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ARID5B, *CEBPE* and *PIP4K2A* Germline Genetic Polymorphisms and Risk of Childhood Acute Lymphoblastic Leukemia in Mexican Patients: A MIGICCL Study

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Background and Aims. Childhood acute lymphoblastic leukemia (ALL) is the leading cause of childhood cancer-related deaths worldwide. Multiples studies have shown that ALL seems to be originated by an interaction between environmental and genetic susceptibility factors. The *ARID5B* polymorphisms are among the most reproducible ALL associated-risk alleles in different populations. The aim of the present study was to examine the contribution of *ARID5B, CEBPE, and PIP4K2* risk alleles for the development of ALL in children from Mexico City and Yucatan, Mexico.

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Methods. A study was conducted with a total of 761 unrelated subjects. Two hundred eighty five ALL cases (111 from Yucatan and 174 from Mexico City) and 476 healthy subjects. Genotyping included the rs7088318 (*PIP4K2A*), rs10821936 (*ARID5B*), rs7089424 (*ARID5B*) and rs2239633 (*CEBPE*) polymorphisms.

Results. Associations between ALL and rs10821936 and rs7089424 *ARID5B* SNPs were found (OR = 1.9, 95% CI (1.5–2.4) and OR = 2.0, 95% CI (1.6–2.5), respectively). Moreover, a higher risk was observed in the homozygous risk genotypes of carriers from Mexico City (OR = 3.1, 95% CI (2.0–4.9) and OR 3.1, CI 95% (2.0–4.8), respectively). Otherwise, the rs7088318 (*PIP4K2A*) and rs2239633 (*CEBPE*) polymorphisms were not associated with ALL risk.

Conclusions. Our analysis suggests that *ARID5B* confers risk for childhood ALL in a Mexican population. © 2016 IMSS. Published by Elsevier Inc.

Key Words: Association study, *ARID5B*, *PIP4K2A*, *CEBPE*, Childhood acute lymphoblastic leukemia, Mexican.

Acute lymphoblastic leukemia (ALL) is the most frequent subtype of childhood cancer worldwide (1–3). The etiology of childhood ALL has not been established; however, many studies support the hypothesis that genetic polymorphisms influence racial differences in ALL incidence, either when the frequency of an ALL-predisposing genetic polymorphism differs by ethnicity or when these variants are associated with ALL in a race-specific manner (4–7). Genome-wide association studies (GWAS) have identified ALL-susceptibility *loci* at 7p12.2, 9p21.3, 10p12.2, 10q21.2 and 14q11.2 (8,9). The most consistent across studies is the 10q21.2 *locus*, which harbors the AT-rich interactive domain 5B (AR*ID5B*) gene. AR*ID5B,* which is involved in regulation of embryonic development, cell growth and B-lymphocyte progenitor differentiation, bears germline single nucleotide polymorphisms (SNP) located in intron 3 that are strongly associated with risk of pediatric ALL including rs10821936 and rs7089424. Although its specific role in the pathogenesis of ALL remains unknown, one of the highlighted findings is the association between *ARID5B* SNPs with ALL susceptibility in multiple investigated populations. Interestingly, differences in the frequencies of the risk alleles among Caucasian, African, Asian and Hispanic derived populations have been found, being the highest in Hispanic descendent populations (9–12). As an example, the frequency of the rs10821936C risk allele was lower in control populations of African ancestry (0.13 in ASW and 0.2 in YRI) than in populations of European ancestry (0.33) (6).

Likewise, the CCAAT/enhancer-binding protein epsilon (*CEBPE*) and phosphatidylinositol-5-phosphate 4-kinase, type II, alpha (*PIP4K2A*) genes have been added to the list of risk genes associated with the development of childhood ALL in other populations (11–14). It is interesting to note that Hispanics have shown a worse prognosis, often need more intensive ALL treatment regimens, show older ages at diagnosis, and exhibit higher frequencies of the *ARID5B* ALL-risk variants (also linked to poorer outcomes) than non-Hispanic Whites (5,15). Mexican as well as Hispanic populations are characterized by a very complex genetic background due to the different contributions from Native American, Caucasian and African populations during the conquest (16). Nowadays, the Mexican population is comprised by Mestizos (94%) and Amerindians (6%) (17,18).

ALL has higher incidence rates in Hispanics than in other ethnic groups and is the leading cause of mortality for cancer in Mexican children (3). It is possible that differences in genetic susceptibility loci could explain the higher observed ALL incidence rates in Mexican population.

The aim of the present study was to examine the contribution of *ARID5B, CEBPE,* and *PIP4K2* risk alleles for the development of ALL in children from Mexico City and Yucatán, Mexico.

Methods

Subjects

We conducted a study in a sample of 761 unrelated Mexican subjects recruited in Merida, Yucatan and Mexico City. Cases were <18 years of age diagnosed with ALL, recruited from two hospitals from Merida, Yucatan and three tertiary level hospitals in Mexico City. Diagnosis of ALL was based on morphology and immunophenotype studies. ALL patients were classified as standard risk (age 1–9.99 years and initial white blood cell count (WBC) $<50 \times 10^9$/L) or as high risk (NCI HR) (age $<$ 1 year or ≥ 10 years and initial WBC $\geq 50 \times 10^9$/L) according to the National Cancer Institute (NCI) Risk Classification (19).

Controls corresponded to healthy adults from Mexico City recruited in the General Hospital of Mexico and Hospital Juarez of Mexico City. Children from Yucatan were included from the Unidad Médica de Alta Especialidad (UMAE)-IMSS, Mérida, Yucatan (third-level hospital). Only individuals self-reported as having not been diagnosed with autoimmune, inflammatory, hematological diseases