# STIM1 mutations: new mutations and different phenotypes

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## Tab.1:clinical and genetic characteristics

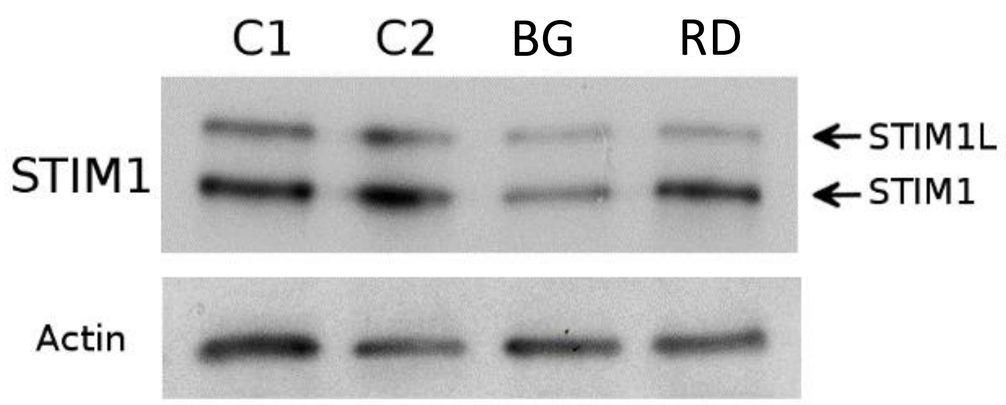
| Mutation | SC c.252T>A/p.D84E | GN c.326A>G/p.H109R | PA c.312A>T/p.K104N | BG c.2246G>A/p.R749H | RD c.1889C>T/p.S630F | GB c.1894_1897del/p.H632fs*0 | TD c.412G>A/p.V138I |
|---|---|---|---|---|---|---|---|
| Gender | M | F | M | M | M | M | M |
| Age of onset | 15 months | Infantile onset | Infantile onset | 39 yrs | 54 yrs | Birth | 6 months |
| Age at last examination | 44 yrs | 32 yrs | 32 yrs | 57 yrs | 56 yrs | 32 yrs | 26 yrs |
| Muscle weakness | Diffuse and marked muscle weakness | Limb-girdle muscle weakness | Limb-girdle muscle weakness | Proximal muscle weakness in upper limbs<br>Distal muscle weakness in lower limbs | - | Ptosis<br>Shoulder girdle weakness<br>Scapular winging | Diffuse muscle weakness (with distal limb predominance) |
| Myalgia | + | + | - | - | + | - | - |
| Walking | with support | Normal | Normal | with support, waddling gait | Normal | Normal | Foot drop, unable to walk on heels |
| Contractures | Diffuse and severe: limited mouth opening, rigid spine, limited all proximal and distal joints movement | Elbows, wrists, heels | Knees and Achilles tendons | - | - | - | - |
| Respiratory dysfunction | sestrictive defect | - | - | sleep apnoea syndrome | - | - | maximal Expiratory Pressure reduction |
| Cardiac dysfunction | - | - | - | - | - | Mitral valve prolapse<br>left anterior fascicular block | - |
| Ophthalmic findings | ptosis<br>Reduced lateral and upward gaze keratoconus, miosis | Corneal transplantation | - | - | - | - | - |
| Dermatologic findings | - | - | - | - | - | - | - |
| CK level (X normal) | 12 x | 4 X | 4 x | 5 x | 8 x | 3 x | normal |
| Asplenia | + | - | - | - | - | - | - |
| Thrombocytopenia | + | + | - | - | - | - | - |
| Hypocalcemia | + | - | - | - | - | - | - |
| Muscle CT imaging | severe involvement of cervical and spinal extensors, subscapularis, hamstrings, and posterior lower leg muscles | fatty replacement of pelvic muscles and thigh muscles, particularly in the anterior compartment | | fatty replacement of glutei, all tight muscles (symmetrical) and leg muscles with sparing of popliteus and posterior tibialis | not done | not done | fatty replacement of paravertebral muscles, vastus intermedius and anterior compartment of thigh muscles |
| Histology | Tubular aggregates, fiber size variability, internal nuclei, type I fiber predominance | tubular aggregates | tubular aggregates | severe muscle dystrophy with inflammatory infiltrates | type I fiber atrophy, rimmed vacuoles in some fibers and cores in others | mild variation in fiber size | congenital fiber type size disproportion |
| Additional features | short stature<br>low MCHC levels<br>migraine | epilepsy<br>sensory neural hearing loss<br>hypotyroidism | - | MGUS | lumbar stenosis | Gilbert syndrome<br>sensory neural hearing loss | - |

## Background and Objective

STIM1 is a reticular Ca2+ sensor composed of a luminal and a cytosolic domain. Dominant mutations in the *STIM1* gene cause three allelic conditions: tubular aggregate myopathy, York platelet dysfunction syndrome, and Stormorken syndrome (a complex phenotype including myopathy, hyposplenism, hypocalcaemia and bleeding diathesis).

## Methods

We tested blood DNA for the coding exons and flanking introns of 241 neuromuscular genes using a targeted multiexon amplicon panel (SureSelect, Agilent technology). Data were analyzed using a routine bioinformatic pipeline that adopts the Ingenuity Variant analysis suite (Qiagen, https://apps.ingenuity.com). Sanger sequencing was used to confirm mutations and assess segregation in the families. Western blotting was performed in skeletal muscle using a commercially available monoclonal antibody ab57834 (Abcam).




## Results and Conclusions

In the clinical study and molecular characterization of 332 patients with neuromuscular disorders tested with a multigene panel in NGS, we identified rare variants in 305 cases. Herein we report on seven patients (age ranged 26-57 years) who harbored mutations in the *STIM1* gene (Table 1). The age of onset of the affected patients ranged from birth to adulthood. Two patients presented clinical characteristic compatible with Stormorken syndrome, 3 out of 7 presented with congenital muscle weakness, 1 with adult onset of non-specified myopathy, and a single case referred only myalgia. The ability to walk was quite conserved in all patients. The mutations we identified (Fig. 1) satisfied canonical criteria for pathogenicity, were distributed throughout the gene (Fig. 2), and five out of 7 were novel. The three-dimensional model of the functional domains presenting missense variants is shown in Fig. 1. Of interest, variant p.D84E is a recurrent mutation in Stormorken syndrome. Muscle biopsy showed the presence of tubular aggregates in 3 patients, and type I fibe atrophy in 2 patients. Two presented non-specific myopathic signs (Fig. 3). Our work expand the heterogeneity of *STIM1* mutations and the associated phenotypes.

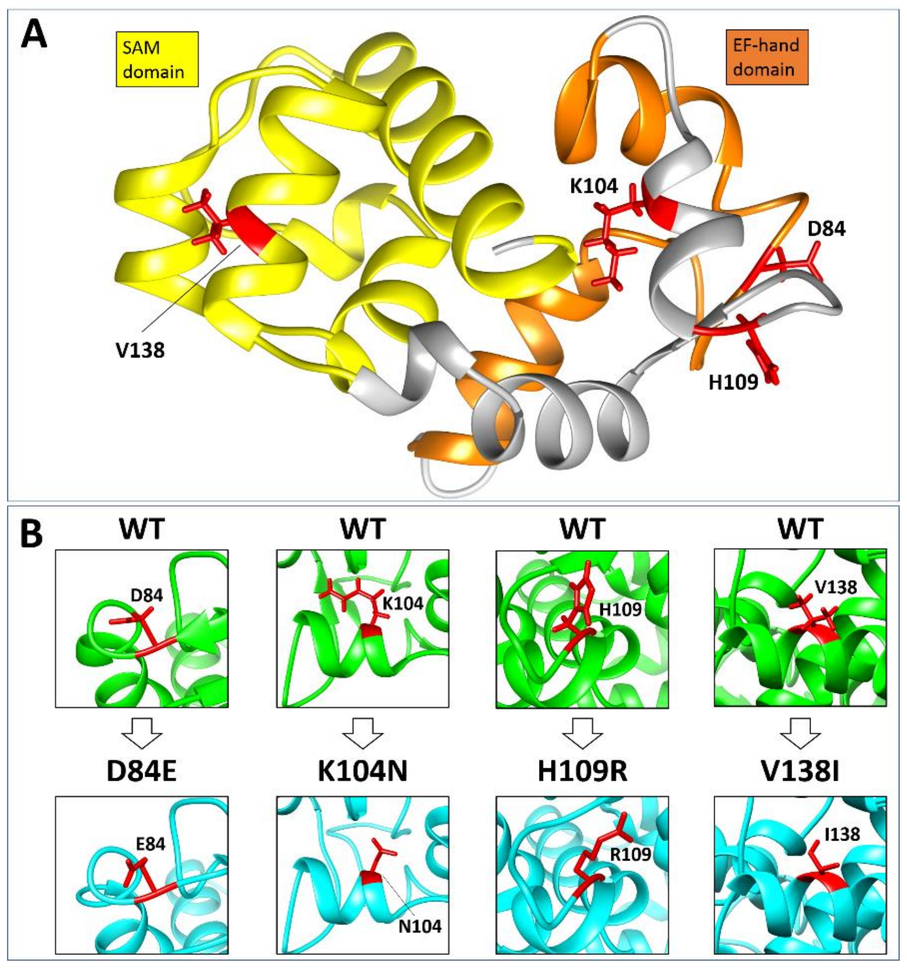



Fig. 1: Three dimensional modeling. **A.** View of the three dimensional model of the Ca2+ - sensing region of STIM1 (PDB entry: 2K60, residues 58-201) consisting of the EF-hand and sterile alpha motif (SAM) domains (Stathopulos et al, 2008). Mutated residues are highlighted in red. **B.** Close view of the structure around residues 84, 104, 109 and 138 in wild-type and mutated STIM1.


Fig. 2: Scheme of the protein structure (https://prosite.expasy.org/cgi-bin/prosite/PSImage.cgi)

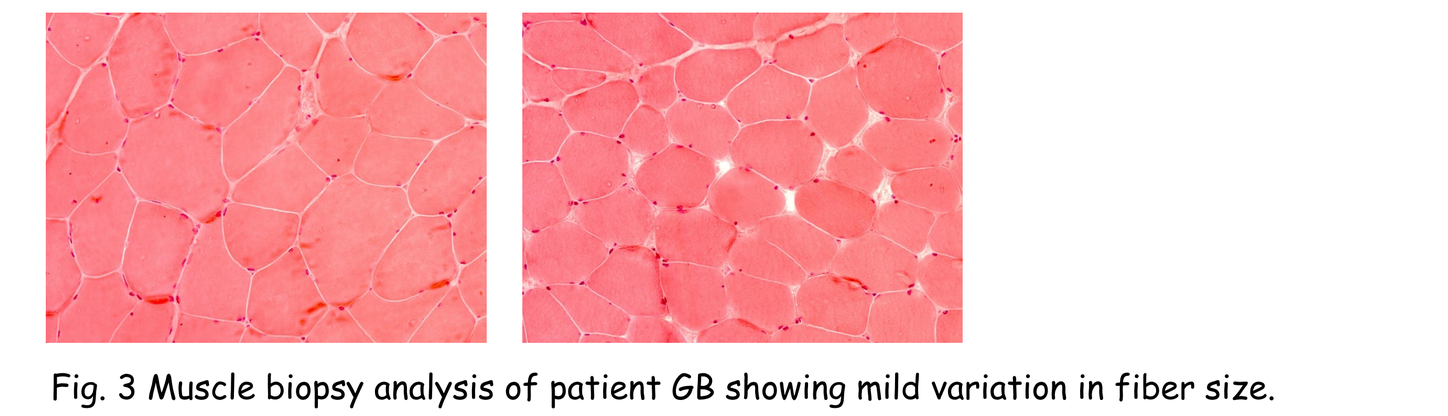


Fig. 3 Muscle biopsy analysis of patient GB showing mild variation in fiber size.