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**MUSCLE ACTION POTENTIAL SCANS AND ULTRASOUND  
IMAGING IN NEUROFIBROMATOSIS Type 2**

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# MUSCLE ACTION POTENTIAL SCANS AND ULTRASOUND IMAGING IN NEUROFIBROMATOSIS Type 2

## ABSTRACT

*Introduction:* The neuropathy in patients with neurofibromatosis type 2 (NF2) is difficult to quantify and to follow-up. This study compared three methods which may help to assess motor axon pathology in NF2 patients.

*Methods:* Nerve conduction studies in median nerves were supplemented by deriving motor unit number estimates (MUNE) from compound muscle action potential (CMAP) scans, and by high resolution ultrasound (US) peripheral nerve imaging.

*Results:* CMAP amplitudes and nerve conduction velocity were normal in the vast majority of affected individuals, but CMAP scan MUNE revealed denervation and reinnervation in many of the peripheral nerves in NF2 patients. In addition, US nerve imaging enabled to monitor the size and number of schwannoma-like fascicular enlargements in the median nerve trunks.

*Conclusion:* In contrast to conventional nerve conduction studies, CMAP scan MUNE in combination with US nerve imaging can quantify the NF2-associated neuropathy and may help to monitor disease progression and drug treatments.

**Key words:** neurofibromatosis type 2, MUNE, denervation, reinnervation, ultrasound nerve imaging, neuropathy

## INTRODUCTION

Neurofibromatosis type 2 (NF2) is a hereditary tumor syndrome caused by loss of function mutations or deletion of the neurofibromatosis type 2 gene (*NF2*) located on chromosome 22q12.<sup>1</sup> This gene encodes merlin, a multi-functional cellular protein (see<sup>2</sup> for a recent review). Symptoms of neuropathy are common in NF2 as there are paresthesias, sensory loss, weakness, and muscle atrophy. Neuropathic pain, however, occurs in few patients only.<sup>3-7</sup> The aim of the present study was to test novel methods which may help to quantify and follow up the NF2-associated neuropathy. For example, in the last few years, attempts to treat NF2 with pharmacological tools have led to the discovery that the anti-vascular antibody bevacizumab can at least stop the growth of tumors in many NF2 patients (e.g.<sup>8-10</sup>). In addition, it has been described, recently, that an anti-angiogenesis treatment can improve the neuropathy in a murine sciatic nerve model of NF2.<sup>11</sup> However, the effect of pharmacological treatment strategies on the NF2-associated neuropathy in patients has not yet been described. One reason for this may be the lack of methods suitable to quantify motor axon pathology in NF2.

A conventional electrophysiological examination of peripheral nerves includes, among other parameters, the determination of the amplitude of CMAPs. This parameter, however, offers only a rough estimation of the number of functionally intact motor axons in peripheral nerves. Reinnervation by collateral sprouting may keep the amplitude constant in spite of a loss in the number of motor units and axons.<sup>12, 13</sup> In fact, apparently normal CMAPs have been recorded in amyotrophic lateral sclerosis (ALS) although the number of intact motor axons was reduced by 50 %.<sup>14</sup>

In the last years, several methods have been developed to estimate the number of intact motor units in a peripheral nerve (MUNE).<sup>15-17</sup> It is now an accepted view that concurrent tracking of declines in MUNE and changes in single motor unit size over time have proven useful for research into the natural history of denervating disease, as well as the compensatory effects of collateral reinnervation.<sup>17</sup>

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3 Muscle action potential scans (CMAP scans), too, have been found to be useful in  
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5 several types of motor neuron diseases and neuropathies.<sup>18,19</sup> In the present study, we have  
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7 used the MScanFit program, recently developed by one of the authors (HB) to model a CMAP  
8  
9 scan.<sup>20</sup> Here we demonstrate that this analysis software can reveal denervation, but also  
10  
11 reinnervation in peripheral nerves and muscles in NF2 patients.  
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14 Peripheral nerve imaging carried out by high resolution ultrasound techniques can be  
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16 performed with high spatial resolution<sup>21</sup> and findings on the median nerve have already been  
17  
18 described.<sup>e.g. 22-24</sup> It has been shown that his method allows the detection and quantification of  
19  
20 schwannomas in peripheral nerves.<sup>25</sup> In the present study, we have combined CMAP scan  
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22 MUNE with ultrasound imaging (US) to test whether these methods may help to quantify and  
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24 to follow-up the NF2-associated neuropathy.  
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## MATERIALS and METHODS

### Patients

The study is based on measurements of 19 NF2 patients aged between 12 to 70 years (mean  $\pm$  SE:  $34.5 \pm 2.9$  years; 12 males, 7 females). The diagnosis of NF2 in these patients was established on the basis of the modified NIH criteria for definite NF2<sup>26</sup> and verified by genetic testing. Other concurring causes for a neuropathy such as diabetes mellitus, alcoholism etc. were excluded by means of medical history and laboratory testing. All procedures were approved by the local ethics committee of Hamburg University Hospital and all patients gave written formal consent. Not all patients were examined by both, electrophysiology and nerve ultrasound imaging on both arms. This is due to organizational reasons (studies in two clinical departments), a change in the study design from one arm to both arms, and insufficient CMAP recordings (see Results for details).

### Electrophysiology

The CMAP scans were performed in the neurofibromatosis outpatient clinic of the Hamburg-Eppendorf University Hospital. QTRACW software (© Institute of Neurology, London) was available on a laptop with a Windows7 operating system. The other components of the set-up were the DS5 isolated bipolar constant current stimulator (Digitimer Ltd; Welwyn Garden City, UK), National Instruments USB-6251-BNC data acquisition device (National Instruments Munich; Germany), the Hum Bug 50 Hz noise eliminator (Science Products; Hofheim, Germany), and a Grass LP511 AC amplifier; bandwidth: 3 – 3 kHz. Self adhesive electrodes (Kendall ECG electrodes, H92SG) with a round conducting area of 15 mm in diameter were used for both stimulation and recording. The position of these electrodes were as in conventional use, stimulating the median nerve at the wrist, and recording CMAPs from the motor point of abductor pollicis brevis. For grounding, Neuroline 71410-M/1 electrodes (Ambu; Bad Nauheim, Germany) were used.

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3 In addition, conventional electrodiagnostic testing of the median nerve (in particular  
4 determination of nerve conduction velocities in the upper and the forearm) was performed in  
5 the neurophysiology laboratory of the Hamburg-Eppendorf University Hospital by using a  
6 Nihon Kohden Neuropack X1. In median motor nerve studies, the recording site was the  
7 abductor pollicis brevis muscle. Stimulation sites were chosen at the wrist, the antecubital  
8 fossa, and the axilla.

### 15 **Muscle action potential scans**

16  
17 Previously, the principles of CMAP scans or electrophysiological muscle scans have been  
18 described.<sup>18, 19</sup> These authors tested the importance of variables, such as stimulation  
19 frequency, stimulus duration, and the number of stimulus steps.<sup>27</sup> The analysis of CMAP  
20 scans is, however, not yet standardized. The method used in the present study (MScanFit) has  
21 been described in detail.<sup>20</sup> MScanFit is available as part of the threshold tracking software  
22 QTRACW (© Institute of Neurology, University College London, distributed by Digitimer  
23 Ltd at [www.digitimer.com](http://www.digitimer.com)). It was chosen for its convenience and speed. In brief, the peak  
24 CMAP amplitude was recorded while stimuli were delivered at a frequency of 2 Hz. The  
25 stimulus current was decreased from just supramaximal in 0.2% steps to a current strength  
26 just below the one necessary for the smallest measurable surface muscle action potential. The  
27 data plots were fitted by a model, in which the CMAP was made up of a number of SMUPs,  
28 each described by an amplitude, threshold and relative spread (or coefficient of variation) of  
29 threshold. From this fitted model, the following derived parameters were used for the  
30 analyses: (1) number of SMUPs, (2) mean SMUP amplitude, and (3) largest SMUP  
31 amplitude.

### 51 **Ultrasound peripheral nerve imaging**

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53 Ultrasound examinations were performed using a GE Healthcare LOGIQ E9 with a L8 18i  
54 linear hockey stick probe. To improve image quality, CrossXBeam and compound imaging  
55 software was used. Median nerves were scanned in the transverse plane along their entire  
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3 accessible length from axilla to wrist. Cervical roots and the plexus cervicobrachialis were not  
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5 scanned and, therefore, not included in the analysis. The cross-sectional area (CSA) of the  
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7 median nerve was recorded at predetermined sites: at the carpal tunnel, at 1/3 of the forearm,  
8  
9 at the elbow, at 1/2 of the upper arm. Fascicle diameters were measured in each median nerve  
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11 at three different sites, to generate normal diameter values ( $0.6 \pm 0.13$  mm; mean  $\pm$  SD).  
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13 All “nerve lesions” within the scanned segments of the median nerve were included in the  
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15 further analysis. Nerve lesions were defined as focal well defined masses inside the  
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17 epineurium with a middle to low homogeneous echogeneity, which allowed a clear  
18  
19 differentiation of the lesion from unaffected fascicles. Only masses inside the epineurium with  
20  
21 an enlargement of the fascicle diameter  $> 2$ fold in comparison to the mean fascicle diameter  
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23 were defined as focal “nerve lesions” or schwannoma-like fascicular enlargements. Since  
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25 small nerve lesions did not results in an increase of the CSA of the affected nerve segment,  
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27 the CSA was not used to define nerve lesions.  
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### 31 32 **Statistics**

33  
34 GraphPad Prism and statistical analysis software in QTRACP were used for basic statistics  
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36 and scatter plots regression lines.  
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## RESULTS

### **MScanFits reveal number of functionally intact motor axons**

CMAP scans were recorded from 27 median nerves of 19 patients with NF2. The analysis is restricted to recordings with a stable amplitude of the maximal CMAP amplitude during the recording period with the maximal stimulus strength., a biphasic shape of the CMAP, no measurable responses to stimuli with low stimulation strength, the absence of disturbing 50 Hz noise, and no voluntary movements. Representative examples of such recordings are illustrated in Fig. 1. Illustrated in the left column of Fig. 1 are CMAPs taken at different stimulation strengths. These representative examples illustrate the shape of the CMAPs. A superposition of all traces (up to several hundred) would reduce the clarity. The MScanFit analyses shown in the center and right column estimated not only the number of functionally intact motor units, but also the relative amplitudes of the component SMUPs. Note that the maximal amplitudes of the CMAPs in the three examples of Fig. 1 are within a normal range of 5 - 8 mV (from base to peak amplitude). In contrast, the numbers of functionally intact motor axons differ clearly (from 35 to 120). It can also be seen that there is an inverse relationship between the number and the mean amplitude of the SMUPs.

We also tested for a correlation between the estimated number of functionally intact motor fibers and other parameters (see Fig. 2). The graph in Fig. 2A shows, not surprisingly, that larger CMAP amplitudes tended to be made up of higher numbers of SMUPs. On the other hand, it can be seen that some CMAPs of normal amplitudes are seen in CMAP scans with a rather low number of functionally intact motor units.

No clear relationship was found between the number of motor units and the conduction velocity of the median nerve in the upper or lower arm (Fig 2B). The conduction velocity in all patients was within a normal range. On the other hand, a strong negative correlation was found between the number of functionally intact motor units and the voltage

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3 amplitude of SMUPs (Fig. 2C): peripheral nerves with a reduced number of motor axons  
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5 show larger amplitudes of both the mean and the largest amplitude of SMUPs. This finding  
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7 can be explained by reinnervation (see Discussion).  
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10 The MScan MUNE data from the NF2 patients were compared with recordings  
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12 obtained from 18 control subjects (age 20-67 years; mean  $\pm$  SE :  $38.6 \pm 3.5$ ; 12 females, 6  
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14 males; 26 median nerves). A summary of the findings is illustrated in Fig. 3. In several of the  
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16 NF2 patients, the number of functionally intact motor units is below 70 in spite of a CMAP  
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18 amplitude above 5 mV. It can be seen that an increase in the mean amplitude of SMUPs is the  
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20 underlying factor.  
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### 23 24 25 **Ultrasound peripheral nerve imaging in neurofibromatosis type 2.**

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27 The cross sectional areas along the right and left median nerves of 14 NF2 patients were  
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29 measured at the carpal tunnel, at 1/3 of the forearm, at the elbow, and at 1/2 of the upper arm.  
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31 A summary of the findings is given in Table 1. These data from NF2 patients can be  
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33 compared with reference values for ultrasonography data of median nerves in control subjects.  
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35 <sup>22, 23</sup> According to these data, we did not find a general enlargement of the CSA in the median  
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37 nerves of NF2 patients.  
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41 On the other hand, a rather common observation in ultrasonographic images of NF2  
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43 patients was the presence of schwannoma-like fascicular enlargements. These are focal well-  
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45 defined masses inside the perineurium with a middle to low homogeneous echogeneity, which  
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47 allowed a clear differentiation from unaffected fascicles (see Fig. 3). All schwannoma-like  
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49 fascicular enlargements (“nerve lesions”) were in direct relationship to the median nerve. A  
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51 centric location inside the median nerve was observed in 95% whereas 5% had an eccentric  
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53 location. The contour exhibited well defined margins in 72%, poorly defined margins were  
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55 found in 28%. The shape was fusiform in 87%, an oval shape was found in 13%. The internal  
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57 echogeneity was homogeneous hypoechoic in 92%, a hyperechoic echogeneity was found in  
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3 8%. An echogenic capsule, cystic changes, target signs or microlobulations were not found in  
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5 any of the “lesions”. They were distant from each other and separated by nerve segments with  
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7 normal fascicular structure. We did not detect any “nerve lesions” with diffuse and  
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9 multilobular enlargement, which is characteristic for plexiform neurofibromas.  
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11 Schwannoma-like fascicular enlargements (“nerve lesions”) were seen in 15 median  
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13 nerves of the 26 median nerves studied in 14 patients. The number of these fascicular  
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15 enlargements varied between one and more than five in affected nerves. Table 2 summarizes  
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17 the number and size of the “nerve lesions”. The diameter varied from >1.6 mm to 7 mm. For  
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19 comparison, Schreiber et al.<sup>22</sup> reported, for controls, a fascicular diameter in the forearm  
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21 median nerve of  $0.60 \pm 0.21$  mm (mean  $\pm$  SD).  
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#### 27 **Do schwannoma-like fascicular enlargements correlate with CMAP scan MUNE?**

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29 In 14 NF2 patients, both CMAP scan MUNE and high resolution US images were obtained  
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31 from 19 median nerves. We tested whether the number and size (diameter) of the  
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33 schwannoma-like fascicular enlargements are correlated with the loss of functionally intact  
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35 motor axons in the median nerves of these NF2 patients. The data are illustrated in Fig. 4.  
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37 There was a correlation between the number of lesions and the loss of functionally intact  
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39 motor units. However, the regression line did not reach significance ( $p = 0.065$ ). This may be  
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41 due to some patients in which denervation of the thenar muscle, but no “nerve lesions” were  
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43 found. Furthermore, the diameter of the largest schwannoma-like fascicular enlargements  
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45 clearly did not show a statistically significant correlation with the loss of functionally intact  
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47 motor units. There might be more and larger “nerve lesions” in more proximal parts of the  
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49 motor nerve fibers not covered by the US imaging in the present study.  
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## DISCUSSION

In the present study of NF2 patients, parameters of conventional neurography (maximal amplitude of the CMAP and nerve conduction velocity (CV)) were supplemented by CMAP scan MUNE and US imaging. The low amplitudes of the CMAP in some patients, together with normal CVs (Fig. 2), are in accordance with the description of an “axonal” type of neuropathy in NF2 patients.<sup>3, 5, 6</sup> In comparison to conventional techniques, however, the CMAP scan analyses can provide more quantitative data about the number of functionally intact motor axons in peripheral nerves and can help to quantify the extent of denervation. For example, a rather low number of motor units can be seen although the maximal amplitude of the CMAP is in the normal range (Fig. 2A).

In addition, denervation is correlated with an increase in the voltage amplitude of SMUPs. In fact, the mean amplitude of SMUPs is larger in nerves with low as compared to high numbers of functionally intact motor fibers (Fig.2C). This observation is similar to earlier reports about the characteristics of SMUPs in NF2<sup>3</sup> and other partially denervated muscles such as in ALS, CMT, diabetic neuropathy and chronic demyelinating neuropathies.<sup>12,19, 28-31</sup> According to these studies, it is very likely that reinnervation of denervated muscle endplates by means of axonal collateral sprouting<sup>12</sup> is the underlying mechanism in NF2 patients, too. Taken together, the combination of a low number of functionally intact motor units and an increase in the mean amplitude of SMUPs (see Fig. 3) may help to support the diagnosis of neuropathy in NF2 patients.

The high resolution ultrasonography nerve images revealed the presence of “nerve lesions” (i.e. schwannoma-like fascicular enlargements) in many NF2 patients (Fig. 4). These lesions might be small tumors (schwannomas) composed of proliferating Schwann cells as described in histological studies of sural nerve biopsies in NF2 patients.<sup>3-6, 32</sup> It has been described already that nerve schwannomas can be detected by ultrasound imaging and a case

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3 report of a single NF2 patient has been published.<sup>25,33</sup> Furthermore, multiple schwannomas  
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5 along peripheral nerve trunks have been found in a recently developed murine model of NF2.  
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7<sup>34</sup> It is, however, important to note that US imaging in the present study is restricted to the  
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9 trunk of the median nerve between wrist and axilla. On the other hand, the follow-up of such  
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11 known “nerve lesions” may be sufficient, for example, to monitor the effect of drug  
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13 treatments on the size of peripheral nerve tumors in NF2.  
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17 The second parameter tested by US imaging in our study was the cross sectional areas  
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19 of several regions in the median nerves outside schwannoma-like fascicular enlargements.  
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21 The CSA data, however, did not differ from recently published reference values for  
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23 ultrasonography of peripheral nerves (Table 1).<sup>22, 23</sup> It remains unclear, therefore, why nerve  
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25 lesions/tumors in NF2 patients are restricted to few nerve regions only.  
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28 By demonstrating specific ultrasound changes in NF2 patients our study shows, that  
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30 high resolution ultrasound can support the differential diagnosis of NF2-associated  
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32 neuropathies from other hereditary or acquired neuropathies and also entrapment syndromes.  
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34 In contrast to hereditary demyelinating neuropathies, e.g. CMT-1a and CMT-1b, we did not  
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36 see a diffuse and extensive enlargement of the cross sectional area or fascicular diameter of  
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38 the median nerve.<sup>22, 24, 35</sup> In NF2 patients, CSA values and fascicular diameter did not differ  
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40 from standard values in unaffected nerve segments. Nerve segments at entrapments sites, e.g.  
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42 the carpal tunnel, were similarly not affected in NF2 patients, allowing a differentiation from  
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44 patients with hereditary neuropathy with liability to pressure palsies (HNPP) or entrapment  
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46 syndromes.<sup>24</sup>  
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50 Focal nerve enlargements are also described for acquired inflammatory  
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52 demyelinating neuropathies, e.g. chronic inflammatory demyelinating polyradiculoneuropathy  
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54 (CIDP). In CIDP patients either diffuse (37-41%) or multifocal enlargement of nerves is  
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56 reported.<sup>35, 36</sup> Another ultrasound pattern seen in CIDP patients are large nerves with hypo-  
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58 and hyperechoic fascicles.<sup>37</sup> As discussed above we did not find similar diffuse or multifocal  
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3 enlargements of the nerves / fascicles or changes in echogenicity in NF2 patients. In the NF2  
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5 cohort, increased CSA values were only detectable in short and clearly defined segments  
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7 associated with schwannoma-like fascicular enlargements.  
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10 Only few reports describe ultrasound images of tumors associated with large  
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12 sensomotoric peripheral nerves in NF1.<sup>38-40</sup> These appear with low homogeneous  
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14 echogeneity in single or multiple fascicles. Recently, possible criteria to distinguish  
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16 neurofibroma from schwannoma in high resolution US nerve images have been discussed.<sup>41</sup>  
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18 We would like to emphasize that all patients in our study were diagnosed as NF2 according to  
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20 current diagnostic criteria.  
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23 The pathogenesis of neuropathy in NF2 patients is unclear. We, therefore, have  
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25 analyzed our data to see whether they may support one of the hypotheses. One possible factor  
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27 is the cumulative nerve compression caused by small tumors (schwannomas) or fascicular  
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29 microlesions as discussed in earlier studies.<sup>3-7, 32</sup> Our data can give some support for this  
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31 view. They indicate that the number of “nerve lesions” is higher in nerves with a loss of  
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33 functionally intact motor axons (Fig. 5). The statistical analysis of this correlation, however,  
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35 does not reach significance (Fig. 5). This may indicate that some tumors remain undetected by  
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37 the nerve US imaging applied in the present study, which was restricted to the median nerve  
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39 distally from the axilla. Also, we cannot exclude the possibility that other factors produce  
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41 denervation in NF2 patients. Indeed, a clinical study describes that NF2 may affect peripheral  
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43 nerve structures in a manner distinct from a compressive schwannoma.<sup>42</sup>  
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47 Referring to this, it has been described that the loss or diminution of merlin in  
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49 peripheral nerve fibers may cause the neuropathy in NF2 patients independently from the  
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51 presence of Schwann cell tumors.<sup>43-45</sup> The authors discuss an important role of merlin in  
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53 neuronal cell types concerning neuromorphogenesis, axon structure maintenance and  
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55 communication between axons and Schwann cells. It is possible, therefore, that NF2-related  
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57 neuropathy is of multifactorial origin (Helen Morrison in<sup>46</sup>). Also, there might be a  
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3 combination of several factors. For example, small lesions due to proliferating Schwann cells  
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5 may be atypically destructive to axons with abnormal expression of merlin. Such a  
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7 combination of factors could explain why there is an asymmetric dysfunction of motor axons  
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9 in some NF2 patients and why the functionally intact axons retain the ability for collateral  
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11 sprouting.  
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14 In summary, our data show that CMAP scan MUNE and high-resolution US  
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16 peripheral nerve imaging are useful complimentary methods for assessing neuropathy in NF2  
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18 patients. These non-invasive methods may be helpful not only for the diagnosis but also to  
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20 follow-up the time course of muscle denervation and reinnervation. In addition, repeated  
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22 nerve imaging would enable to observe the development in the number and size of  
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24 schwannoma-like fascicular enlargements. From a practical point of view, these methods  
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26 would be feasible for routine use in specialized centers.  
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**Abbreviations**

<b>APB</b>	M. abductor pollicis brevis
<b>ALS</b>	amyotrophic lateral sclerosis
<b>CIDP</b>	chronic inflammatory demyelinating polyradiculoneuropathy
<b>CMAP</b>	compound muscle action potential
<b>CMT</b>	Charcot-Marie-Tooth neuropathy
<b>CSA</b>	cross sectional area
<b>CV</b>	conduction velocity
<b>HNPP</b>	hereditary neuropathy with liability to pressure palsies
<b>MScan</b>	muscle action potential scan
<b>MUNE</b>	motor unit number estimate
<b>NF1</b>	neurofibromatosis type 1
<b>NF2</b>	neurofibromatosis type 2
<b>SMUP</b>	single motor unit action potential
<b>US</b>	ultrasound



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**TABLE 1.**

Cross sectional areas along the median nerves of NF2 patients.

<b>cross sectional area</b>	<b>NF2</b>		
<b>CSA</b>	<b>patients</b>		
<b>right median nerve</b>	<b>number</b>	<b>mean (mm<sup>2</sup>)</b>	<b>± SD</b>
carpal tunnel	13	7.77	1.64
1/3 of the forearm	14	7.79	2.72
at the elbow	14	8.86	2.74
½ of the upper arm	14	8.64	2.10
<b>left median nerve</b>			
carpal tunnel	12	9.33	4.40
1/3 of the forearm	12	7.33	1.30
at the elbow	12	9.00	2.30
½ of the upper arm	12	9.83	2.82

**TABLE 2.**

Number and size of schwannoma-like fascicular enlargements  
in the median nerves of NF2 patients

<b>nerve lesions number</b>	<b>NF2 patients</b>	<b>diameter 1.6 – 2.5 mm</b>	<b>diameter 2.6 – 5.0 mm</b>	<b>diameter &gt; 5.0 mm</b>
<b>right median nerve</b>	n = 14			
no lesion	5			
1	3	1	2	
2	3	3	3	
3	1	1	1	1
4	1	1	2	1
≥ 5	1	3	4	2
<b>left median nerve</b>	n = 12			
no lesion	6			
1				
2	1	1	1	
3	3	3	6	
4	1	2	2	
≥ 5	1	6	2	3



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3 **FIGURE LEGENDS**  
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7 **FIGURE 1.** Examples of CMAP scan analyses in three NF2 patients (**A, B, C**). The left  
8 column illustrates examples of CMAPs recorded from APB after stimulation of the median  
9 nerve at the wrist with subthreshold to supramaximal stimulation. The peak amplitudes  
10 (measured from base to the negative maximum) of all CMAPs are plotted for the various  
11 stimulation strengths (middle column). In the right column, the MScanFit program was used  
12 to derive a model with several SMUPs of different amplitudes to match the stimulus-response  
13 plots in the center column. The maximal number of functionally intact motor units and the  
14 mean voltage amplitude of the SMUPs for patients A, B, and C are given as insets in the  
15 middle and right column.  
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29 **FIGURE 2.** Statistical analyses. The number of functionally intact motor units was tested for  
30 a possible correlation with other parameters. The insets in all graphs show the results of the fit  
31 with regression lines. Low numbers of SMUPs in APB do not show a correlation with the  
32 nerve CV in the forearm or upper arm (**B**). There is, however, a statistically significant  
33 correlation with the peak amplitude of the CMAP, the mean amplitude of SMUPs, and the  
34 voltage amplitude of the largest SMUP.  
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45 **FIGURE 3.** Summary of MScan MUNE data in NF2 patients and from 26 median nerves of  
46 18 control subjects. The maximal amplitude of the CMAP, the number of functionally intact  
47 motor units, and the mean amplitude of SMUPs are illustrated in scatter (**A, C**) and dot plots  
48 (**B, D**). The bars in **B, D** indicate mean  $\pm$  SE.  
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56 **FIGURE 4.** Examples of “nerve lesions” (i.e. schwannoma-like fascicular enlargements) in a  
57 NF2 patient. Longitudinal (a, b, c) and transverse (d, e, f) sonograms of the right median  
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3 nerve reveal well defined “lesions” of different diameters: (d) > 7 mm, (e) about 4 mm, (f)  
4 about 2 mm. The “lesions” show a middle to low homogeneous echogeneity and are located  
5 in direct continuity of the nerve inside the hyperechogenic epineurium. The outer borders of  
6 the nerve and the schwannoma-like fascicular enlargements are marked by yellow dotted  
7 lines.  
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16 **FIGURE 5.** Correlation of findings in high resolution US nerve imaging with the number of  
17 functionally intact motor units detected by CMAP scan MUNE. The number (A) and the  
18 diameters of the largest schwannoma-like fascicular enlargements (B) in an affected nerve are  
19 illustrated. (A) Data from 20 median nerves of 14 NF2 patients. (B) Data from schwannoma-  
20 like fascicular enlargements detected in 11 median nerves from 9 NF2 patients. The insets  
21 show egression line statistics.  
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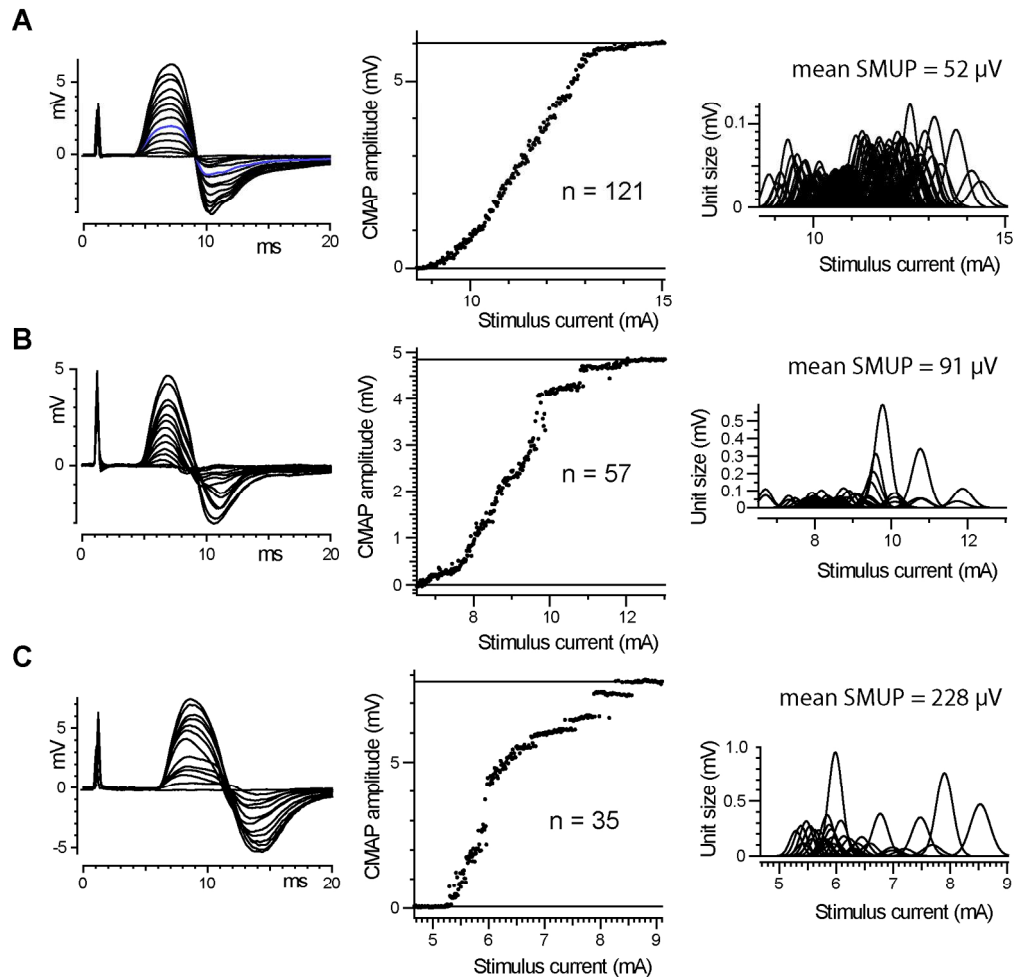


FIGURE 1. Examples of CMAP scan analyses in three NF2 patients (A, B, C). The left column illustrates examples of CMAPs recorded from APB after stimulation of the median nerve at the wrist with subthreshold to supramaximal stimulation. The peak amplitudes (measured from base to the negative maximum) of all CMAPs are plotted for the various stimulation strengths (middle column). In the right column, the MScanFit program was used to derive a model with several SMUPs of different amplitudes to match the stimulus-response plots in the center column. The maximal number of functionally intact motor units and the mean voltage amplitude of the SMUPs for patients A, B, and C are given as insets in the middle and right column. 169x165mm (300 x 300 DPI)

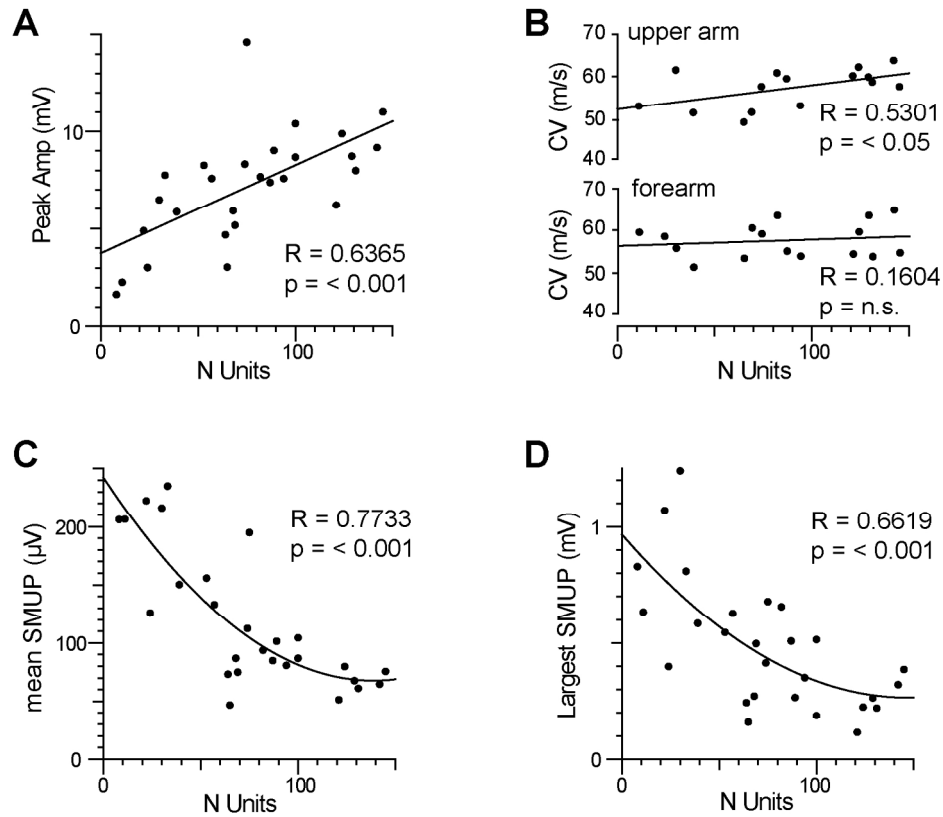


FIGURE 2. Statistical analyses. The number of functionally intact motor units was tested for a possible correlation with other parameters. The insets in all graphs show the results of the fit with regression lines. Low numbers of SMUPs in APB do not show a reduction of the nerve conduction velocity in the forearm or upper arm (B). There is, however, a statistically significant correlation with the peak amplitude of the CMAP, the mean amplitude of SMUPs, and the voltage amplitude of the largest SMUP (A, C, D).

171x157mm (300 x 300 DPI)

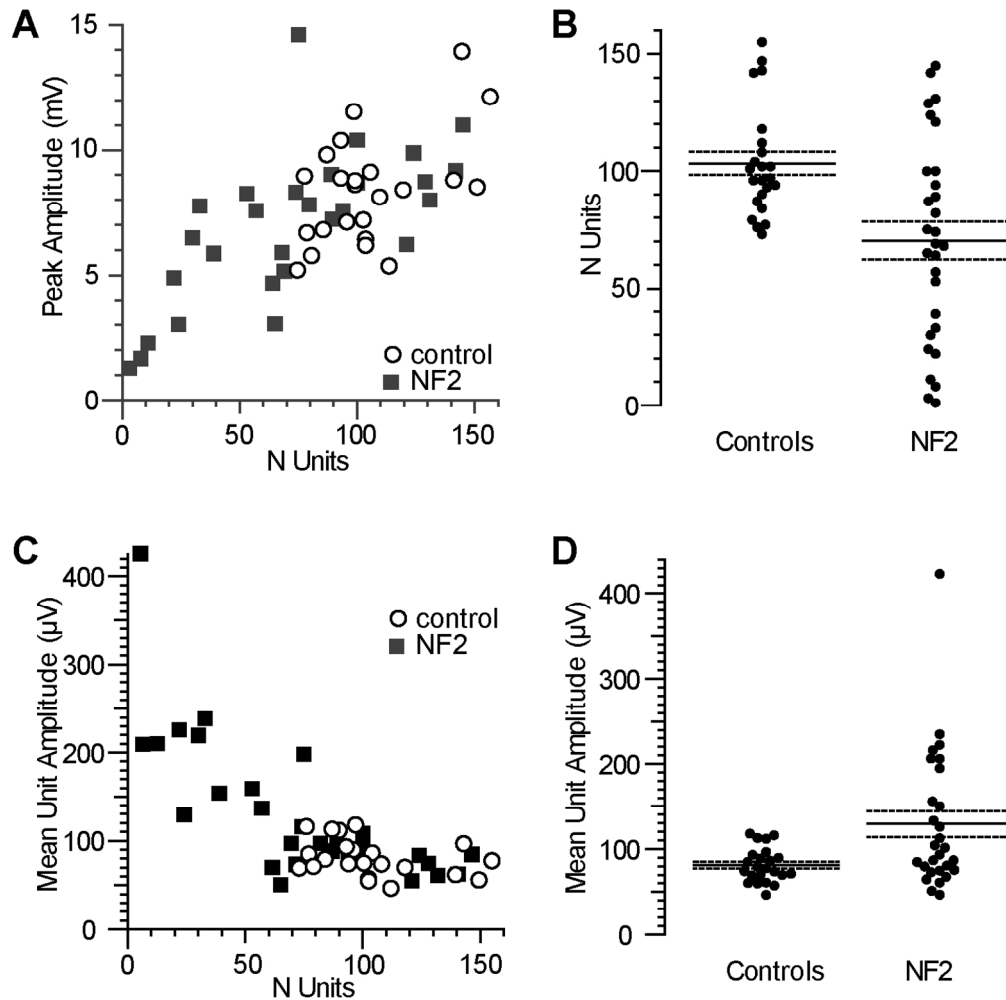


FIGURE 3. Summary of MScan MUNE data in NF2 patients and from 26 median nerves of 18 control subjects. The maximal amplitude of the CMAP, the number of functionally intact motor units, and the mean amplitude of SMUPs are illustrated in scatter (A, C) and dot plots (B, D). The bars in B, D indicate mean + SE.

127x128mm (300 x 300 DPI)

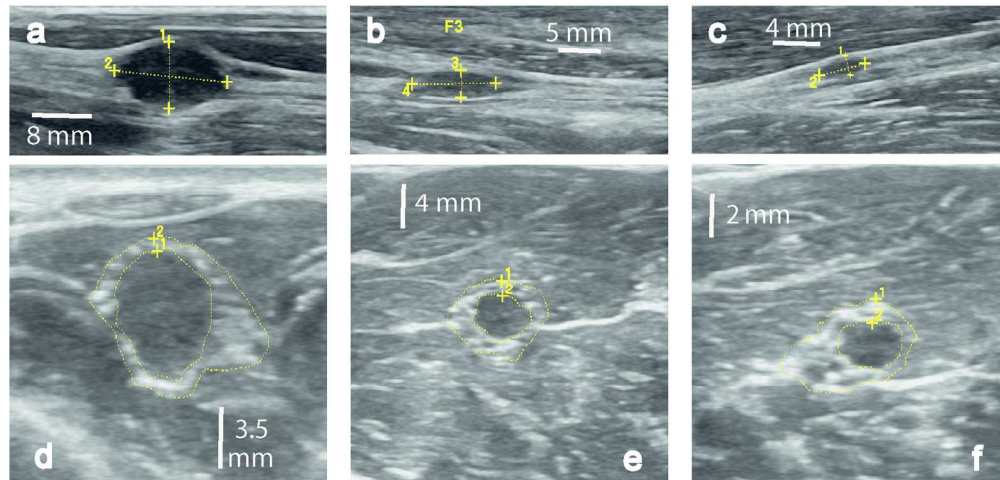


FIGURE 4. Examples of “nerve lesions” (i.e. schwannoma-like fascicular enlargements) in a NF2 patient. Longitudinal (a, b, c) and transverse (d, e, f) sonograms of the right median nerve reveal well defined “lesions” of different diameters: (d) > 7 mm, (e) about 4 mm, (f) about 2 mm. The “lesions” show a middle to low homogeneous echogeneity and are located in direct continuity of the nerve inside the hyperechogenic epineurium. The outer borders of the nerve and the schwannoma-like fascicular enlargements are marked by yellow dotted lines.

151x72mm (300 x 300 DPI)

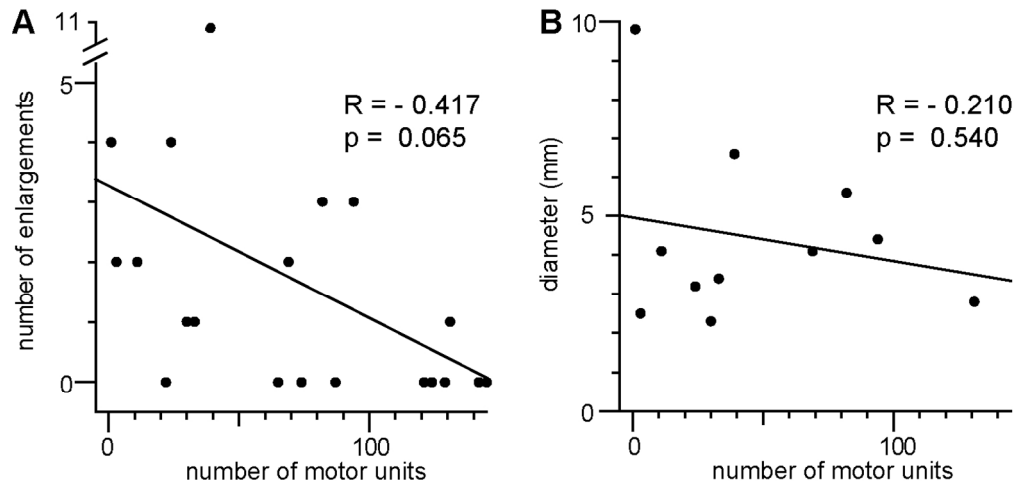


FIGURE 5. Correlation of findings in high resolution US nerve imaging with the number of functionally intact motor units detected by CMAP scan MUNE. The number (A) and the diameters of the largest schwannoma-like fascicular enlargements (B) in an affected nerve are illustrated. (A) Data from 20 median nerves of 14 NF2 patients including those patients without a "nerve lesion". (B) Data from schwannoma-like fascicular enlargements detected in 11 median nerves from 9 NF2 patients. The insets show regression line statistics.  
128x61mm (300 x 300 DPI)