tendon reflexes (Table 1). CK levels were elevated in all (650 – 4547 IU/L). Muscle biopsy in 4 patients was suggestive of muscular dystrophy. RNS showed decrement response in probands from family 3 and 4. Pyridostigmine and Salbutamol were started in family 4, and they showed significant improvement in fatigue and weakness. Genetic analysis revealed identical missense mutation c.1000G>A (p.Asp334Asn) in exon 9 of GMPPB gene in 6 patients tested of all four families. This mutation was previously reported in a compound heterozygous form in two patients of Asian origin (Pakistan and India) in published literature. However, the phenotype described in these two cases was Congenital muscular dystrophy with CNS involvement. While, in all our patients the mutation was present in homozygous form and had a milder, slowly progressive phenotype consistent with Limb girdle myasthenic syndrome. This indicates the milder effect of the mutation which may require a different mutation to cause severe phenotype. As of now this variant has not been reported from other geographical regions. Furthermore, the allele frequency of c.1000G>A among south Asian population is 0.0005 and has zero frequency in other populations in ExAC database. Hence, we suspect a possible founder affect for this mutation in South Asia and needs to be further explored. Table 1: Clinical features. **Conclusion:** This report further expands the emerging phenotypic spectrum of GMPPB associated dystroglycanopathies and indicates a probable South Asian founder mutation with milder effect in its homozygous form.

Family	Year	Gender	Age	Onset	Clinical features	Creatine kinase	RNS	Family History
1	2004	M	50	42	Weakness: Proximal>distal, truncal weakness; Fatigue +; Scapular winging; Calf hypertrophy; Fatigue +; DTRs: 2+	650	Significant decrement (>20%)	3 siblings affected
2	2006	F	35	30	Weakness: Proximal; fatigue +; calf hypertrophy; DTRs 2+	1583		elder sister affected
3	2016	F	32	22	Weakness: Proximal; fatigue +; calf hypertrophy; DTRs 2+	1790	Significant decrement (>20%)	Negative
4	2017	F (younger sister)	45	28	Weakness: Proximal and truncal weakness; chewing difficulty; fatigue +; mild ptosis (fatigable) and facial weakness; calf hypertrophy; DTRs 2+	4547	Mild Decrement (<10%)	Maternal 1st cousin affected (M/44; onset: 18 yrs)
	2017	F (elder sister)	46	36	Weakness: Proximal and truncal weakness; chewing difficulty; fatigue +; facial weakness; calf hypertrophy; DTRs 2+	2107	Significant Decrement (>20%)	

PS1Group1-045 / #480

Topic: *Group 1 – Muscle Diseases of Genetic Origin and Acquired Myopathies: Clinical Features, Pathophysiology, Therapy*

NFAT5 AND P38 MAPKS INTERACT IN MUSCLE CELLS RESPONDING TO OSMOTIC AND INFLAMMATORY STRESS AND IN POLYMYOSITIS

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Background: The transcription factor Nuclear Factor of Activated T-cells 5 (NFAT5) is the key regulator of cells' responses to osmotic stress, but is also implicated in inflammatory muscle disease. NFAT5 most likely is regulated by Mitogen-activated protein kinases (MAPKs) and the four members of the p38 family of MAPKs, termed MAPK11 (p38β), MAPK12 (p38γ), MAPK13 (p38δ) and MAPK14 (p38α), have known associations with inflammation. **Methods:** We study MAPKs mRNA expression and protein activation in an in vitro muscle inflammation model, and in muscle from polymyositis patients. **Results:** We observe that in muscle cells in culture, exposure to increased salt concentrations and

pro-inflammatory cytokines influence NFAT5 mRNA expression and translocation to the nucleus. A maximal 4-fold increase of NFAT5 messenger levels in myotubes treated with IL1β and IFNγ+IL1β for 24h is detected, in the latter condition accompanied by a moderate increase of MAPK12 and MAPK13 phosphorylation. Neither MAPK14 expression nor phosphorylation is substantially altered by cytokines and increased NaCl concentrations. Longer exposure of myotubes in culture to cytokines does not increase NFAT5 nor MAPK14 expression, yet hyperosmotic conditions lead to a time-dependent increase of expression, reaching 9-fold (NFAT5) and 18-fold (MAPK14) after 72h. At this stage, culture densities decrease substantially, disfavoring the differentiated multinucleated cells and leaving myoblasts as the remaining cell developmental stage. In muscle tissues, levels of phosphorylated MAPK11/12/14 relative to actin content, increase from 0.52±0.24 in normal (n=4), to 0.87±0.23 in polymyositis (n=4), but this difference does not reach statistical significance (p=0.08). Immunofluorescent localization studies show expression in blood vessel endothelium and in a subset of small, most often CD56+ (regenerating) muscle fibers. **Conclusion:** We identify p38 MAPKs as possible phospho-activators of NFAT5 in muscle cell's responding to inflammatory stress, and put forward MAPK12 as a likely regulator relevant to inflammatory myopathy.

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Topic: *Group 1 – Muscle Diseases of Genetic Origin and Acquired Myopathies: Clinical Features, Pathophysiology, Therapy*

IMPLICATION OF THE BREAKPOINTS POSITION IN PATIENTS WITH THE MACRODELETION OF EXONS 45 TO 55

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Background: Duchenne muscular dystrophy (DMD) is a severe myopathy that affects to 1 out of 3500 -5000 newborn boys and it is responsible of severe disability and early death, caused by mutations in the DMD gene. Becker muscular dystrophy, is an allelic form, which manifest a benign phenotype. Sixty five per cent of the mutations in the DMD consist on intragenic deletions that disrupt the reading frame of the gene, while in BMD the reading frame is preserved. An emerging gene therapy in DMD patients consist on inducing skipping of an exon that recover the reading frame in a restrictive group of cases. Multiexon skipping is another approach that can be achieved with the new Crispr-Cas9 technology. In particular, 63% of DMD mutations are located between exons 45 to 55 and it has been observed the existence of a spontaneous deletion spanning that region in asymptomatic subjects or variable Becker phenotype. Our aim is to analyze the diverse clinical profile and to refine the underlying molecular mechanisms in a cohort of subjects with a 45-55 deletion. Our hypothesis is that the different location of the intronic breakpoint positions of these patients might be responsible of their clinical phenotype. **Methods:** We analyzed the exact position of the intronic breakpoints in 8 index patients with this deletion. We performed an array, and multiple PCRs in order to restrict the area of the breaking points in the introns 44-45 and 55-56, following by amplification and sequencing of the deletion junction to detect the exact breakpoint We also checked the clinical features of the patients in an attempt to correlate them with their sequences. **Results:** A group of 6 patients shared the same breakpoints in both introns. These patients presented variable clinical manifestation (2 asymptomatics, 2 mild BMD, 1 BMD and 1 with cardiomyopathy). In one of the other 2 patients, the deletion affected the regulatory regions of the dystrophin isoform Dp140 and in fact the patient presented ADHD (attention deficit hyperactivity disorder), dyslexia and dysgraphia. The last patient presented a proximal insertion of a stretch from a deleted region in the 44-45 intronic breakpoint. This patient showed an early onset cardiomyopathy. **Conclusion:** We cannot certainly affirm that t the position of the intronic breakpoints in patients with deletion 45-55 is related with the clinical features of these patients, nevertheless we found some associations. We detected a major hotspot, where 6 of 8 patients share the same breakpoints and present variable clinical manifestations, where we can find asymptomatic patients (suggesting that there are other factors that may have