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REDES COLABORATIVAS Y COMPARTIR DATOS EN ENFERMEDADES GENÉTICAS NEUROMUSCULARES

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In this roundtable, we will discuss opportunities for data sharing and scientific collaborations in the field of genetics of neuromuscular diseases in Latin America. Dr. Michel Naslavsky from Universidade de São Paulo, will present the initiative "*Arquivo Brasileiro Online de Mutações*" (ABraOM) and he will discuss how such databases could contribute to the field. Dr. Florencia Giliberto (Universidad de Buenos Aires) will discuss the experience with next generation sequencing for the diagnosis of small mutation in *DMD* gene in Argentina. Dr. Fernando Suárez-Obando from Pontificia Universidad Javeriana, Colombia will present the efforts for building registries/databases for Duchenne muscular dystrophy in the country. Dr. Alberto L. Rosa (Universidad Católica de Córdoba) will present recent studies on facioscapulohumeral muscular dystrophy in Argentina, and Dr. Jorge Bevilacqua (Univesidad de Chile) will present the situation for molecular diagnosis of limb girdle muscle dystrophy (LGMD) in Chile together with recent characterization of these patients in the country. The coordinator of the round table Dr. Jonas Saute, from Universidade Federal do Rio Grande do Sul, Brazil, will conduct the discussion also pointing to some recent collaborative studies in Brazil on LGMD, trying to stimulate the creation/consolidation of potential databases for sharing genetic information of Latin American individuals with neuromuscular diseases, aiming the promotion of regional scientific progress in this field.

CAN THE "ARQUIVO BRASILEIRO *ONLINE* DE MUTAÇÕES" (ABRAOM) CONTRIBUTE TO THE NEUROMUSCULAR GENETICS FIELD?

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Sequencing datasets are an important resource to assess allelic frequency of rare variation and improve pathogenicity interpretation in molecular diagnosis. To further assess the incidence of putative loss of function previously assigned as pathogenic or likely pathogenic variants, a census-based cohort of 1,172 unrelated Brazilian individuals aged 60 or over as an extension of the Online Brazilian Archive of Mutations (ABraOM – *Arquivo Brasileiro Online de Mutações*). We have filtered 106 genes associated to muscular disorders, specifically limb-girdle and congenital muscular dystrophies, in a whole genome sequencing dataset. Initial filtering by an allelic frequency cutoff of 1% within the cohort provided a high confidence list of 637 variants in 82 genes with splicing, stop gain/loss and frameshift predicted consequences. 6% were not previously described elsewhere, 30 had been asserted as pathogenic or likely pathogenic at ClinVar and present in up to 5 heterozygous individuals. Although sarcopenia can be found within this cohort of elderly individuals, early-onset muscular phenotypes are not represented and the sample may be biased towards health fitness and overall survival. It is possible that pathogenicity classification can be overestimated; their true effects might be modulated by complex genomic interactions resulting in reduced penetrance. Healthy elderly cohorts can play a role as a tool for filtering candidate variants as causes to Mendelian early- and adult-onset disorders.

THE EXPERIENCE WITH WES FOR DIAGNOSIS OF SMALL MUTATIONS IN DMD IN ARGENTINA

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Las Distrofinopatías son enfermedades neuromusculares de herencia recesiva ligadas al cromosoma X, generadas por mutaciones en el gen *DMD*. La más frecuente y severa de ellas es la Distrofia Muscular de Duchenne (DMD). Si bien aún no existe un tratamiento efectivo para estas enfermedades, se están desarrollando varios abordajes terapéuticos. El objetivo de esta exposición es compartir nuestra experiencia de más de 25 años en los estudios moleculares que llevamos realizando, describir nuestro algoritmo diagnóstico, difundir los conocimientos adquiridos sobre la secuenciación de exoma completo (WES) y enfatizar sobre la importancia de reportar las variantes identificadas, así como trabajar colaborativamente con otros centros de referencia. A lo largo de estos años hemos analizados más de 2.000 muestras, confirmando el diagnóstico, detectando portadoras, realizando estudios prenatales y estableciendo el protocolo terapéutico que aplica a la mutación identificada. Hasta el momento llevamos realizados más de 120 exomas de individuos con distrofia muscular, en su mayoría DMD, con una taza de detección de ~92%. Las variantes que identificamos en nuestra población son compartidas en la base de datos pública LOVD (*Leiden Open Variation Database*) - *Human Variome Project*. La importancia de caracterizar la alteración molecular no solo es necesario para determinar el mejor estándar de cuidado para el paciente, sino que permite a la familia recibir un adecuado asesoramiento genético que colabore con una responsable planificación familiar.

DISTROFIA MUSCULAR DE DUCHENNE. REGISTROS Y BASES DE DATOS EN COLOMBIA

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La distrofia muscular de Duchenne (DMD) es una miopatía hereditaria, recesiva, ligada a X, con una incidencia de uno por cada 3.500 hombres y una prevalencia global de 4,78 por cada 100.000. Los registros de enfermedades de baja prevalencia como la DMD tiene como objetivos optimizar la monitorización del progreso de los pacientes sobre el curso de la enfermedad, a través de la recolección del estado clínico y la aplicación de escalas de incapacidad, fatiga y estado de salud y bienestar, independientemente del tipo de tratamiento que éste reciba. El registro colombiano de DMD tiene como objetivo identificar aspectos relacionados con la variabilidad en la presentación clínica que pudieran relacionarse con variables del manejo, terapéutico, aspectos sociodemográficos y bases genéticas. La primera etapa del registro incluyó 62 pacientes con sospecha clínica de DMD, los cuales tuvieron confirmación molecular de la enfermedad (75% con deleción/Duplicación; 25% con mutaciones puntuales). Se pretende con este tipo de iniciativas, estimar de forma adecuada la frecuencia de la enfermedad, comprender la variabilidad, progresión y evolución natural de las manifestaciones clínicas, así como diseñar estrategias de seguimiento individualizadas, optimizando los recursos de salud disponible, mejorando la calidad asistencial e incentivar la utilización de las guías de práctica clínica dentro del contexto de la atención clínica de paciente con DMD. Se expone la estructura del registro y su extensión hacia el monitoreo de otras enfermedades de baja prevalencia.

STUDIES ON FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN ARGENTINA

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Facioscapulohumeral muscular dystrophy (FSHD), together with myotonic dystrophy, are the second more frequent inherited human myopathies. FSHD, clinically underdiagnosed worldwide, develops following a complex interplay of genetic and epigenetic events. The more frequent genetic form (FSHD1) is associated with deletions of a tandem repeat (D4Z4) at chromosome 4q35, a specific 4q35 subtelomeric haplotype (4qA) and decreased cytosine methylation at the residual D4Z4 units. On the other hand, a ~5% of FSHD individuals (FSHD2), that carry mutations at the gene SMCHD1, also carry a 4qA haplotype and decreased cytosine methylation at D4Z4. Each D4Z4 element contains a copy of the gene called DUX4, which has a pseudogene-like structure and is located on repetitive DNA. The elusive nature of both the DUX4 transcript and the DUX4 protein was unveiled in year 2007, on a seminal publication from our laboratory. We proposed that aberrant expression of DUX4, a nuclear-located transcription factor, is the causative pathogenic protein in FSHD. In year 2010, a unifying model for the pathogenesis of FSHD was proposed showing that the permissive 4qA haplotype is a DUX4-mRNA polyadenylation signal that allows stable translation of the muscle toxic protein DUX4. This molecular mechanism of disease highlights the epigenetic nature of the FSHD pathogenesis and connect the pathogenic pathways of FSHD1 and FSHD2. Current pharmacological trials are aimed to control DUX4 gene expression and/or the activity of the DUX4.

PRELIMINARY DATA ON THE GENETICS OF LIMB GIRDLE MUSCLE WEAKNESS IN CHILE

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In Chile it is estimated that about 6,000 patients suffer of a hereditary myopathy (HM), however there are no systematic registries of the number of patients or the different forms of myopathy that they have. In part, the scarceness of information comes from the fact that until today there are no laboratories performing genetic diagnosis for these diseases in the country. The only genetic analysis that is performed commercially in Chile is MLPA for DMD. After 7 years of screening of adult patients HM (*i.e.* older than 15), searching first for dysferlin-related myopathy and next for patients with limb girdle muscle weakness phenotype, allowed the definite molecular diagnosis of 101 patients. These results, coming mainly from a single neuromuscular reference clinic based in Santiago, show that adult patients with LGMW in Chile are more frequently affected with dysferlin-related myopathy (48%), for which gene four recurrent mutations demonstrated to have a founder effect, followed by calpainopathy (7%), dystrophinopathy Becker type (6%), titinopthy (5%), collagen 6 related myopathy (5%) and desminopathy (4%). The other HM identified don't show any particular frequency and are present in small number of patients comprising dystrophies, congenital muscular dystrophies and spinal muscle atrophy.

These preliminary show a biased first analysis of the relative prevalence of adult myopathy forms in the country; further collaborative work to integrate data from different centres across Chile is urgently needed.