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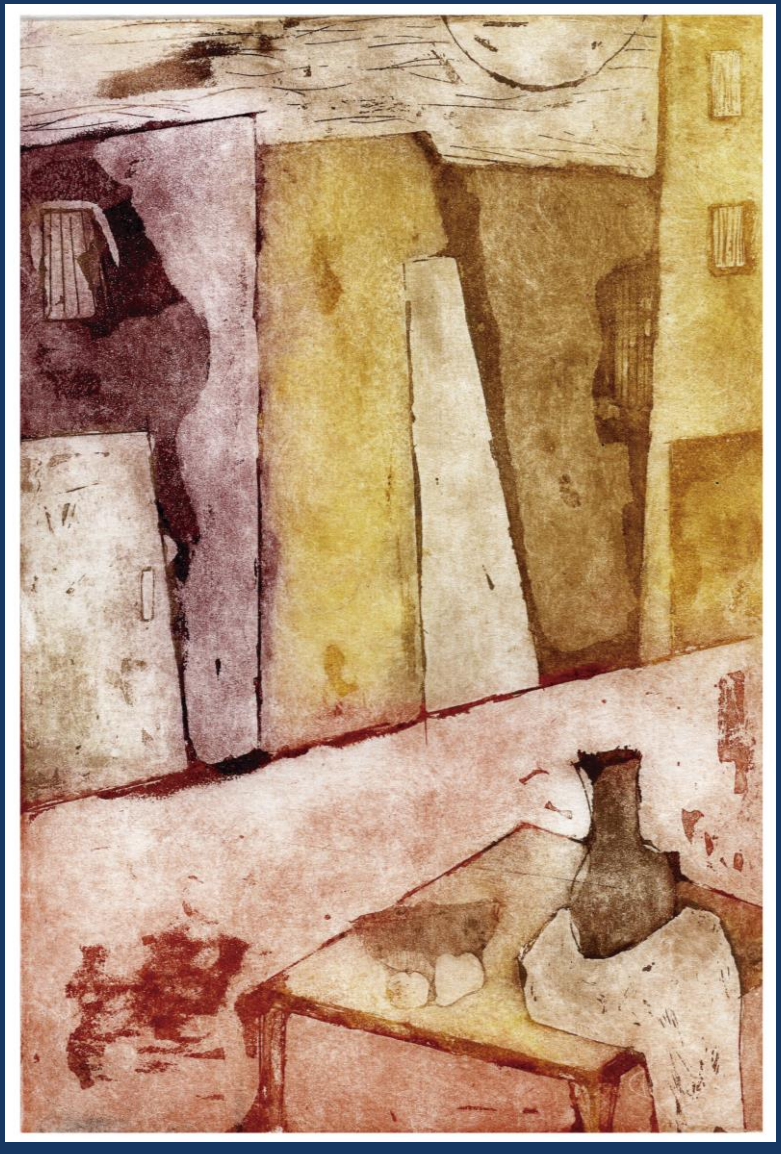

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La Tapa (Ver pág. 4)
Atardecer en la tarde
Antonella Ricagni

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Sociedad Argentina de Investigación Clínica (SAIC)

LI Reunión Anual de la
Asociación Argentina de Farmacología Experimental (SAFE)

XXI Reunión Anual de la
Sociedad Argentina de Biología (SAB)

XXXI Reunión Anual de la
Sociedad Argentina de Protozoología (SAP)

IX Reunión Anual de la
Asociación Argentina de Nanomedicinas
(NANOMED-ar)

VI Reunión Científica Regional de la Asociación Argentina de Ciencia y Tecnología de Animales de Laboratorio (AACyTAL)

con la participación de
The Histochemical Society

13 - 16 de noviembre de 2019
Hotel 13 de Julio - Mar del Plata

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0109 - DIVING THE OCEAN OF VARIANTS IN PURSUIT OF A MUSCULAR DYSTROPHIES DIFFERENTIAL DIAGNOSIS

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Abstract/Resumen: Muscular dystrophies (MD) are a group of rare inherited diseases that cause weakness and progressive degeneration of skeletal muscle. They are caused by mutations in genes encoding structural skeletal muscle proteins or proteins necessary for the stability and proper functioning of muscle fibers. However, the clinical symptoms of these pathologies overlap, hindering differential diagnosis, which is of paramount importance to establish the standard of care. Therefore, it is important to carry out molecular studies to be able to differentiate between each type of MD. Here, we focus on the case of Limb-Girdle MD, which are frequently misdiagnosed as Dystrophinopathies, the most frequent type of MD and caused by mutations in the DMD gene. The present work aims to detect molecular alterations in MD genes in patients with a presumptive dystrophinopathy clinical diagnosis but no DMD mutation identified. A cohort of 106 Dystrophinopathy suspected males, with no alteration detected in DMD by MLPA, was referred to our laboratory for WES analysis. In a subset of 21, no small mutation in the DMD gene was detected. Therefore, we deepened the screening to all the MD genes included in the Gene Table of Neuromuscular Disorders. For recessive MD disorders, when only one mutation was identified, MLPA (SGCA, SGCB, SGCD, SGCG and FKRP) was implemented for deletion/duplication screening. Dystrophinopathy mutations were detected in the DMD gene in 81.1 % of patients. Further analysis of the WES results of the remaining individuals, allowed us to identify possibly pathogenic molecular alterations, in other MD associated genes, in 11 of them (10.4 %). Thus, reaching a WES detection rate of 91.5 %. We found 2 large deletions in SGCA and SGCD by MLPA. Finally, our work highlights the importance of extending the mutation screening to all the MD associated genes in patients without alterations in DMD, given that a misdiagnosis could lead to an error in the selection of the standard of care.

0110 - HOW TO SURPASE THE WES TSUNAMI OF VARIANTS: THE IMPORTANCE OF THE HUMAN FACTOR

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Abstract/Resumen: Dystrophinopathies are neuromuscular X-linked recessive diseases caused by mutations in the DMD gene. Molecular alterations in this gene are large deletions/duplications in 80 % of cases, identified by MLPA, and small mutations in the remaining 20 %, detected by whole exome sequencing (WES). The use of next generation sequencing (NGS) techniques generates a large quantity of data that is analyzed by a bioinformatics pipeline. However, this analysis can lead to errors in the variant calling. The present work aims to emphasize the importance of the human factor in order to detect these errors. A cohort of 106 patients with presumptive clinical diagnosis of dystrophinopathy and negative MLPA results was analyzed by WES. Raw data was evaluated using the Integrative Genomics Viewer (IGV) software. Sanger sequencing was used to corroborate the identified variants. Two cases have been selected as an example to illustrate variant calling errors. Even though the WES technique and its bioinformatic pipeline proved to be fruitful, allowing us to identified pathogenic variants in muscular dystrophy genes in 91.5 % of patients, we detected 2 variant calling errors among the studied individuals. In other words, the VCF results did not resemble the alteration observed in the raw data analysis. These discordances were due to the presence of deletions in the DMD gene, which caused problems in the alignment process. In both cases, alignment and annotation had to be manually re performed. While one of the patients carries a small delins, the other one has a complex rearrangement, a deletion and a 20 pb insertion in the same allele. Specific primers were design to corroborate these findings. Finally, this work highlight the importance of analyzing the NGS raw data, corroborating the identified mutations by an alternative technique and the expertise of the scientist in charge of the study, so as to detect the occurrence of variant calling errors and provide reliable results to the patient.

0250 - A NOVEL HUMAN HETEROZYGOUS STAT5B VARIANT LEADS TO GROWTH AND DEVELOPMENTAL DEFECTS IN ZEBRAFISH EMBRYOS

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Abstract/Resumen: Signal transducer and activator of transcription 5B (STAT5B) has been identified as a key downstream mediator of Growth Hormone (GH) signaling in somatic growth. Autosomic recessive human mutations in STAT5B lead to severe growth retardation associated to immune dysregulation. On the other hand, some heterozygous STAT5B mutations have been associated to a milder form of the disease. The aim of our study was to evaluate the functional consequences of a novel heterozygous human STAT5B variant (K632N), described in a child presenting short stature with mild immunological dysfunction, during zebrafish embryo development to determine its pathogenicity. To do this, we microinjected 100 and 200 pg of wildtype (WT) and mutant mRNA into zebrafish embryos and measured the embryo length at 72 hours post fertilization (hpf). In addition, we characterized the morphological phenotypes observed in these embryos. Zebrafish embryos microinyected with 100 and 200 pg of mutant mRNA show a dose dependent significant reduction of body length at 72 hpf compared to those microinyected with the same dose of WT mRNA ($p<0.001$) for both 100 and 200 pg. Moreover, the body length is significantly shorter in those embryos injected with 200 pg ($p<0.001$) compared with 100 pg of mutant mRNA. In addition, a significant number of embryos injected with mutant mRNA show developmental defects including pericardial edema, bent spine, and cyclopia compared to those injected with WT mRNA ($p<0.01$). These morphological phenotypes also increase with the mutant mRNA dose. In conclusion, our study was able to evidence the pathogenic nature of the STAT5B K632N variant since it leads to growth and developmental defects in zebrafish embryos. The zebrafish, and its conserved GH-IGF-I axis, constitutes an ideal in vivo model for characterizing the functional effect of genetic variants in ortholog human genes.

0560 - PORPHYRINOGENICITY OF DRUGS IN ACUTE INTERMITTENT PORPHYRIA: ARE THE CYP-450 POLYMORPHISMS THE ANSWER?

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CENTRO DE INVESTIGACIONES SOBRE PORFIRINAS Y PORFIRIAS (CIPYP)