ABSTRACTS COLLECTION

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P01

Reproductive Genetics

P01.002.B PPARG1 gene methylation in granulosa cells relation to hyperinsulinemia and hyperandrogenism in women with polycystic ovary syndrome

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Background/Objective: one of the most prevalence endocrine disorders in women is Polycystic Ovary Syndrome (PCOS). This syndrome is heterogeneous, and recent evidence suggested that epigenetic events could responsible for the occurrence of this syndrome. one of the most significant epigenetic modifications is DNA methylation, which could decrease gene expression. There is a close connection between energy metabolism and female fertility. PPARG gene plays an important role in lipid and glucose metabolism, and it shows significant role in the evolution of the reproductive system growth and development in embryonic stage. This study aimed to investigate the frequency PPARG1 gene methylation in granulosa cells in PCOS patients with hyperinsulinemia and hyperandrogenism.

Methods: The follicular fluid of 30 normal individuals, 25 women with polycystic ovary syndrome only, 20 PCO women with hyperandrogenism (HA), and 20 PCO women with insulin resistance (IR) were collected. After isolation of granulosa cells from follicular fluid, genomic DNA extracted and after bisulfite DNA treatment, CpG-rich region in PPARG1 gene promoter was selected and methylation-specific polymerase chain reaction (MS-PCR) was performed on bisulfite DNA.

Results: The results analysis revealed a significant difference between the methylation of the PPARG1 gene in four patient groups ($P < 0.005$), indicating that the PPARG1 gene promoter is hypermethylated more significantly in PCO-IR and PCO-HA patients.

Conclusion: The frequency of PPARG1 gene promoter methylation in PCO-IR and PCO-HA individuals were higher than in other groups. So higher methylation would decrease PPARG1 gene expression in ovary, which could cause PCO-IR and PCO-HA in women in reproductive age.

Conflict of Interest: None declared

P01.004.D Severe premature ovarian insufficiency: don't forget about men

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P10.100.D STUB1 variants in ataxia with and without intermediate TBP repeat expansion

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Background: Pathogenic variants in *STUB1* cause both recessive (SACR16) and dominant (SCA48) forms of spinocerebellar ataxia. Because of this, difficulties may arise in the interpretation of variants, especially when the family history is unclear. Furthermore, a digenic inheritance pattern in SCA48 with intermediate repeat expansion in *TBP* (SCA17) has recently been described. Here we present 5 families with *STUB1* variants, identified during routine clinical testing.

Methods: Exome analysis of genes involved in movement disorders was performed (Agilent Sureselect XT Human All Exon V7 capture, paired-end Illumina sequencing). In addition, repeat expansion testing was performed for *ATN1, ATXN1, ATXN2, ATXN3, ATXN7, FMR1, PPP2R2B, TBP, FXN* and *CACNA1A*.

Results: Three families showed an autosomal dominant inheritance pattern of a progressive cerebellar syndrome with cognitive decline, starting between 45-60 years. In these three families, a heterozygous *STUB1* variant was identified (c.146A>G, c.256G>C and c.453+4_453+6delAGT), without intermediate *TBP* expansions. In another family, compound heterozygosity for c.433A>C and c.196C>T was found in a patient with early onset cerebellar syndrome. The patient also carried a heterozygous pathogenic repeat expansion in *FXN*. In the last family, progressive neurological symptoms (ataxia, pyramidal signs and cognitive decline) started at age 26. A heterozygous start loss (c.1A>G) was identified together with an intermediate TBP repeat expansion (n = 47).

Conclusions: These families illustrate the diverse inheritance patterns in *STUB1* related ataxia. Our data suggest that intermediate *TBP* expansions are not a requisite for developing symptoms in SCA48. Whether other genetic factors (such as *FXN* repeat expansions) are involved, needs further research.

Conflict of Interest: None declared

P11 Neuromuscular Disorders

P11.001.A Spinal muscular atrophy testing: A clinical laboratory perspective

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Spinal Muscular Atrophy (SMA) is a degenerative disease of the lower motor neurons and brain stem nuclei characterized by progressive and symmetrical muscle weakness and atrophy. Targeted treatments for SMA have emerged within the past decade, prompting the United States federal government to include SMA on the Recommended Uniform Screening Panel for Newborn Screening programs (NBS), as early diagnosis and initiation of treatment before motor neuron death increases the likelihood of positive outcomes. Given the benefits of early detection, a historical review of positive cases identified in our laboratory was undertaken to ascertain whether enhanced population screening practices outside of NBS would be beneficial. From 2016-2022, we identified 228 cases with zero copies of *SMN1* through prenatal screening, diagnostic testing, and carrier screening. Indications for prenatal screening (n = 120) included a positive family history or known parental carrier status. Approximately 90% of these pregnancies would be expected to result in more severe and earlier onset of disease, including one pregnancy in which one parent was a SNP negative silent carrier of SMA. Among postnatal cases, the reasons for testing included positive family history, known carrier parents, clinical symptoms of disease, and screening. The age of postnatal cases ranged from newborn to 63 years. Predictably, age at testing was generally correlated with *SMN2* copy number, but a surprising number of cases (13.9%; 15/108) were identified through screening. Taken together, these data suggest that broader population screening may be beneficial to identify pre-symptomatic adults and inform decisions regarding prenatal screening for reproductive partners.

Conflict of Interest: Jennifer Reiner Labcorp, Robert Pyatt Labcorp, Lynne Rosenblum Labcorp, Zena Wolf Labcorp, Winnie Xin Labcorp, Zhaoqing Zhou Labcorp, Hui Zhu Labcorp, Natalia Leach Labcorp

P11.002.B Clarifying the diagnosis: Genomic findings in a cohort with suspected multiple sclerosis

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Multiple sclerosis (MS) is a neuroinflammatory condition characterized by demyelination of the central nervous system, likely resulting from a combination of genetic and environmental factors. Symptoms of this condition are variable but include muscle weakness, ataxia, sensory dysfunction, bladder and bowel neurogenic dysfunction, and optic neuritis. Although there are no known monogenic causes of MS, exome or genome sequencing (ES or GS) may have utility in clarifying diagnosis. There are several genetic disorders that mimic the symptoms of MS, which raises the possibility of misdiagnosis. Therefore, we sought to summarize the genomic findings in a cohort of individuals with MS symptoms to determine the utility of testing in such individuals.

A total of 268 individuals with symptoms of MS underwent ES or GS from 2017-2022.

Seventeen individuals (6.3%) received a report with genetic findings related to their neurological symptoms: 3 had pathogenic (P) findings, 4 had likely pathogenic (LP) findings, and 10 had high-priority variants of uncertain significance. Two individuals (0.75%) had LP/P variants associated Charcot-Marie-Tooth disease (*MFN2, MME*) and one had an LP variant in *CSF1R*, which is associated with hereditary diffuse leukoencephalopathy with spheroids. Eight individuals (3.0%) had a LP/P variant in an ACMG secondary finding gene (*SCN5A, HFE, BRCA2, KCNQ, RYR1, PMS2, TP53*).

Here we summarize the molecular findings in a cohort of individuals with suspected MS. Our findings highlight the utility of incorporating ES/GS into clinical evaluation for patients with MS in terms of clarifying diagnosis and providing accurate recurrence risk counseling and medical management.

Conflict of Interest: None declared

P11.003.C Three heterozygous GAA cases mimicking late-onset Pompe disease

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Background: Late-onset Pompe disease (LOPD) is a recessive disorder caused by acid α-glucosidase (GAA) deficiency. Carriers of one *GAA* pathogenic variant are asymptomatic. There are several cases reported, where only one pathogenic *GAA* variant has been identified. Here, we present three unrelated cases with suspected LOPD carrying one pathogenic *GAA* variant together with other heterozygous variant(s) related to glycogen storage or structural muscle protein.

Methods: All patients were examined by a neurologist and underwent WGS (60x, PCR-free, PE150). The GAA enzyme activity was measured in dried blood spot, leukocytes and/or in fibroblasts (also used for total RNA sequencing, PE75).

Results: The phenotype of all three patients included adolescent to adult disease onset, proximal weakness and myalgia. GAA was decreased, and creatine kinase was normal to mildly elevated. WGS revealed following heterozygous phenotype-related variants: Patient 1 maternal *GAA* c.-32-13T>G (pathogenic), paternal *PHKB* (VUS) and *AMPD1* (VUS); Patient 2 *GAA* c.-32-13T>G and *AMPD1* (VUS; same variant as in Patient 1); Patient 3 *GAA* c.1082C>T p.(Pro361Leu) (pathogenic) and *FHL1* (VUS). In fibroblasts of Patient 1, the activity of GAA was 0.83 (NR 6.04-17.06) nmol/min/mg protein and RNA sequencing confirmed abnormal transcripts due to c.-32-13T>G but no other splicing defects in *GAA*.

Conclusion: There may be a small cohort of LOPD-like cases where a symptomatic heterozygosity or digenic/oligogenic inheritance can be considered.

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Conflict of Interest: None declared

P11.004.D Objective evaluation of clinical actionability for genes involved in myopathies: 63 genes with a medical value for patient care

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Background/Objectives: The generation of large amounts of mutational data though the diagnostic implementation of high-throughput diagnostic sequencing has been associated to complexification of interpretation and related long delays of genetic results. It has been important to prioritize certain analyses, particularly those of "actionable" genes in diagnostic situations, involving specific treatment and/or management. In this French national project, we carried out an objective assessment of the clinical actionability of genes involved in myopathies, for which only few data obtained methodologically exist to date.

Methods: We applied the ClinGen Actionability criteria to evaluate and score the clinical actionability of all 199 genes implicated in myopathies published by FILNEMUS for the "National French consensus on gene Lists for the diagnosis of myopathies using next generation sequencing".

Results: 63 myopathy genes were objectified as actionable based on the ClinGen Actionability criteria, with the currently available data. Among the 36 myopathy genes with the highest actionability scores, only 8 had been scored to date by ClinGen.

Conclusion: Our work presents the first systematic evaluation of clinical actionability for genes involved in myopathies. The data obtained through these methodological tools are an important resource for strategic choices in diagnostic approaches and the management of genetic myopathies. The clinical actionability of genes has to be considered as an evolving concept, in relation to progresses in disease knowledge and therapeutic approaches.

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Conflict of Interest: None declared

P11.005.A DEPISMA: a prefiguring newborn screening project for spinal muscular atrophy in France

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Spinal Muscular Atrophy (SMA) is a genetic disorder of the nervous system, affecting about 1 in 7000 births and mainly due to