

Three brothers with lower extremity weakness



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***Department of Neurology**

'Department of Pathology

#Undiagnosed Disease Network

University of California, Los Angeles



History

- ▶ F.R. is a 17 year male who presents with lower extremity weakness
- ▶ History:
 - ▶ Born via C-section due to breech presentation
 - ▶ “legs tend to flop to the side”
 - ▶ Started crawling only on his arms at 8 months of age
 - ▶ Walked poorly at age 2 years of age
 - ▶ Tendency to fall, noted with abnormal gait
 - ▶ Was never able to run



Developmental history

- ▶ He was born to a G2P1 mom via cesarean section due to breech presentation. There was no known complication during delivery. Birth weight was 8 pounds.
- ▶ Milestones:
 - ▶ Sit at 6-7 months
 - ▶ Walk at age 2
 - ▶ First word by 1 year of age, 100 words (Japanese) by 19 month

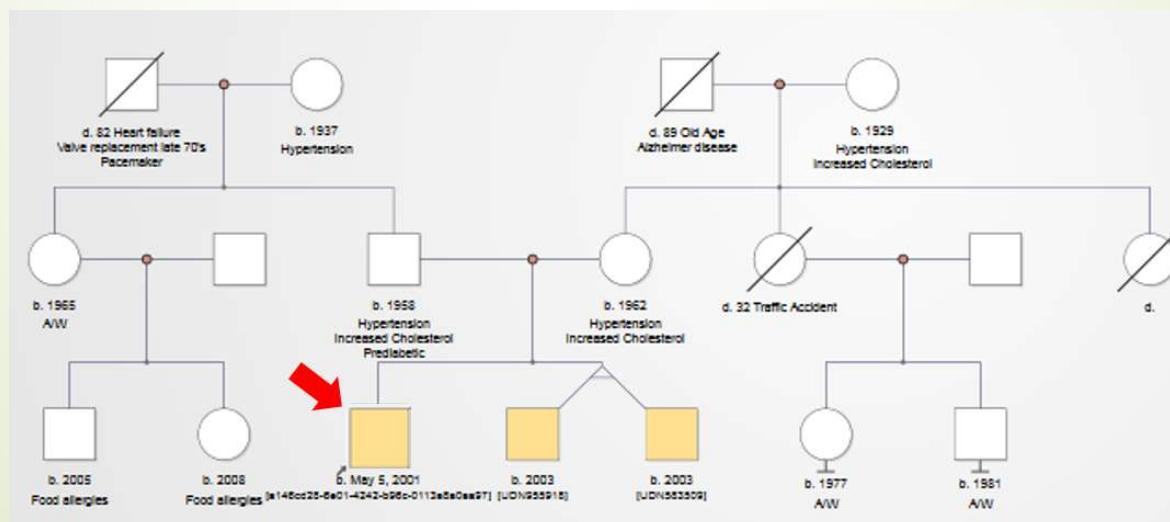


Other medical history:

- ▶ PMH: as above
- ▶ Meds: none
- ▶ Allergies: NKDA
- ▶ Social History: lives at home with family, attend age-appropriate grade

Family history

- ▶ Two younger twin brothers (identical) who also have same phenotype
- ▶ Both parents are healthy, they are both Japanese
- ▶ no other family history of significant neuromuscular disorders



Physical Exam

- ▶ **Vital Signs:** normal
- ▶ **General Exam:** atrophy of bilateral lower extremity
- ▶ **Mental Status:** normal
- ▶ **Cranial Nerves:** normal
- ▶ **Sensory Exam:** normal to light touch, vibration, pin-prick, and cold touch
- ▶ **Reflex (left/right):**
 - ▶ Biceps :2/2
 - ▶ Triceps: 2/2
 - ▶ Patellars 0 / 0
 - ▶ Achillies: 0 /0

Motor Exam (left/right)

- ▶ Upper extremity
- ▶ Shoulder Abduction 5/5
- ▶ Elbow flexion 5/5
- ▶ Elbow extension 5/5
- ▶ Wrist flexion 5/5
- ▶ Wrist extension 5/5
- ▶ Finger flexion 5/5
- ▶ Finger extension 5/5

- ▶ Lower extremity
- ▶ Hip flexion: 4+/4+
- ▶ Hip extension: 5/5
- ▶ Knee flexion 4+/4+
- ▶ **Knee extension 2/2**
- ▶ Dorsi-flexion 4+/4+
- ▶ **Plantar-flexion 3/3**

Motor examination:

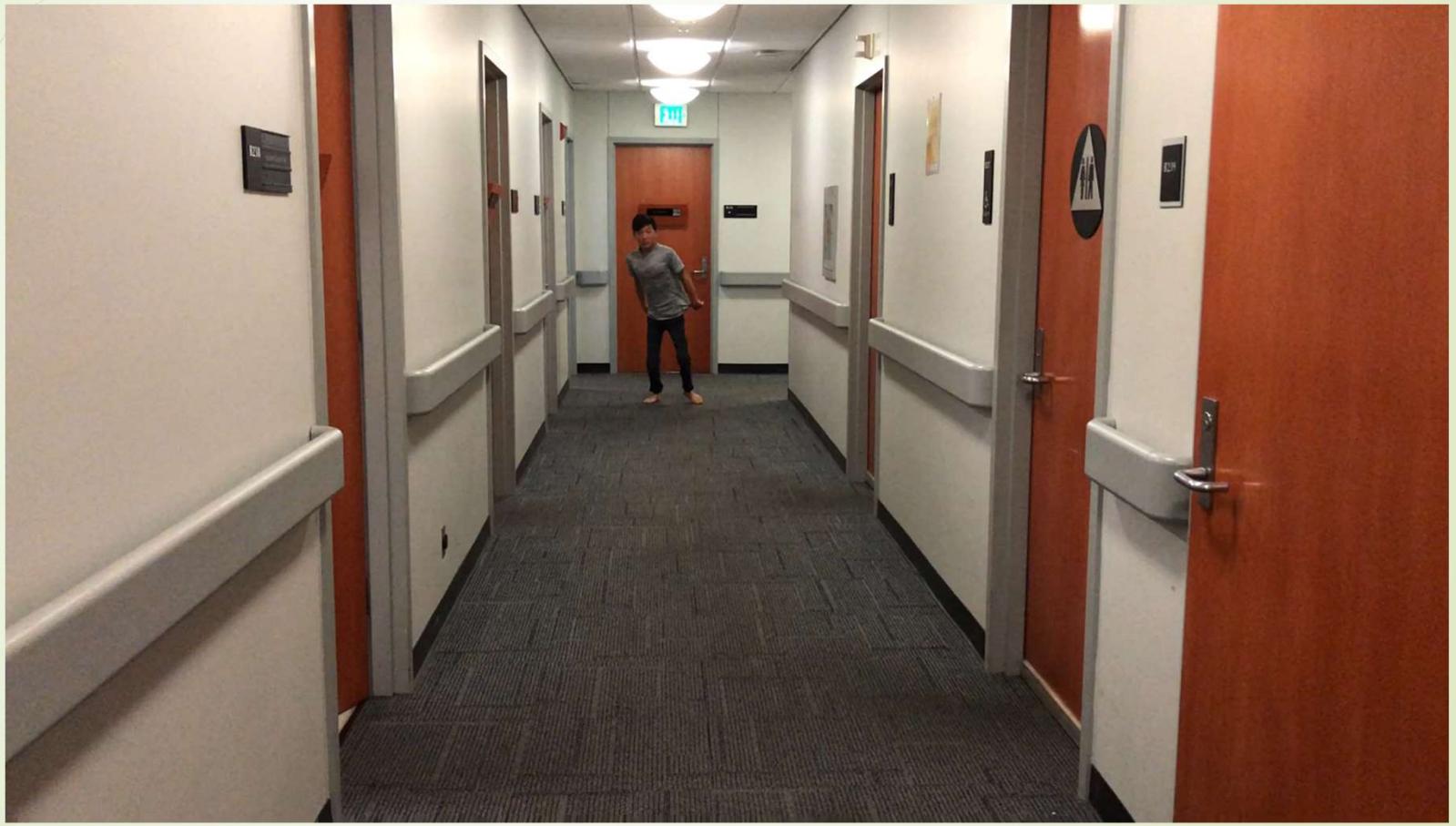


Motor Examination (continued):





GAIT



Exam summary

- ▶ Motor: Prominent quadriceps weakness
- ▶ Contracture of knees
- ▶ Unusual gait with excessive forward lean
- ▶ Absent reflex in lower extremities
- ▶ Normal sensory exam
- ▶ Normal cognition



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Prior Work up:

- ▶ CK 348 (at 2 year of age)
- ▶ NCS/EMG:
 - ▶ NCS: no clear abnormality per report
 - ▶ EMG: notable for decreased recruitment of polyphasic large-amplitude motor unit action potentials in the lower extremity muscles
- ▶ Gene testing: SMA negative

EMG

| Side | Muscle | Nerve | Root | Ins Act | Fibs/PSW | Fasc | Other | Amp | Dur | Poly | Recr |
|------|--------------|----------------|-----------|---------|----------|------|-------|-----------|-----|------|------------|
| Left | AntTibialis | Dp Br Peron | L4-5 | Nml | None | None | None | >10 mV | Nml | Nml | 3+ Decr |
| Left | PostTibialis | Tibial | L5, S1 | Nml | None | None | None | >10 mV | Nml | Nml | Nml |



MRI of the right thigh

- ▶ Significant anterior compartment atrophy
- ▶ Preserved medial and posterior compartment



MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

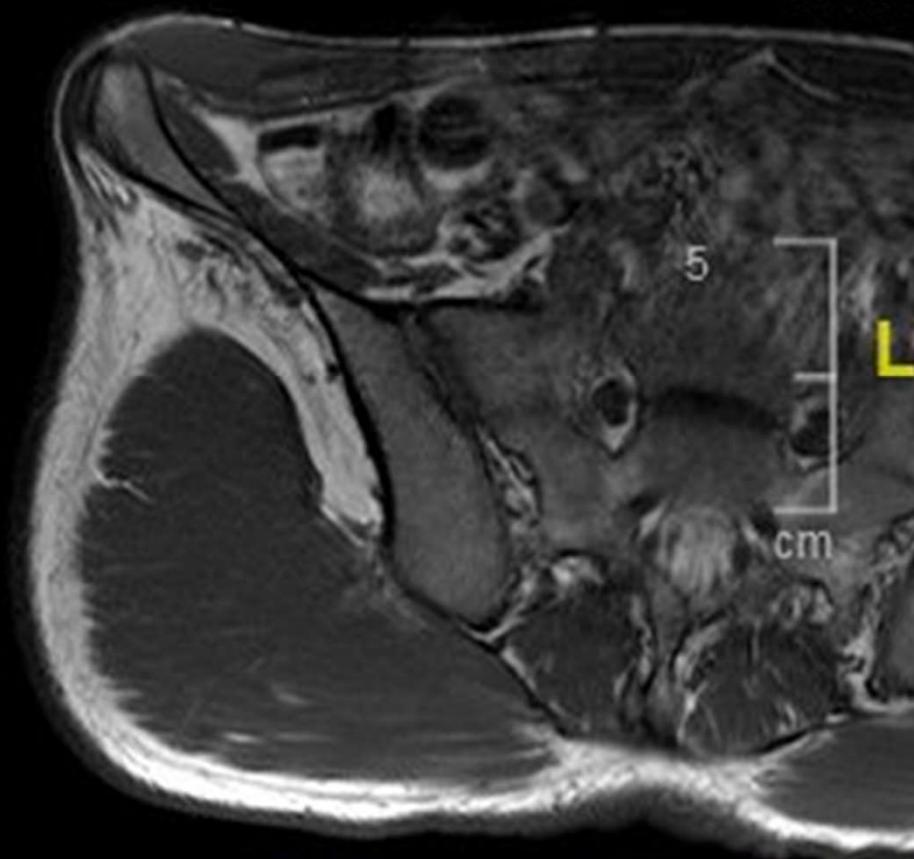
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13-Feb-2017

Im:12/90

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R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RI

AH

COMPARISON

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Westwood Rad

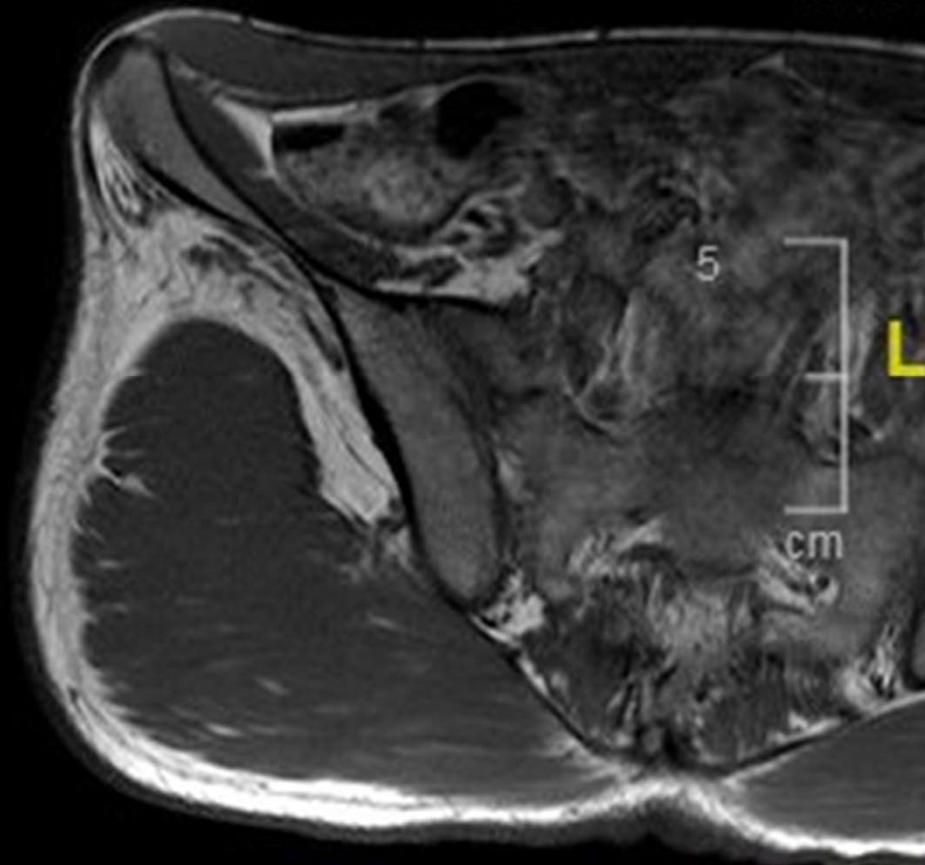
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R



PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

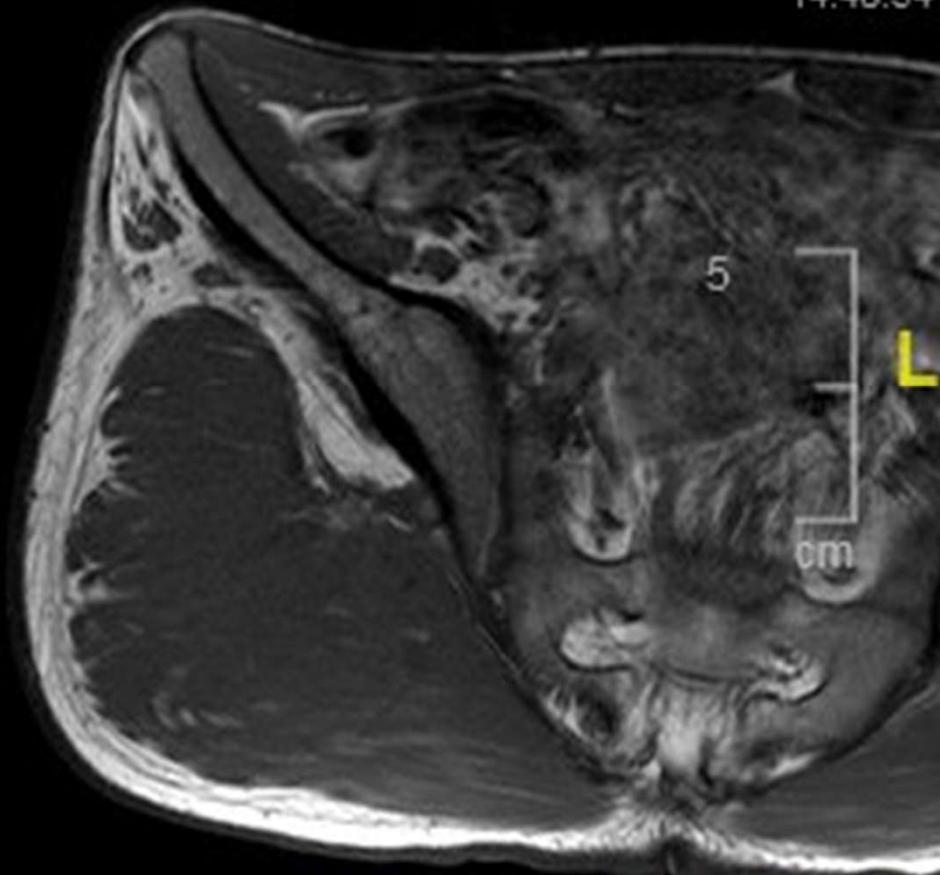
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R



PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

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Westwood Rad

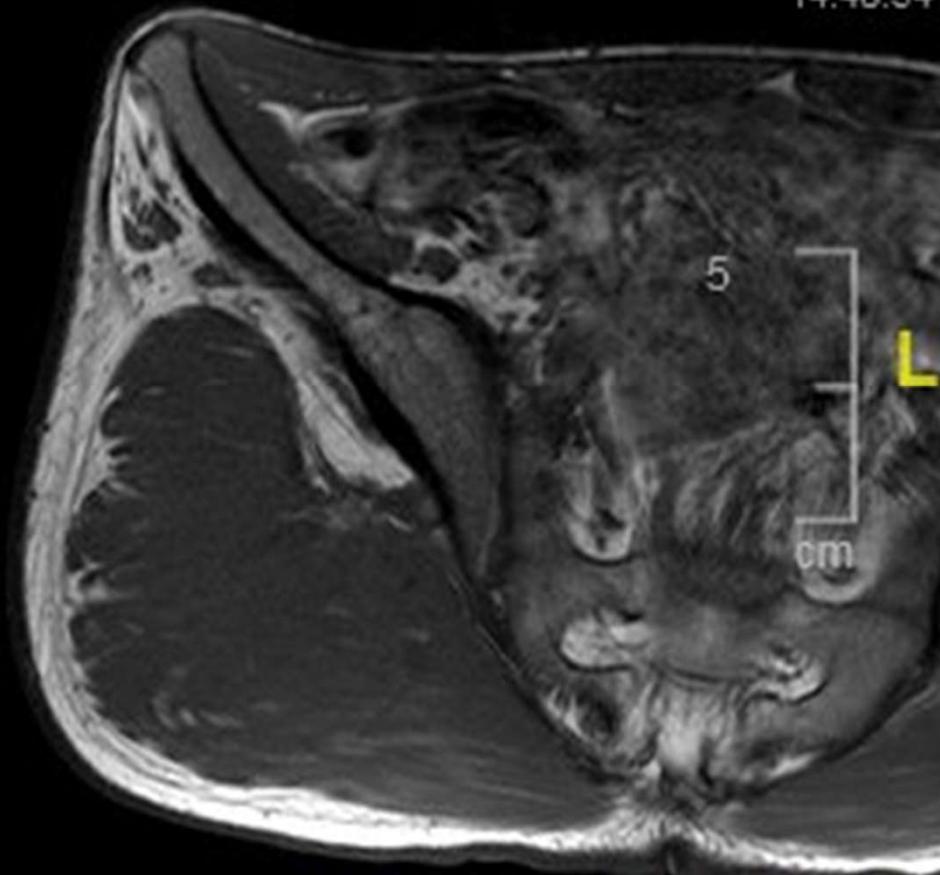
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PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

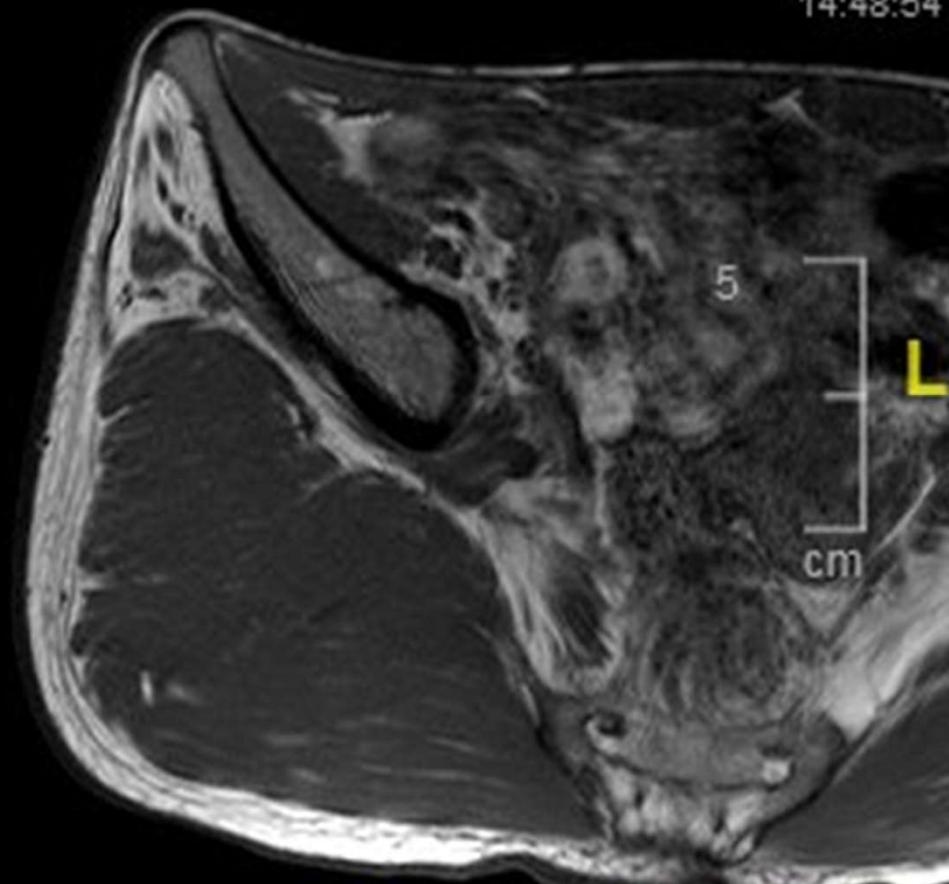
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PF

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MR FEMUR WO CONTRAST RI

AH

COMPARISON

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Westwood Rad

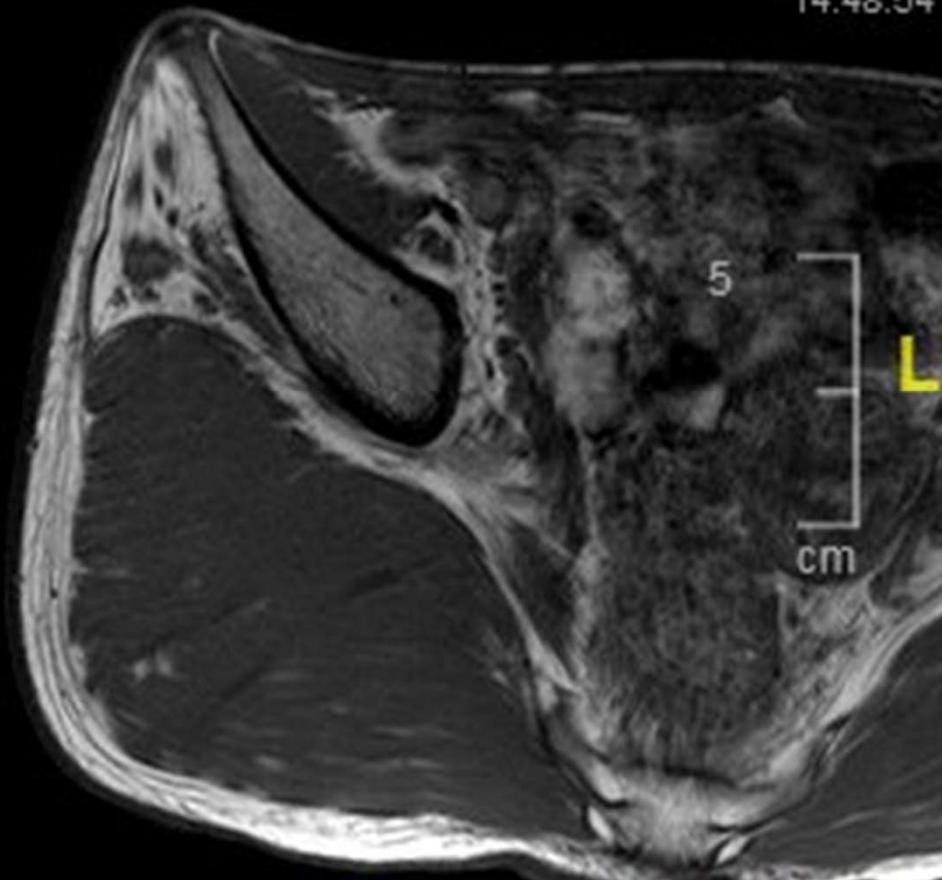
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PF

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MR FEMUR WO CONTRAST RI

AH

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

COMPARISON

Westwood Rad

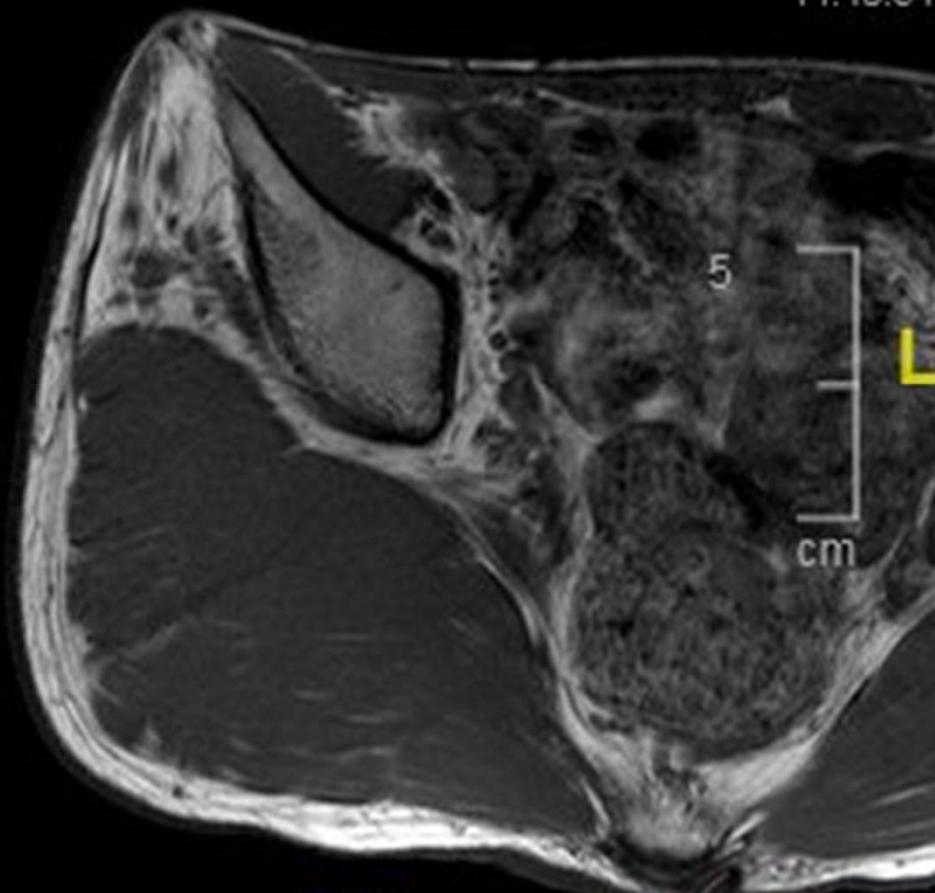
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PF

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MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

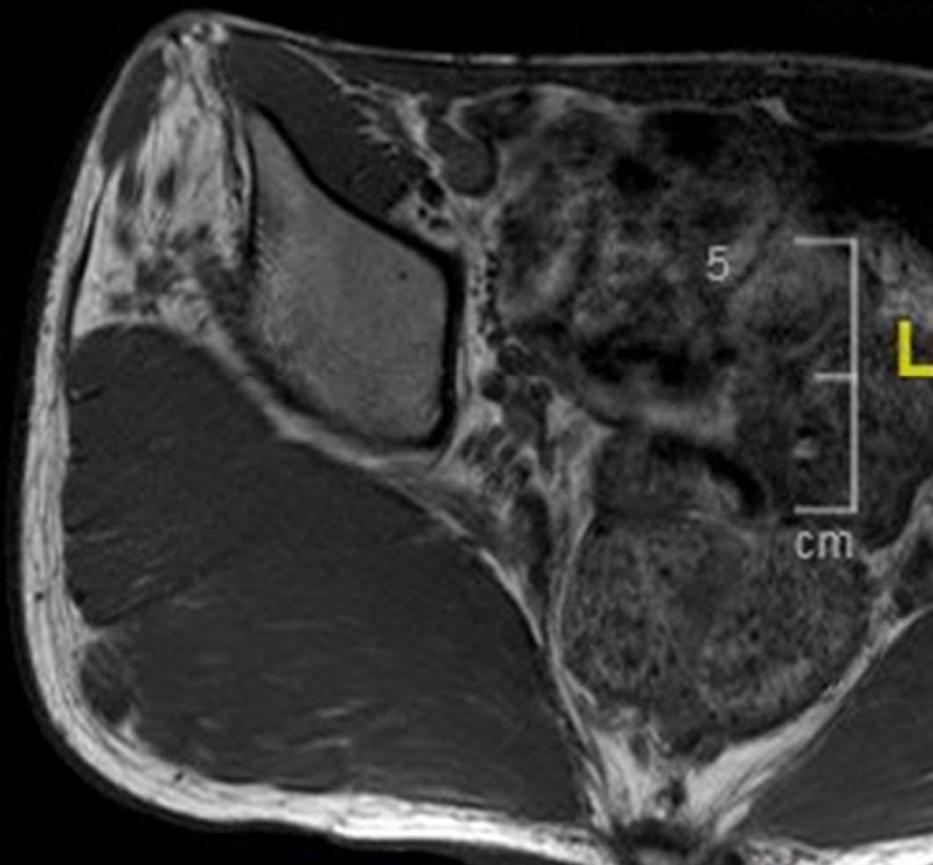
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PF

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MR FEMUR WO CONTRAST RI

AH

COMPARISON

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Westwood Rad

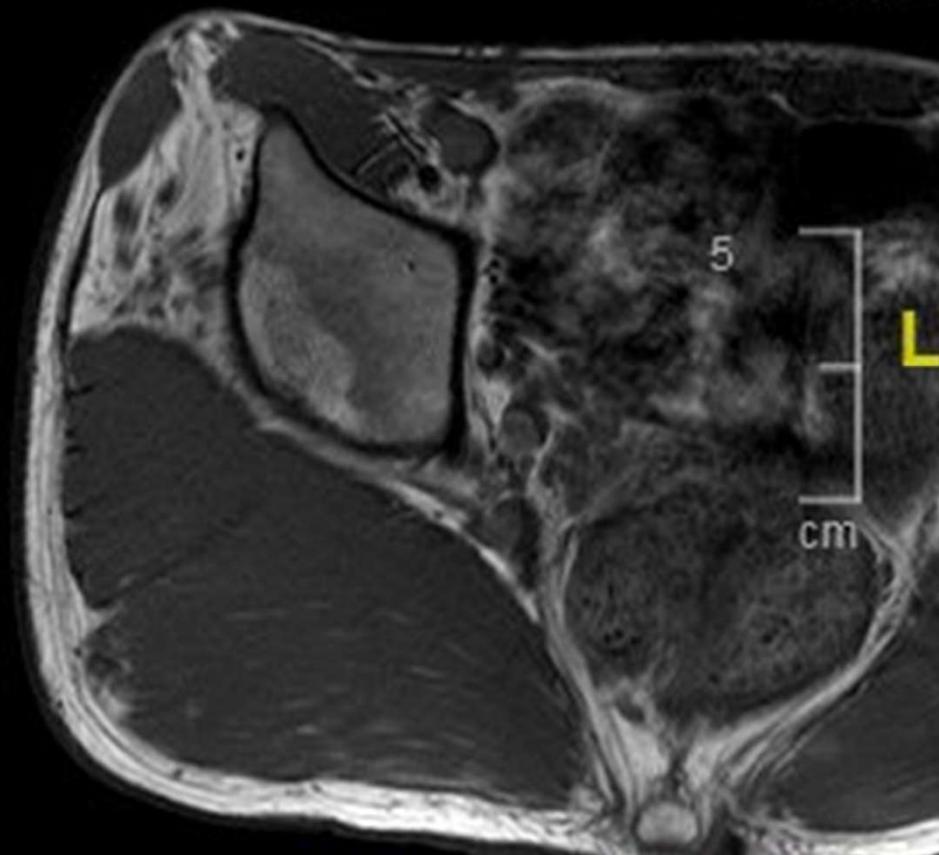
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PF

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MR FEMUR WO CONTRAST RI

AH

COMPARISON

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Westwood Rad

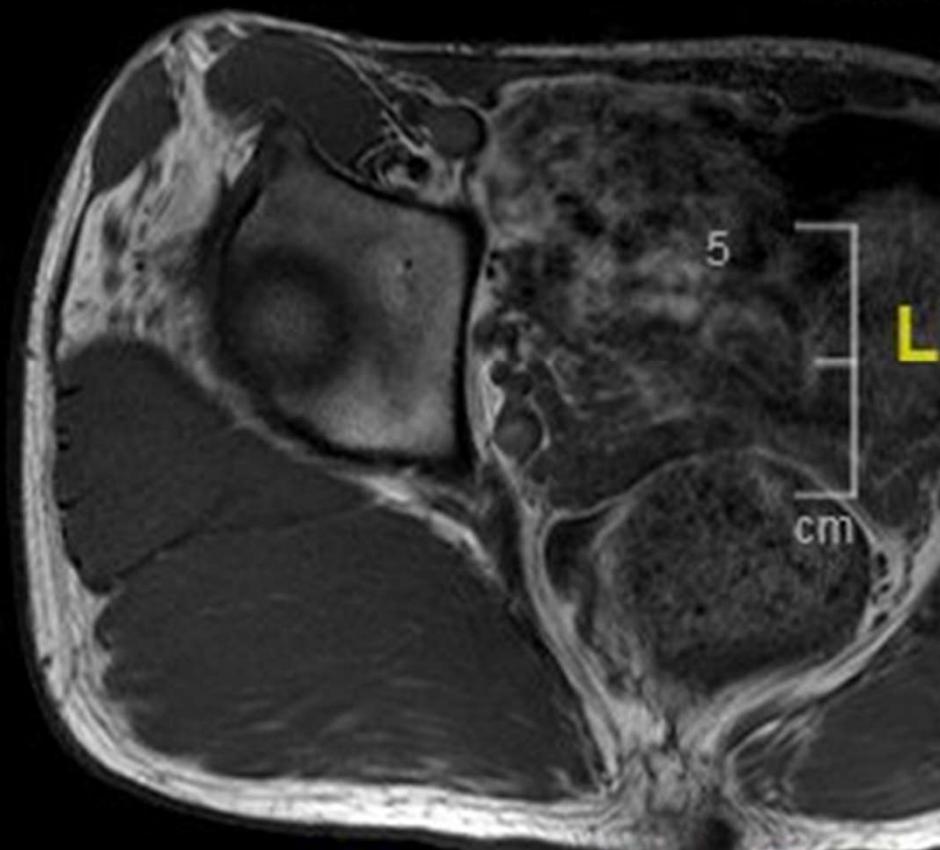
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PF

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MR FEMUR WO CONTRAST RI

AH

COMPARISON

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Westwood Rad

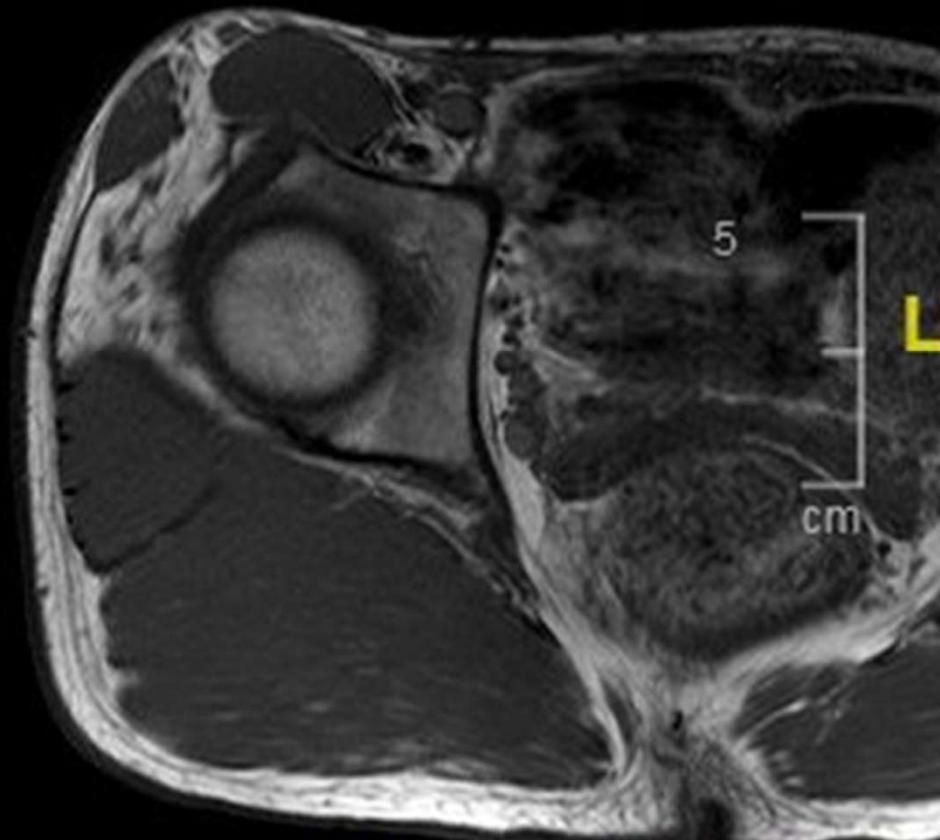
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R



WL:381 - WW:876

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Se:21
Im:24/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

Se:21

13-Feb-2017

Im:25/90

14:48:54

R



PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

Se:21

13-Feb-2017

Im:28/90

14:48:54

R



PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

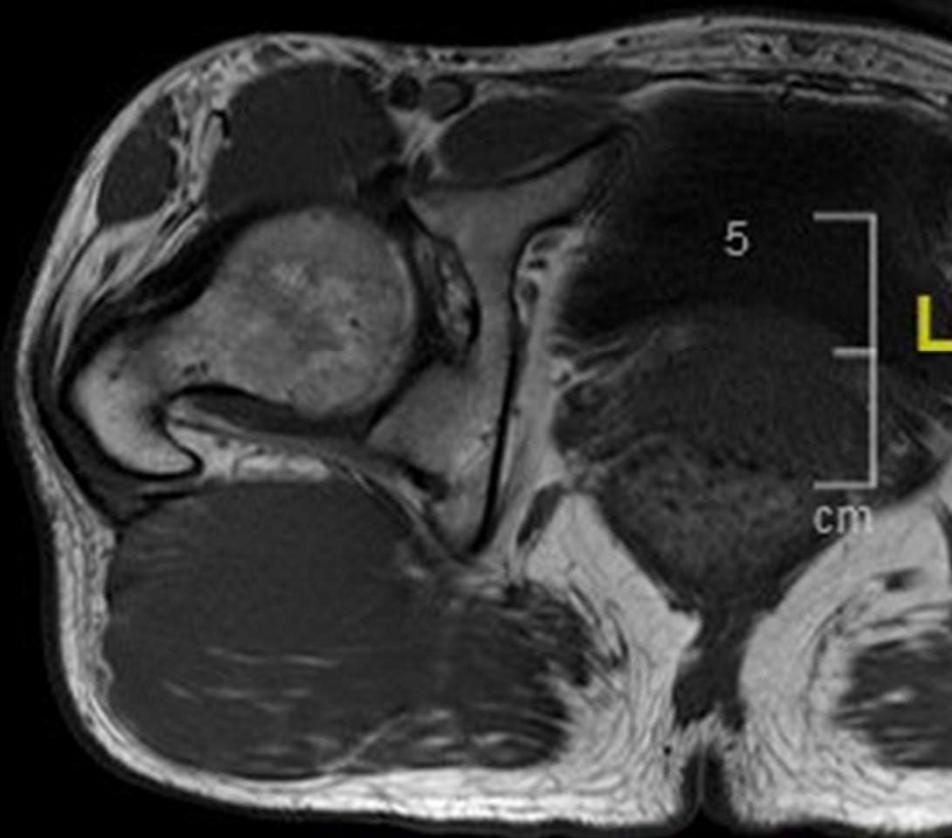
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PF

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MR FEMUR WO CONTRAST RI

AH

COMPARISON

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Westwood Rad

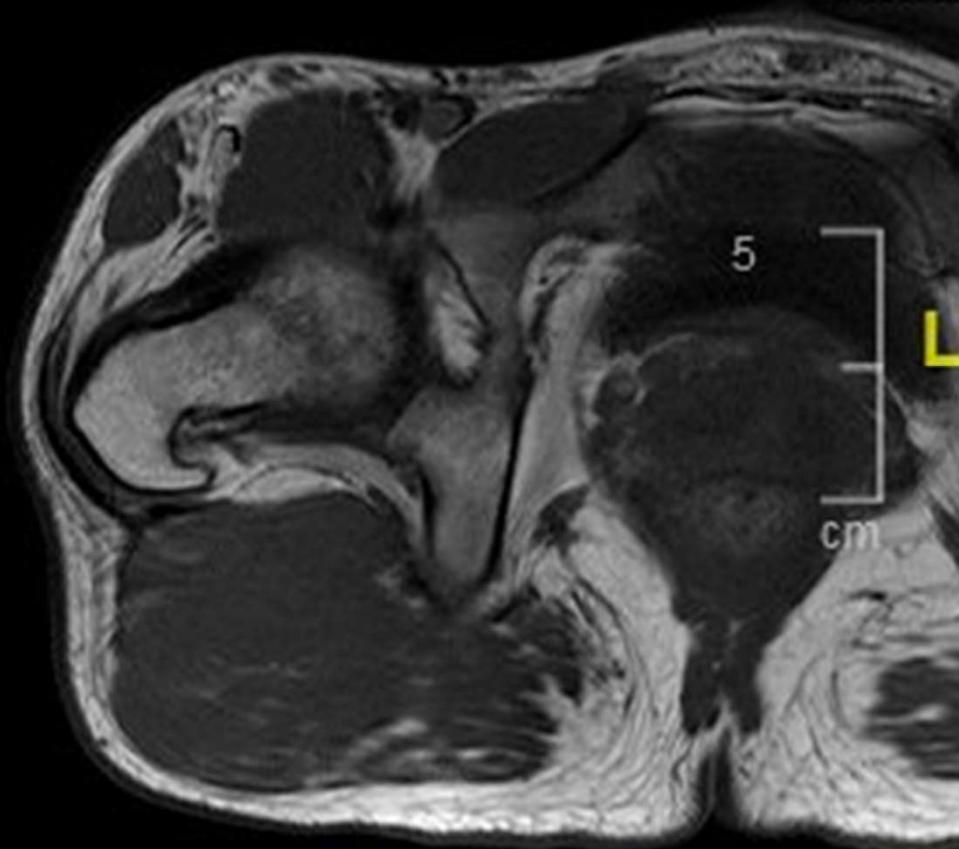
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R



PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

Se:21

13-Feb-2017

Im:29/90

14:48:54

R

5

cm

L

PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

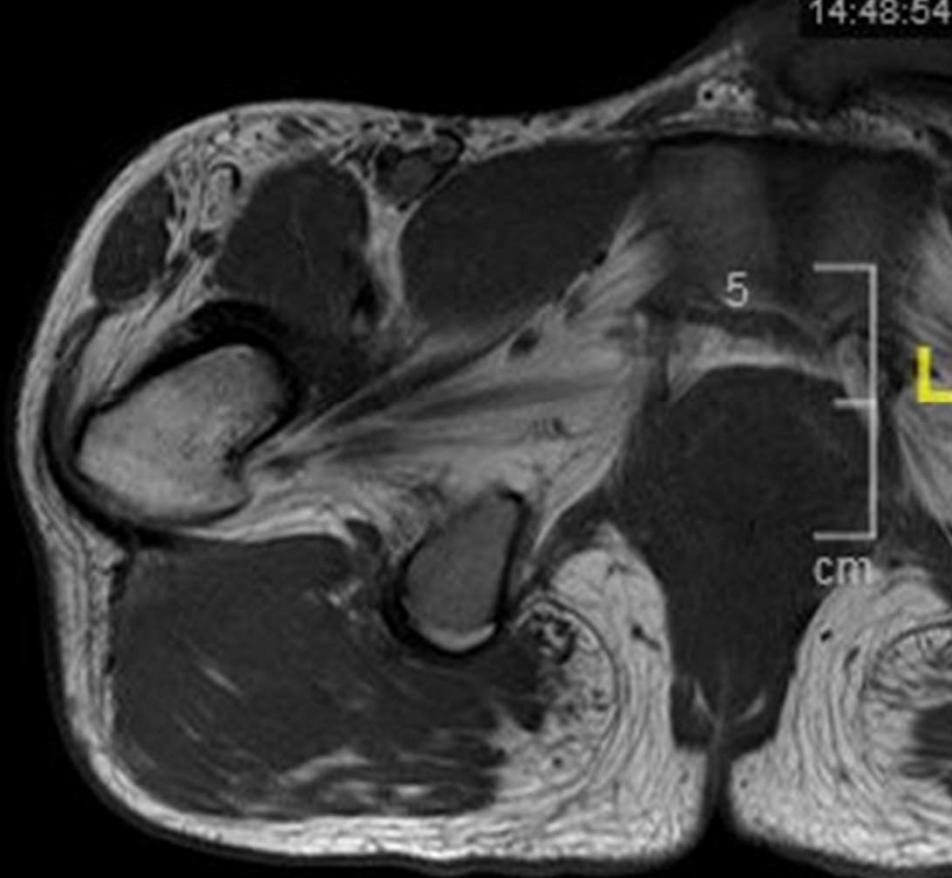
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R



PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

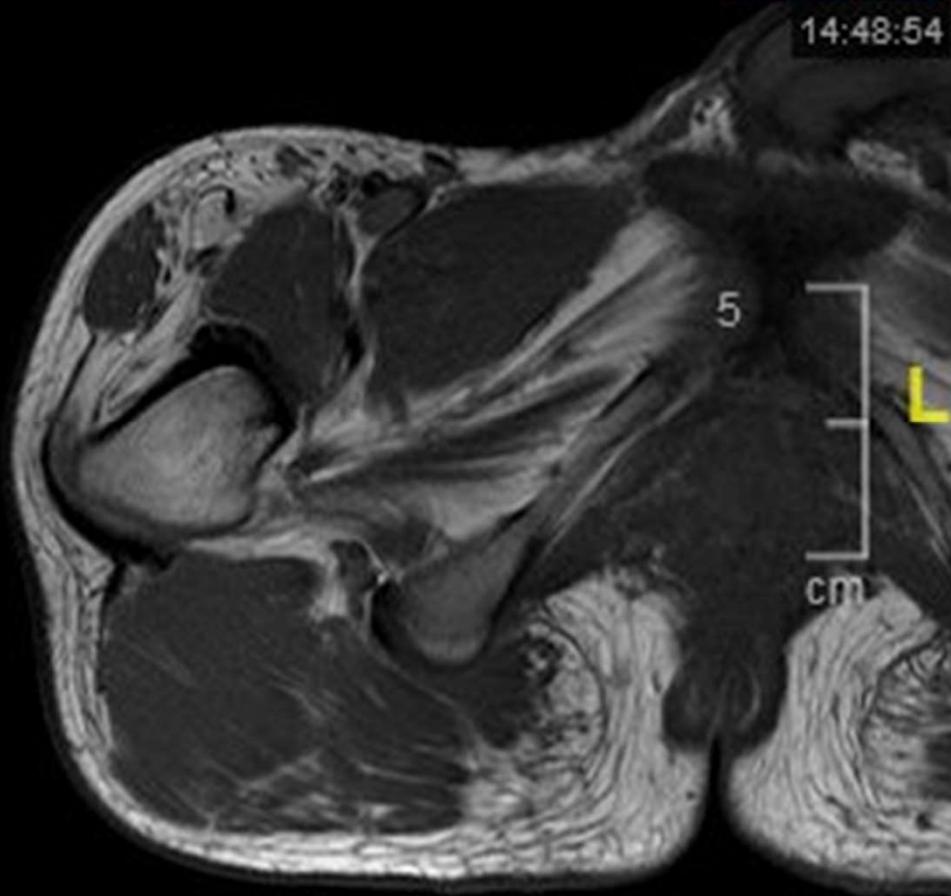
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R



PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

Se:21

13-Feb-2017

Im:32/90

14:48:54

R

5

cm

L

PF

WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

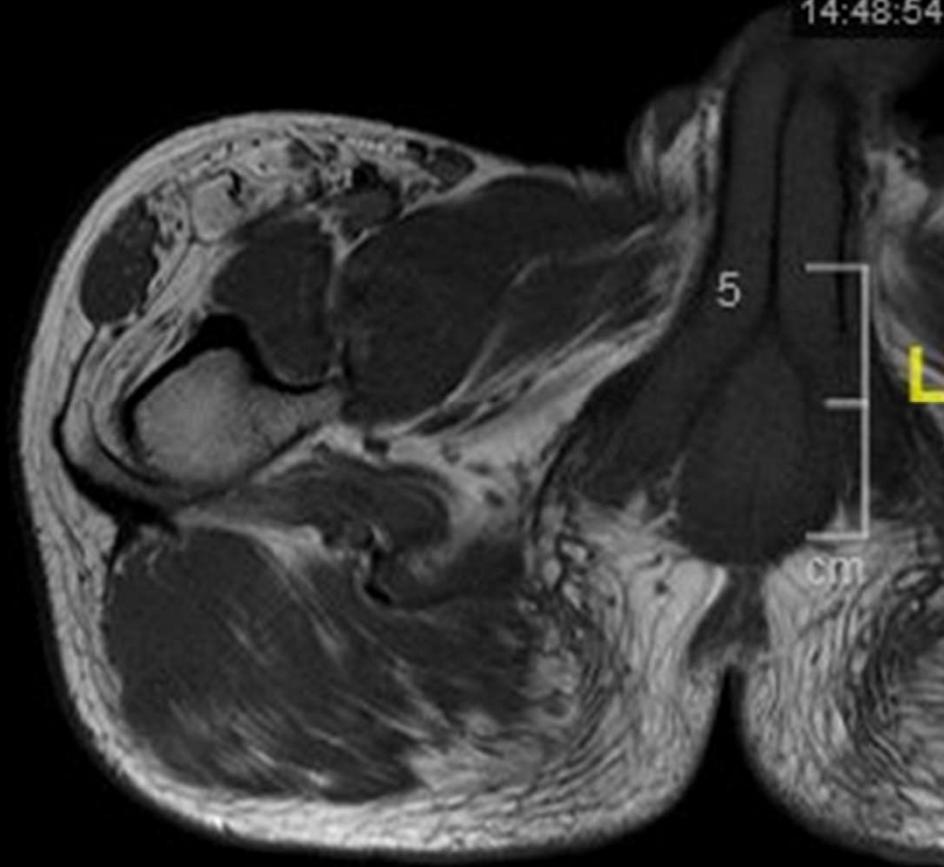
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R



PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

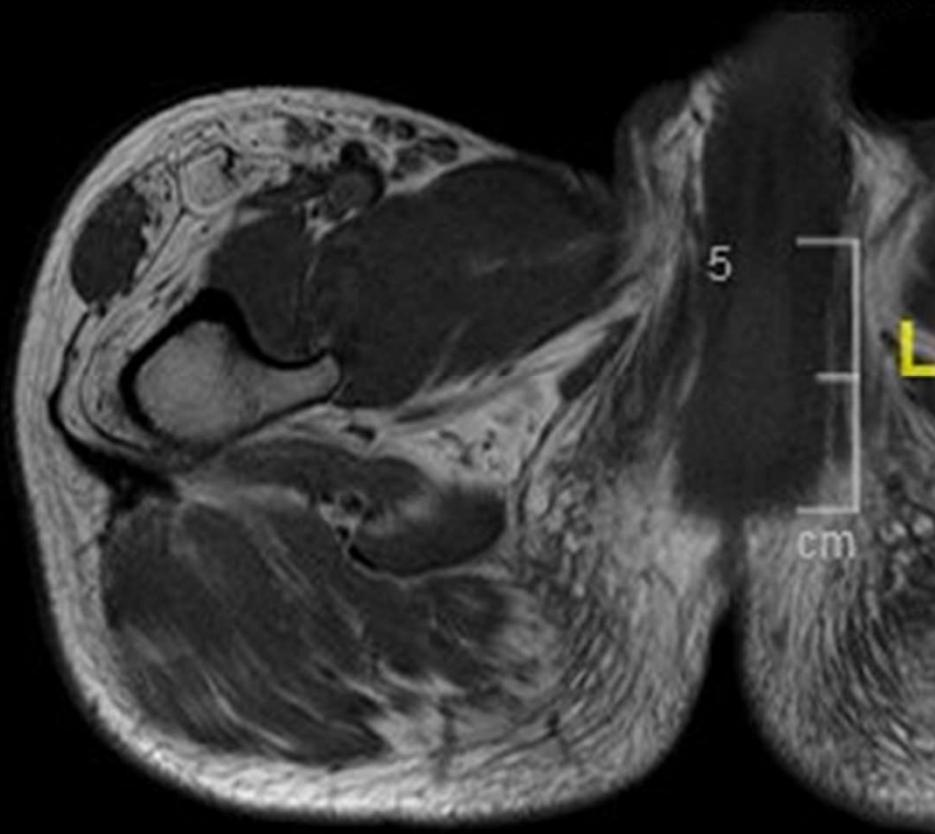
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PF

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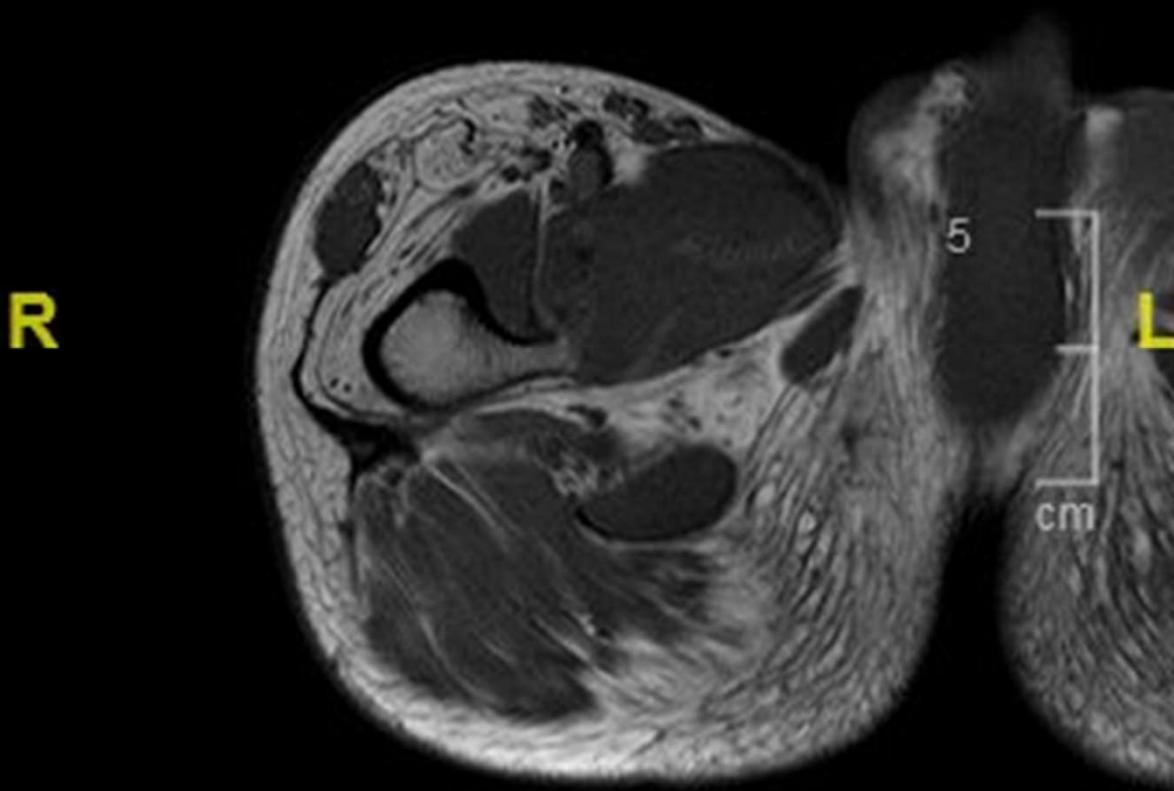
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Se:21
Im:35/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

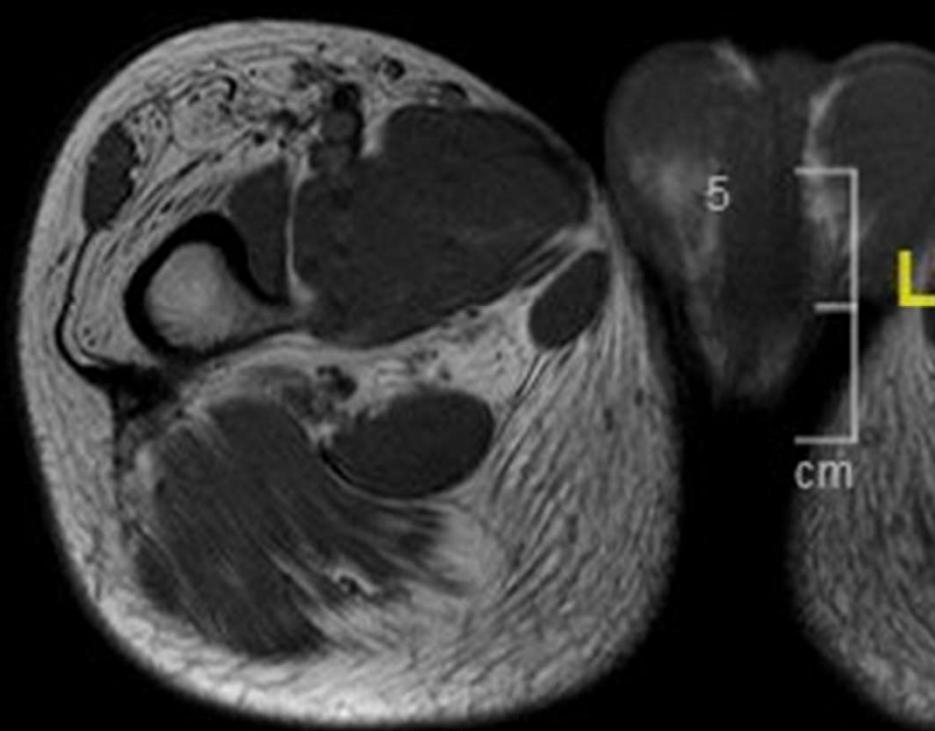
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R



PF

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MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

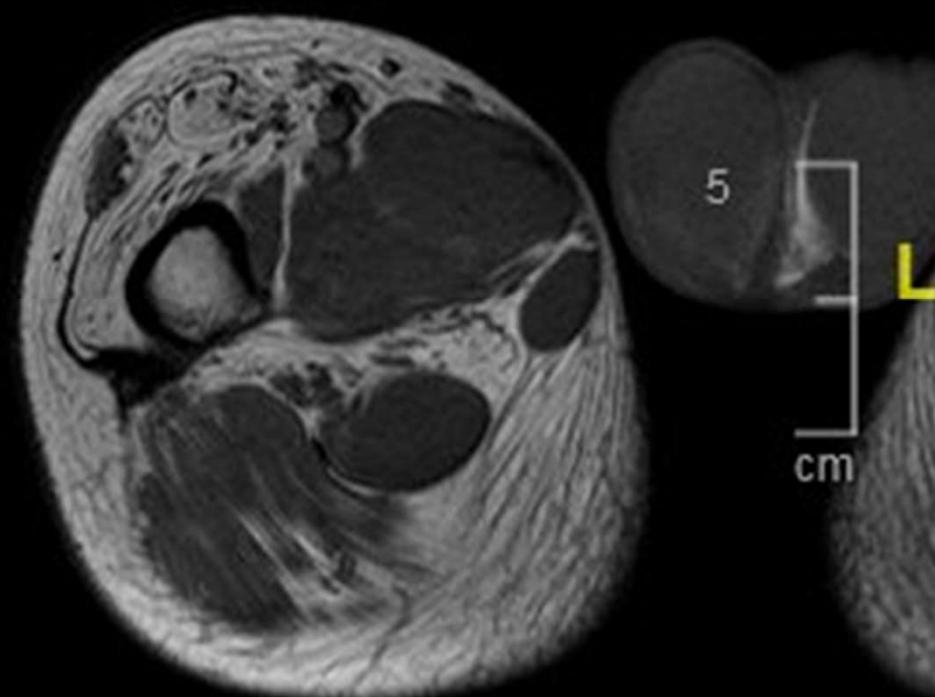
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R



PF

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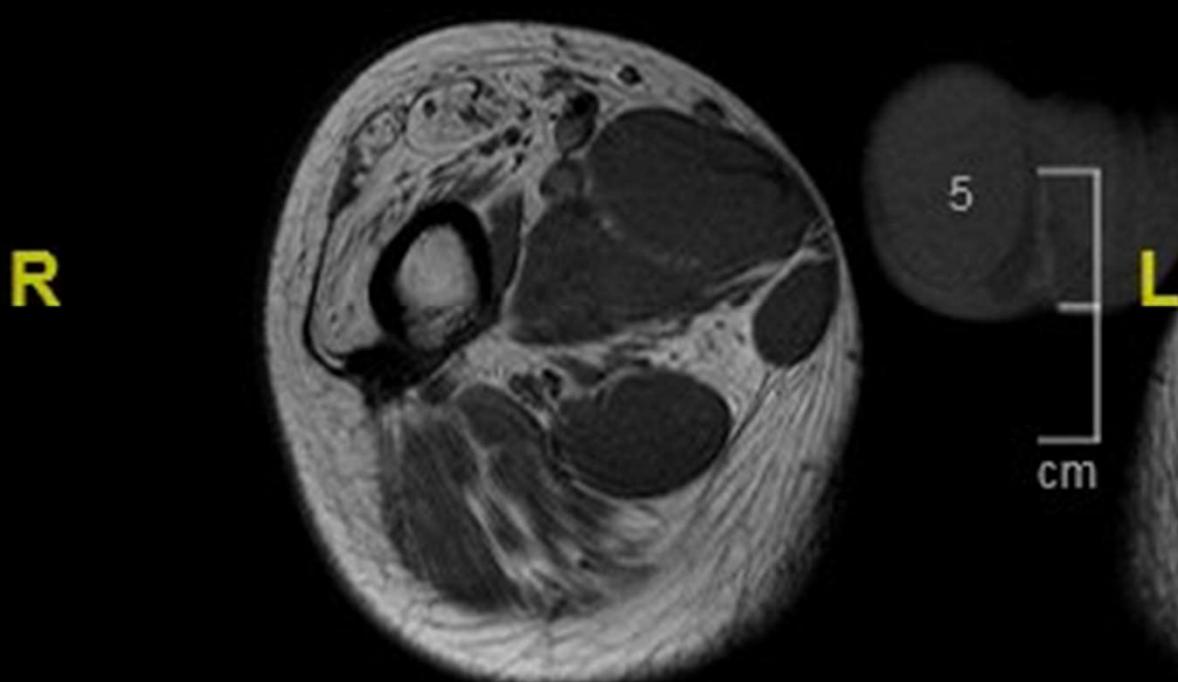
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Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:38/90

COMPARISON

Westwood Rad

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14:48:54



• WL:381 - WW:676

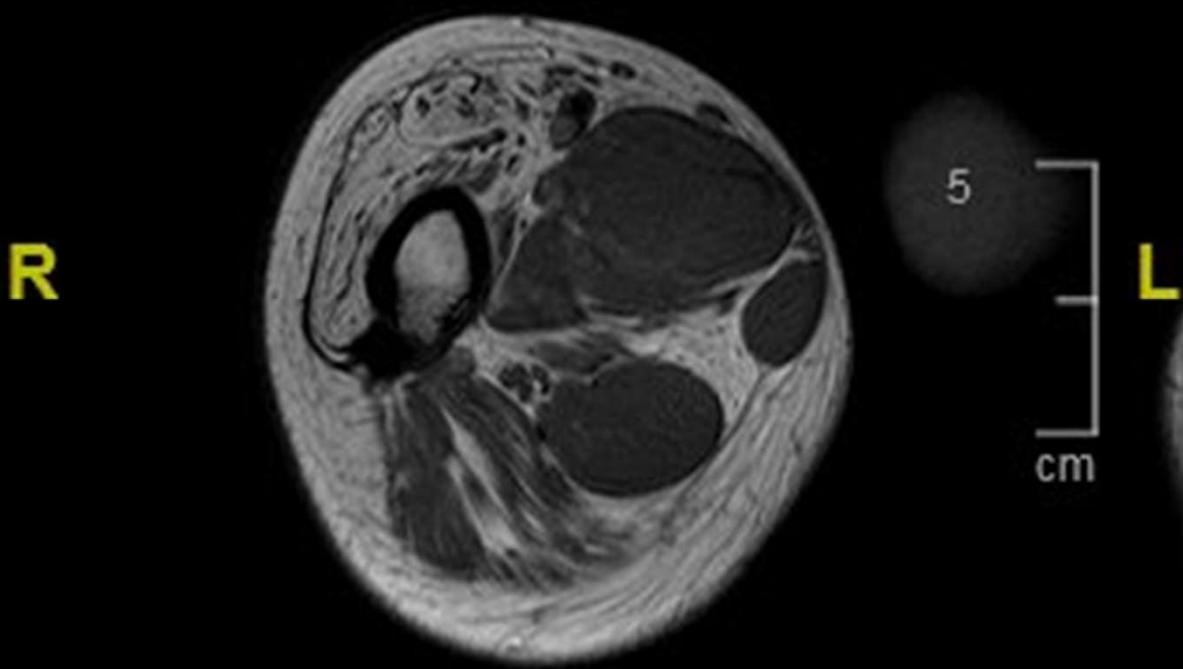
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Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:39/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



• WL:381 - WW:876

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Im:40/90

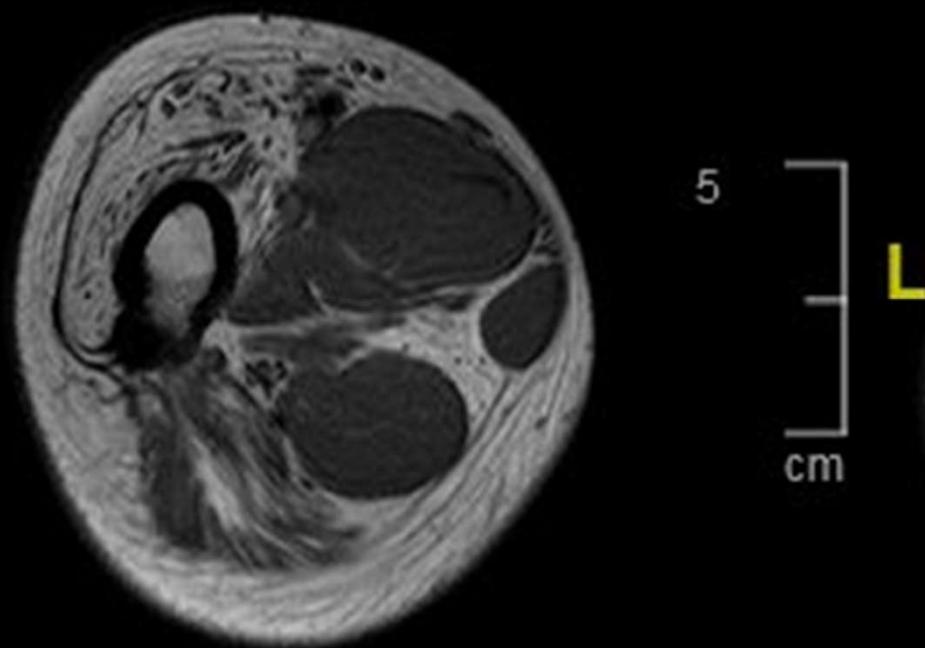
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:676

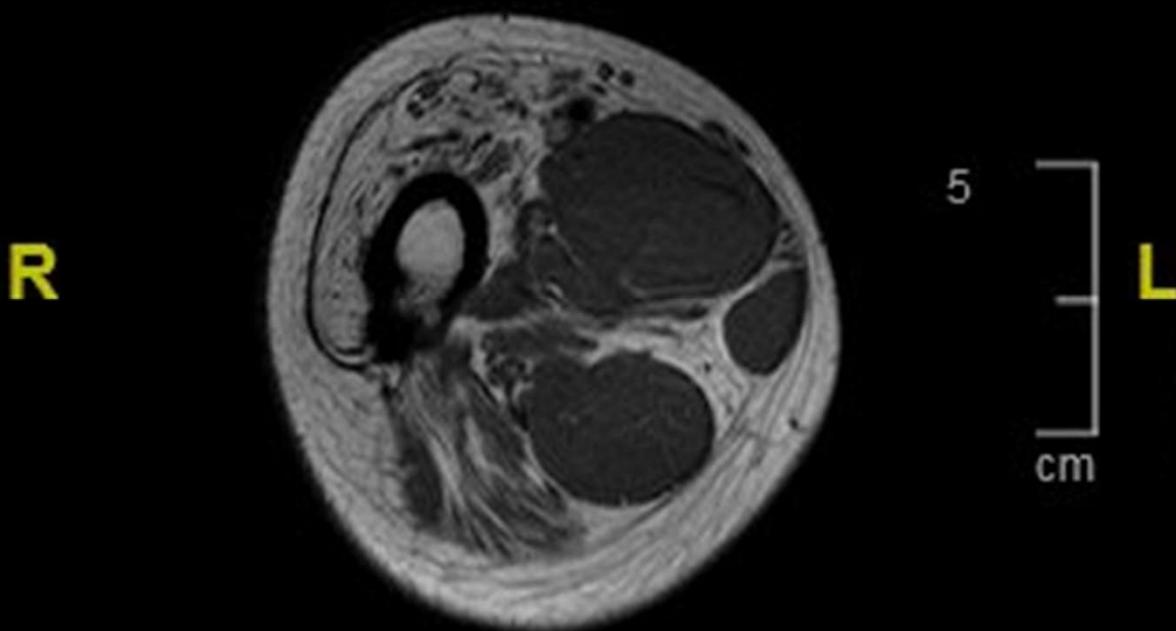
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Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:41/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



5
cm

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:42/90

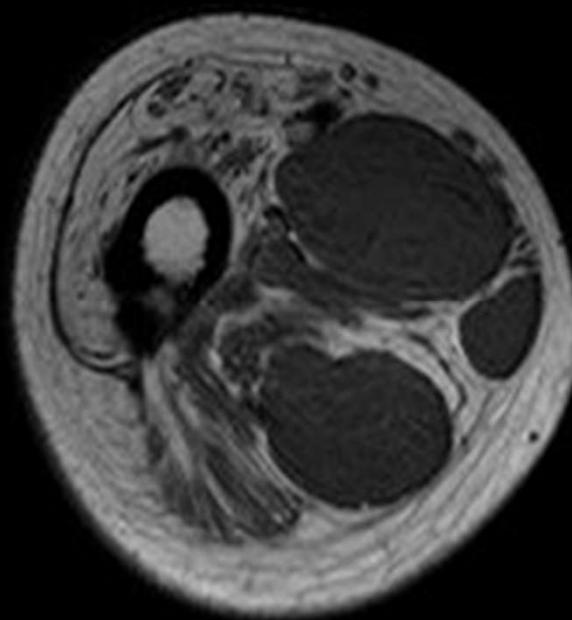
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:43/90

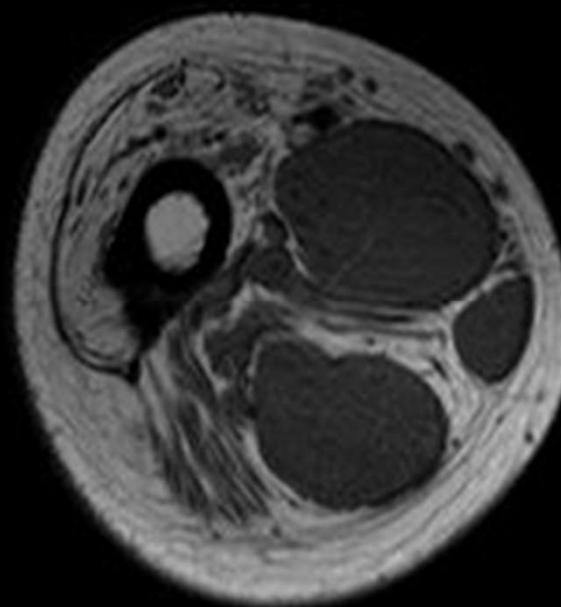
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:44/90

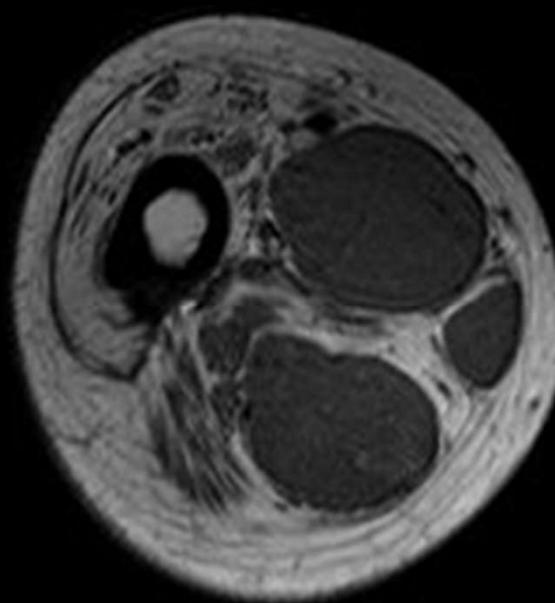
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:45/90

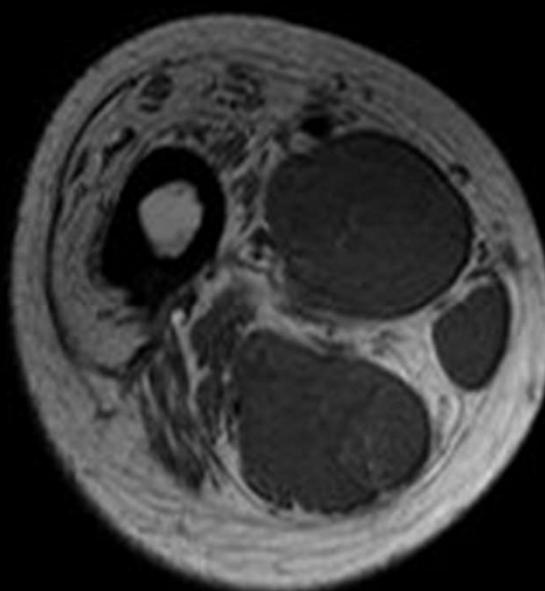
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:48/90

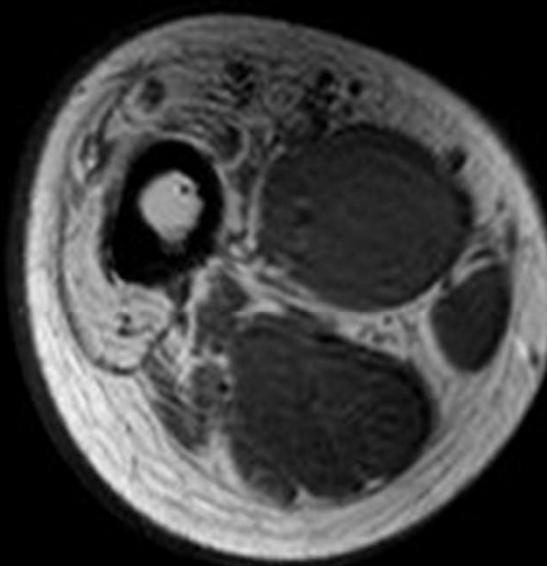
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:878

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
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Im:47/90

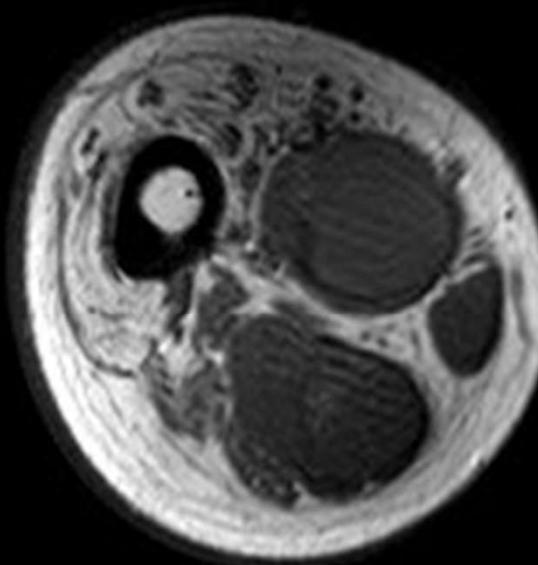
COMPARISON

Westwood Rad

13-Feb-2017

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R



5
cm

L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

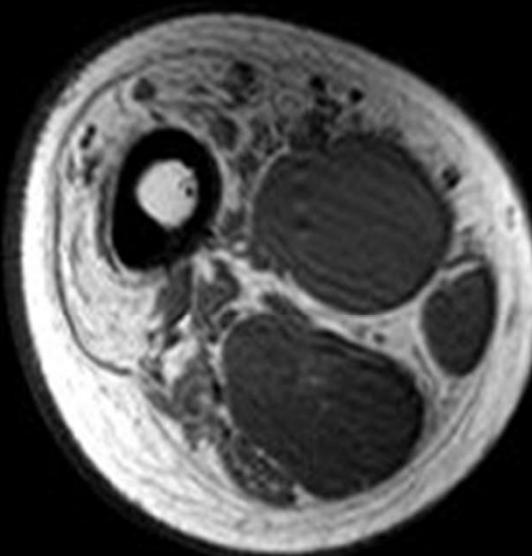
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Im:48/90

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R



5
cm

L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:49/90

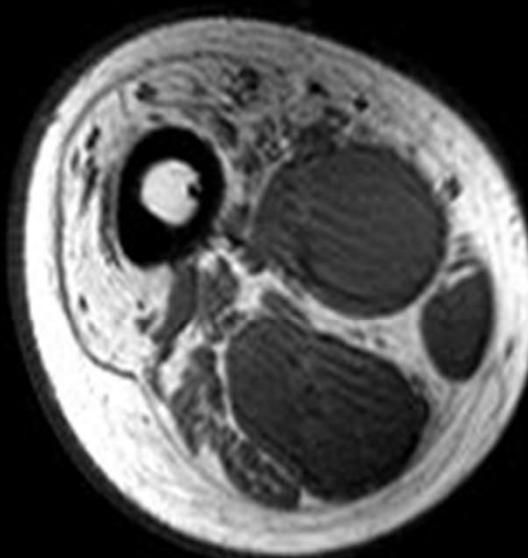
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RIGH
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Im:50/90

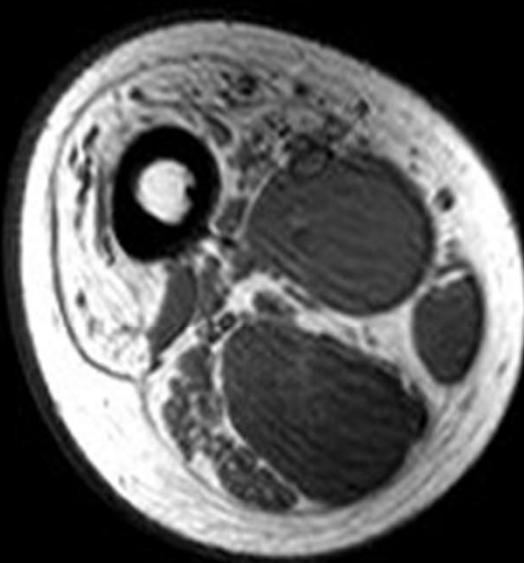
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:51/90

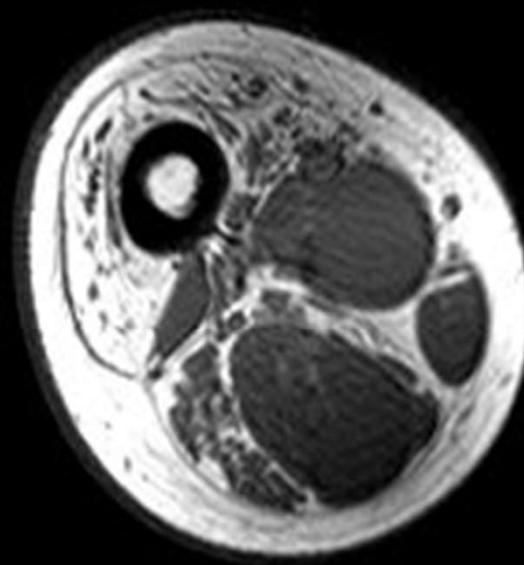
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:52/90

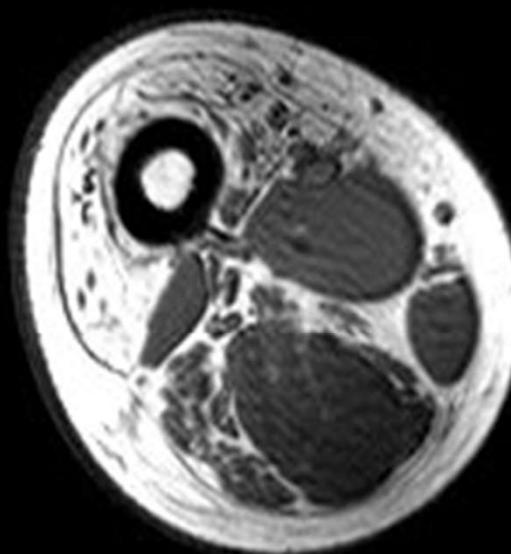
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm **L**

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
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Im:53/90

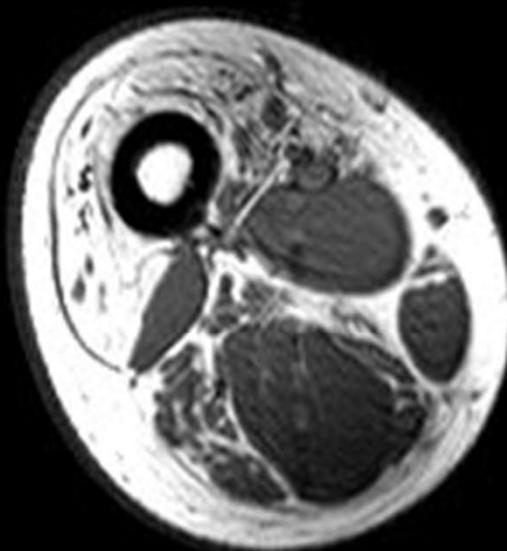
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

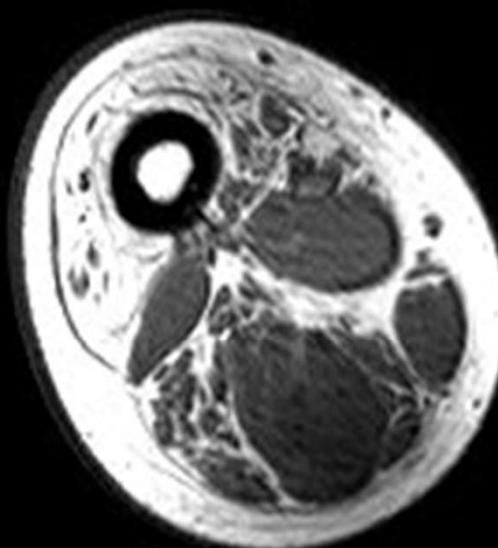
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Im:54/90

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R



5
cm

L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

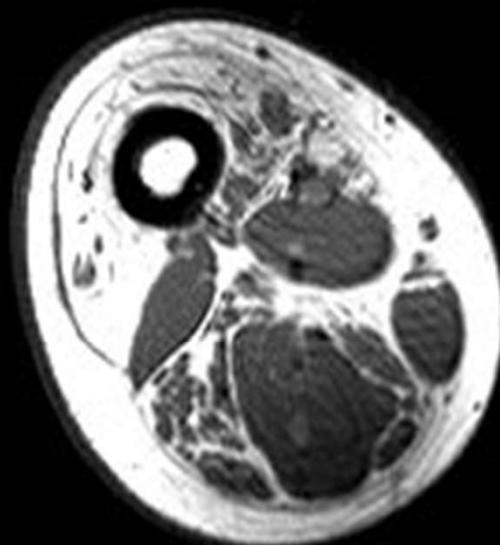
Se:21

13-Feb-2017

Im:55/90

14:48:54

R



5
cm

L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:58/90

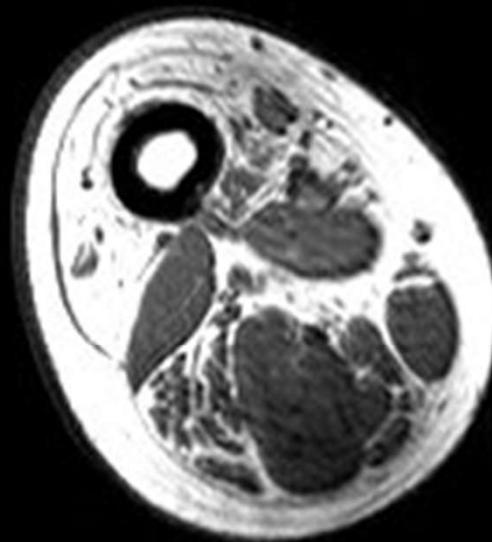
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:676

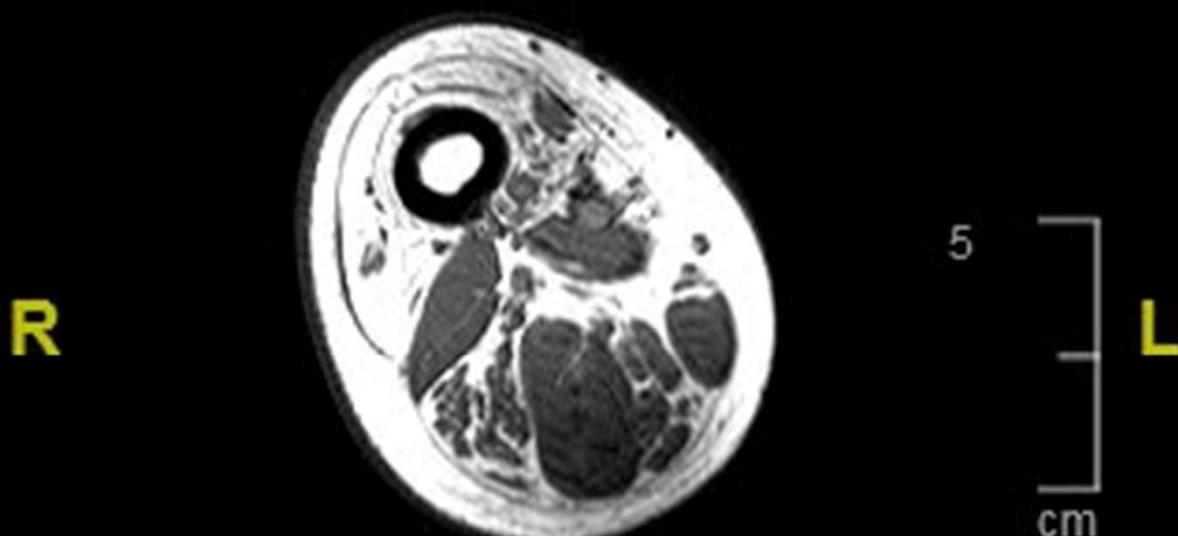
MR FEMUR WO CONTRAST RI
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:57/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



5
cm

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:58/90

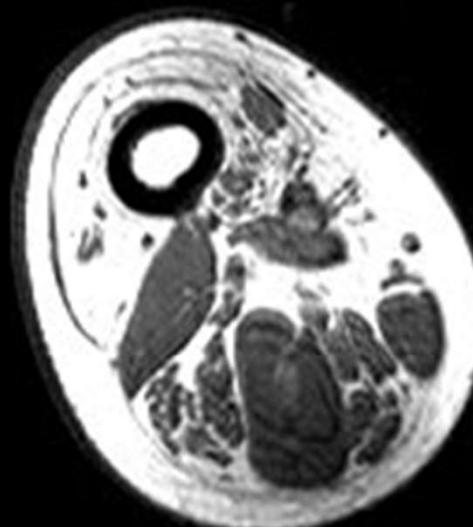
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:59/90

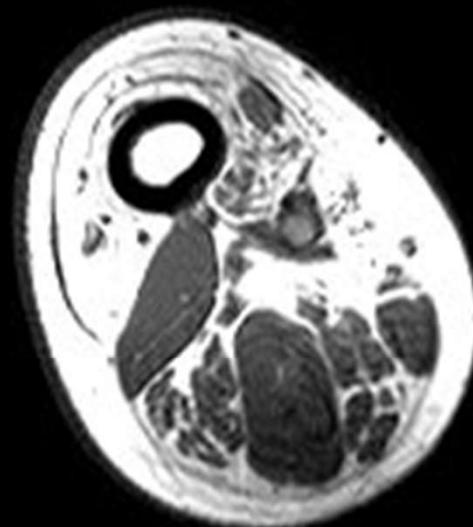
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

AH

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:60/90

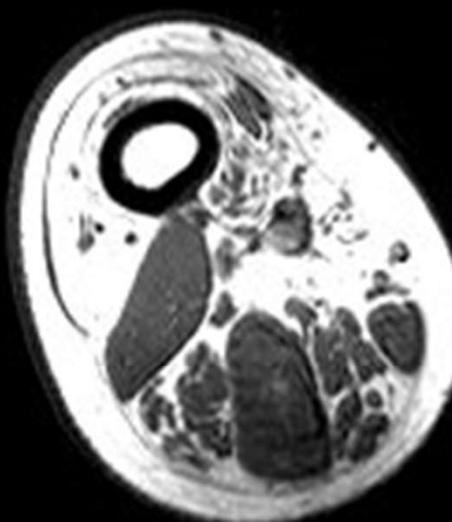
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:61/90

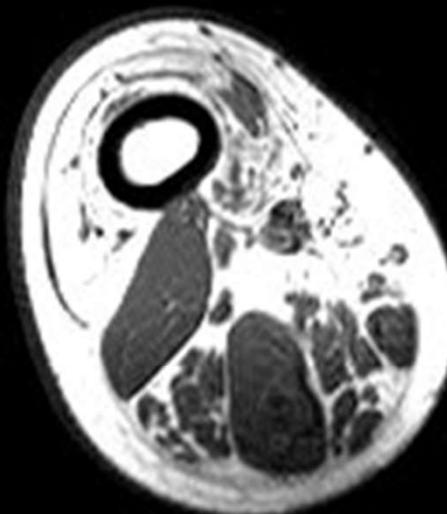
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:62/90

AH

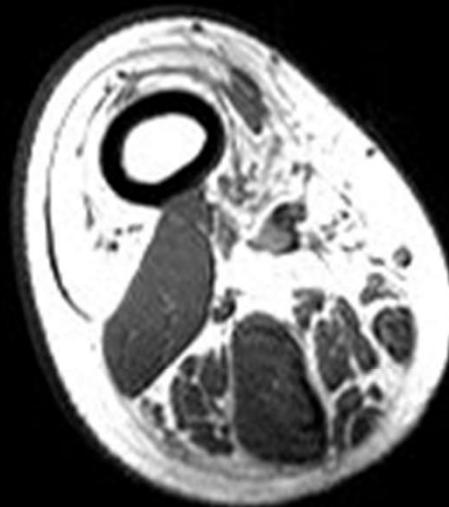
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:63/90

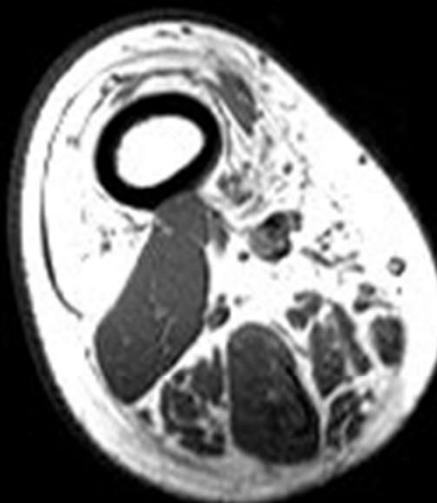
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:64/90

AH

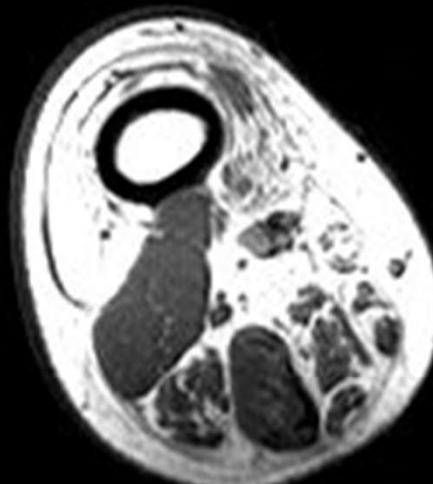
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:676

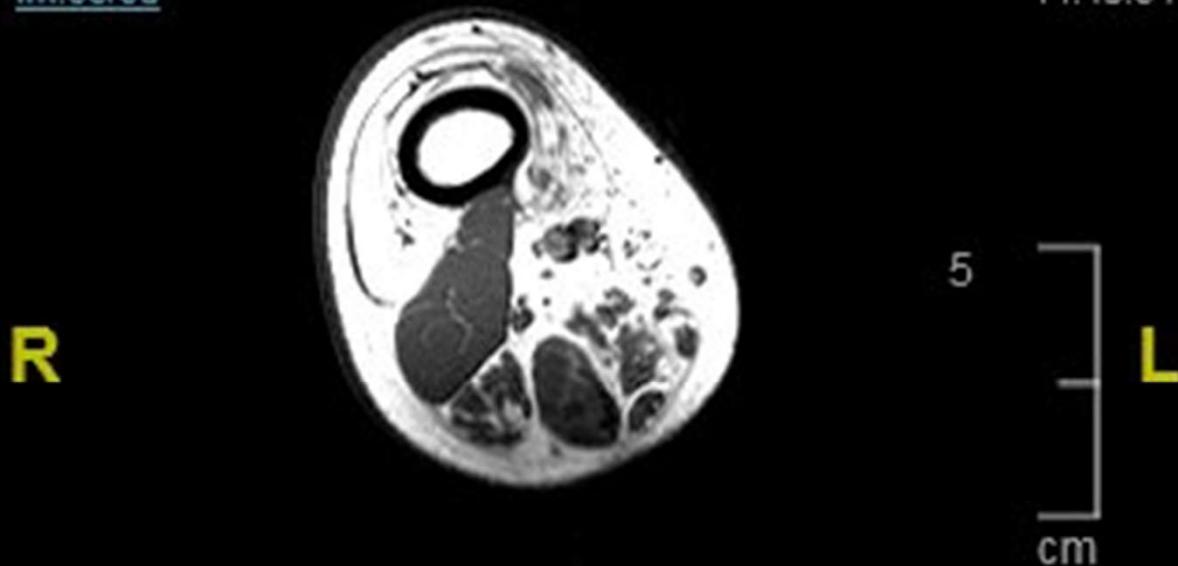
MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:65/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



PF

• WL:381 - WW:676

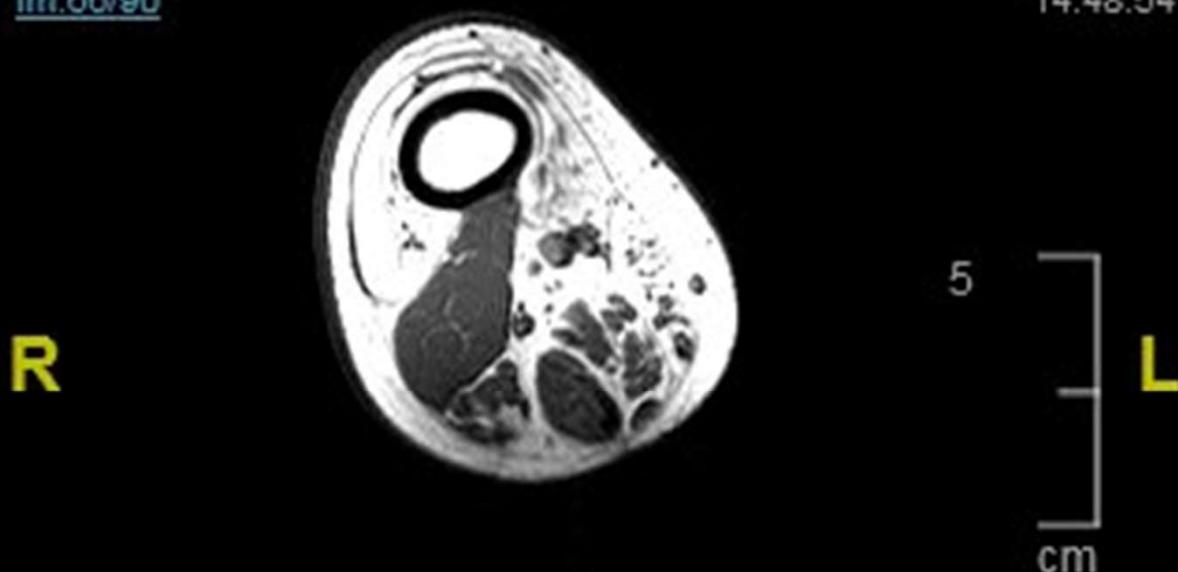
MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:68/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



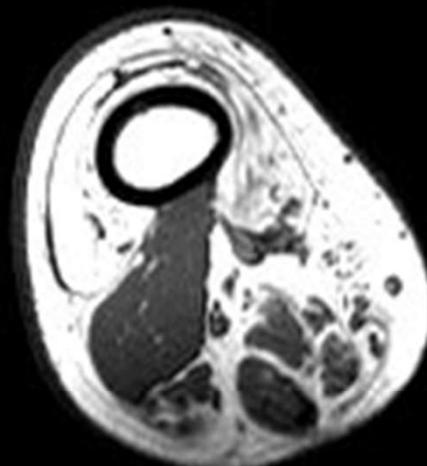
R

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:67/90

R



PF

COMPARISON

Westwood Rad

13-Feb-2017

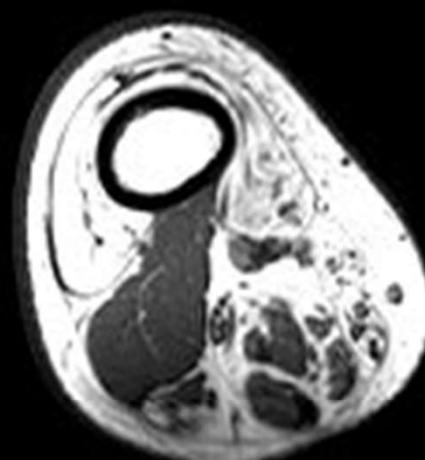
14:48:54

5
cm

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:68/90

R



PF

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

5
cm

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:69/90

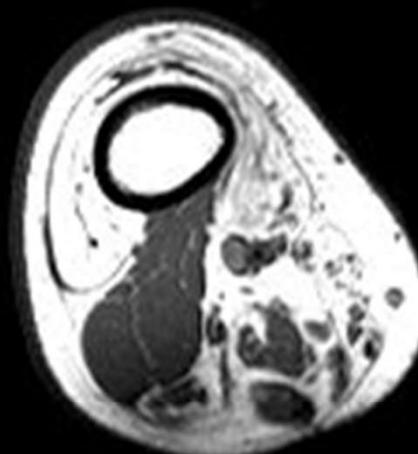
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

AH

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:70/90

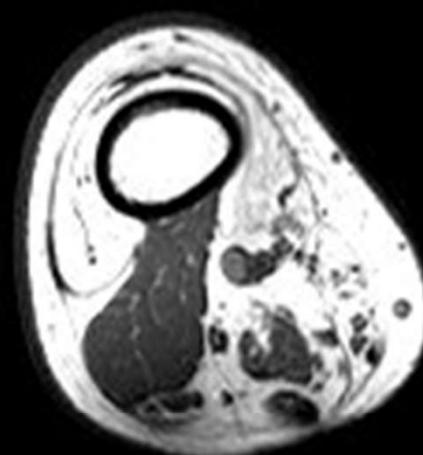
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:676

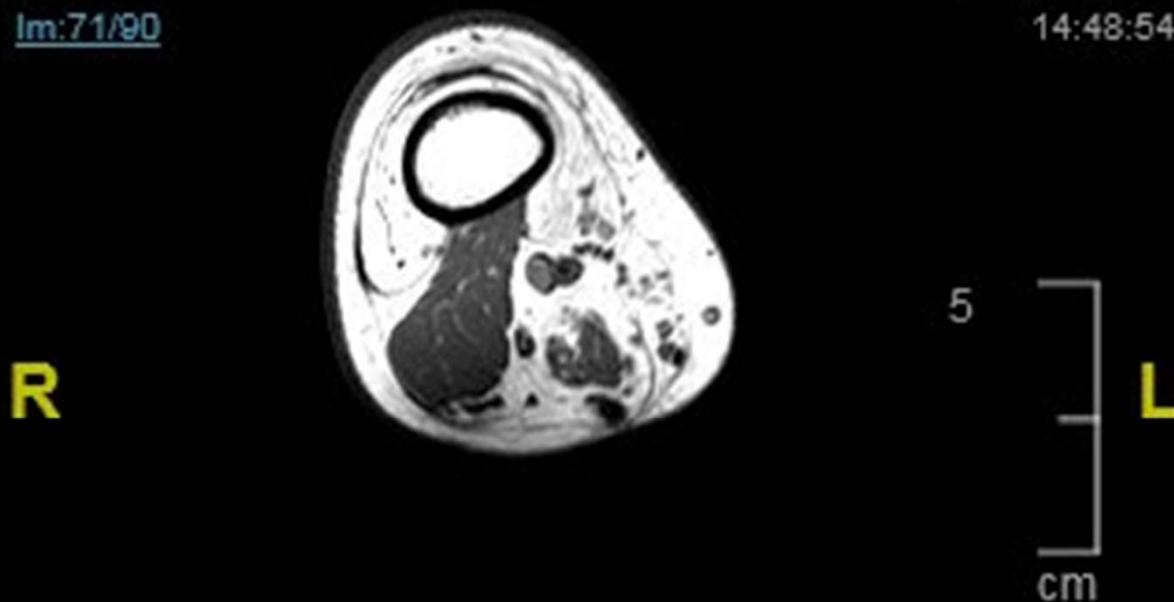
MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:71/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



R

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:72/90

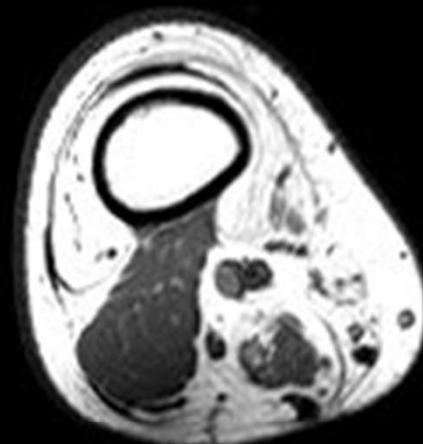
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm
L

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:73/90

AH

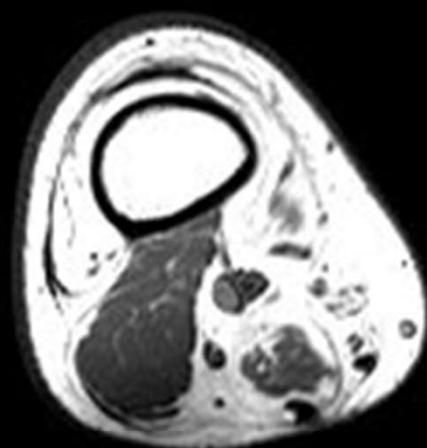
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:676

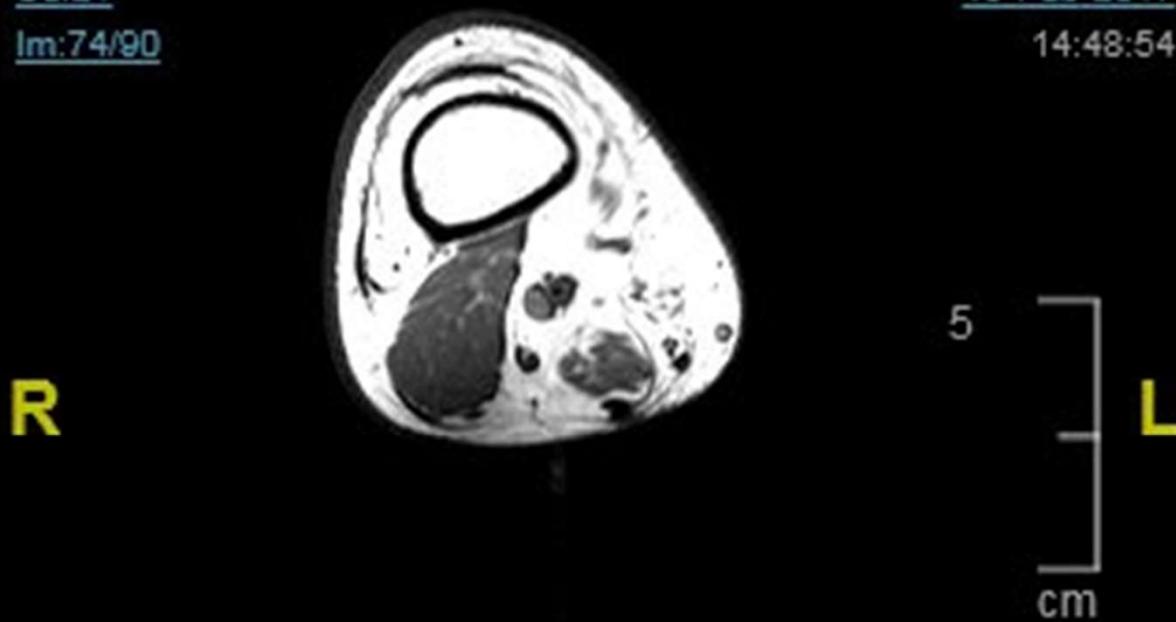
MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:74/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



R

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:75/90

AH

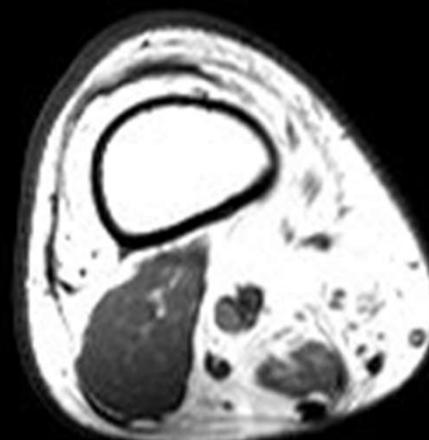
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:76/90

AH

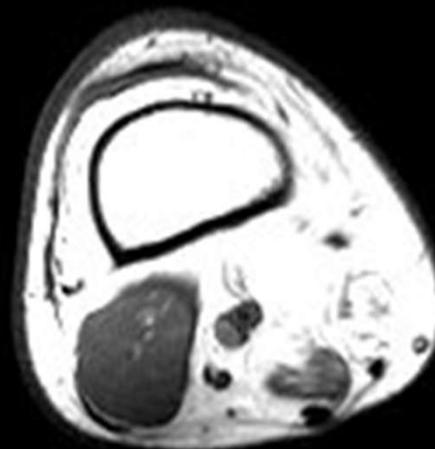
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

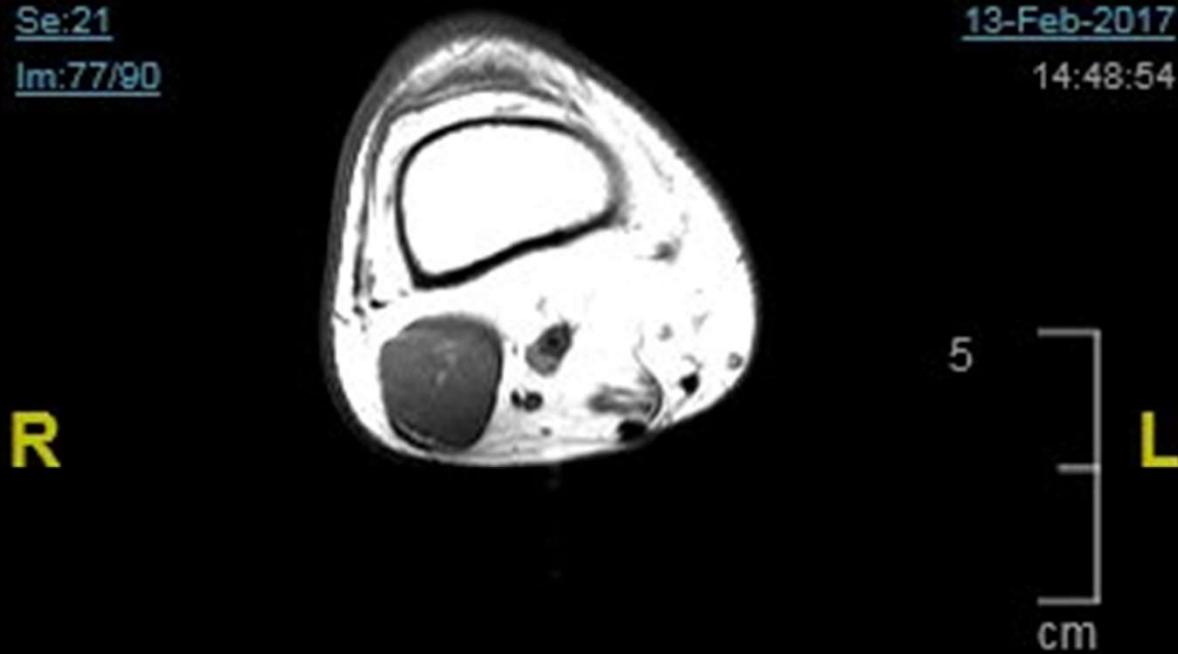
PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI **AH**
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:77/90

COMPARISON

Westwood Rad
13-Feb-2017
14:48:54



PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

AH

COMPARISON

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Westwood Rad

Se:21

13-Feb-2017

Im:78/90

14:48:54

R



5
cm

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:79/90

AH

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:876

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:80/90

AH

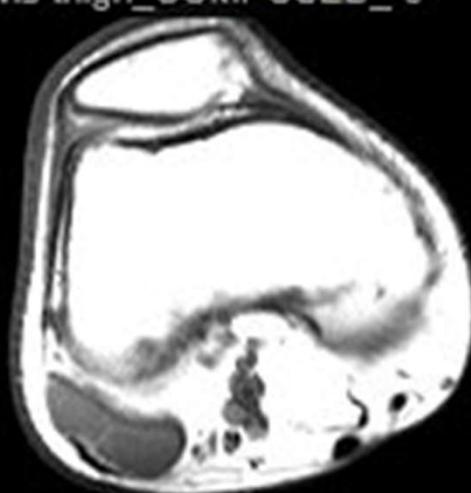
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

PF

• WL:381 - WW:676

MR FEMUR WO CONTRAST RI

Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9

Se:21

Im:81/90

AH

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5
cm

L

PF

• WL:381 - WW:876



MRI of the right leg

- ▶ Atrophy: posterior compartment
- ▶ Preservation: mostly anterior compartment



MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

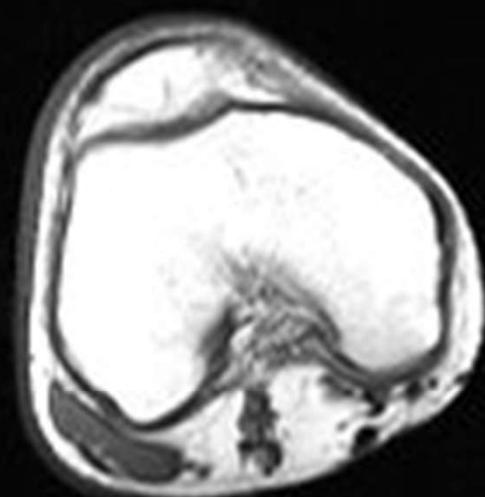
Se:22

13-Feb-2017

Im:9/66

14:52:20

R



5

cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

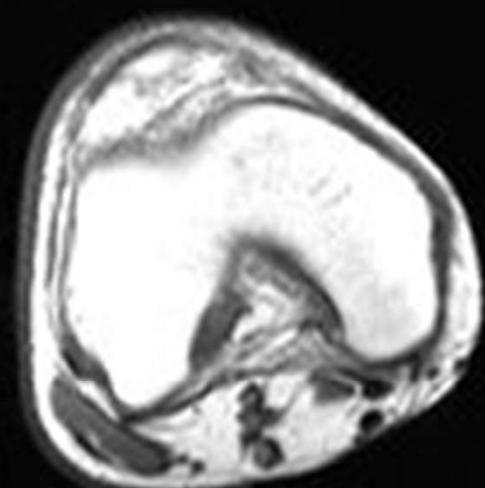
Se:22

13-Feb-2017

Im:10/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

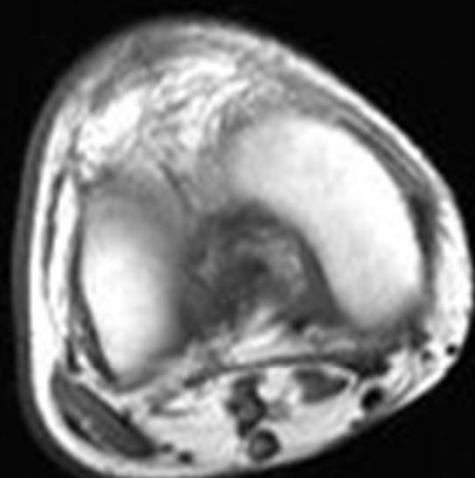
Se:22

13-Feb-2017

Im:11/86

14:52:20

R



5
cm

L

P

• WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

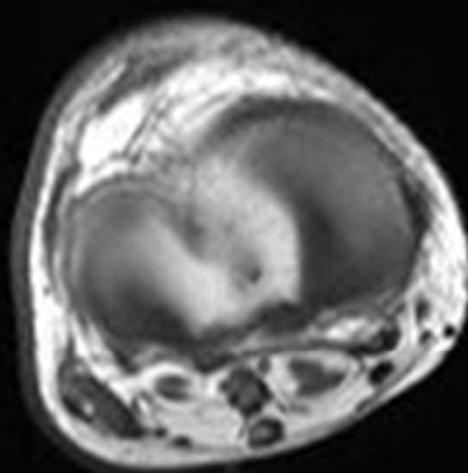
Se:22

13-Feb-2017

Im:12/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

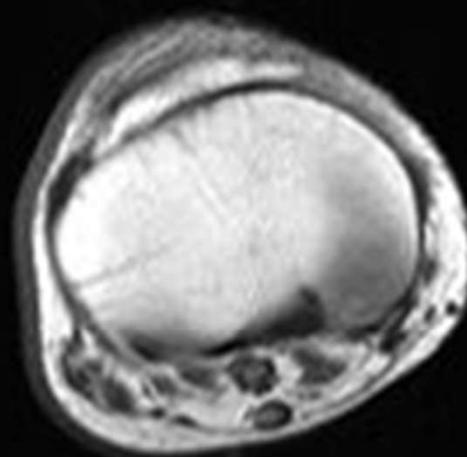
Se:22

13-Feb-2017

Im:13/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

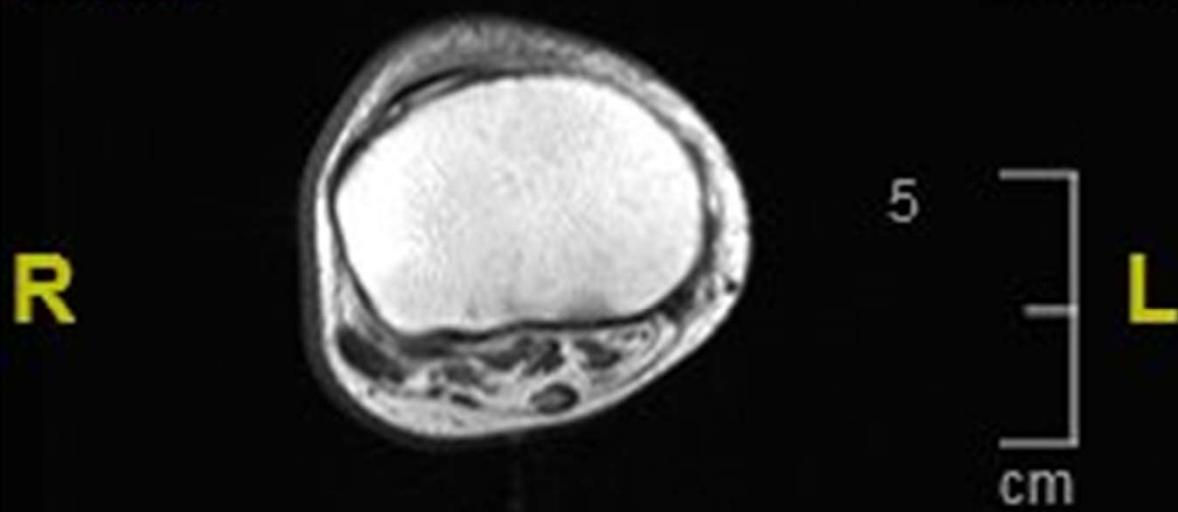
Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

Se:22

13-Feb-2017

Im:14/86

14:52:20



P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

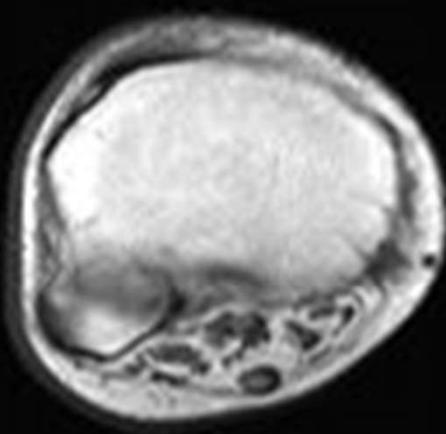
Se:22

13-Feb-2017

Im:15/86

14:52:20

R



5
cm

L

P

• WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

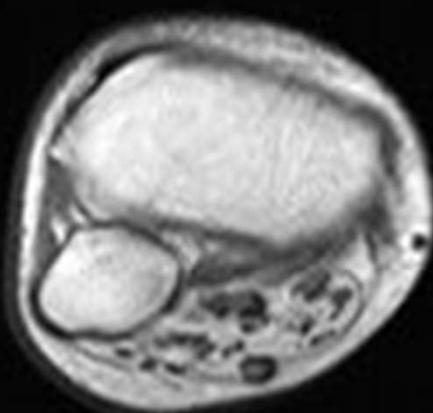
Se:22

13-Feb-2017

Im:16/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

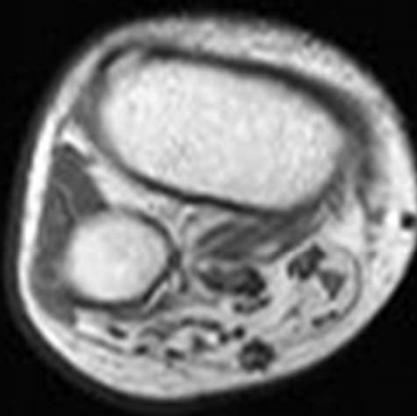
Se:22

13-Feb-2017

Im:17/86

14:52:20

R



5
cm
L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

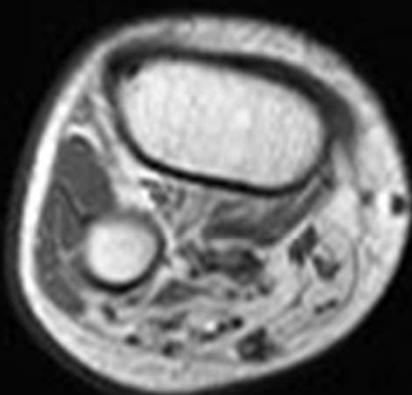
Se:22

13-Feb-2017

Im:18/86

14:52:20

R



5
cm
L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

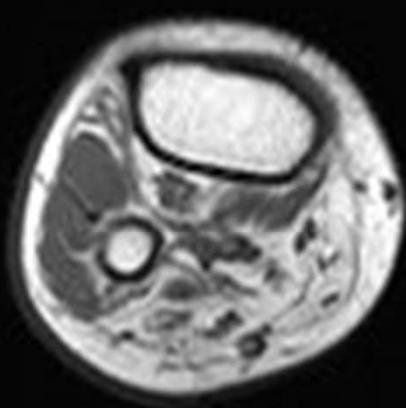
Se:22

13-Feb-2017

Im:19/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

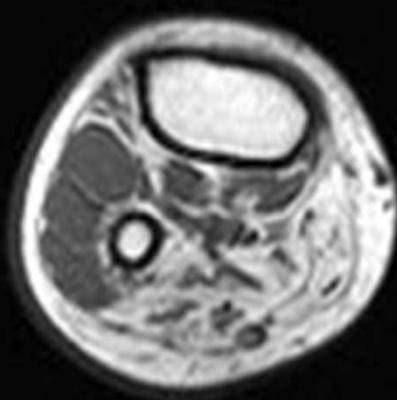
Se:22

13-Feb-2017

Im:20/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

Se:22

13-Feb-2017

Im:21/86

14:52:20

R



5

cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

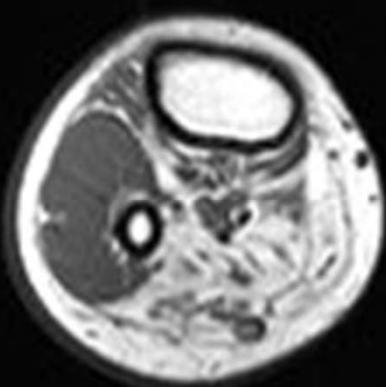
Se:22

13-Feb-2017

Im:22/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST **A** RIGHT

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

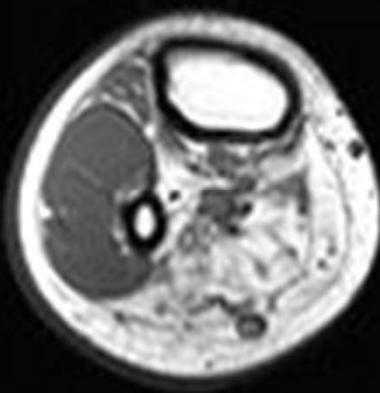
Se:22

13-Feb-2017

Im:23/86

14:52:20

R



5
cm **L**

P

• WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

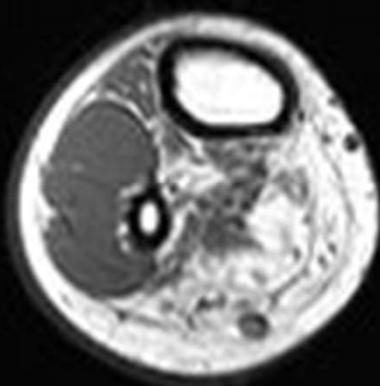
Se:22

13-Feb-2017

Im:24/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

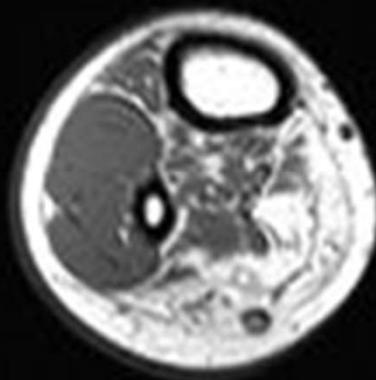
Se:22

13-Feb-2017

Im:25/86

14:52:20

R



5

cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

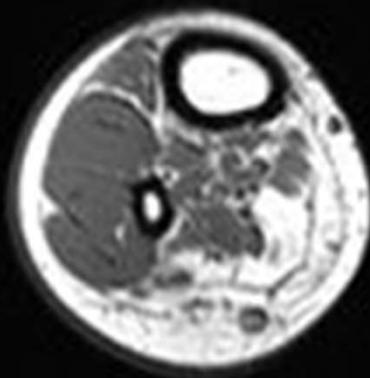
Se:22

13-Feb-2017

Im:26/86

14:52:20

R



5

cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

Se:22

13-Feb-2017

Im:27/86

14:52:20

R



5

cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

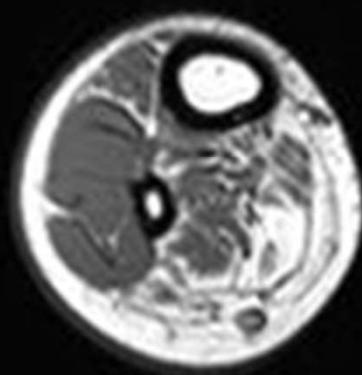
Se:22

13-Feb-2017

Im:28/86

14:52:20

R



P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

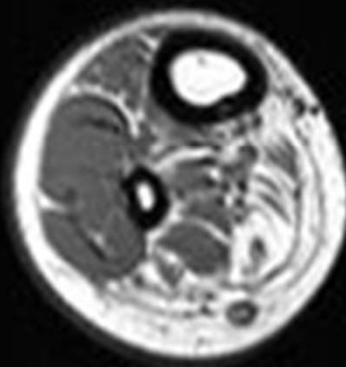
Se:22

13-Feb-2017

Im:29/86

14:52:20

R



P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

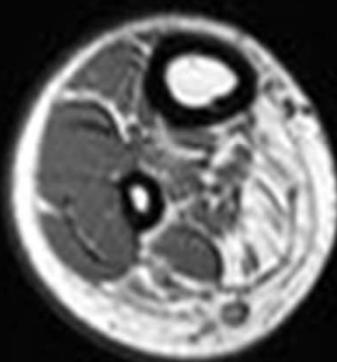
Se:22

13-Feb-2017

Im:30/86

14:52:20

R



P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

Se:22

13-Feb-2017

Im:31/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

RIGHT Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

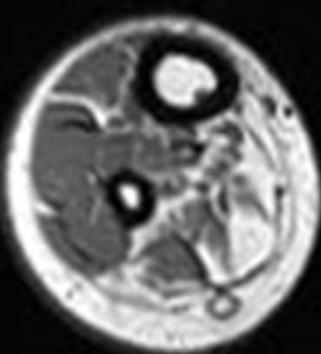
Se:22

13-Feb-2017

Im:32/86

14:52:20

R



5
cm

L

P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST

A

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

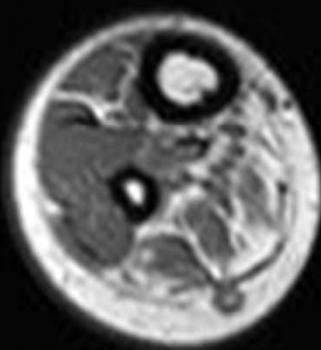
Se:22

13-Feb-2017

Im:33/86

14:52:20

R



5
cm

L

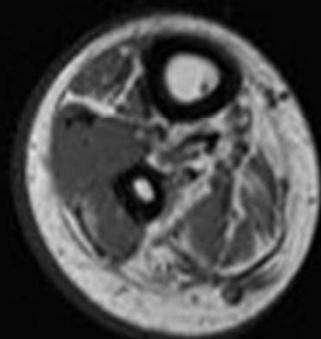
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WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIGT
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:34/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm
L

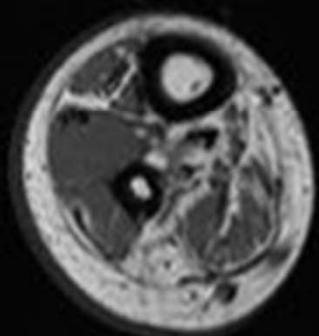
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MR TIB-FIB WO CONTRAST RIGT
Rt_t1_tse_tra calves_COMPOSED_-11
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Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm
L

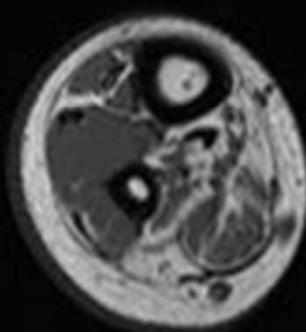
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Im:38/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

L

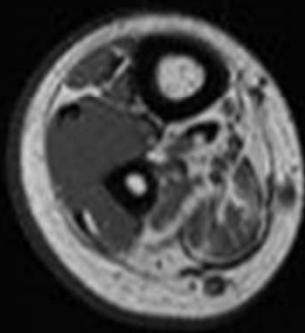
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Im:37/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

L

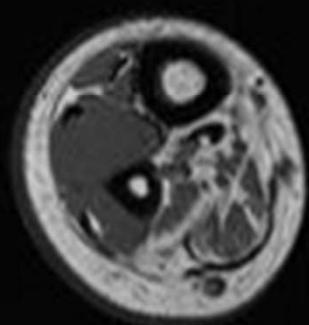
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Rt_t1_tse_tra calves_COMPOSED_-11
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Im:38/66

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm
L

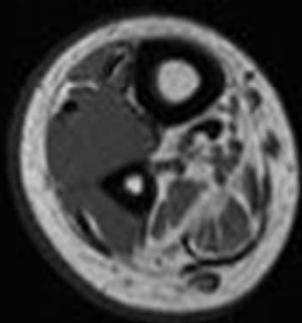
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Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

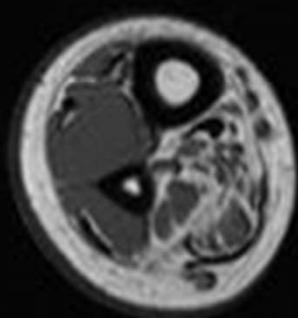
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Im:40/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm
L

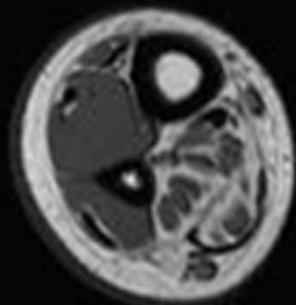
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MR TIB-FIB WO CONTRAST RIGT
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Im:41/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

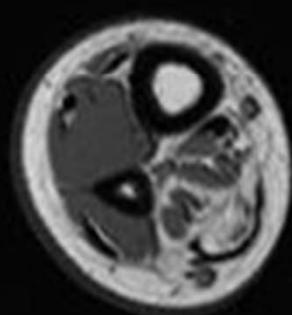
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Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm
L

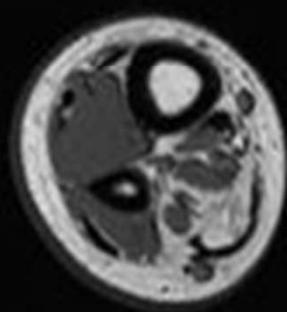
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MR TIB-FIB WO CONTRAST RIGT
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Im:43/66

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm
L

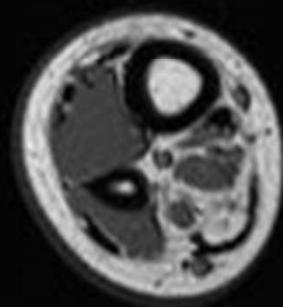
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MR TIB-FIB WO CONTRAST RIGT
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Im:44/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

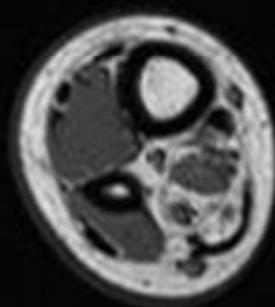
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Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:45/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm
L

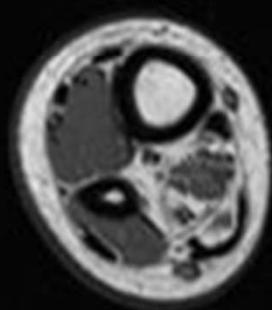
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MR TIB-FIB WO CONTRAST RIGT
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Se:22
Im:48/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

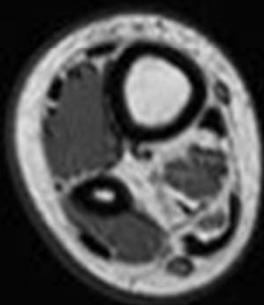
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MR TIB-FIB WO CONTRAST RIGT
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:47/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

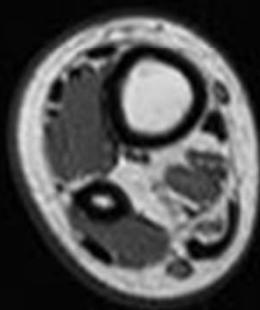
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MR TIB-FIB WO CONTRAST RIGA
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:48/66

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

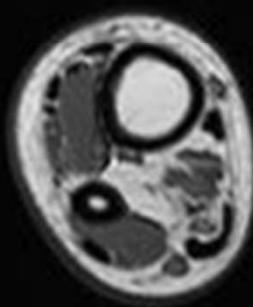
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Im:49/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

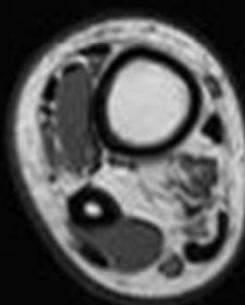
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MR TIB-FIB WO CONTRAST RIGT
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:50/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

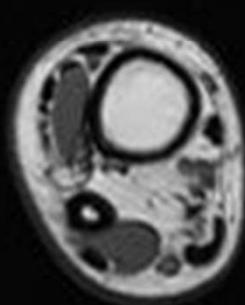
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MR TIB-FIB WO CONTRAST RIGT
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Im:51/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

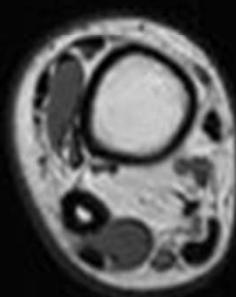
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Primary
Westwood Rad
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14:52:20

R



5
cm

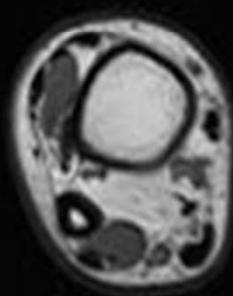
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MR TIB-FIB WO CONTRAST RIGHT
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Im:53/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

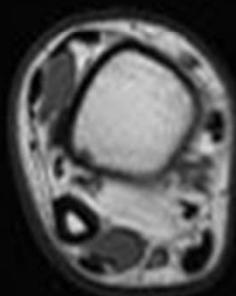
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WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIGT
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Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

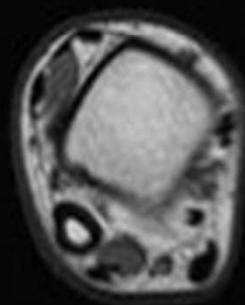
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WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIGHT
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Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

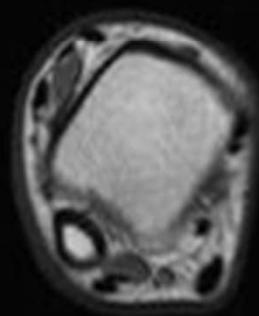
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MR TIB-FIB WO CONTRAST RIGT
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Im:58/86

Primary
Westwood Rad
13-Feb-2017
14:52:20

R



5
cm

P

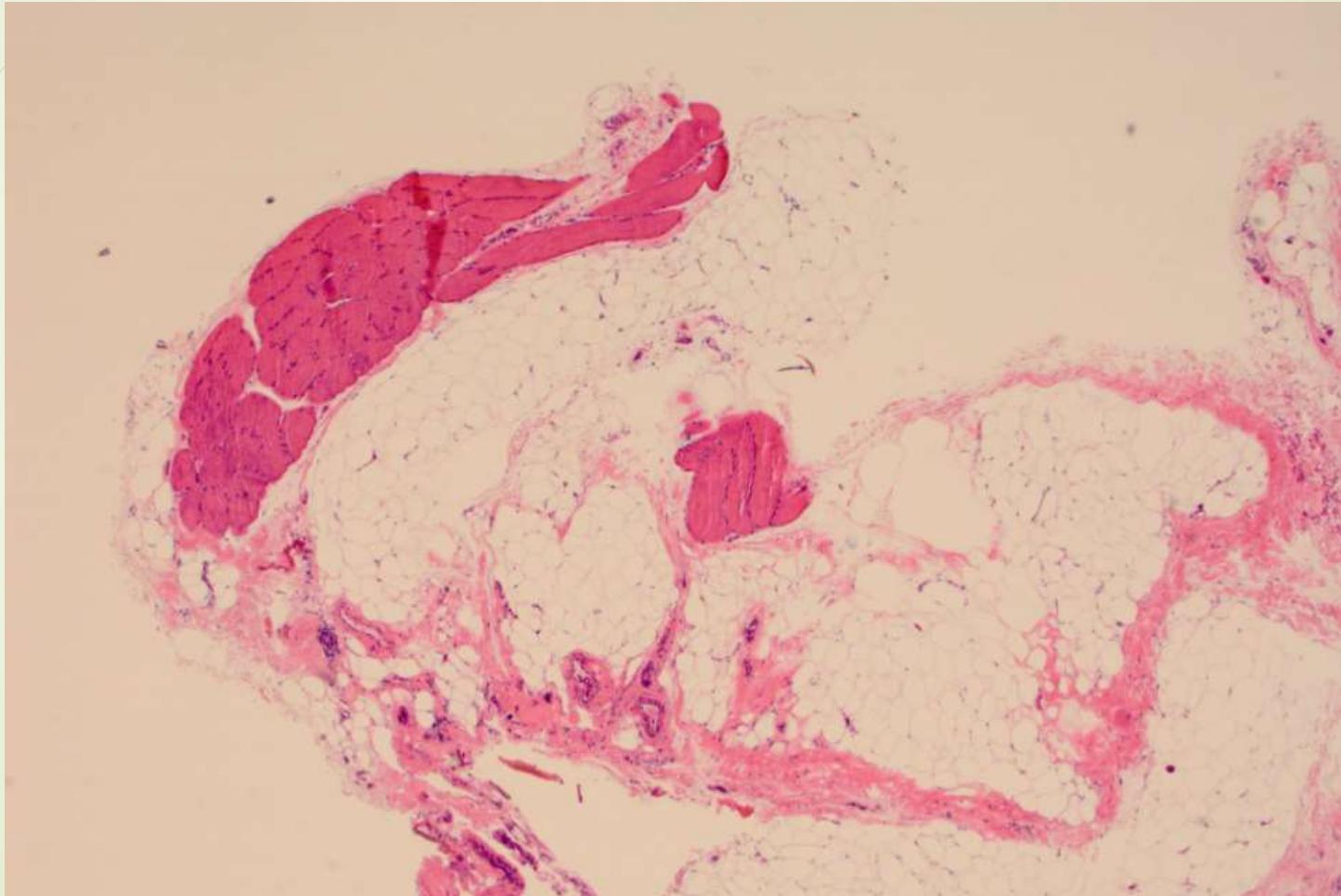
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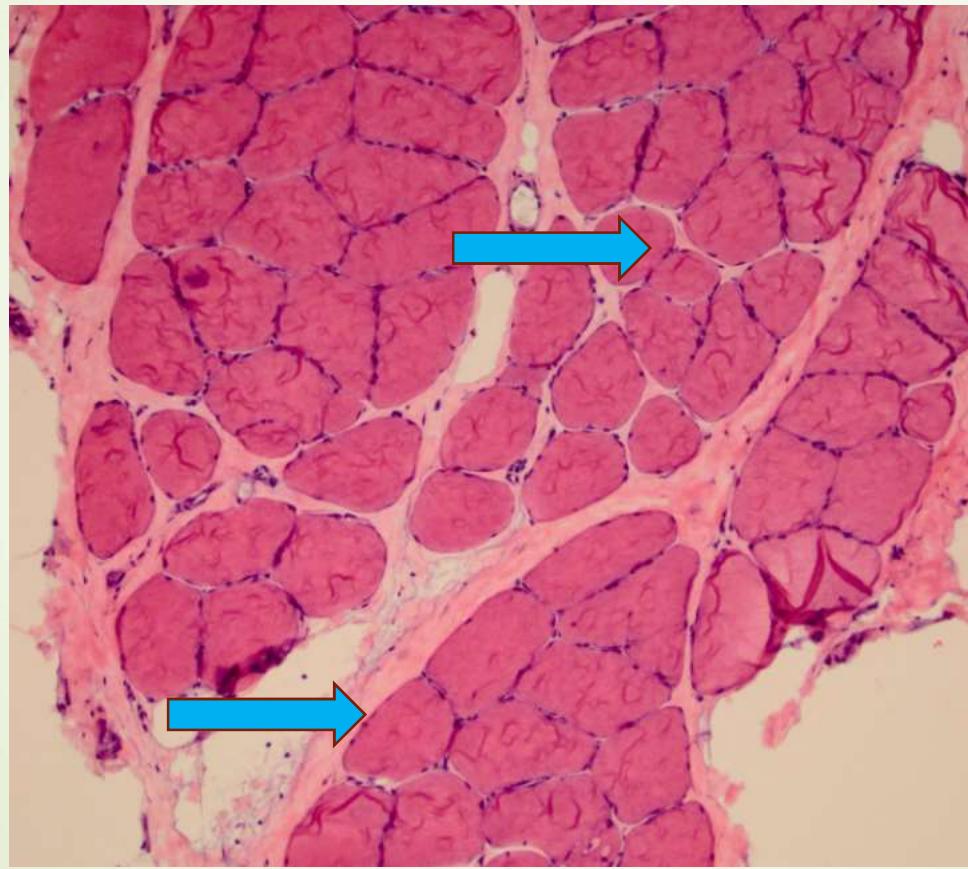
The three brothers: same phenotype



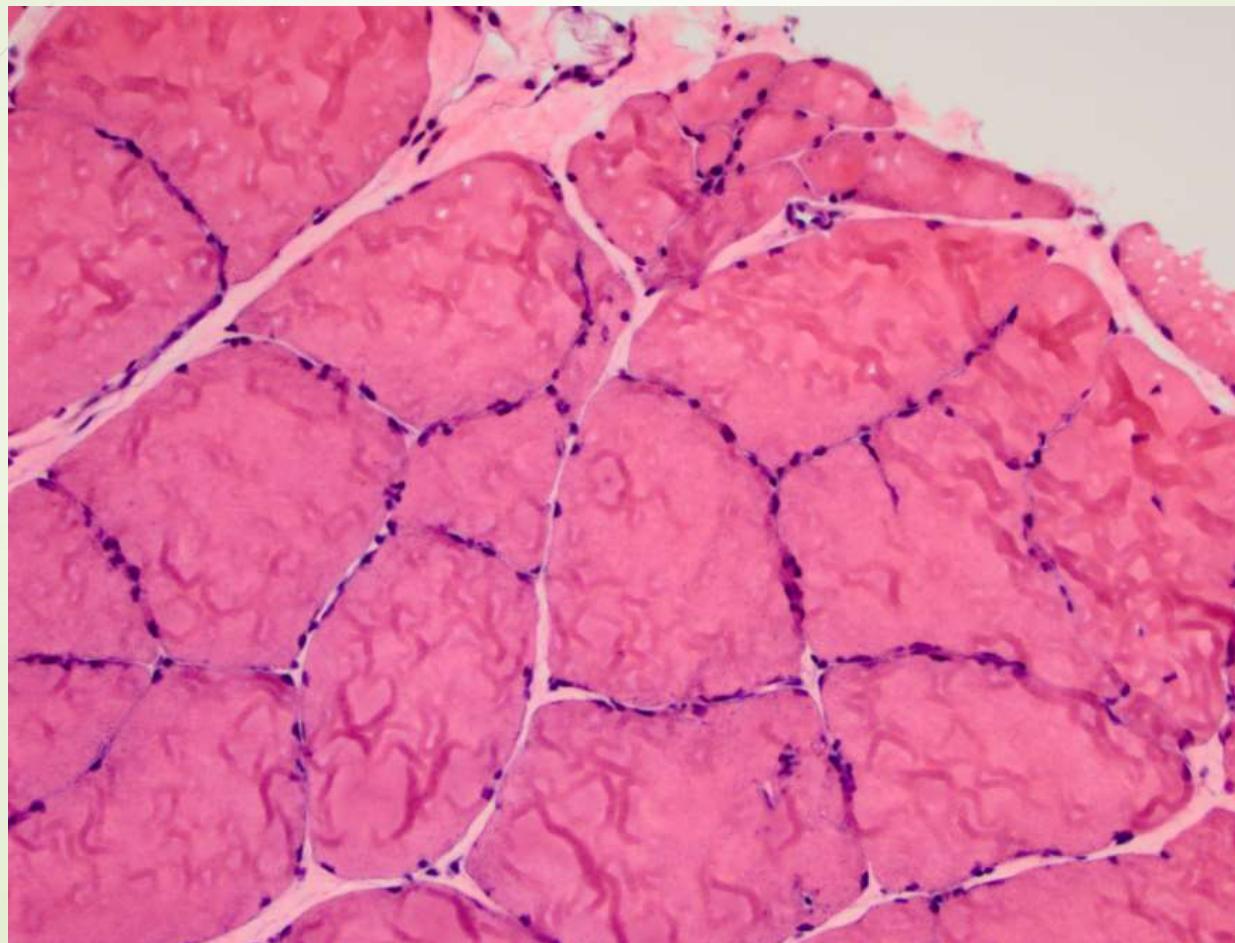
Biopsy: tibialis anterior



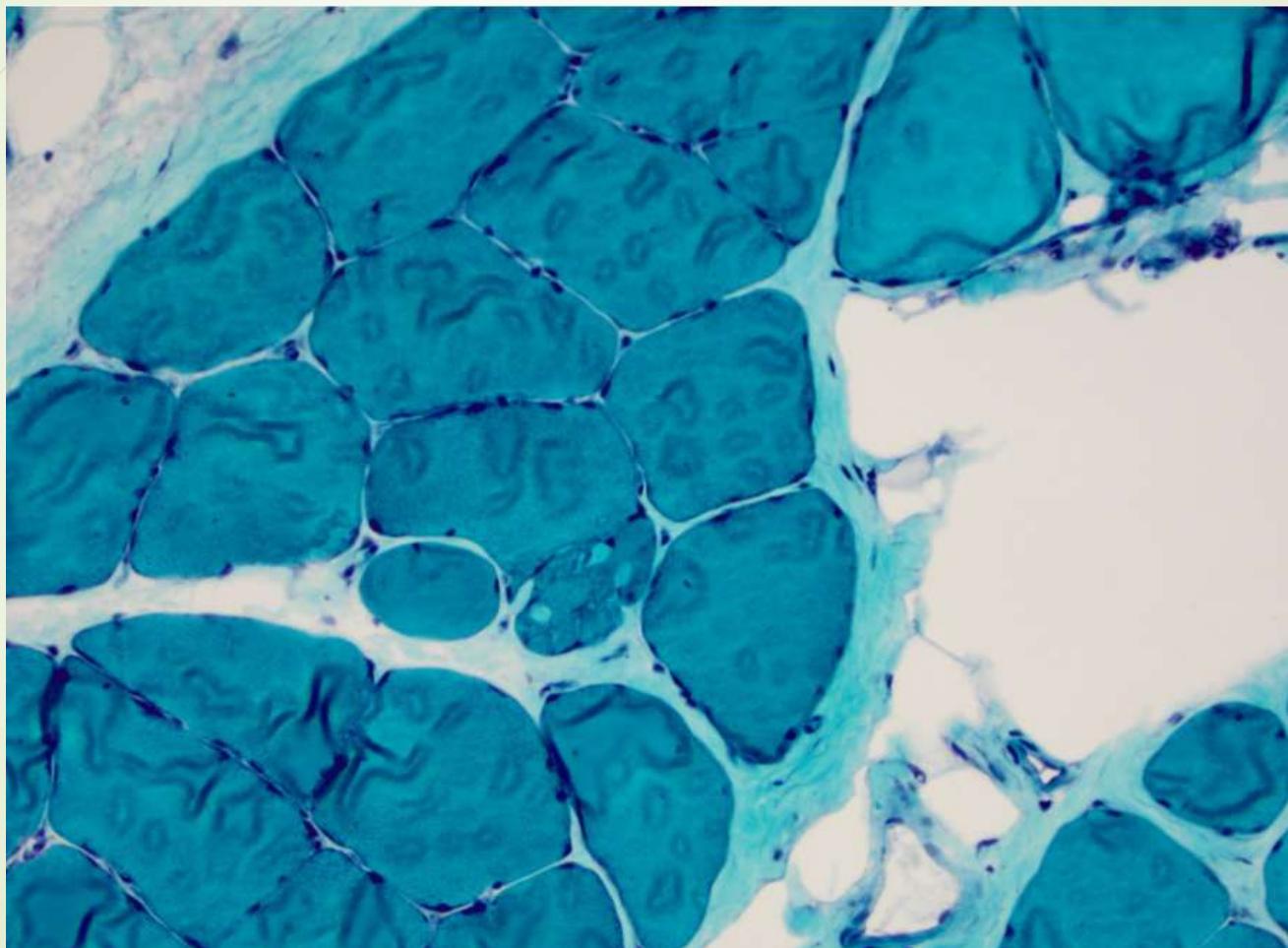
H/E



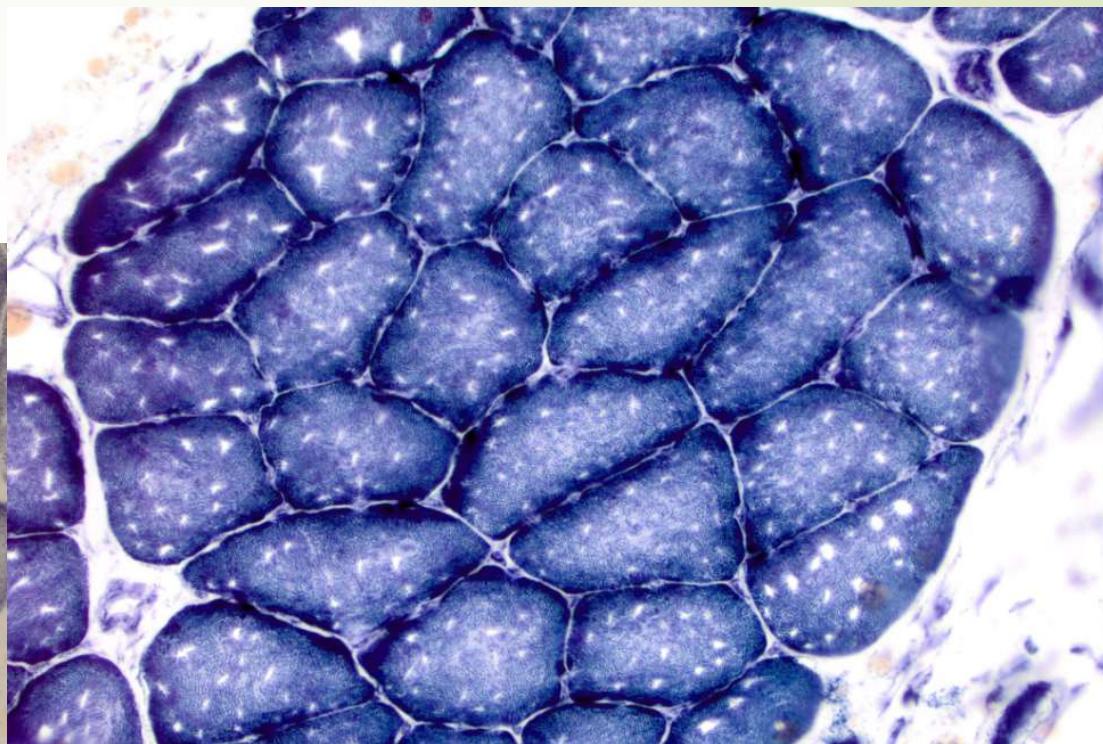
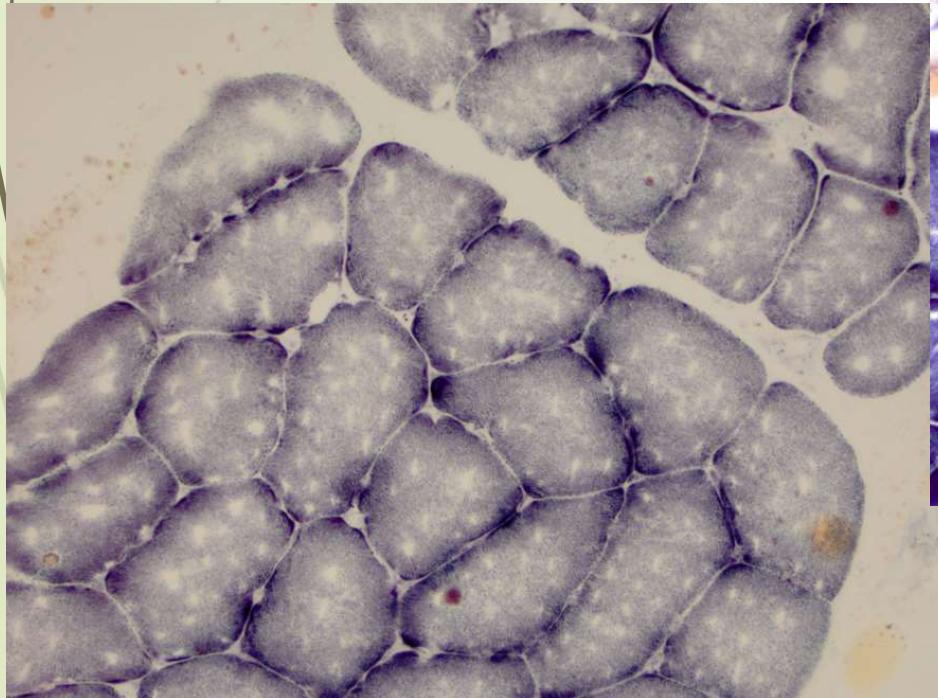
H/E



Gömöri trichrome

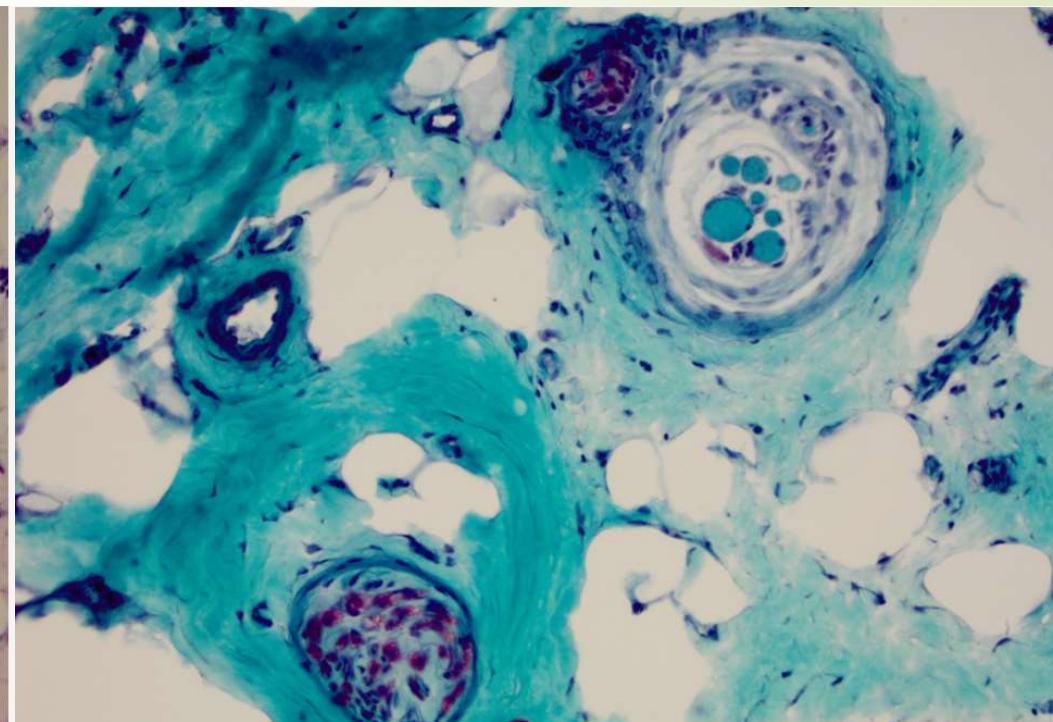
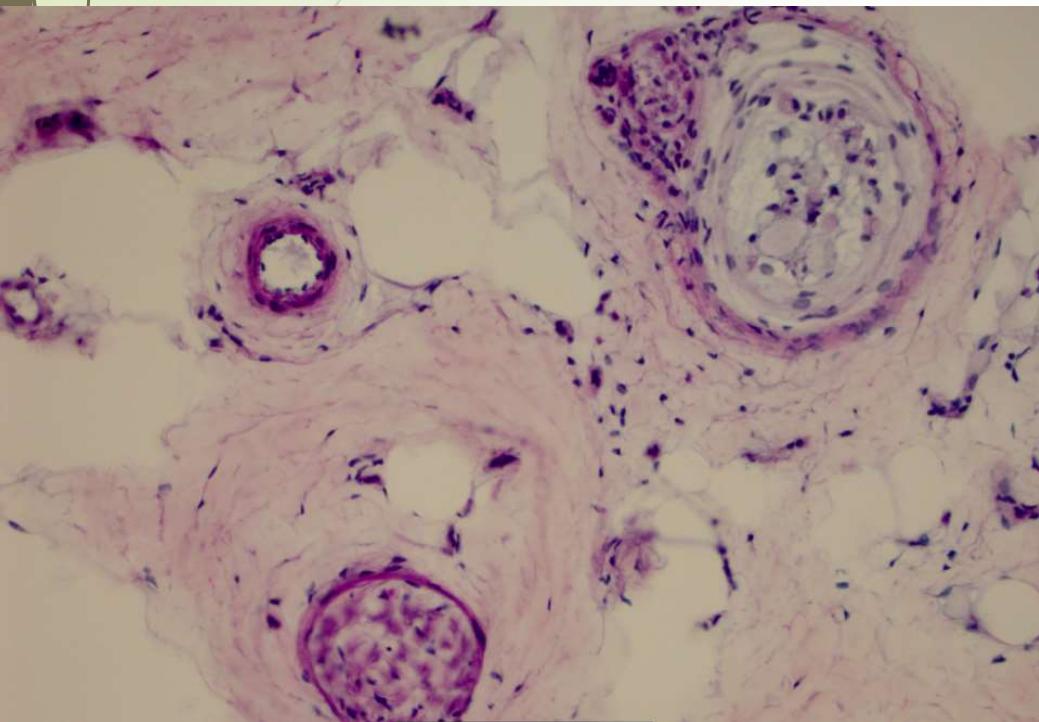


SDH/NADH stain

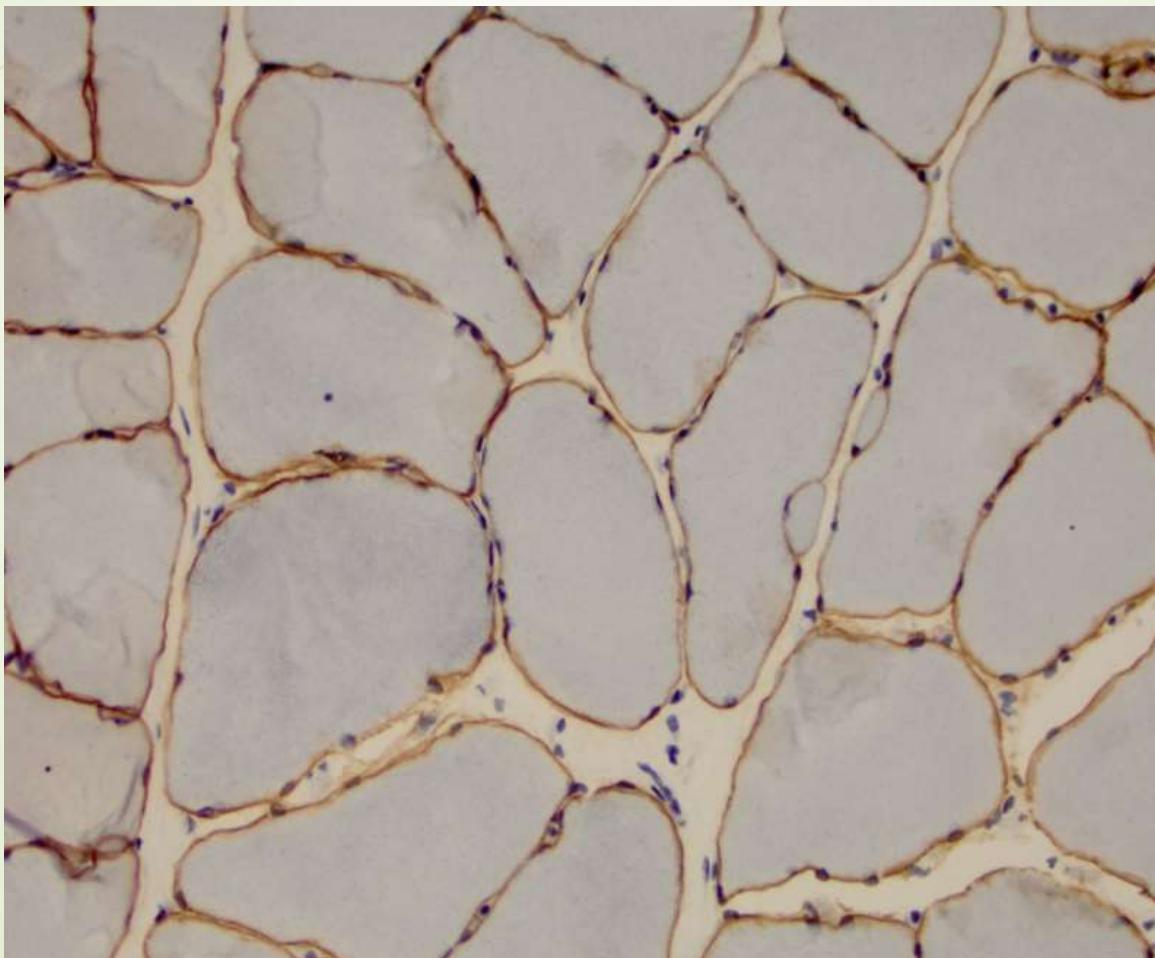


ATPase 9.2, 4.6, 4.2- exclusive type 1 fiber only

Nerve



Dystrophin stain





Immunohistochemistry

| ANTIBODY/PROBE: | RESULT/COMMENT |
|------------------------------|----------------|
| ► Dystrophin I – Rod domain | Positive |
| ► Dystrophin II – C terminus | Positive |
| ► Merosin (laminin alpha 2) | Positive |
| ► Alpha sarcoglycan | Positive |
| ► Beta sarcoglycan | Positive |
| ► Gamma sarcoglycan | Positive |



Open discussion of diagnosis: What do you think?





Further work up: Distal hereditary motor neuropathy panel (next-gen sequencing)

- ▶ Gene sequenced: ATP7A, BSCL2, DCTN1, DNMT1, FIG4, GARS, HINT1, HSPB1, HSPBB, IGHMBP2, LAS1L, MEGF10, REEP1, STX, SLC5A7, TRPV4
- ▶ FIG4 VUS
 - ▶ Heterozygous c.181C>T (p.Gln61*) Variant of unknown significance
- ▶ FIG4 (CMT4J, ALS11) is supposed to autosomal recessive
- ▶ Twin brothers were tested, and were negative for this mutation
- ▶ Trio exome sequencing: no clinical significant variants



Whole genome sequencing performed on patient, twin brothers, and parents

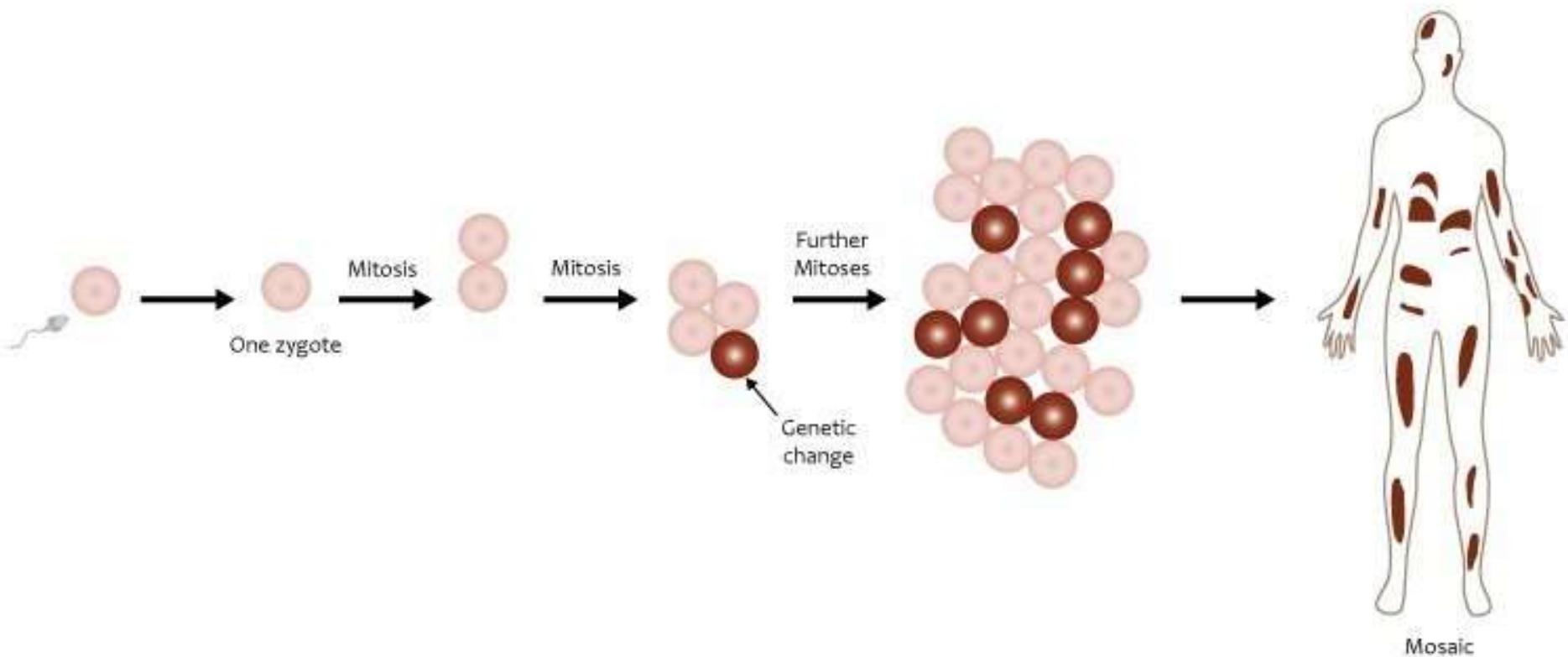
- ▶ DYNC1H1 gene (AD Lower extremity predominant SMA)
 - ▶ variant c.2327C>T (p.Pro776Leu)
 - ▶ Twin brothers also tested positive for this mutation
 - ▶ Father is also tested positive for this mutation
 - ▶ It appears that it is inherited from Father who does not have phenotype

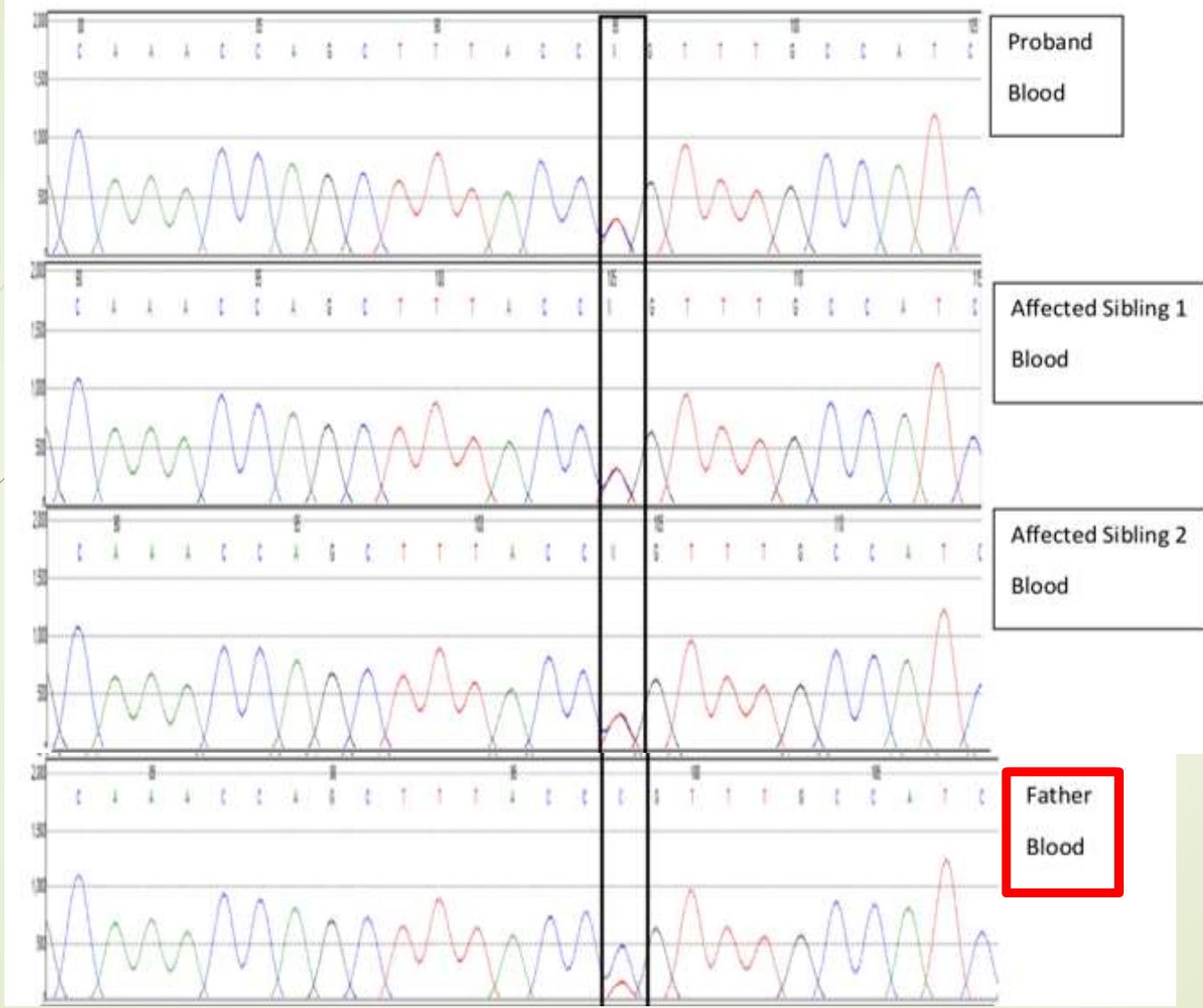


Whole Genome Sequencing: allele imbalance observed

- ▶ Allele imbalance observed in father's DYNC1H1 mutation
- ▶ Suspect that the father is actually mosaic for that mutation (mutation load is <50%)
- ▶ Therefore this could explain that although father carries the mutation, he does not have the phenotype

Genetic mosaicism

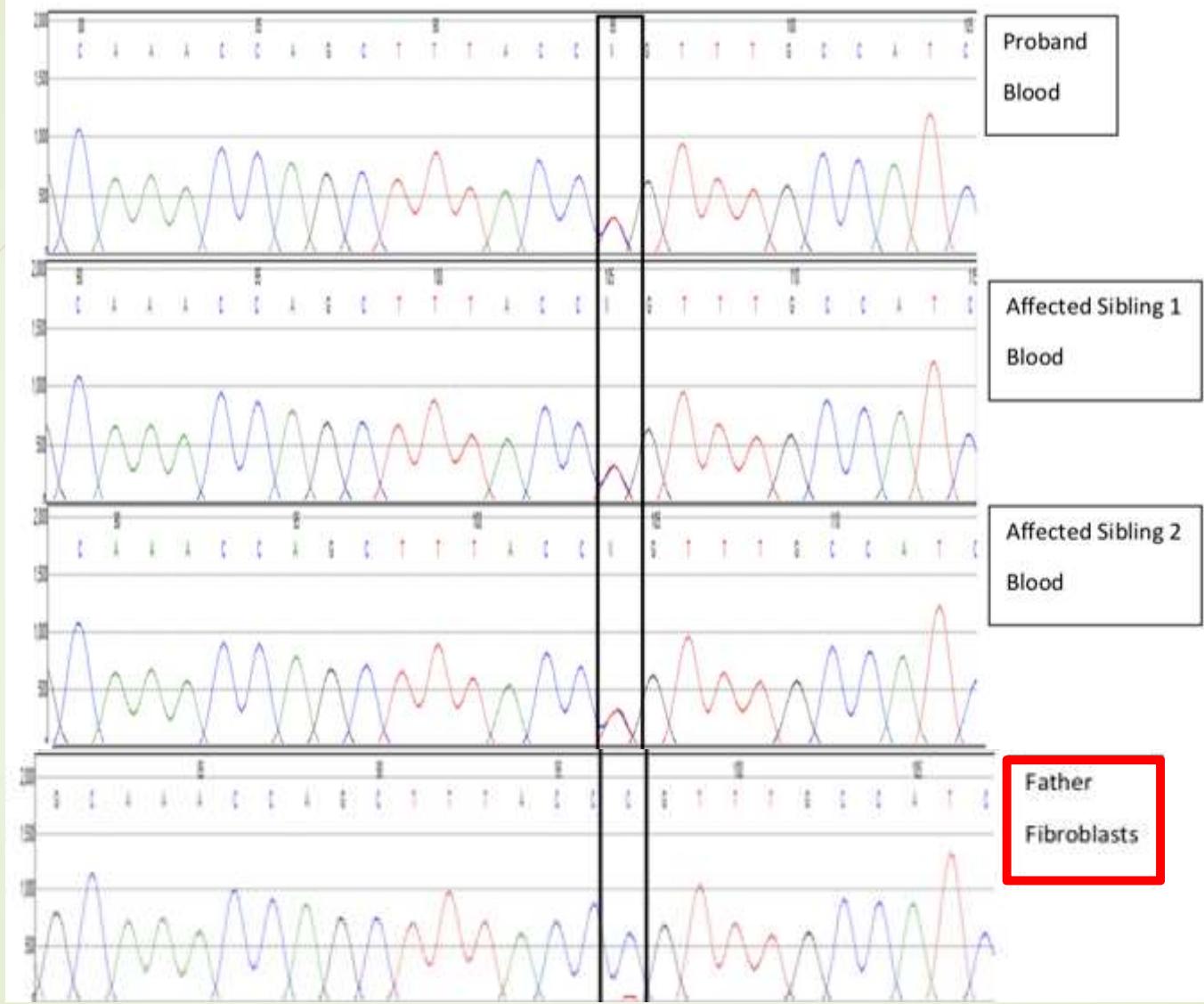


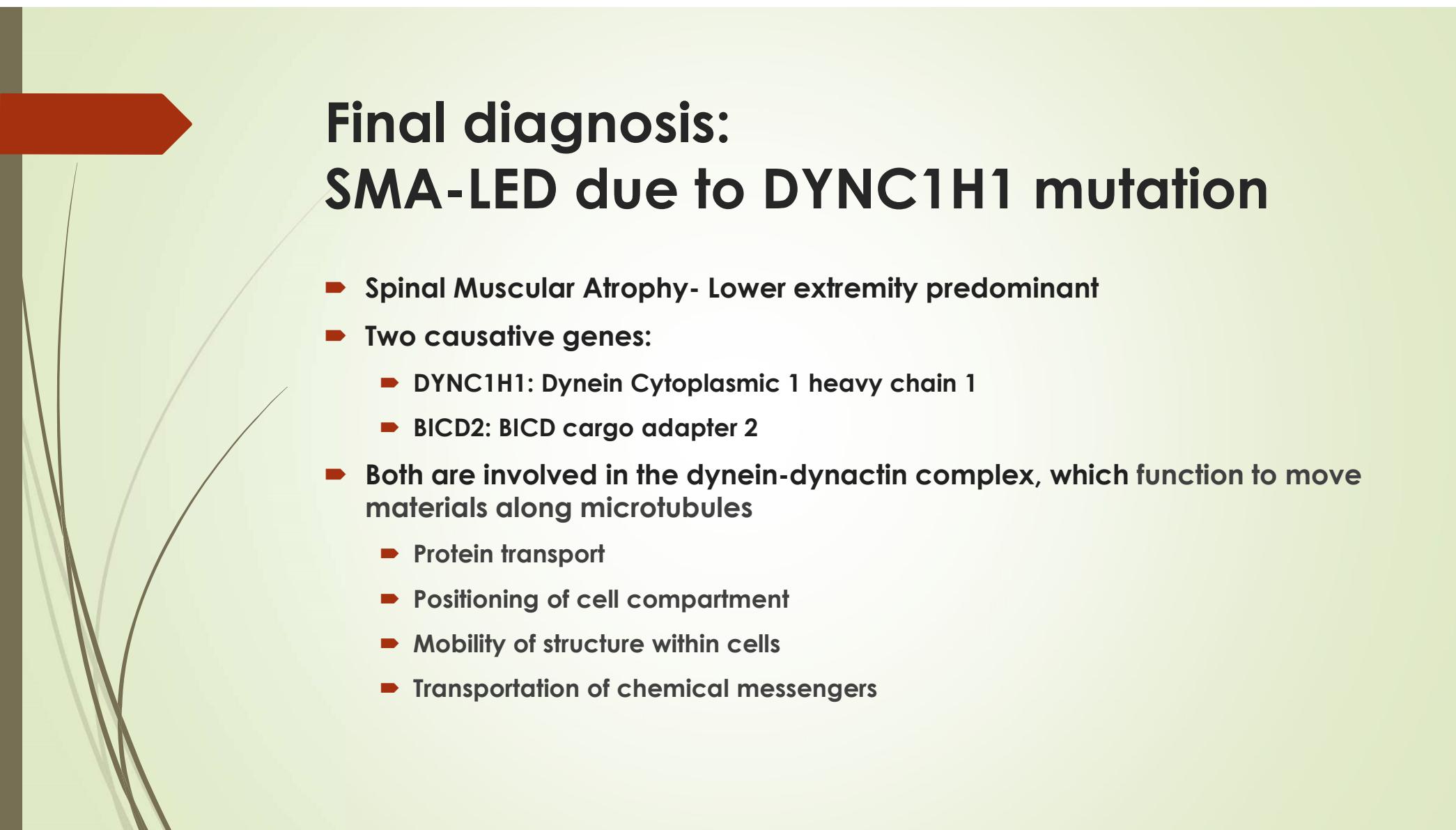




Confirmation with second tissue analysis: fibroblast

- ▶ Targeted sequencing was performed on second tissue sample on the family: fibroblast
- ▶ Three boys have 50% of DYNC1H1 allele
- ▶ 0% in mother
- ▶ Almost no detectable in father
- ▶ Confirm mosaicism



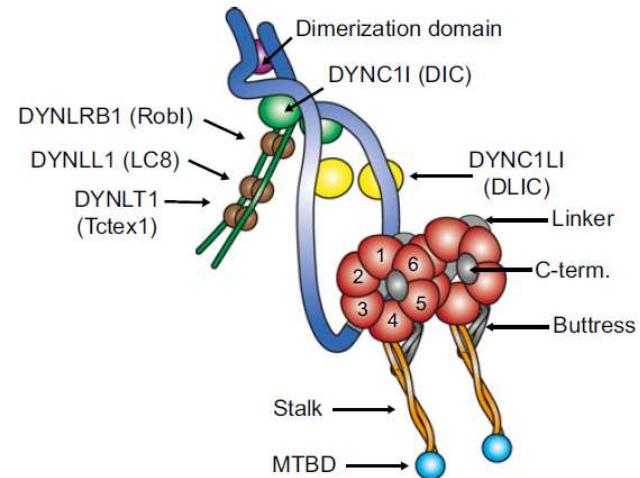


Final diagnosis: SMA-LED due to DYNC1H1 mutation

- ▶ Spinal Muscular Atrophy- Lower extremity predominant
- ▶ Two causative genes:
 - ▶ DYNC1H1: Dynein Cytoplasmic 1 heavy chain 1
 - ▶ BICD2: BICD cargo adapter 2
- ▶ Both are involved in the dynein-dynactin complex, which function to move materials along microtubules
 - ▶ Protein transport
 - ▶ Positioning of cell compartment
 - ▶ Mobility of structure within cells
 - ▶ Transportation of chemical messengers

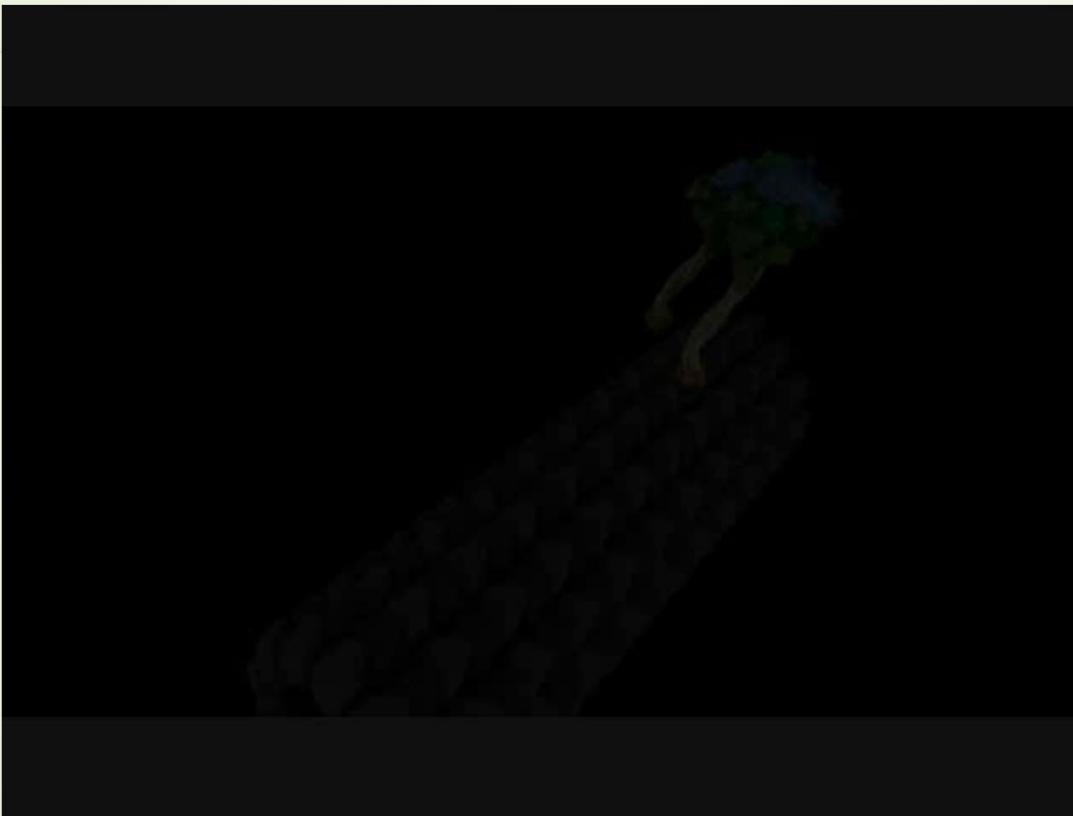
Dynein-Dynactin complex

- ▶ Dynein-Dynactin complex consists of 2 heavy chain, one intermediate chain, and three light chains
- ▶ The heavy chain contains a motor domain which translocate the protein complex across microtubules



DYNC1H1 mutations associated with neurological diseases compromise processivity of dynein-dynactin- cargo adaptor complexes
 Ha Thi Hoanga, Max A. Schlagerb,1, Andrew P. Carterb, and Simon L. Bullocka,2

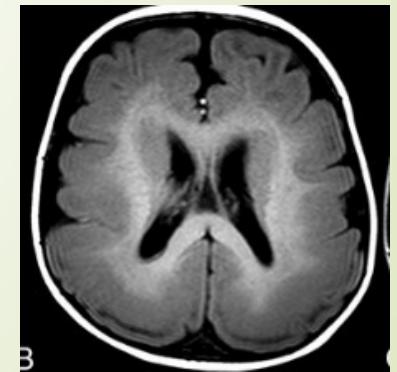
Dynein-Dynactin complex



Animation created by Janet
Iwasa, Harvard Medical School

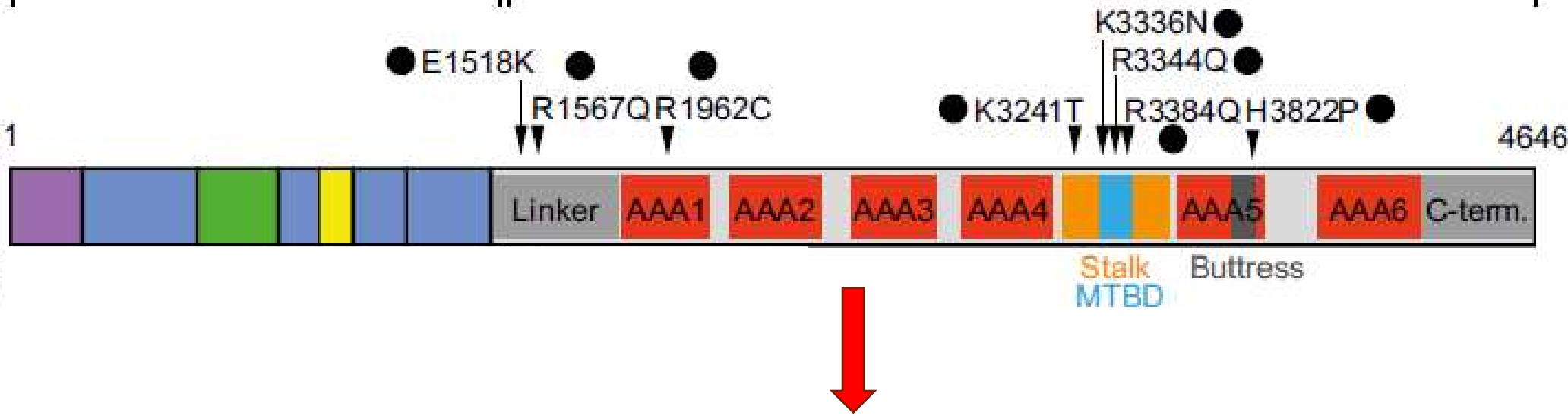
Clinical significance of DYNC1H1 mutation

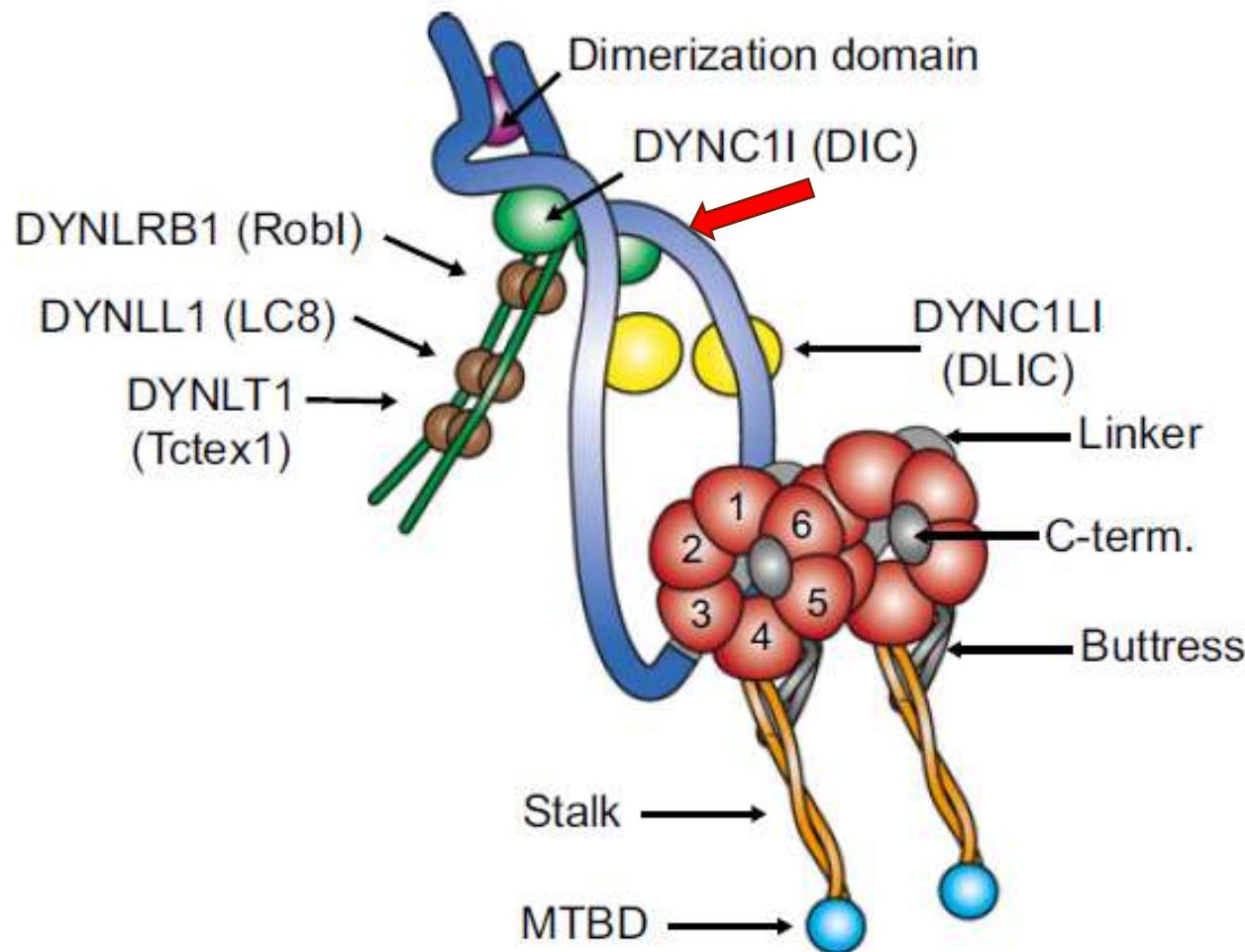
- ▶ Spinal muscular atrophy-Lower Extremity predominant (SMA-LED)
 - ▶ Muscle weakness in the legs
- ▶ Malformation of Cortical Development (MCD)
 - ▶ Due to defective neuronal proliferation or migration
 - ▶ Associated with severe intellectual disability and epilepsy



Tail

Motor





Summary

- ▶ This case characterizes the phenotype of a patient with SMA-LED
- ▶ De novo mutations may result in a mosaic parent, which can present significant challenges in making diagnosis based on genomic data

▶ **THANK YOU**

Acknowledgement

- ▶ Stanley F. Nelson, UCLA Human Genetics
- ▶ Undiagnosed disease network
- ▶ Negar Khanlou, UCLA Pathology
- ▶ Perry Shieh, UCLA Neuromuscular



David Geffen
School of Medicine