Research Abstracts for 2018 CLIC-I4C Joint Meeting

Abstract Number, Presenting Author (Last, First) – Title

Legend
* = Presenting author
† = Presenting author is a young investigator
§ = Authors contributed equally

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MOLECULAR EPIDEMIOLOGY OF PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA IN BRAZIL. Francianne G Andrade†, Suellen V. Moura Feliciano, Ingrid Sardou-Cezar, Daniela Palheiro Mendes-de-Almeida, Paulo Chagas Neto, Marceli S. Santos, Maria S. Pombo-de-Oliveira *(Pediatric-Hematology-Oncology Program (PHOP) Research Center, National Cancer Institute (INCA), Brazil)*

Background: Acute promyelocytic leukemia (APL) presents well-characterized mechanisms of pathogenesis with distinctive acquired fusion gene. The incidence rate of APL seems to vary among geographic regions, being higher in the Latino population, underlying genetic background that plays a role along with environmental factors. Our aim was to establish the incidence rate of APL among children and adolescents according to hospital-based and population-based cancer registries (PBCR) in Brazil. We also aim to describe the molecular features of APL to provide insight into molecular epidemiology potentially associated with APL development. **Methods**: APL cases (<19 years old) were assessed from a dataset of hospital-based registry from a central laboratory (PHOP, INCA) that is a reference for leukemia diagnostic assistance (2002-2017) and from 18 PBCR in Brazil. Diagnostic algorithm included morphology, immunophenotype, and PML-RARa identified by FISH/RT-PCR. Additionally, FLT3, KRAS, NRAS, and PTPN11 mutations were analyzed. **Results**: In the PHOP-based registries, 149 patients out of 734 myeloid malignancies (MM, 20.3%) were diagnosed with APL, while in the PBCR 45 out of 1.421 (3.2%) MMs were APL. The incidence rate based on PBCR showed that APL was highest in Southeast/South (1.60 per million) compared with other Brazilian regions (0.9 per million). MM rate of unspecified cell-type in PBCRs was about 50% and the coverage of PHOP was estimated in 95% of PBCRs. Patients were similarly distributed among age ranges >2-10 and >10-21 years old (47.3% and 50%, respectively); no sex differences were observed, but a remarkable decrease in Blacks (10.5%) vs. Non-Black (90.5%) was found. PML-RARA was identified in the great majority of cases; RAS mutations were observed in 55% of APLs, including FLT3 (45.2%), NRAS (7.3%), KRAS (2.5%) and PTPN11 (rs61736914, a silent aminoacid substitutions=4.9%). **Conclusions**: APL is the most frequent MM subtype highly associated with FLT3 mutations, reflecting the profile of the disease in Brazil. Future studies should explore these association with environmental exposures.

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INCREASED PENETRANCE OF ACUTE LYMPHOBLASTIC LEUKEMIA SUSCEPTIBILITY LOCI IN CHILDREN WITH DOWN SYNDROME. Adam J. de Smith†§, Austin L. Brown§, Vincent U. Gant§, ME Scheurer, KM Walsh, N Winick, NA Heerema, AJ Carroll, MJ Borowitz, BL Wood, WL Carroll, EA Raetz, E Feingold, W Yang, M Devidas, CG Mullighan, SP Hunger, C Pui, M Loh, LM Morimoto, T Whitehead, HM Hansen, AY Kang, D Sinnett, P Thompson, JM Birch, JW Taub, ME Zwick, MS Pombo-de-Oliveira, C Metayer, X Ma, BA Mueller, SL Sherman, JL Wiemels, MV Relling, JJ Yang, Philip J. Lupo§, Karen R. Rabin§ *(Department of Preventative Medicine, Keck School of Medicine, University of Southern California, California, USA)*

Down syndrome (DS) is one of the strongest risk factors for acute lymphoblastic leukemia (ALL), the most common pediatric malignancy, as children born with trisomy 21 have an approximately 20-fold increased risk of disease. ALL in children with DS (DS-ALL) is associated with inferior outcomes and unique somatic characteristics, including a high frequency of CRLF2 overexpression. However, the role of inherited genetic variation in DS-ALL is unknown. To this end, we performed the first genome-wide association study (GWAS) of DS-ALL, including four independent case-control studies comprising 542 DS-ALL cases and 1192 DS controls. We carried out genome-wide imputation of autosomal and disomic single nucleotide polymorphisms (SNPs), and combined results from all studies using fixed effects meta-analysis. Genome-wide significant SNPs were identified at four loci previously associated with non-DS ALL, including: rs58923657 near IKZF1 (odds ratio [OR] = 2.02, Pmeta=5.32x10-15), missense SNP rs3731249 in CDKN2A (OR=3.63, Pmeta=3.91x10-10), rs7090445 in ARID5B (OR=1.60, Pmeta=8.44x10-9), and rs3781093 in GATA3 (OR=1.73, Pmeta=2.89x10-8). Case-case analyses comparing the frequency of ALL risk alleles (at IKZF1, CDKN2A, ARID5B, GATA3, CEBPE, BMI1, and PIP4K2A) in DS-ALL versus non-DS ALL (n = 3082 cases) revealed significantly higher risk allele frequencies in DS-ALL cases for SNPs in CDKN2A (OR=1.58, Pmeta=4.08x10-4), GATA3 (OR=1.34, Pmeta=4.38x10-5), and IKZF1 (OR=1.18, Pmeta=0.015). Genetic risk scores (GRS) calculated from the seven susceptibility loci were also significantly higher in DS-ALL cases than in non-DS ALL cases (weighted GRS, P=3.33x10-6), indicating that DS-ALL cases harbor significantly more risk alleles than non-DS cases. Furthermore, among controls without ALL, neither the GRS nor any individual ALL risk alleles were associated with DS status, suggesting that the higher risk allele frequencies in DS-ALL cases represents a larger magnitude of effect for known ALL risk loci in the genetic background of trisomy 21. Finally, shRNA knockdown of IKZF1 in lymphoblastoid cell lines (LCLs) revealed significantly higher proliferation rates in DS LCLs versus non-DS LCLs, as measured by serial counts (P<0.05) and proportion of cells in S-phase (P<0.05). Our results support a higher penetrance of ALL susceptibility loci in the DS population, and may inform surveillance strategies for children with DS who are at the greatest risk of developing ALL.

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ADMIXTURE AND THE RISK OF ACUTE LEUKEMIA: THE ADMIRAL STUDY. Logan G. Spector*, Michael E. Scheurer* *(Division of Epidemiology/Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA; Baylor College of Medicine, Texas Children's Cancer Center, Texas, USA)*

There is a strong case, based on multiple lines of evidence, that the lower incidence of acute lymphoblastic leukemia (ALL) in children with substantial African ancestry compared to those with other continental ancestries is largely or primarily genetic. This evidence includes the comparatively low risk both in African and in African diaspora populations; our report of intermediate risk in children with mixed ancestry; SEER analyses which indicate lower incidence compared to white children in all socioeconomic strata; and the persistence of lower risk despite greater exposure to putative environmental risk factors for ALL among African-American children. Common variation described to date incompletely accounts for the difference in incidence compared to white children, suggesting a substantial, undiscovered genetic contribution. Lastly, African and European populations have many divergent hematopoietic and immune traits which are due to genetic differences. Admixture mapping is useful for discovery of loci underlying ancestry-related differences in risk, with power proportional to the magnitude of the difference. Pediatric ALL, particularly B-cell ALL, displays greater than a two-fold difference in risk, making admixture mapping particularly attractive even with modest sample sizes. The collective preliminary data suggest we are similarly likely to find loci and genes that explain the lower risk of ALL in AA children. We have therefore assembled 1,120 African-American children with ALL and existing data or DNA samples, with another 309 samples anticipated over the life of the study, to form the Admixture and Risk of Acute Leukemia (ADMIRAL) study. This research holds the potential to answer a long-standing mystery by revealing critical genes or loci that explain the comparative deficit of ALL in African-American children. In addition, we may uncover genes or variants associated with the worse characteristics at presentation in African-American patients as well as with worse survival, which will indicate avenues for improving outcome in this population.

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NON-CHROMOSOMAL CONGENITAL ANOMALIES AND RISK OF CHILDHOOD LEUKAEMIA: AN ITALIAN POPULATION-BASED CASE-CONTROL STUDY. Carlotta Malagoli, Tommaso Filippini, Marcella Malavolti, Stefano Volpato, Gianni Astolfi, Giovanni Palazzi, Marco Vinceti* *(Environmental, Genetic and Nutritional Epidemiology Research Center (CREAGEN), University of Modena and Reggio Emilia, Modena, Italy; Department of Epidemiology, Boston University School of Public Health, Boston, USA)*

Introduction: The association between chromosomal conditions such as Down syndrome and increased CL risk of childhood leukemia (CL) is well established, while the association between non-chromosomal birth defects is far less clear. We conducted a population-based case-control study in two provinces of Northern Italy to evaluate CL risk in children born with non-chromosomal anomalies. **Methods**: We identified all leukemia cases diagnosed in children (<15 years) in the Modena and Reggio Emilia provinces through the Italian National Childhood Cancer Register in the period 1998-2013. For each case, we randomly selected four population controls matched by age, sex, province of residence and calendar year. Through the Emilia-Romagna Region population-based Birth Defects Registry, we retrieved information about occurrence and type of congenital malformations for each study subject. We computed the odds ratio (OR) of CL for children affected by non-chromosomal birth defects using a multivariable conditional logistic regression model. **Results**: We eventually included 132 cases and 528 controls, 5 of which (2 cases and 3 controls) were affected by a non-chromosomal congenital malformation. We found an increased risk of CL in children born with non-chromosomal anomalies, with an OR of 2.7 (95% confidence interval 0.4–16.0). **Conclusions**: Despite the limited stability of the risk estimates and the risk of unmeasured and residual confounding, our study appears to suggest an association between non-chromosomal birth defects and risk of childhood leukemia.

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EARLY INFECTION WITH CYTOMEGALOVIRUS AND RISK OF CHILDHOOD HEMATOLOGICAL MALIGNANCIES. Joseph Wiemels*, Mats Talbäck, Stephen Francis, Maria Feychting *(Center for Genetic Epidemiology, Department of Preventive Medicine, USC Keck School of Medicine, Los Angeles, California, USA)*

A primary etiologic factor for childhood acute lymphoblastic leukemia (ALL) involves patterns of infection during childhood. Until recently, no specific infection was implicated. Prenatal cytomegalovirus (CMV) infection was recently identified as a risk factor for childhood ALL by its presence in in ALL blast cells; CMV sequences were also detected in neonatal blood spots of children who later contracted leukemia. In the current study, we asked whether clinically identified CMV infection prior to hematological malignancies (including ALL) and central nervous system tumors may be an etiologic factor, using high quality Swedish population-based registries. CMV infection was identified with appropriate ICD9 or ICD10 codes in the Patient and Medical Birth Registries, and childhood malignancies below the age of 15 were identified in the Cancer Registry, among 2,782,507 children born in Sweden 1982 to 2015. While active screening for vertical CMV infection indicates incidence at birth at around 0.15-2% around the world (including Sweden), clinical identification of CMV is far rarer. The frequency was 0.0066% for CMV detection at birth among normal children but 0.088% for those contracting hematologic malignancy. Observing all CMV infections registered earlier than 6 months prior to malignancy diagnosis including the pregnancy period, an increased hazard ratio (HR) of CMV-related infections, adjusting for congenital malformations, deformations, and chromosome abnormalities, was detected for hematological malignancies (HR=12.1, 95%CI: 5.8-21.5). Cox proportional hazard ratio for having congenital viral infections, excluding CMV is 0.91(95% CI: 0.59 - 1.42), therefore indicating that CMV is the culprit infection. Central nervous system tumors exhibited no relationship with prior CMV infection. The data are compatible with an in utero infection of CMV leading to increased risk of childhood hematological malignancies. Further conformation and elucidation of the role of CMV in the etiology of childhood hematologic malignancies is warranted.

Abstracts not Available for the Following Posters:

Altaf, Sadaf† – *Cytogenic Etiology in Acute Myeloid Leukemia and its Association with Outcomes in Pediatric Patients in Pakistan*

Heck, Julia E. – *Parental Occupation and the Risk of Childhood Retinoblastoma: A Danish Population-Based Registry Study*

Investigators, International Childhood Cancer Cohort Consortium – *International Childhood Cancer Cohort Consortium (I4C: Rationale, Cohorts, Ascertainment of Childhood Cancer, Available Data, and Harmonization)*

Núñez Enriquez, Juan Carlos† -- *Electromagnetic Fields and Risk of Childhood B-lineage Acute Lymphoblastic Leukemia in a City with High Incidence of Leukemia and an Elevated Exposure to Electromagnetic Fields: A Population-Based Study from the Mexican Inter-Institutional Group for the Identification of the Causes of Childhood Leukemia (MIGICCL)*

Patel, Deven† – *Parental Occupational Exposure to Pesticides, Farm Animals, and Organic Dust and Childhood Cancer Risk: Findings from the International Childhood Cancer Cohort Consortium (I4C)*

Petridou, Eleni – *Quality of Childhood Cancer Registration to Facilitate CLIC+ Research: Preliminary Results from Two NARECHEM-ST Projects*

Ramakrishnan, Rema† – *Placental Weight, Birth Weight: Placental Weight Ratio and Childhood Cancer in the International Childhood Cancer Cohort Consortium (I4C)*

Rashed, Wafaa M.† – *Risk Factors for Childhood Acute Lymphoblastic Leukemia (ALL)*

Withrow, Diana† – *Trends in Pediatric Central Nervous System Tumors Incidence in the United States*, 1998-2013