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REUNIÓN CONJUNTA DE SOCIEDADES DE BIOCIENCIAS

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LIII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN BIOQUÍMICA Y BIOLOGÍA MOLECULAR (SAIB)

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13-17 de noviembre de 2017
Palais Rouge– Buenos Aires

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JOINT MEETING OF BIOSCIENCE SOCIETIES

LXII ANNUAL MEETING OF ARGENTINE SOCIETY OF CLINICAL INVESTIGATION (SAIC)

LIII ANNUAL MEETING OF ARGENTINE SOCIETY OF BIOCHEMISTRY AND MOLECULAR BIOLOGY (SAIB)

LXV ANNUAL MEETING OF ARGENTINE SOCIETY OF IMMUNOLOGY (SAI)

MEETING OF ARGENTINE SOCIETY OF ANDROLOGY (SAA)

XLVI ANNUAL MEETING OF ARGENTINE SOCIETY OF BIOPHYSICS (SAB)

XIX ANNUAL MEETING OF ARGENTINE SOCIETY OF BIOLOGY (SAB)

XLIX ANNUAL MEETING OF ARGENTINE SOCIETY OF EXPERIMENTAL PHARMACOLOGY (SAFE)

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MEETING OF ARGENTINE SOCIETY OF HEMATOLOGY (SAH)

XXIX ANNUAL MEETING OF ARGENTINE SOCIETY OF PROTOZOOLOGY (SAP)

November 13 -17, 2017
Palais Rouge– Buenos Aires

(1) Instituto de Patobiología, CICVyA-CNIA, INTA. (2) CONICET. (3) Instituto de Genética, CICVyA-CNIA, INTA

Brucella melitensis is the etiological agent of brucellosis in goats and is the main cause of human brucellosis. The selection of resistance-related genes is considered one of the best long-term means to improve control to bacterial infection in livestock animals. We performed a candidate gene association study to test if polymorphisms at bacterial-infection related genes influence the resistance to *Brucella* infection in goats.

Using the NCBI dbSNP database and a literature review, we identified polymorphic INDELs lying in five host genes linked to *Brucella* spp. and other bacterial infections: IRF3-rs540, FKBP5-rs294, TIRAP-rs561, PTPRT-rs588 and KARLN-rs989 (GENE-marker). DNA samples from 64 cases (seropositive) and 78 controls were used. INDELs were resolved by PCR-capillary electrophoresis and genetic associations were determined by the Fisher's exact test.

Allelic frequencies were significantly different between cases and controls at IRF3-rs540 and KARLN-rs989 ($p \leq 0.01$). Moreover, IRF3-rs540, KARLN-rs989 and TIRAP-rs561 genotypes were associated with presence/absence of *Brucella*-specific antibodies in goats ($p \leq 0.01$). The major homozygous genotype (AA) at IRF3-rs540 was associated with susceptibility to *Brucella* infection (OR=0.45). Using RegRNA, we observed that the allele A introduce a premature stop codon in an IRF3 uORF. The KARLN-rs989 minor allele (b) was almost exclusively present in the controls. Furthermore, Bb/ bb genotypes were associated with resistance to *Brucella* spp. infection (OR=9.54). The heterozygous genotype at TIRAP-rs561 (Cc) was also associated with resistance (OR=4.44). We hypothesize that KARLN-rs989 and TIRAP-rs561 might be in linkage disequilibrium with missense SNPs at KARLN exon 8 and TIRAP exon 4, respectively. This study contributes to the understanding of genetic variation in host control of *Brucella* infection.

Keywords: *Brucella*, goats, genetic resistance, polymorphisms.

(337) **PATHOGENICITY ANALYSIS OF SMALL IN-FRAME DELETIONS IN DMD/DMB PATIENTS: REACHING CERTAINTY OF UNCERTAINTY**

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Duchenne Muscular Dystrophy (DMD) and Becker Muscular Dystrophy (BMD) are X-linked genetic diseases caused by mutations in the *DMD* gene. DMD is a severe dystrophy that occurs due to absence of dystrophin and affects 1:3.500 born males, whereas BMD is less severe due to less expression or function of the protein and affects 1:18.000. Molecular alterations in *DMD* gene are gross deletions/duplications in 80% of cases and small mutations in 20%. Large rearrangements are identified by Multiplex Ligation-dependent Probe Amplification (MLPA), while point mutations are detected by gene sequencing. The "reading frame theory" establishes a correlation between phenotype and mutation type, which agrees with the observed phenotype in 92% of cases. According to this theory, patients carrying a mutation causing a disruption on the translational reading frame (out-of-frame mutation) show a clinical progression to DMD, while patients with a genetic alteration that do not affect the translational reading frame (in-frame mutation) develop a milder phenotype, BMD-like.

From a cohort of 175 patients with clinical diagnosis of DMD/BMD, analyzed by MLPA and 40 of them also studied by Next Generation Sequencing (Whole Exome Sequencing), we have detected two small in-frame variants c.10101_10103delAGA and c.120_131delCTTCAGTGACCT in two patients with a DMD phenotype. As the observed phenotype did not adjust to the "reading frame theory" and there were none or scarce cases carrying these mutations previously reported, our aim was to increase the predicted pathogenic effect of these two mutations found. Two different strategies were implemented, an intrafamilial segregation analysis and a functional and structural bioinformatic analysis of the dystrophin protein. This work offers an example of different methodologies to corroborate the pathogenic effect of Variants of Unknown Significance (VUS), one of the major challenges of the Next Generation Sequencing data interpretation.

Keywords: Dystrophinopathies, Variant of Unknown Significance, Structural bioinformatic analysis, Segregation analysis

(702) **CCR5 AND CCR2 POLYMORPHISMS AND THEIR ASSOCIATION WITH CHRONIC CHAGAS CARDIOMYOPATHY (CCC) IN ARGENTINIAN POPULATION**

Natalia Juiz, Elkyn Estupiñán (1), Daniel Hernandez (2), Alejandra Garcilazo (3), Raul Chadi (3), Gisela Morales Sanfurgo (3), Silvia Longhi (4), Alejandro Schijman (4), Clara Gonzalez (1)
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Several studies have proposed different genetic markers as chemokines and cytokines genes for susceptibility to develop CCC. Many genes may be involved, each one making a small contribution. Thus, an appropriate approach for this problematic is to study numerous SNPs in individuals sharing genetic background.

Our aim was to analyze *CCR2* and *CCR5* SNPs located in the promoter region by TaqMan allelic discrimination assay, and their association with CCC in Argentinean populations.

A case-control study was carried in 480 *T. cruzi* seropositive adults from Gran Chaco endemic region and patients attending Buenos Aires hospitals. They were classified in 2 groups according to the Consensus on Chagas-Mazza Disease: non-demonstrated (non-DC) or demonstrated (DC) pathology groups.

Due to our studied population did not fit Hardy-Weimberg equilibrium, we subclassified them according to geographical/ethnic origin. Thereby, SNPs frequencies between creole population from endemic regions and Buenos Aires patients were similar but differ from wichi population from Gran Chaco. The association analysis showed that the T allele in rs1800024 was more represented in non-DC than in DC group ($p=0.041$) in non-wichi population, becoming a protective factor. Among wichi individuals the G allele in rs1800023 was more frequent in DC group ($p=0.016$) and may be a risk factor to CCC. Moreover, we found that only in wichi population the HHE haplotype displayed a higher prevalence in non-DC group.

These results are consistent with a previous study showing that although wichi and creoles live in the same geographical area, they are genetically different and for this reason, the results differed according to the population studied. It is tempting to speculate an association between the above described genetic differences and the clinical manifestations of CCC. Indeed, right bundle-branch block, the most frequent abnormality in CCC, had a clear tendency for lower prevalence in the wichi population.

Keywords: CHAGAS DISEASE, Trypanosoma cruzi, POLYMORPHISMS, CHRONIC CHAGAS CARDIOMYOPATHY

(731) **THE IL-17F rs763780 SNP IS ASSOCIATED WITH HUMAN TUBERCULOSIS SUSCEPTIBILITY AND DISEASE SEVERITY IN ARGENTINA.**

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Mycobacterium tuberculosis (*Mtb*) causes nearly 10 millions of new tuberculosis disease cases annually. However, most individuals exposed to *Mtb* do not develop tuberculosis, suggesting the influence of a human genetic component. In this work, we investigated the