Do PTK2 gene polymorphisms contribute to the interindividual variability in muscle strength and the response to resistance training? A preliminary report

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Muscle force is transmitted to the tendon along the length of a muscle fiber and also laterally via attachments to the surrounding matrix of connective tissue (27). It has been suggested that an increase in lateral attachments after resistance training might result in enhanced muscle specific force [maximum force per unit physiological cross-sectional area (PCSA)] (7, 12). Such attachments have been identified as intrasarcosomal protein complexes known as “costameres” (19), which are associated with the lateral transmission of muscle fiber force (6). Therefore, costameres could enable each muscle fiber to act as multiple force-generating units, thus increasing the specific force of the whole muscle.

Mechanical tension is essential in regulating costameric protein expression (29) and resistance training is known to modulate the expression of costameric proteins, such as desmin (32), alpha-1-syntrophin, and dystrophin (14) in humans, while focal adhesion kinase (FAK) and paxillin expression and activity are increased in stretch-induced hypertrophied rooster skeletal muscle (11). The integrin-associated tyrosine kinase, FAK, has been shown to play a major role in costamere formation and turnover (4, 20), and FAK expression is controlled at the level of the protein tyrosine kinase-2 (PTK2) gene. Therefore, polymorphisms of the PTK2 gene could potentially underpin the considerable interindividual variability reported in untrained human muscle specific force [ranging from 22 to 40 N/cm² (8)], and in the training-induced relative change in specific force, which varies between −5% and +39% (9).

As muscle strength and training responses are important from a clinical perspective, e.g., the response to rehabilitation following injury, we aimed to elucidate whether single-nucleotide polymorphisms (SNPs) of the PTK2 gene were associated with in vivo muscle specific force and functional measures of strength, both before and after resistance training. We hypothesized that two PTK2 SNPs (the intronic rs7843014 and the 3'-UTR rs7460 SNP) would be associated with quadriceps femoris (QF) muscle specific force and with the change in specific force following training.

MATERIALS AND METHODS

Participants. Fifty-one untrained Caucasian males [aged 20.3 ± 3.1 yr, height 178.1 ± 5.6 cm, body mass 75.4 ± 10.6 kg, body mass index (BMI) 23.7 ± 2.6 (means ± SD)] provided written informed consent before their involvement in the study, which complied with the Declaration of Helsinki and was approved by the local ethics committee of the Manchester Metropolitan University.

Habitual physical activity rating. The habitual physical activity rating (PAR) of each participant was assessed by questionnaire (2) immediately before the training period. The overall PAR was scored using a scale from 1 to 5 points, where 1 was the least active, 3 was intermediate, and 5 was extremely active. Participants were asked to maintain their PAR and habitual dietary intake over the course of the study.

Experimental design. Maximum patellar tendon force, QF muscle volume, physiological cross-sectional area (PCSA), and specific force were determined in the right limb (as described in method 2 of Ref. 8) before and after 9 wk of high-intensity unilateral knee extension...
resistance training (10) in 51 previously untrained men. In addition, all participants had blood samples isolated, which were genotyped for the PTK2 rs747640 A/T and rs7483041 A/C SNPs.

Progressive resistance training. The supervised resistance training protocol has been described in detail elsewhere (10). Briefly, supervised knee extension training was performed unilaterally three times per week for 9 wk. The maximum training load that could be lifted once only (1-RM) throughout the full range of knee extension (110° to 20° of knee flexion; 0° = full knee extension) was assessed at the beginning of the training program and reevaluated at the start of each week on a standard knee extension machine (Technogym, Gambettola, Italy). The training intensity was set in relation to the 1-RM and was therefore progressively increased throughout the 9 wk of training. Each session comprised a warm-up set of 10 knee extension repetitions at 40% of the revised 1-RM, followed by four sets (2 min rest between each) of 10 repetitions at 80% 1-RM. Compliance with the training protocol was 100%, with each participant completing all 27 training sessions.

Maximum patellar tendon force. The method used to assess maximum patellar tendon force has been explained in detail elsewhere (8). In summary, participants performed isometric knee extension maximal voluntary contractions (MVCs) on a dynamometer (Cybex Norm, Cybex International, Ronkonkoma, NY) at optimum knee joint angle, which ranged from 70 to 90° knee flexion. Participants were seated with a hip angle of 85° (supine = 180°) and were fixed with inextensible straps to the strength-testing chair. Contraction torque of the antagonist muscles during knee extension MVC was calculated by comparing electromyographic activity of the biceps femoris muscle during maximal isometric knee extension and maximal isometric knee flexion (21). Two bipolar silver chloride surface electrodes (Neuroline, Medicotest, Rugmarken, Denmark) were placed 20 mm apart along the sagittal axis over the muscle belly (the location was recorded on an acetate for further tests) and one reference electrode was positioned over the lateral tibial condyle. The root mean square of the raw EMG signal was calculated over 1 s around the peak torque during each maximum voluntary isometric knee extension and flexion at optimum joint angle and the torque produced by the hamstrings during knee extension was estimated assuming a linear relationship between torque and EMG activity (21). The estimated antagonist torque obtained at the optimum knee extension angle was used to calculate the maximum overall knee extension torque. Voluntary QF muscle activation was assessed using the interpolated twitch technique (25), whereby the participant received a supramaximal twitch (Digitimer stimulator model DS7, Welwyn Garden City, UK) via two 7.5 cm × 12.5 cm self-adhesive electrodes (Versastim, Conned, New York, NY) placed distally (anode) and proximally (cathode) over the QF muscle, once before MVC (control twitch) and once during MVC. True maximum torque (TMT) was calculated as TMT = MVC(C) × (1 − r/T)−1, where r is the amplitude of the superimposed twitch, T is the value of the twitch before the MVC, and MVC(C) is MVC corrected for antagonist muscle coactivation.

The patellar tendon moment arm (dPT) was determined using a 0.2-T magnetic resonance imaging (MRI) scanner (G-Scan, Esaote Biomedica, Genoa, Italy), as previously described (30). Sagittal and coronal-plane knee scans were acquired using a Turbo 3D T1-weighted sequence with the following scanning parameters: time of repetition 40 ms; time to echo 16 ms; matrix 256 × 256; field of view 180 mm × 180 mm; slice thickness 3.4 mm; interslice gap 0 mm. The knee was scanned at rest with the participant in the supine position and the knee fully extended. Coronal scans were used to identify the appropriate sagittal scans, which were used to locate the center of rotation (COR), i.e., the midpoint of the shortest distance between the two femoral condyles and the tibial plateau, and dPT was defined as the perpendicular distance between the COR and the axis of the patellar tendon (30). Previously reported ratios of dPT at full extension (0° knee flexion) to dPT at 70°, 80°, and 90° knee flexion (3) were used to calculate dPT at optimum knee joint angle in this study. Subsequently, maximum force resolved at the patellar tendon (FP) was calculated as FP = TMT/dPT.

Muscle physiological cross-sectional area (PCSA). QF muscle PCSA was determined from a method that has been described in detail previously (2) method (2 of Ref. 8). In brief, ultrasonography (MyLab25, Esaote Biomedica, Genoa, Italy) was used to identify femur length [the distance from the proximal origin of the vastus lateralis (VL) muscle to the tibiofemoral contact point]. The anatomical cross-sectional area (ACSA) of each of the four constituent QF heads and a series of regression equations. VL muscle fascicle length (Lf) and pennation angle (θp) were measured during knee extension MVC at optimum knee angle using ultrasonography at 50% of the muscle length along the mid sagittal plane. Dividing Vm by VL muscle Lf provided QF PCSA [VL Lf has been shown to be representative of the Lf for the whole QF muscle group (8)].

In vivo muscle specific force. QF muscle force is reduced when resolved along the patellar tendon according to the θp. Therefore, QF PCSA was multiplied by the cosine of θp, which provided the reduced QF PCSA. Consequently, specific force was determined by dividing FP by the reduced QF PCSA (8).

Blood sampling. A 10-ml blood sample was drawn into 10-ml EDTA tubes (BD Vacutainer Systems, Plymouth, UK) from a superficial forearm vein. The whole blood was aliquotted into 2-ml tubes (Eppendorf AG, Hamburg, Germany) and stored at −80°C until subsequent analysis.

DNA extraction and determination of PTK2 genotype. Automated DNA extraction was performed using a QIAcube (Qiagen, Crawley, UK) in association with the QIAamp DNA Blood Kit (Qiagen, Crawley, UK), and following the QIAamp spin protocol for DNA purification from whole blood.

Real-time polymerase chain reaction (PCR) was performed to determine the genotype of the PTK2 polymorphisms in each participant. Reactions were carried out on 96-well microtiter plates. Each 10-μl reaction volume contained 5 μl Genotyping Master Mix (Applied Biosystem), Foster City, CA), 4.3 μl nuclease-free H2O (Qiagen, Crawley, UK), 0.5 μl genotyping assay mix (Applied Biosystem), Foster City, CA), plus 0.2 μl sample DNA at a concentration of 30 ng/ml and an A260/A280 ratio of 1.7–1.9. TaqMan rs7483041 and rs7460 SNP genotyping assay mix were used, and each mix included the appropriate TaqMan primers and probes.

For control wells, 0.2 μl nuclease-free H2O replaced the DNA template. Following sealing (Microseal “B” adhesive seal, Bio-Rad Laboratories, Hercules, CA) and centrifugation at 8,000 RPM for 1 min, DNA amplification (Chromo4 Real-Time PCR Detection System, Bio-Rad Laboratories) was performed using the following PCR protocol: denaturation at 95°C for 10 min, followed by 40 cycles of incubation at 92°C for 15 s, then annealing and extension at 60°C for 1 min. PTK2 genotypes were ultimately determined using Opticon Monitor 3.1 software (Bio-Rad Laboratories). All samples were analyzed in duplicate and in all cases there was 100% agreement between genotype for samples from the same participant.

We performed the genotyping in accordance with published genotyping and quality control recommendations (5). These included describing genotyping assays and protocols in detail, producing an overview of sample ID and well number before genotyping, including external control samples, incorporating internal controls by genotyping samples in duplicate (from the same DNA collection), comparing current genotype frequencies with previously published frequencies in a similar population, and evaluating the level of agreement with the Hardy-Weinberg principle. The extent of linkage disequilibrium (LD) between the two PTK2 SNPs was investigated by using freely available software (http://linkage.rockefeller.edu ott/eh.htm) to estimate the haplotype frequencies. The difference between the expected and
The observed haplotype frequencies were then calculated and reported as $D^* \text{ and } R^2$.

Statistical analysis. Genotype frequencies for each PTK2 SNP were tested for compliance with the Hardy-Weinberg principle using $\chi^2$ tests. Repeated-measures ANOVAs [within-subjects factor: time (pre- and posttraining); between-subjects factor: group (3 genotype levels)] were used to detect associations between each PTK2 SNP and the interindividual variance in muscle specific force, for both the rs7843014 (ANOVA, genotype $P = 0.659$; Table 1) and the rs7460 (ANOVA, genotype $P = 0.740$; Table 2) SNPs. Furthermore, the PTK2 rs7843014 A/C and rs7460 A/T allele frequencies were similar to those reported elsewhere for Cau-

### RESULTS

**PTK2 genotypes.** The genotype frequencies for the PTK2 rs7843014 (AA = 37.3%; AC = 41.2%; CC = 21.6%) and rs7460 (AA = 25.5%; AT = 41.2%; TT = 33.3%) polymorphisms were all in Hardy-Weinberg equilibrium ($P \geq 0.473$). Further, the PTK2 rs7843014 A/C and rs7460 A/T allele frequencies were similar to those reported elsewhere for Cau-

### Table 1. Baseline values and training-induced changes in muscle strength variables in participants according to protein tyrosine kinase-2 (PTK2) rs7843014 genotype

<table>
<thead>
<tr>
<th>Strength Variable</th>
<th>PTK2 rs7843014 Genotype</th>
<th>$P_1$</th>
<th>$P_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA (n = 19)</td>
<td>AC (n = 21)</td>
<td>CC (n = 11)</td>
</tr>
<tr>
<td>Pre 1-RM, kg</td>
<td>55.0 ± 13.2</td>
<td>53.8 ± 9.7</td>
<td>54.1 ± 10.9</td>
</tr>
<tr>
<td>Δ1-RM, %</td>
<td>64.4 ± 31.9</td>
<td>64.6 ± 28.2</td>
<td>77.0 ± 31.9</td>
</tr>
<tr>
<td>Pre-MVC, N·m</td>
<td>252 ± 58</td>
<td>245 ± 52</td>
<td>245 ± 42</td>
</tr>
<tr>
<td>ΔMVC, %</td>
<td>26.7 ± 8.0</td>
<td>25.4 ± 12.5</td>
<td>26.2 ± 11.9</td>
</tr>
<tr>
<td>Pre-SF, N/cm²</td>
<td>27.7 ± 6.4</td>
<td>24.2 ± 3.7</td>
<td>23.9 ± 4.4</td>
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<tr>
<td>ΔSF, %</td>
<td>16.2 ± 10.5</td>
<td>14.7 ± 11.3</td>
<td>20.0 ± 12.4</td>
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</table>

Values are means ± SD. Repeated-measures ANOVA $P$ values are presented for genotype (Pre) and training response (Δ) comparisons for the 3 genotypes ($P_1$), and AA vs. AC + CC ($P_2$). AA, homozygote; AT, heterozygote; TT, homozygote.

### Table 2. Baseline values and training-induced changes in muscle strength variables in participants according to protein tyrosine kinase-2 (PTK2) rs7460 genotype

<table>
<thead>
<tr>
<th>Strength Variable</th>
<th>PTK2 rs7460 Genotype</th>
<th>$P_1$</th>
<th>$P_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA (n = 13)</td>
<td>AT (n = 21)</td>
<td>TT (n = 17)</td>
</tr>
<tr>
<td>Pre 1-RM, kg</td>
<td>54.6 ± 9.7</td>
<td>53.0 ± 10.4</td>
<td>55.7 ± 13.4</td>
</tr>
<tr>
<td>Δ1-RM, %</td>
<td>69.3 ± 32.3</td>
<td>67.7 ± 27.3</td>
<td>65.2 ± 34.0</td>
</tr>
<tr>
<td>Pre-MVC, N·m</td>
<td>243 ± 47</td>
<td>244 ± 51</td>
<td>256 ± 58</td>
</tr>
<tr>
<td>ΔMVC, %</td>
<td>28.7 ± 11.7</td>
<td>25.1 ± 12.6</td>
<td>25.2 ± 7.0</td>
</tr>
<tr>
<td>Pre-SF, N/cm²</td>
<td>24.0 ± 4.0</td>
<td>24.2 ± 3.6</td>
<td>28.1 ± 6.6</td>
</tr>
<tr>
<td>ΔSF, %</td>
<td>20.8 ± 11.9</td>
<td>14.4 ± 11.6</td>
<td>15.5 ± 9.8</td>
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</table>

Values are means ± SD. Repeated-measures ANOVA $P$ values are presented for genotype (Pre) and training response (Δ) comparisons for the 3 genotypes ($P_1$), and TT vs. AT + AA ($P_2$). AA, homozygote; AT, heterozygote; TT, homozygote. Other abbreviations as in Table 1. "Significantly different from TT genotype (post hoc independent t-test: $P = 0.009$)."
the muscles of PTK2 rs7460 TT homozygotes to have higher specific force than AA and AT genotypes (ANOVA, genotype $P = 0.058$; Table 2). When the PTK2 rs7843014 AC and CC genotypes were pooled, the QF muscles of individuals homozygous for the A-allele expressed higher specific force than carriers of the C-allele before training (ANOVA, genotype $P = 0.023$; Table 1; t-test $P = 0.016$; Fig. 1). Similarly, when the PTK2 rs7460 AA and AT genotypes were combined, QF muscle specific force was found to be higher in TT homozygotes than in A-allele carriers before training (ANOVA, genotype $P = 0.017$; Table 2; t-test $P = 0.009$; Fig. 1). However, there was no significant interaction between training and PTK2 genotype concerning QF muscle specific force and both the rs7843014 (ANOVA, time $\times$ genotype $P = 0.601$; time $P < 0.0005$; Table 1) and rs7460 (ANOVA, time $\times$ genotype $P = 0.461$; time $P < 0.0005$; Table 2) PTK2 SNPs, implying that specific force increased similarly among all three genotypes of both SNPs (16.4 ± 11.2% for the whole cohort).

As both SNPs of the PTK2 gene were associated with QF muscle specific force, and a large proportion of participants (33%) possessed both “preferential” genotypes, it was further investigated whether or not the loci and PTK2 alleles were independent from each other. The estimated haplotype frequencies are presented in Table 3, and the deviation of the observed haplotype frequency from the expected frequency was calculated and defined as the linkage disequilibrium (LD). The LD for the two PTK2 polymorphisms was $D' = 0.905$ and $R^2 = 0.700$, which suggests that the two polymorphisms are in LD and are not completely independent from one another.

Both PTK2 SNPs were associated with untrained muscle specific force; therefore the contribution of each SNP to the interindividual variance in the respective muscle phenotype was investigated. On an individual basis, PTK2 rs7843014 genotype correlated with baseline muscle specific force ($R^2 = 0.091$; $P = 0.031$), suggesting that genotype for this SNP alone contributed to ∼9% of the interindividual variability in muscle specific force in the untrained state. PTK2 rs7460 genotype also correlated with baseline muscle specific force ($R^2 = 0.102$; $P = 0.022$), thus implying that genotype for this SNP explained ∼10% of the interindividual variability in untrained muscle specific force. Combining the two PTK2 SNPs in a multiple regression model led to a tendency toward a correlation with untrained muscle specific force ($R^2 = 0.105$; $P = 0.071$). Although this correlation did not reach statistical significance, it is interesting to note that the coefficient of determination was similar to that of the individual PTK2 SNPs, which is probably due to the relatively high LD between the two SNPs.

**DISCUSSION**

We investigated whether associations existed between polymorphisms of the PTK2 gene and human skeletal muscle strength phenotypes before and after resistance training. The two PTK2 gene polymorphisms were significantly associated with the interindividual variability in muscle specific force but did not contribute to the observed interindividual variation in the training response. Thus our results highlight a novel association between sequence variations in the PTK2 gene and the intrinsic force-generating capacity of human skeletal muscle, possibly via influences on lateral force transmission. It should be noted, however, that the data presented in this study are preliminary in that the sample size is a limitation. Thus future studies should attempt to replicate our findings using larger cohorts from the same and other ethnic populations, which would increase both the power of the study and the confidence in our results.

The genotype frequencies for the PTK2 rs7843014 (AA = 37%; AC = 41%; CC = 22%) and rs7460 (AA = 26%; AT = 41%; TT = 33%) SNPs observed in our study were comparable to those reported previously for Caucasian populations (31). Baseline values for our entire cohort were similar to those reported elsewhere for this population concerning 1-RM lifting strength (13), isometric MVC knee joint torque (18), QF muscle PCSA (16) and specific force (16). Our observed 67% increase in 1-RM for the whole cohort was higher than some (22), but less than other (23, 24) reports of 1-RM strength gains following a similar period of knee extensor strength training. The 26% increase in isometric knee extensor MVC strength was less than some (26), but greater than other (1, 17) previously reported gains in isometric strength following a similar duration of knee extensor training. Regarding muscle hypertrophy, our observed 6% increase in QF muscle PCSA was comparable to previous reports of QF muscle size gains following resistance training of similar type and duration (1, 17). The 16% increase in muscle specific force was also comparable to that reported elsewhere following resistance training of the QF muscle, although in older individuals (21).

Focal adhesion kinase (FAK) plays an integral role in the costamere protein complex (4, 20) that is involved in the lateral transmission of force (6). As FAK is encoded by the PTK2

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**Table 3.** Estimates of haplotype frequencies regarding the protein tyrosine kinase-2 (PTK2) rs7843014 (A/C) and rs7460 (A/T) polymorphisms

<table>
<thead>
<tr>
<th>Allele at Locus 1 (rs7843014 A/C)</th>
<th>Allele at Locus 2 (rs7460 A/T)</th>
<th>Haplotype Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>T</td>
<td>0.519</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>0.060</td>
</tr>
<tr>
<td>C</td>
<td>T</td>
<td>0.021</td>
</tr>
<tr>
<td>C</td>
<td>A</td>
<td>0.401</td>
</tr>
</tbody>
</table>

**Fig. 1.** Baseline quadriceps femoris muscle specific force according to non-preferential (white bars) and preferential (black bars) genotypes of the protein tyrosine kinase-2 (PTK2) rs7843014 (preferential genotype: AA) and rs7460 (preferential genotype: TT). *$P = 0.016$, significantly different from pooled PTK2 rs7843014 AC + CC genotypes; **$P = 0.009$, significantly different from combined PTK2 rs7460 AA + AT genotypes.
gene, we hypothesized that polymorphisms of this gene would explain part of the interindividual variability in QF muscle specific force between untrained young men. We determined that individuals homozygous for the rs7843014 A-allele had a higher muscle specific force than carriers of the C-allele, while QF muscle specific force was greater in rs7460 TT homozygotes compared with their A-allele counterparts.

Of the 19 participants who possessed one or both of the preferential PTK2 genotypes (rs7843014 AA or rs7460 TT), 17 people possessed both genotypes. Individually and combined, these two SNPs explained ~10% of the interindividual variability in muscle specific force in the untrained state. Thus these findings suggest that the two SNPs are not independently associated with in vivo muscle specific force but that they are in linkage disequilibrium, which is supported by a D' value of 0.91 and $R^2$ value of 0.70. This opens up several theoretical possibilities: 1) only one locus is functionally important regarding muscle specific force; 2) the SNPs become functional only when they occur together; 3) neither SNP influences muscle specific force but both are in linkage disequilibrium with the true functional variant that was not genotyped. In any case, neither of the PTK2 SNPs investigated in our study are of a kind likely to influence the amino acid sequence of the protein product. However, an alteration in DNA sequence in the 3'-UTR region of a gene (e.g., the PTK2 rs7460 A/T polymorphism) has the potential to alter the level, location, or timing of gene expression, while intronic genomic variants (e.g., the PTK2 rs7843014 A/C polymorphism) generally have the potential to influence gene expression and mRNA stability (28). Therefore, a potential influence of PTK2 gene polymorphisms on the concentration and time course of FAK expression warrants future investigation.

We hypothesized that PTK2 genotype would influence muscle specific force, leading to associations with functional measures of strength, such as maximum dynamic lifting strength (1-RM) and isometric MVC knee joint torque. While we did find PTK2 genotype associations with untrained QF muscle specific force, we observed no association with baseline 1-RM or MVC torque. Although the intrinsic strength of the muscle undoubtedly contributes to both 1-RM and MVC torque, extrinsic factors such as neural drive, moment arm length, muscle size and architecture are also known to influence such strength measures independent of specific force (8), thus potentially masking any genotype associations with 1-RM and MVC torque.

Mechanical tension is known to regulate costameric protein expression (29), and resistance training increases the expression of costameric proteins, such as desmin (32), alpha-1-syntrophin and dystrophin (14) in humans, and FAK in hyper trophyed rooster skeletal muscle (11). Therefore, we hypothesized that PTK2 genotype would influence the previously reported interindividual variability in the training-induced change in muscle specific force, 1-RM, and MVC torque (9), possibly through a genotype-dependent change in costameric density with loading. However, we found no association between either PTK2 SNP and the relative changes in muscle specific force, 1-RM, or MVC torque following 9 wk of resistance training. If any inherent difference between PTK2 genotype in the level of FAK protein expression is not preferentially enhanced with loading, muscle specific force will increase similarly between genotype. The higher muscle specific force at baseline might then be attributable to a greater muscle costameric density, which could be realized by 1) a higher number of costameres per muscle fiber perimeter and/or 2) a larger number of smaller fibers per muscle with a higher fiber perimeter-to-area ratio. Preliminary (unpublished) histological data from our laboratory suggest that people with the “preferential” PTK2 AA genotype do have smaller muscle fiber CSAs than their “nonpreferential” genotype counterparts, and together with a nonassociation between PTK2 genotype and muscle PCSA reported here, this would support the second hypothesis. In this case, a larger loading-induced increase in FAK expression in people with the higher baseline specific force, i.e., people with the preferential PTK2 genotypes, might be offset by a relatively greater loading-induced increase in the perimeter of large compared with small fibers (assuming a similar relative increase in fiber CSA). This would lead to a similar increase in total muscle costameric density between genotype, which in turn would lead to comparable training-induced increases in muscle specific force.

**Summary and conclusions.** The interindividual variability in QF muscle specific force can be partly explained by polymorphisms of the PTK2 gene that encodes FAK, a structural protein involved in the lateral transmission of muscle fiber force. Future experiments should investigate potential associations between PTK2 genotype and FAK expression in skeletal muscle. These results highlight the impact of genetic variation on the intrinsic strength of human skeletal muscle.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

R.M.E., A.G.W., D.A.J., C.E.S., and H.D. conception and design of research; R.M.E. performed experiments; R.M.E. and A.G.W. analyzed data; R.M.E., A.G.W., D.A.J., C.E.S., and H.D. interpreted results of experiments; R.M.E. prepared figures; R.M.E. drafted manuscript; R.M.E., A.G.W., D.A.J., C.E.S., and H.D. edited and revised manuscript; R.M.E., A.G.W., D.A.J., C.E.S., and H.D. approved final version of manuscript.

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