25–29	34	393	Reference (1.00)	Reference (1.00)
30–35	41	330	1.44 (0.89–2.32)	1.29 (0.77–2.17)
35 and above	26	284	1.06 (0.62–1.81)	0.95 (0.50–1.78)
Unknown	20	243		
Maternal Race/Ethnicity				
Non-Hispanic White	58	615	Reference (1.00)	Reference (1.00) ^d
Non-Hispanic Black	9	195	0.49 (0.24–1.00)	0.50 (0.24–1.02)
Hispanic	89	772	1.20 (0.84–1.70)	1.51 (1.02–2.25)
Non-Hispanic Other	8	58	1.47 (0.67–3.24)	1.88 (0.77–4.57)
Paternal Race/Ethnicity				
Non-Hispanic White	56	552	Reference (1.00)	Reference (1.00) ^e
Non-Hispanic Black	7	139	0.50 (0.22–1.11)	0.23 (0.05–0.98)
Hispanic	77	640	1.19 (0.83–1.70)	1.30 (0.72–2.33)
Non-Hispanic Other	3	44	0.67 (0.20–2.23)	---
Unknown	19	245		
Maternal Education				
<High School	51	474	1.09 (0.71–1.66)	1.01 (0.66–1.57)
High School	45	455	Reference (1.00)	Reference (1.00)
>High School	65	681	0.96 (0.65–1.44)	0.97 (0.64–1.46)
Unknown	1	10		
Maternal Nativity				
US Born	122	1,185	Reference (1.00)	Reference (1.00)
Mexico	28	306	0.89 (0.58–1.37)	0.69 (0.43–1.11)
Other Foreign Country	12	126	0.93 (0.50–1.72)	0.71 (0.35–1.43)
Unknown	0	3		
Residence on Mexican Border				
No	149	1,419	Reference (1.00)	Reference (1.00)
Yes	13	183	0.68 (0.38–1.22)	0.56 (0.31–1.03)
Unknown	0	18		

Parental Characteristics and LCH	Cases (n)	Controls (n)	OR (95% CI) ^a	aOR (95% CI) ^b
Maternal Residence				
Urban	143	1,390	Reference (1.00)	Reference (1.00)
Rural	7	68	1.00 (0.45–2.22)	0.99 (0.45–2.22)
Unknown	12	162		
Pre-Pregnancy BMI (2005–2011)				
Underweight (<18.5)	6	30	1.93 (0.75–4.94)	1.91 (0.74–4.91)
Normal (18.5–24.99)	38	364	Reference (1.00)	Reference (1.00)
Overweight (25–29.99)	18	153	1.13 (0.62–2.04)	1.13 (0.62–2.04)
Obese (≥30)	7	145	0.46 (0.20–1.06)	0.46 (0.20–1.06)
Unknown	1	8		
Maternal Smoking During Pregnancy				
No	153	1,503	Reference (1.00)	Reference (1.00)
Yes	7	99	0.69 (0.32–1.52)	0.72 (0.32–1.59)
Unknown	2	18		

n, Number of cases or controls;

^a Adjusted for birth year;

^b Adjusted for birth year, maternal race/ethnicity, and child's sex unless otherwise noted;

^c Adjusted for birth year, maternal race/ethnicity, child's sex, and maternal age;

^d Adjusted for birth year, child's sex, maternal nativity, and residence on Mexican border;

^e Adjusted for birth year, child's sex, maternal nativity, residence on Mexican border, and maternal race/ethnicity.

Table 2

Associations between perinatal characteristics and risk of pediatric LCH in Texas, 1995–2011

Perinatal Characteristics and LCH	Cases (<i>n</i>)	Controls (<i>n</i>)	OR (95% CI) ^a	aOR (95% CI) ^b
Sex of Child				
Male	91	827	Reference (1.00)	Reference (1.00) ^c
Female	71	793	0.81 (0.59–1.13)	0.81 (0.59–1.13)
Size for Gestational Age				
Small	21	217	0.97 (0.60–1.58)	0.95 (0.58–1.55)
Appropriate	124	1,246	Reference (1.00)	Reference (1.00)
Large	16	133	1.21 (0.70–2.10)	1.16 (0.67–2.01)
Unknown	1	24		
Birth order				
1 st	133	1,295	Reference (1.00)	Reference (1.00)
2 nd	19	218	0.85 (0.51–1.40)	0.87 (0.53–1.45)
3 rd	9	85	1.03 (0.51–2.10)	1.09 (0.53–2.22)
Unknown	1	22		
Plurality				
Singleton	157	1,567	Reference (1.00)	Reference (1.00)
2	5	53	0.94 (0.37–2.39)	0.92 (0.36–2.34)
Term of Birth				
Pre- & Early Term (<39 weeks)	76	672	1.28 (0.90–1.81)	1.24 (0.88–1.76)
Full Term (39 weeks <41)	66	745	Reference (1.00)	Reference (1.00)
Late & Post-Term (≥ 41 weeks)	19	167	1.28 (0.75–2.20)	1.32 (0.77–2.27)
Unknown	1	36		
Mode of Delivery				
Vaginal Spontaneous	102	1,062	Reference (1.00)	Reference (1.00)
Vaginal Forceps or Vacuum	6	64	0.97 (0.41–2.31)	0.96 (0.40–2.28)
Cesarean	54	494	1.14 (0.80–1.61)	1.15 (0.81–1.62)
Season of Birth				
Summer	45	463	Reference (1.00)	Reference (1.00)
Fall	37	411	0.93 (0.59–1.46)	0.94 (0.59–1.48)
Winter	37	360	1.06 (0.67–1.67)	1.07 (0.68–1.70)
Spring	43	386	1.15 (0.74–1.78)	1.13 (0.72–1.75)
Hepatitis B Vaccination Prior to Hospital Discharge				
Yes	130	1,214	Reference (1.00)	Reference (1.00)
No	31	392	0.73 (0.49–1.11)	0.76 (0.50–1.16)
Unknown	1	14		
Breastfed at Time of Hospital Discharge (2005–2011)				
Yes	56	541	Reference (1.00)	Reference (1.00)
No	14	159	0.85 (0.46–1.57)	0.87 (0.47–1.61)

n, Number of cases or controls;

^a Adjusted for birth year;

^b Adjusted for birth year, maternal race/ethnicity, and child's sex unless otherwise noted;

^c Adjusted for birth year and maternal race/ethnicity.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Overview of US-based LCH epidemiologic studies

Authors and Year	Years Included	Case Type and Number	Study Design	Primary Findings
Glass and Miller, 1968 ²⁵	1960–1964	270 Letterer-Siwe related Deaths	Retrospective survey of vital records	<ul style="list-style-type: none"> Majority of Letterer-Siwe (high-risk LCH) deaths in first two years of life. Five sibling pairs died with Letterer-Siwe disease in the four year period. 88.9% of death occurred among whites.
Hamre, et al., 1997 ²⁴	1971–1986	177 LCH cases	Matched case-control	<ul style="list-style-type: none"> Solvent exposure, family history of benign tumors, maternal urinary tract infections during index pregnancy, feeding problems during infancy, and blood transfusions during infancy associated with increased LCH risk. Vitamin supplements during pregnancy associated with decreased LCH risk. No comment on risk differences by race/ethnicity.
Bhatia, et al., 1997 ¹⁴	Undisclosed	459 LCH cases	Case-control	<ul style="list-style-type: none"> Thyroid disease in proband or family history of thyroid disease highly associated with LCH. Postnatal exposures including infections, diarrhea and vomiting associated with increased LCH risk. Childhood immunizations suggested as protective. 96.5% of cases were white versus 92.0% of community controls, while 1.6% of cases were black versus 4.6% of community controls.
Jurban, et al., 2005 ²⁶	1984–2001	132 LCH cases	Retrospective chart review	<ul style="list-style-type: none"> Patients with LCH involving only the bones have a significantly better outcome than those with other organ involvement. Patients less than one year of age with multi-organ involvement are at high risk of death. No comment on reactivation differences by race/ethnicity in this Children's Hospital Los Angeles (CHLA) study.
Venkatramani, et al., 2012 ¹³	2007–2009	60 LCH cases	Case-control	<ul style="list-style-type: none"> Family history of cancer, infection during infancy, lack of immunizations, and parental occupational exposure to metal, granite, or wood dust associated with increased LCH risk. In this CHLA study, 18% of LCH cases were white, 53% were Hispanic and 0% were black.
Golpanian, et al., 2014 ¹¹	1973–2010	828 Pediatric Histiocytosis cases	Population-based using Surveillance, Epidemiology, and End Results (SEER) database	<ul style="list-style-type: none"> White children had a higher incidence compared with blacks, $P < 0.05$. Asian and/or Pacific Islander or Native American descent had the highest rate of LCH.

Authors and Year	Years Included	Case Type and Number	Study Design	Primary Findings
Ribeiro, et al., 2015 ¹²	2000–2009	145 LCH cases	Population-based using Surveillance, Epidemiology, and End Results (SEER) database	<ul style="list-style-type: none">Gender and race had no association with survival.Lower age-adjusted incidence rate observed for blacks versus whites overall among those ages 0–19, and particularly for cases diagnosed under the age of 1.Higher age-adjusted incidence rates observed for Hispanics versus non-Hispanics among the entire study population, and among those cases diagnosed <1 of age.Risk of LCH was higher in areas with low educational levels and crowded counties.In particular, LCH incidence according to crowding level was higher among Hispanics in stratified analyses.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript