

Genetic variants associated with neuromuscular disorders in a large cohort of heart transplant recipients due to cardiomyopathy

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BACKGROUND

In hereditary neuromuscular disorders (NMD) cardiac involvement may be the first presenting symptom (1,2,3). Disease-causing genes, particularly *LMNA*, *TTN* and *MYH7*, may cause structural changes and abnormal function within both the skeletal- and cardiac muscle. Deterioration of heart function may progress to a refractory end-stage heart failure requiring advanced therapies such as heart transplantation (HTx), with poor median life expectancy of 6 months to 1 year if untreated. HTx is considered “gold standard” for treatment. However, a definite diagnosis of NMD is traditionally regarded as a relative contraindication for HTx. Neuromuscular symptoms may be subtle and slowly progressive and may appear gradually many years after HTx and could be overlooked in the cardiac follow-up (1, 2). **Our hypothesis:** heart transplant recipients with a prior non-ischemic cardiomyopathy (CM) may have genes associated with an underlying NMD. In the first part of the study, we investigated the prevalence of disease-causing mutations in a large Norwegian cohort of heart transplant recipients with a prior CM diagnosis. We included 196/281 (70 %) HTx recipients with a prior CM. Prior genetic results and updated genetic testing resulted in high diagnostic yield. Pathological genetic mutations (class 4 and 5 variants) were seen in 61% (119/196) of the included subjects, and of those 72 % (86/119) had mutations in genes associated with NMD, mostly in *TTN* and *LMNA*. The rest of those included (n=119) had mutations associated with heart disease only, n=33 (28%).

AIM

To unravel neuromuscular symptoms among HTx recipients with a prior CM that had tested positive for disease-causing mutations in genes associated with NMD.

METHOD

The cohort of genetically positive HTx recipients with a prior CM from the first part of the study (n=119) were divided into two groups:

- NMD group:** that had mutations in genes associated with NMD (n=86).
- Heart group (control group):** that had mutations in genes associated with solely cardiac involvement (n=33).

All patients had the same pre-Tx procedure and diagnostic evaluation (functional lung exam, teeth status, dermatology, psychiatric assessment) and essentially the same medications (immune suppressants, statins and anticoagulants) post-transplantation.

Patients from both groups were invited to:

- Neurologic examination and functional assessment with MFM 32**, a 32-item clinical scale used to evaluate fine and gross motor function in patients with NMDs (4).
- Manual muscle testing: MRC grading (0-5) of 24 muscle groups, and trunk muscles (5).**
- The “ four climb step test”** for functional and ambulatory evaluation for NMDs (5)
- The “ 30 second chair-stand test”** used to assess mobility, leg strength and fall risk (6).

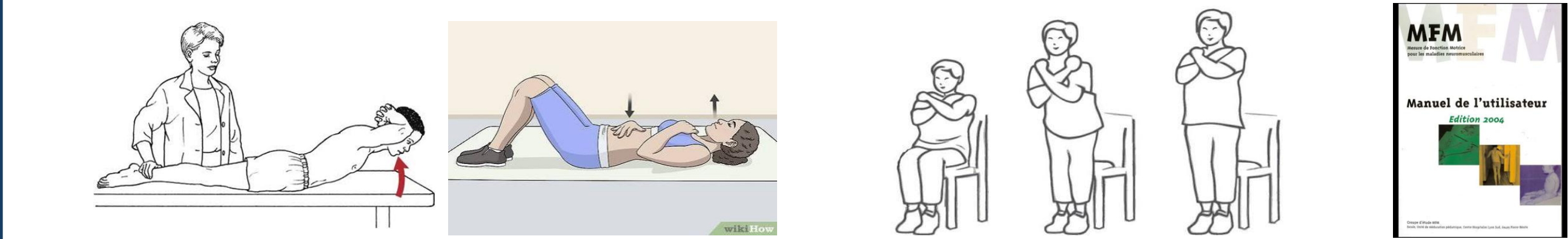
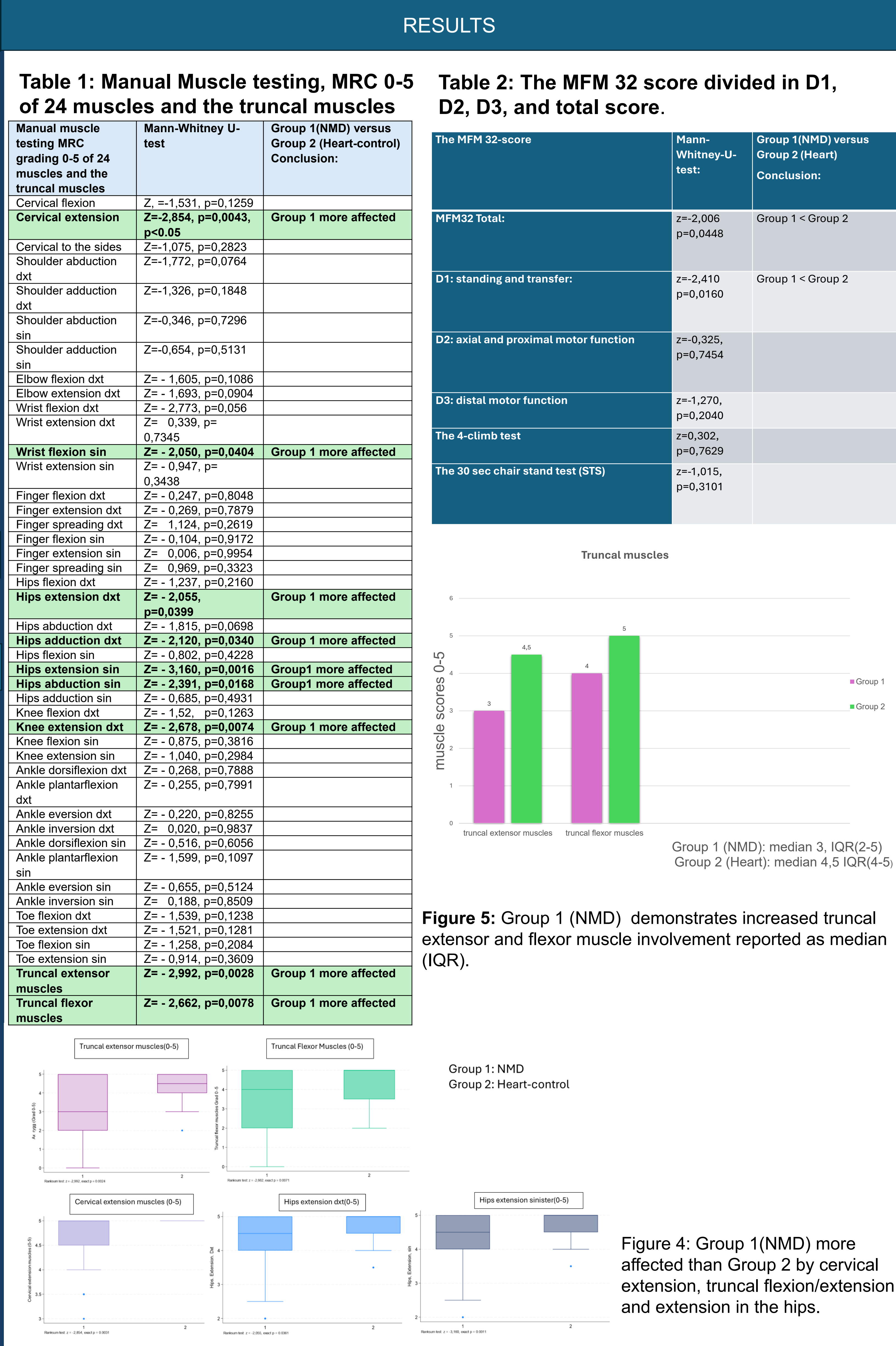
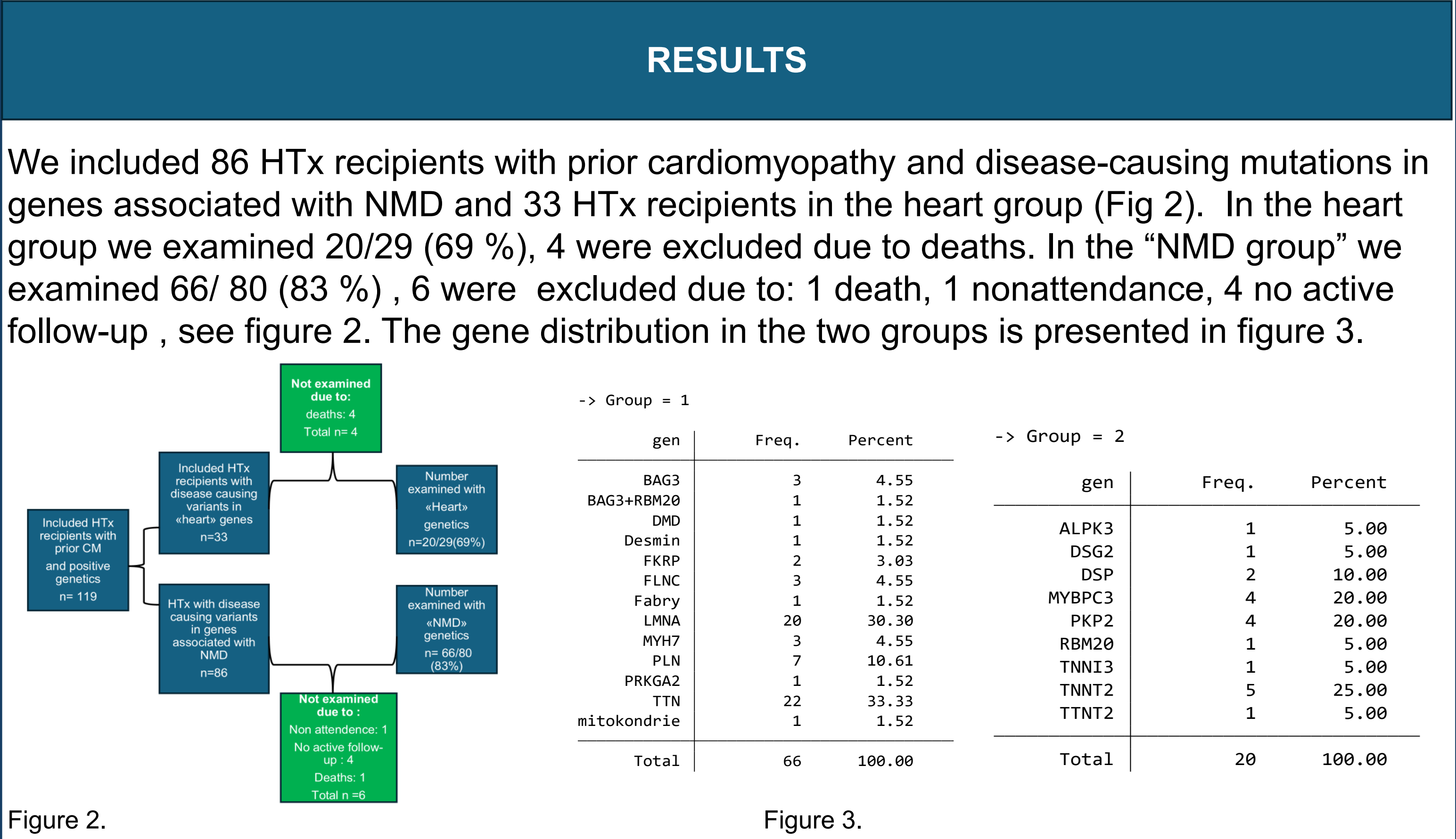


Figure 1: Trunical muscle test (trunical extension and flexion), the “ 30 second chair-stand test” and the MFM 32 manual



CONCLUSION

- Manual Muscle testing** demonstrates **reduced muscle function and weakness** of the **trunc extensor and flexor muscle groups and for cervical extension, but also for hip extension and wrist flexion bilateral** in the NMD group compared to the Heart-control group. This correlates well with the impression of reduced muscle function and weakness by examination in the NMD group.
- In the subdomains of MFM 32**, the D1 (measures standing and transfers) shows that the NMD group is more affected than the Heart group.
- Total score of MFM 32** reflects the overall motor function and was much lower for the NMD group.

TAKE HOME MESSAGE

- HTx recipients with a prior cardiomyopathy that have genes associated with NMD have reduced muscular function in several muscle groups responsible for their overall motor function compared to the Heart group.
- Trunical muscle involvement leads to impaired standing and gait, sitting balance, head control, and may lead to respiratory problems especially if additional proximal involvement.
- HTx recipients that are geno-positive for disease-causing genes associated with NMD should be followed- up by a multidisciplinary team including a neurologist.

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