



Three brothers with lower extremity weakness

Abel Wu, M.D.*, Negar Khanlou, M.D.', Stanley F. Nelson, M.D.#, and Perry B. Shieh, M.D. Ph.D*.

*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

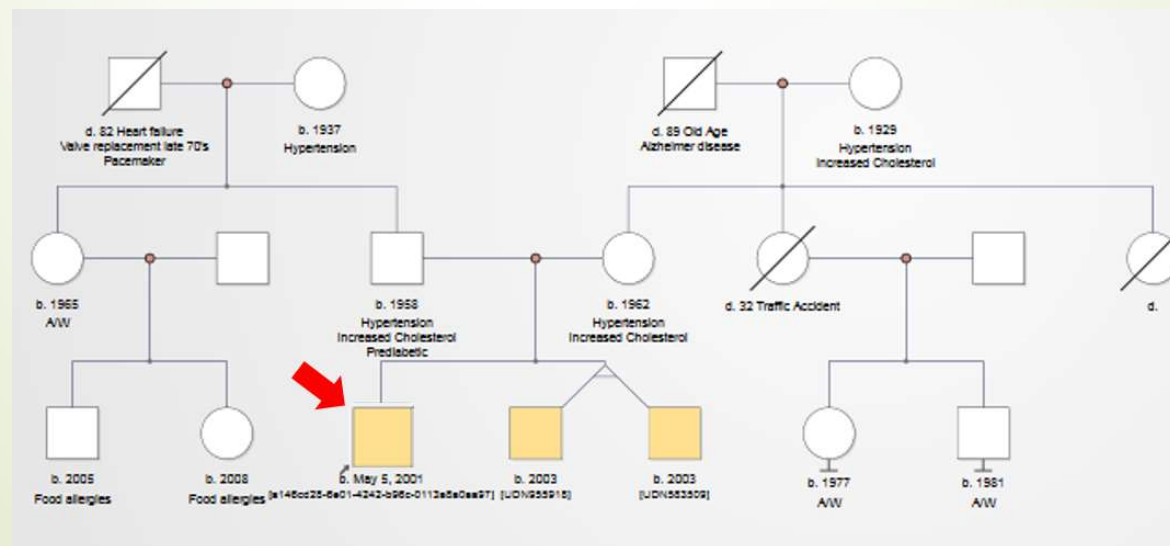


Other medical history:

- **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**



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

Sid e	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 RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:12/90

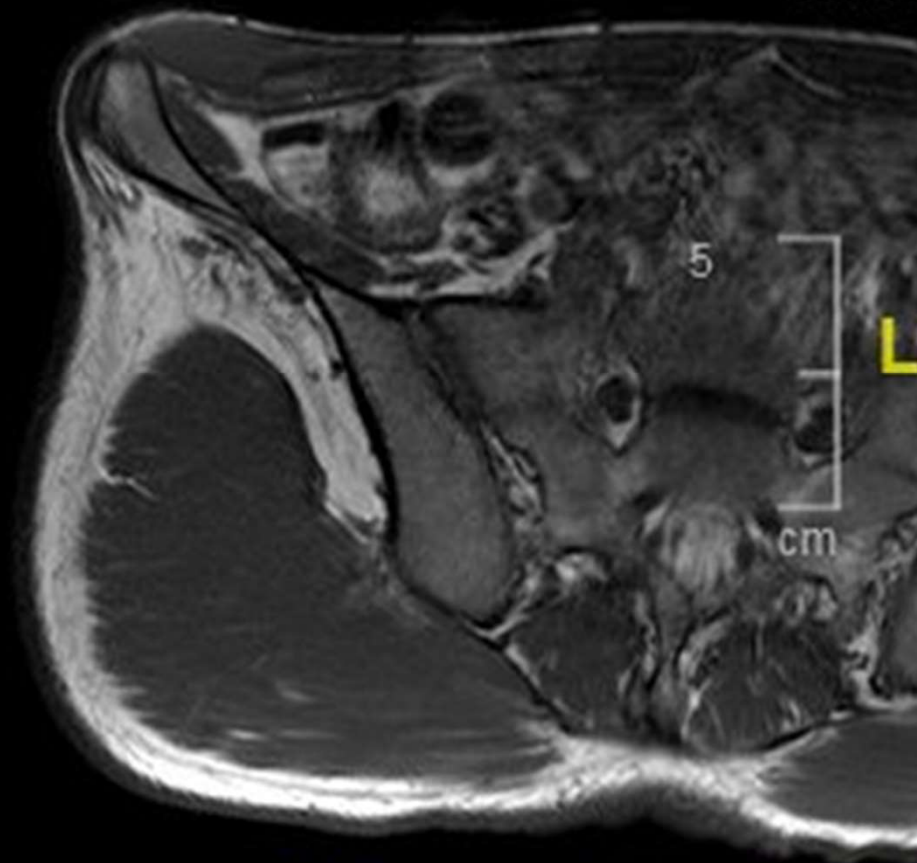
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:13/90

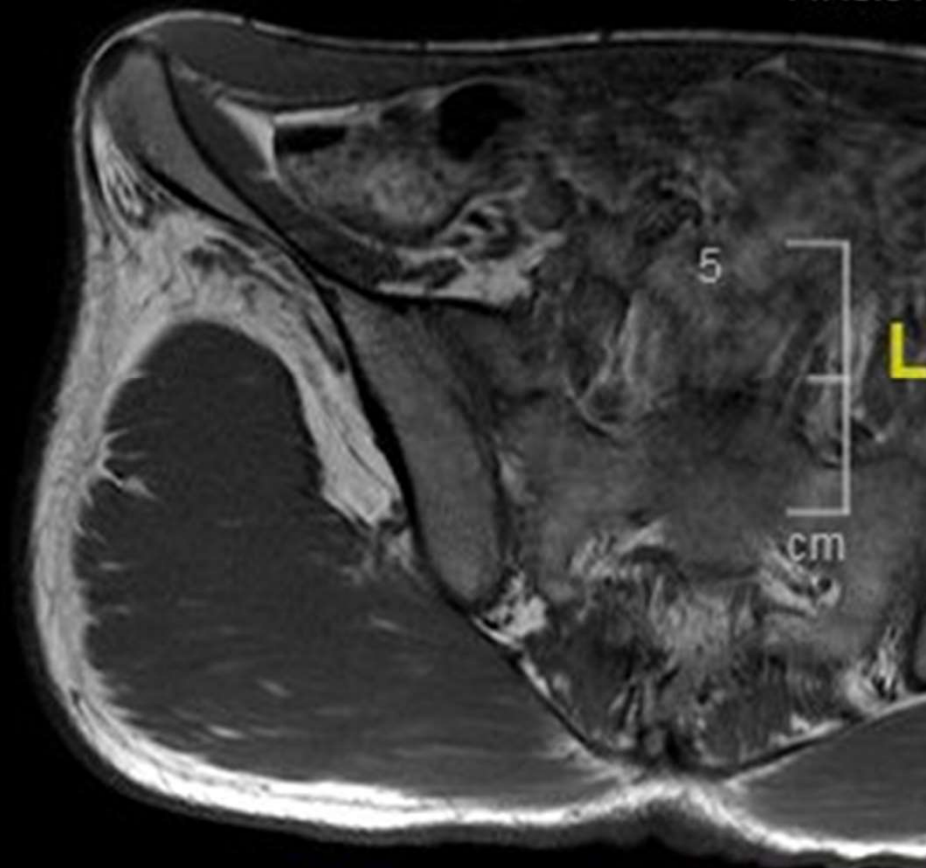
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:15/90

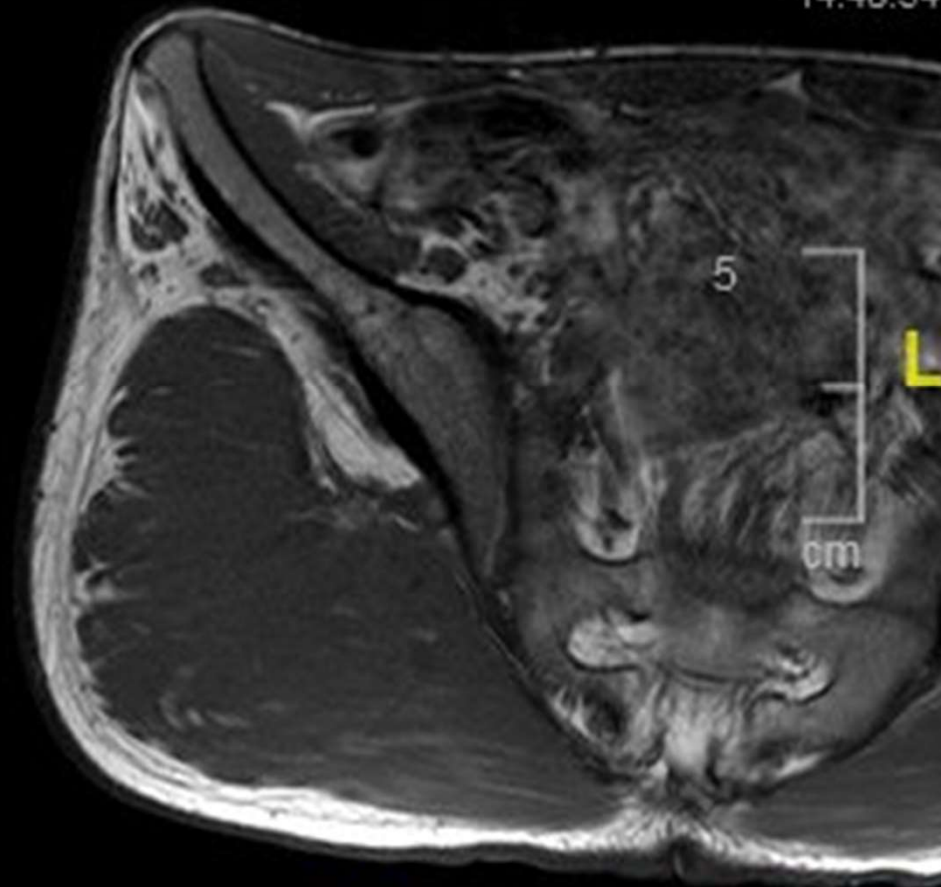
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:15/90

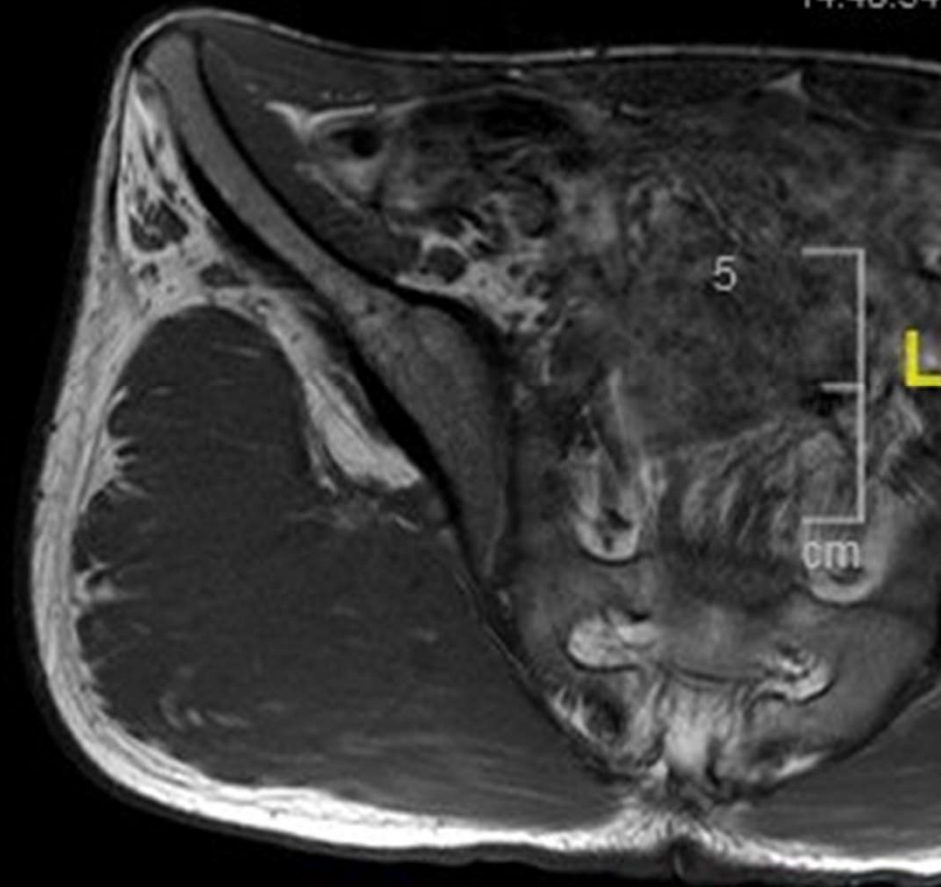
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:17/90

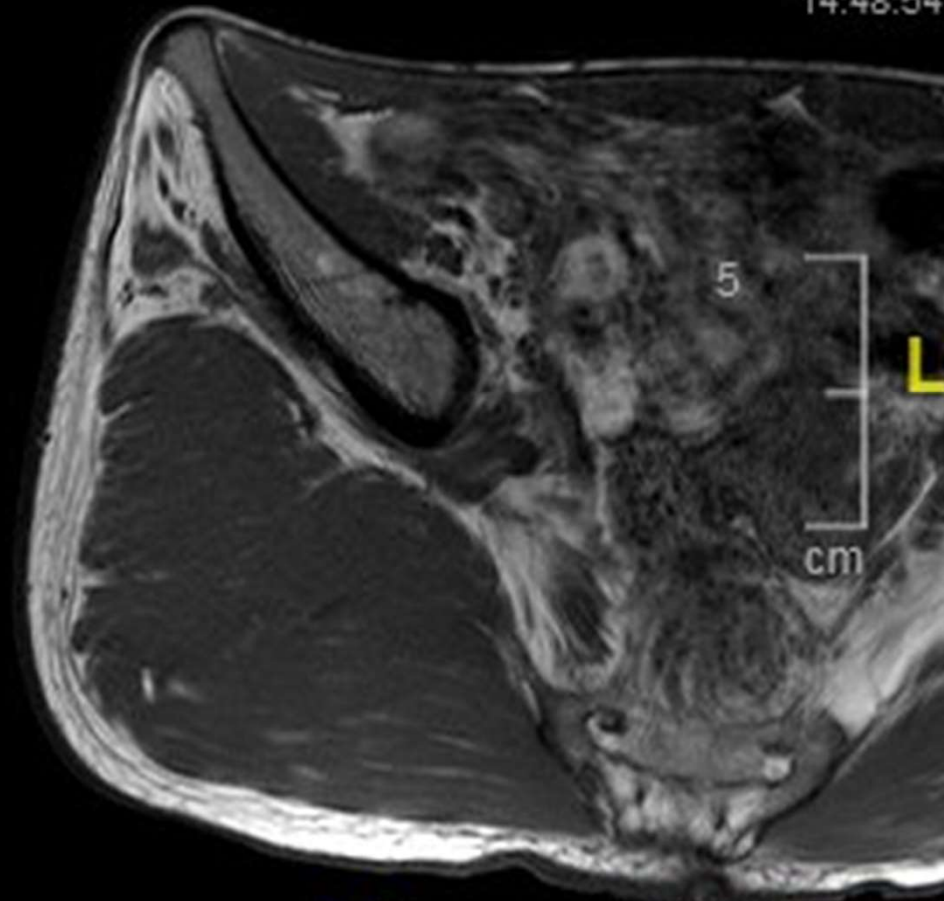
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:18/90

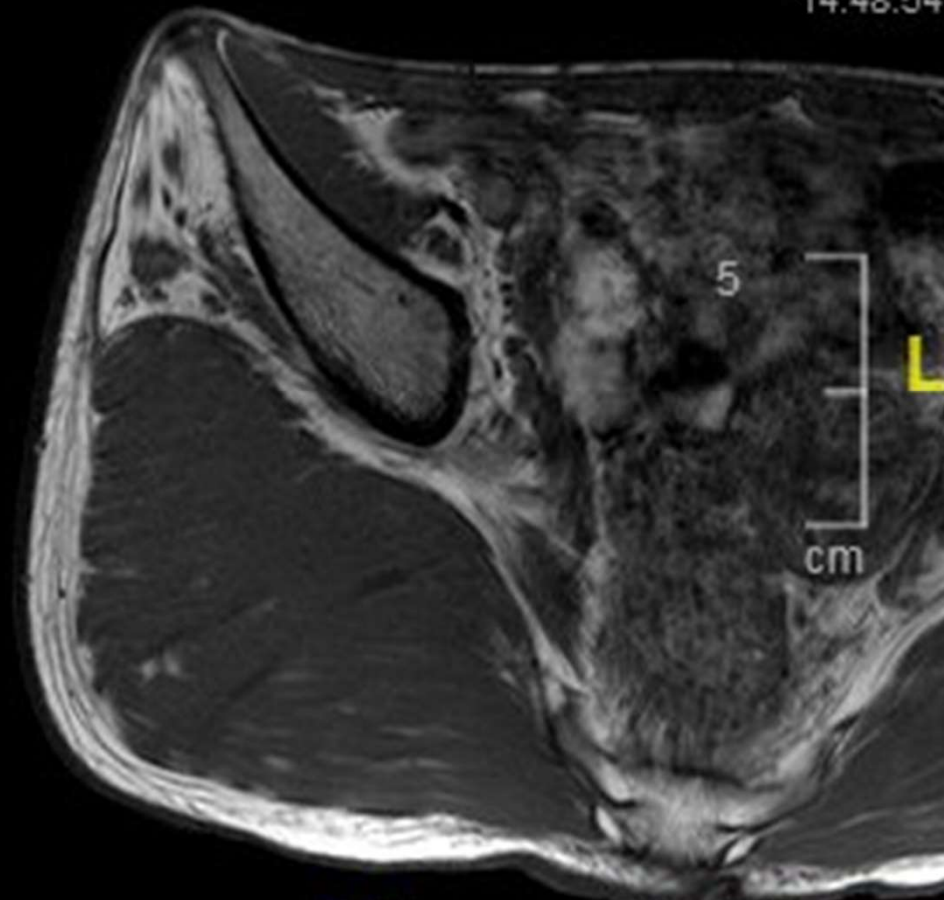
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:19/90

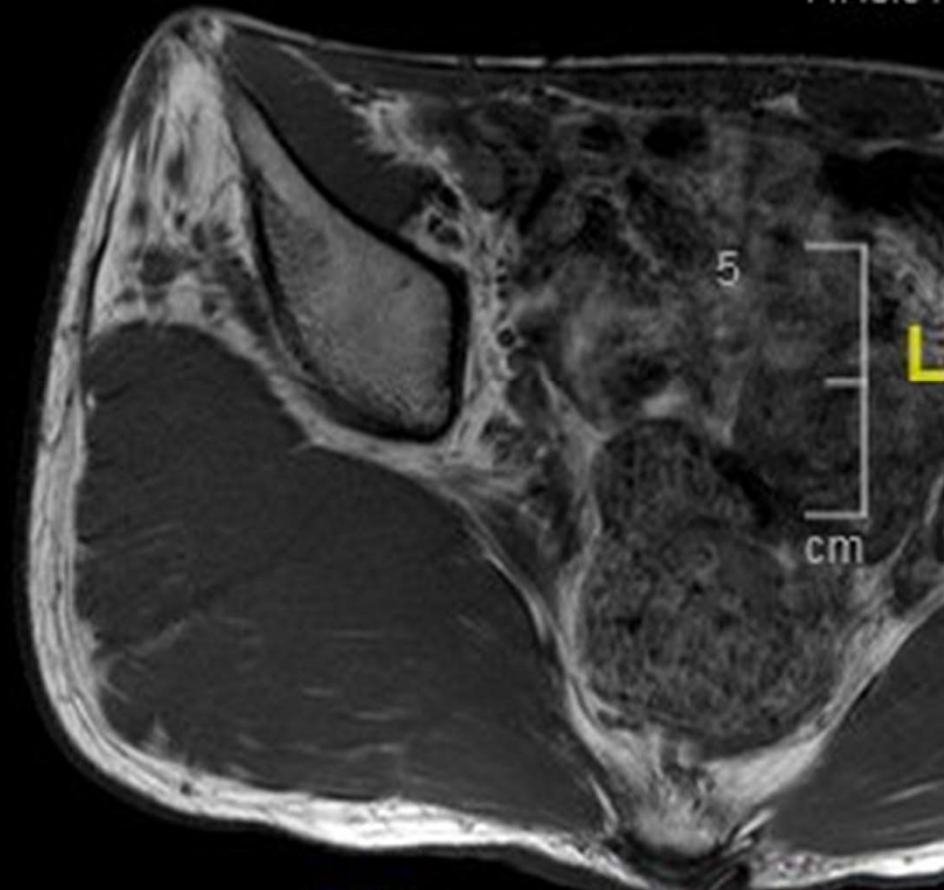
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:20/90

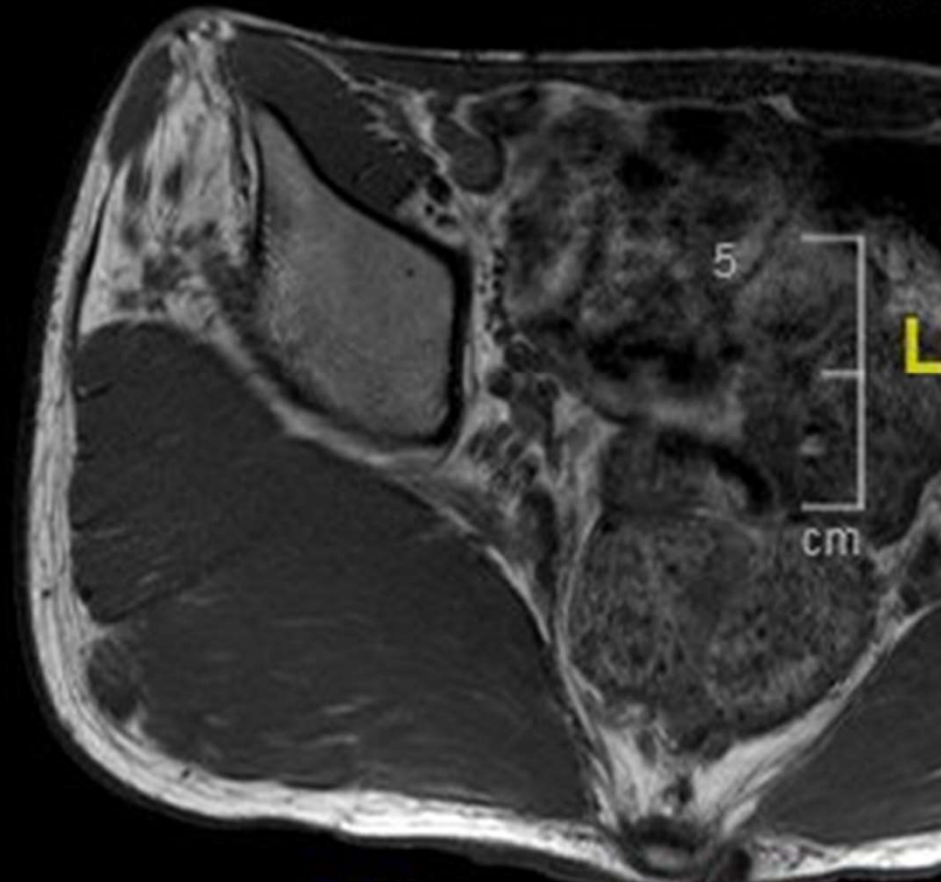
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

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

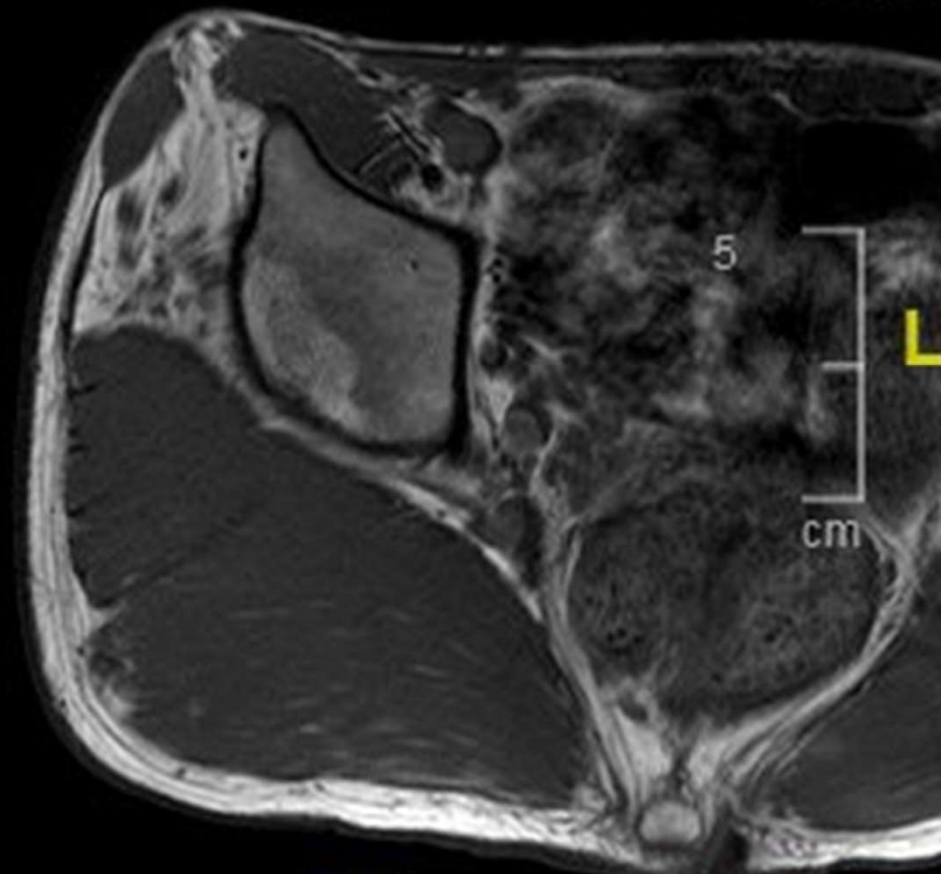
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:22/90

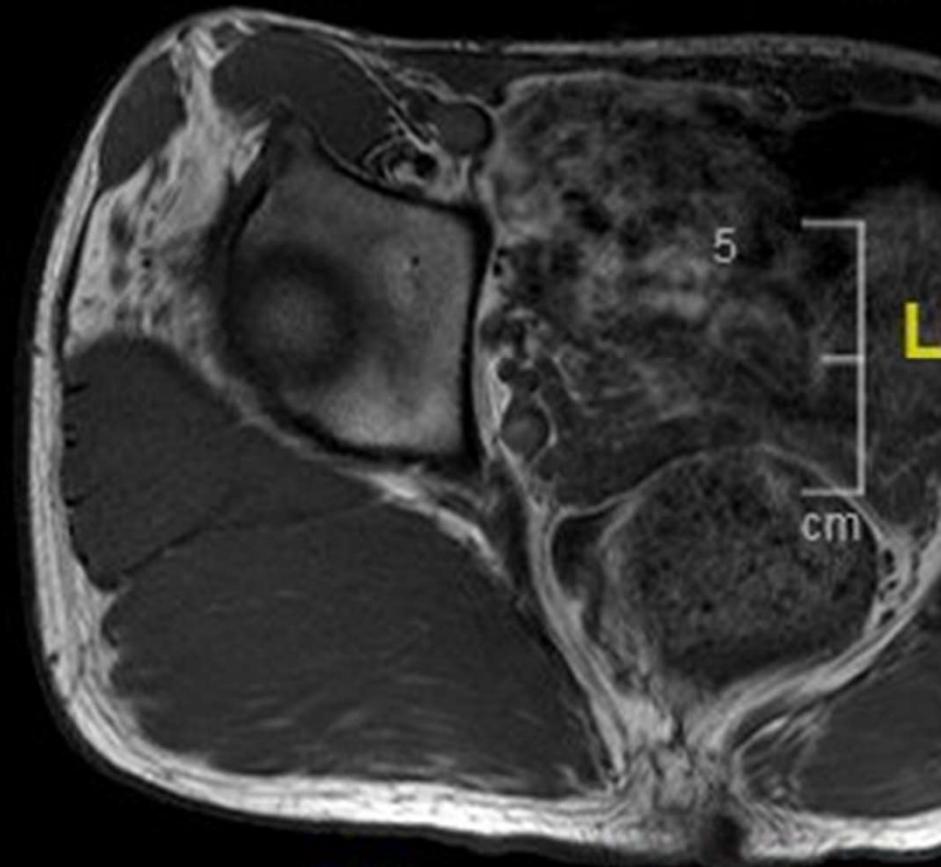
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:23/90

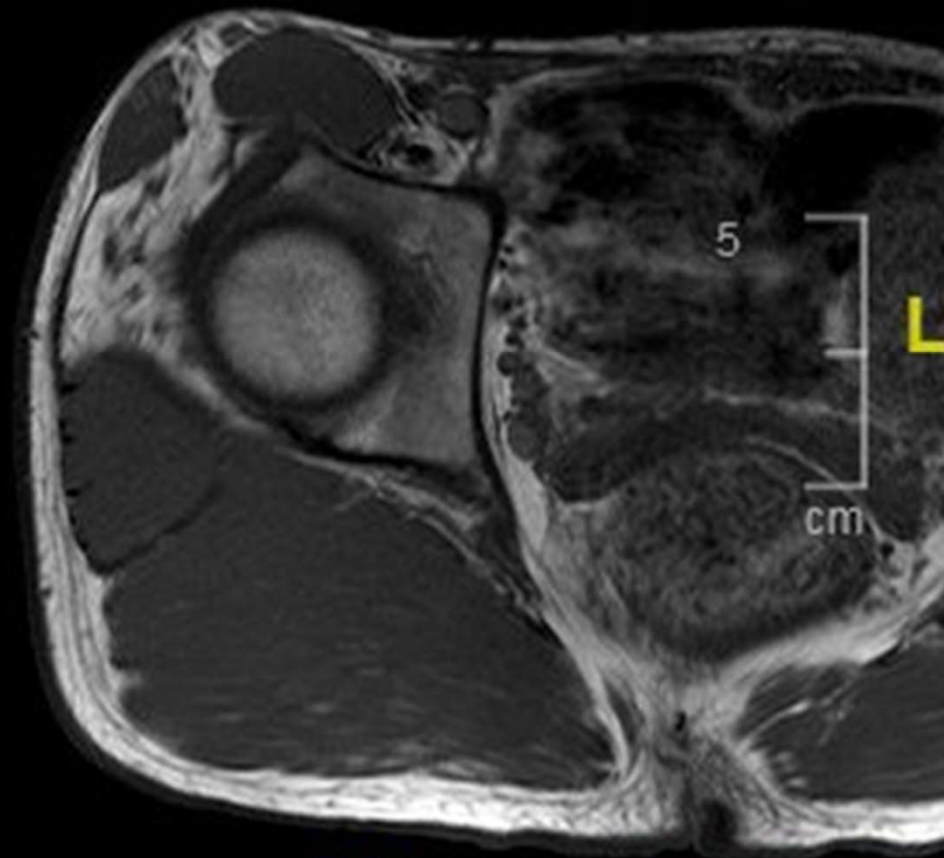
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:24/90

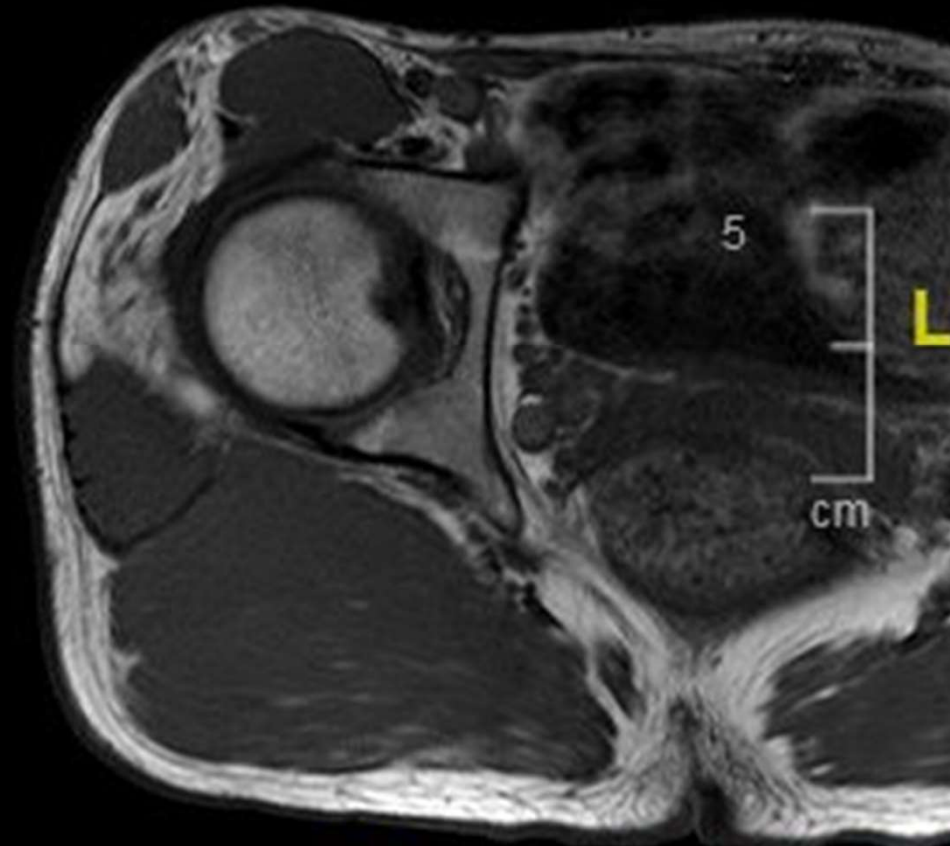
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:25/90

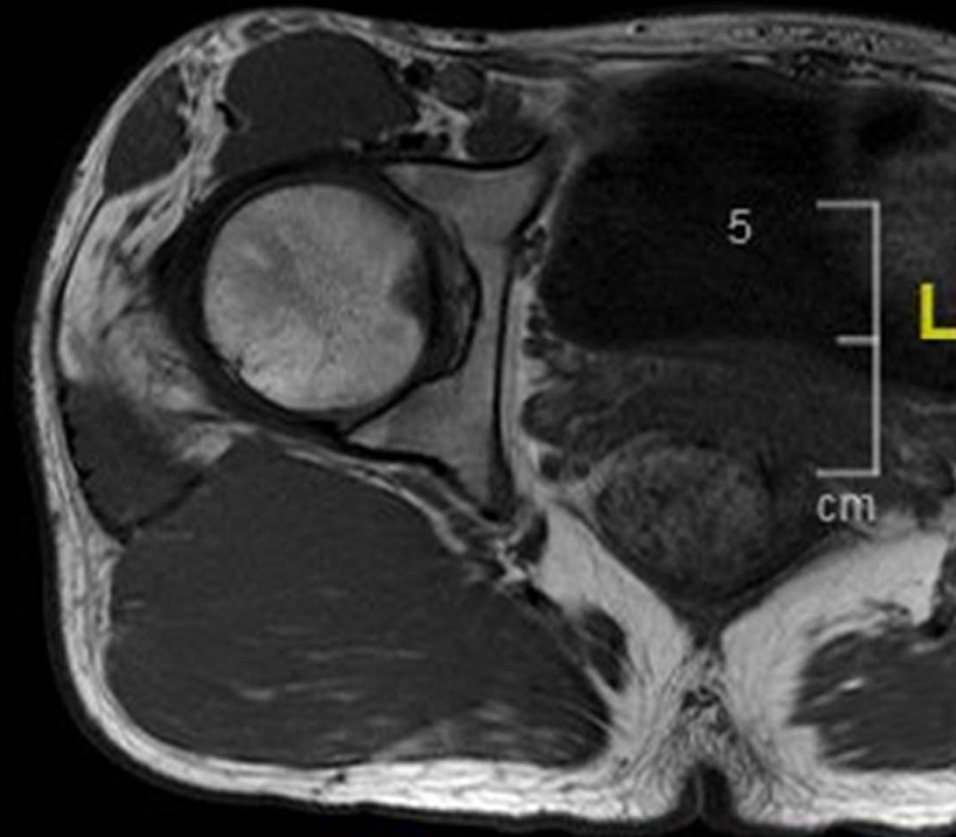
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:26/90

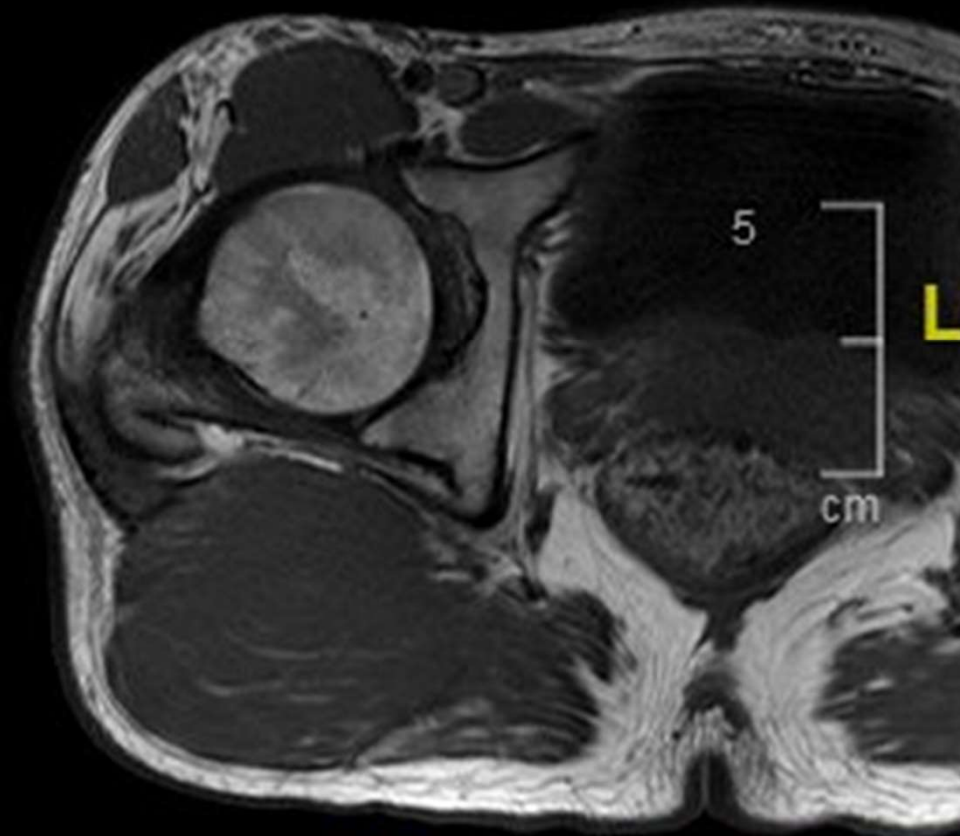
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:27/90

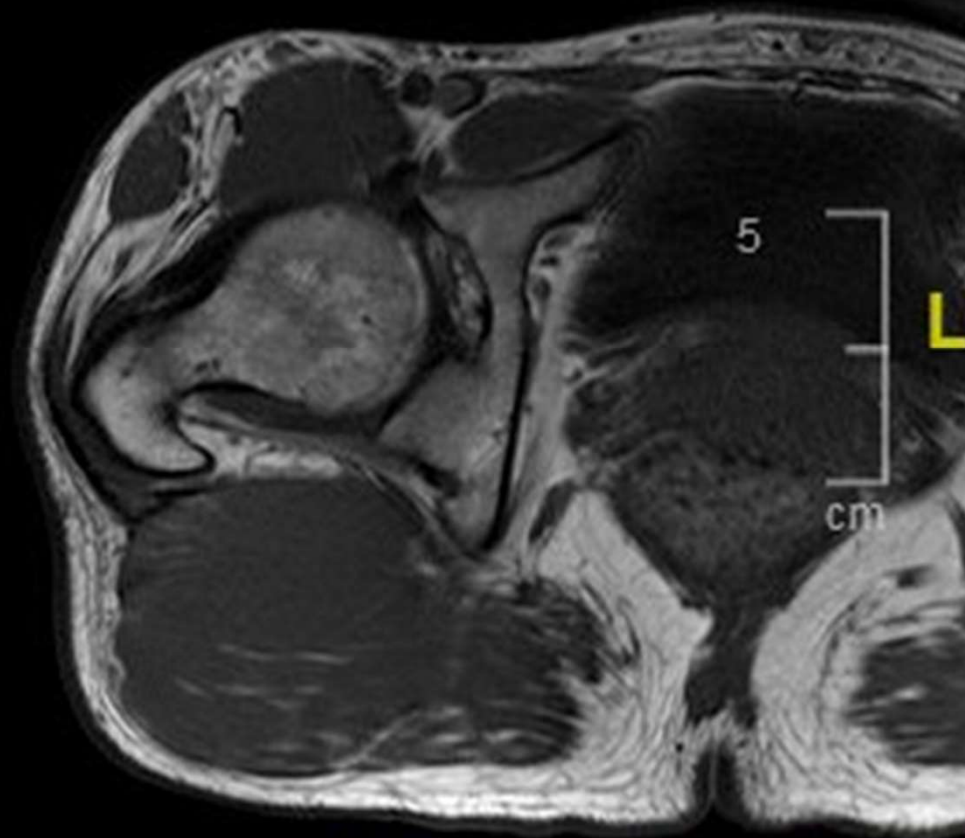
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:28/90

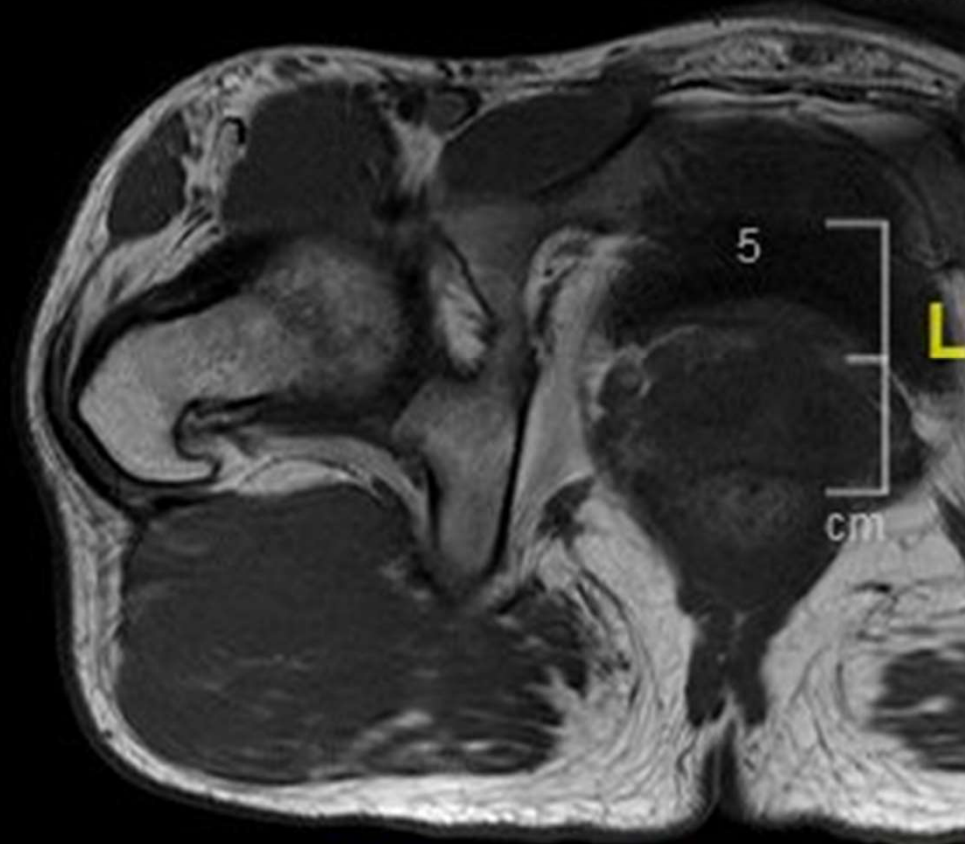
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:29/90

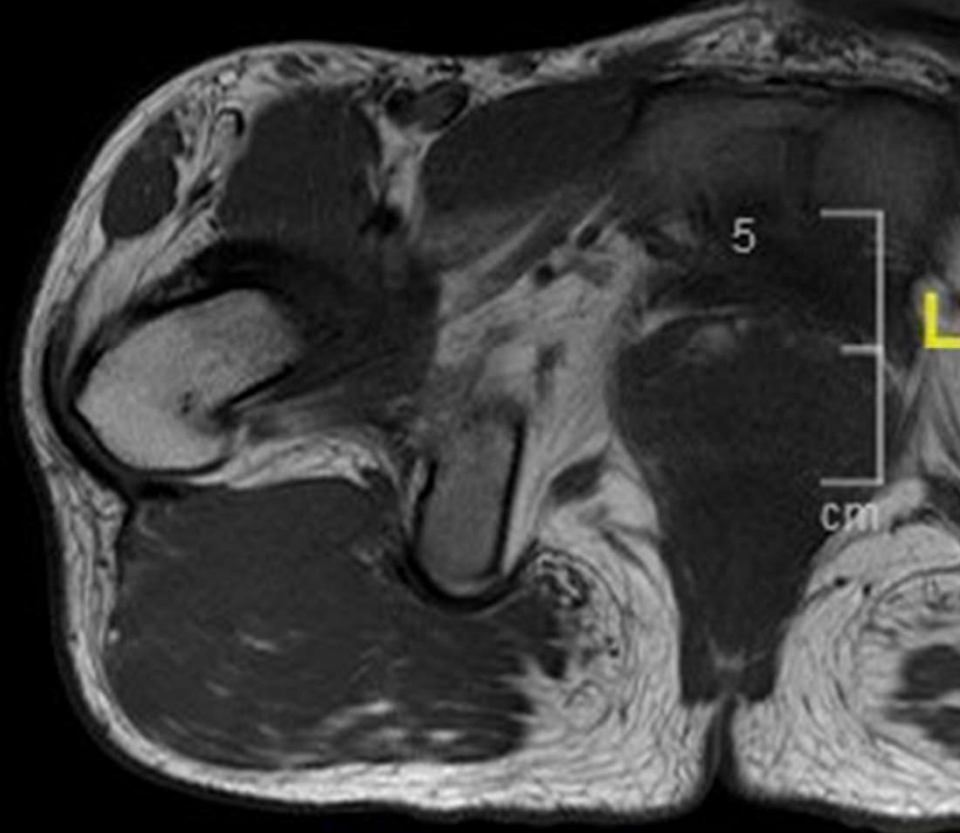
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:30/90

AF **COMPARISON**

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:31/90

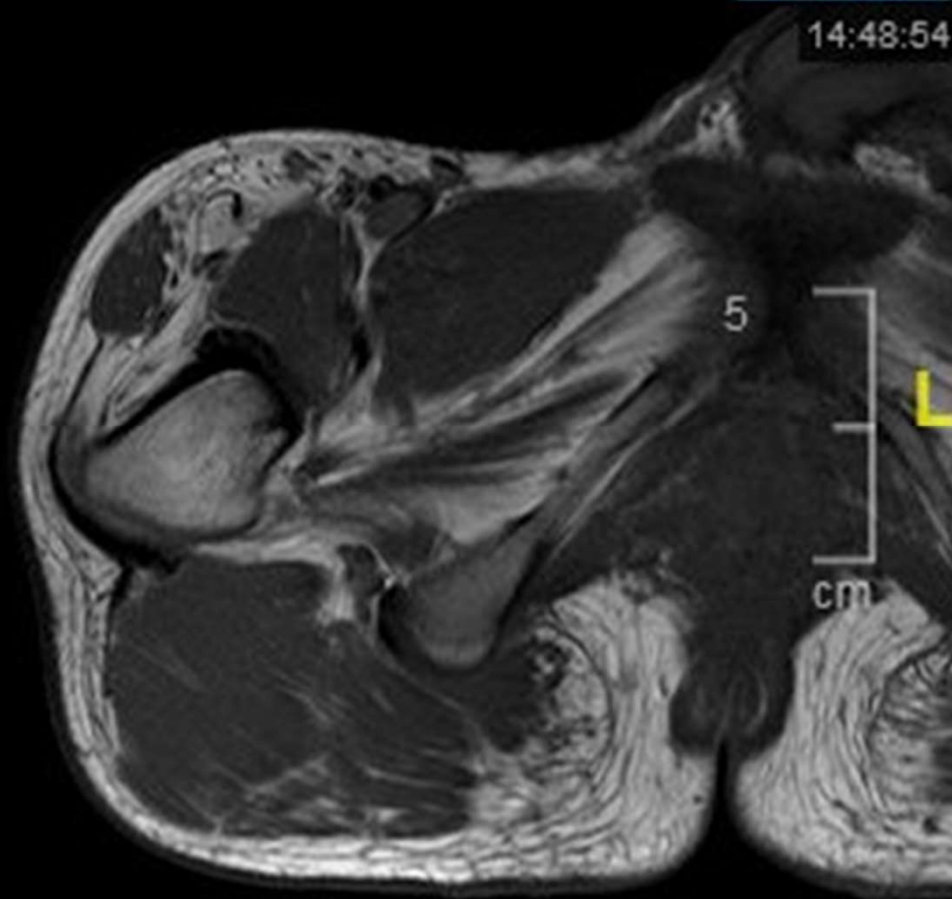
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:32/90

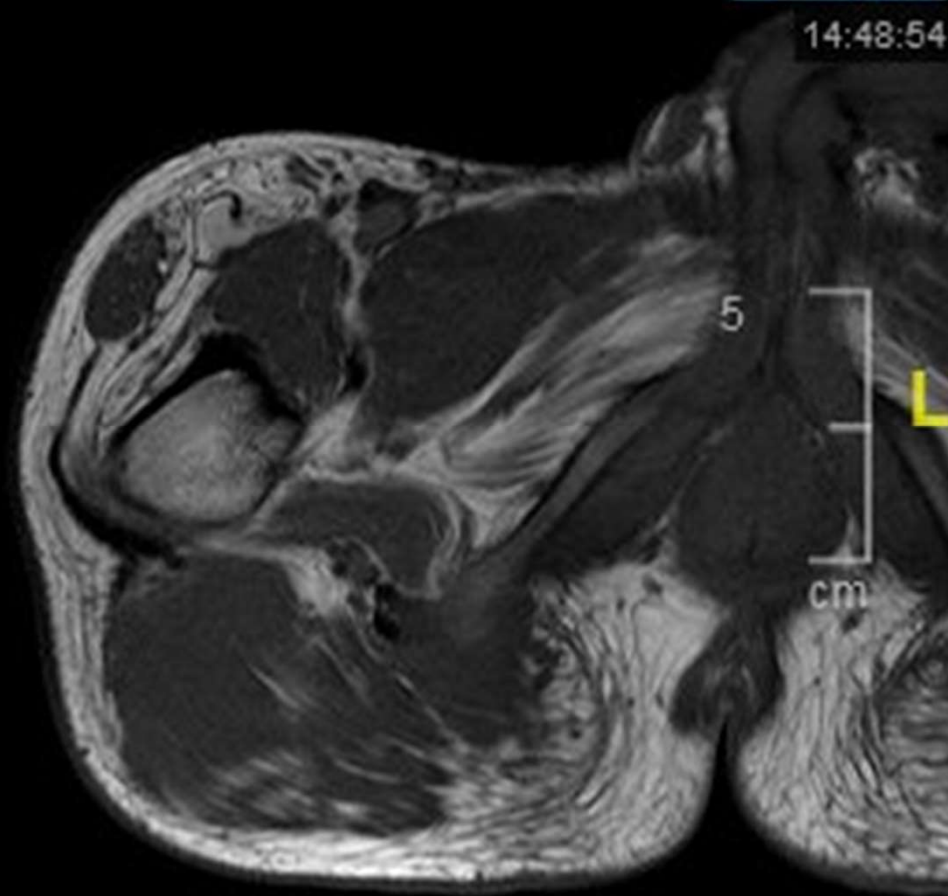
AF **COMPARISON**

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:33/90

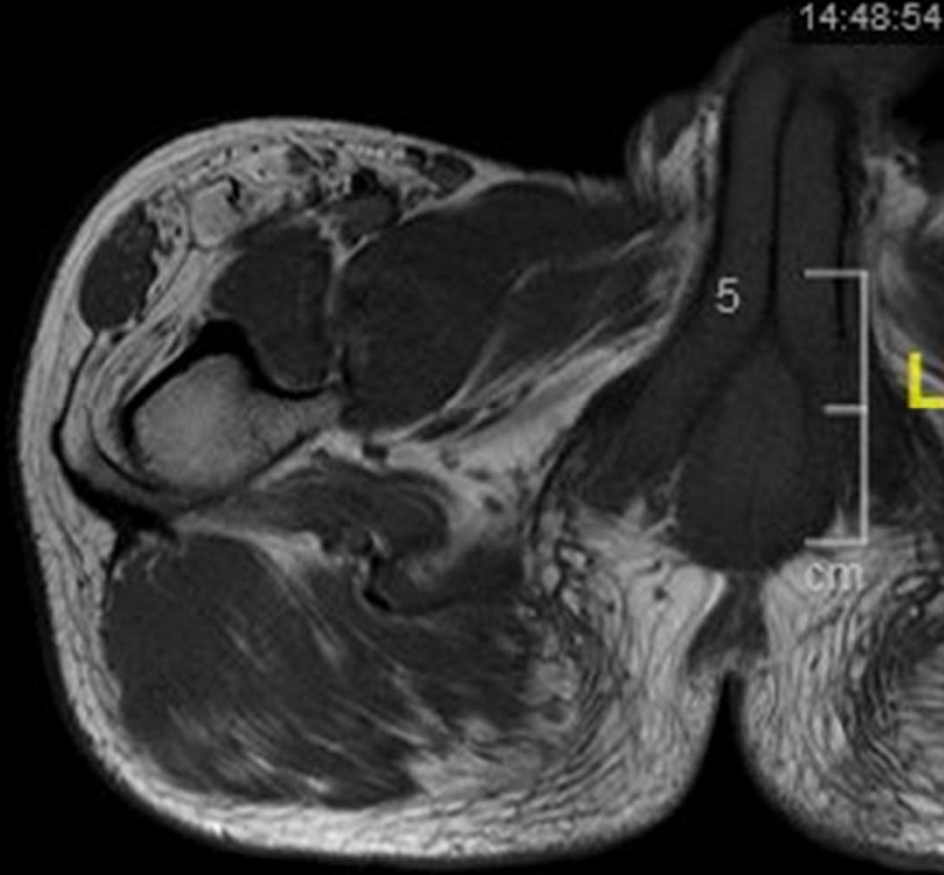
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:34/90

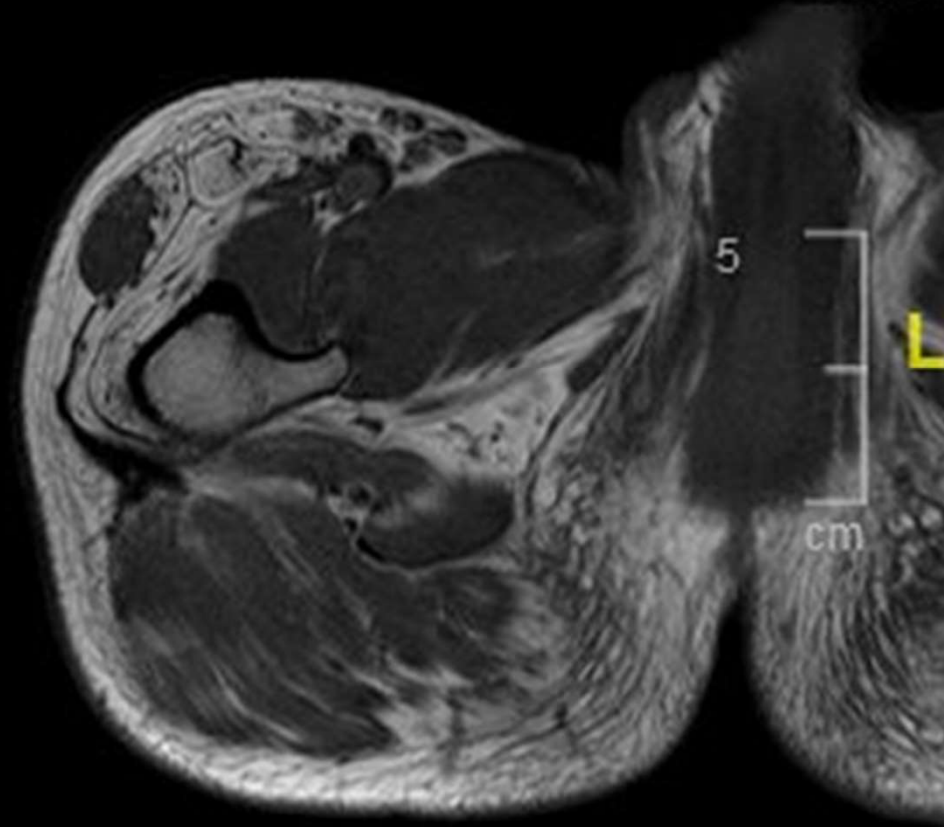
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:35/90

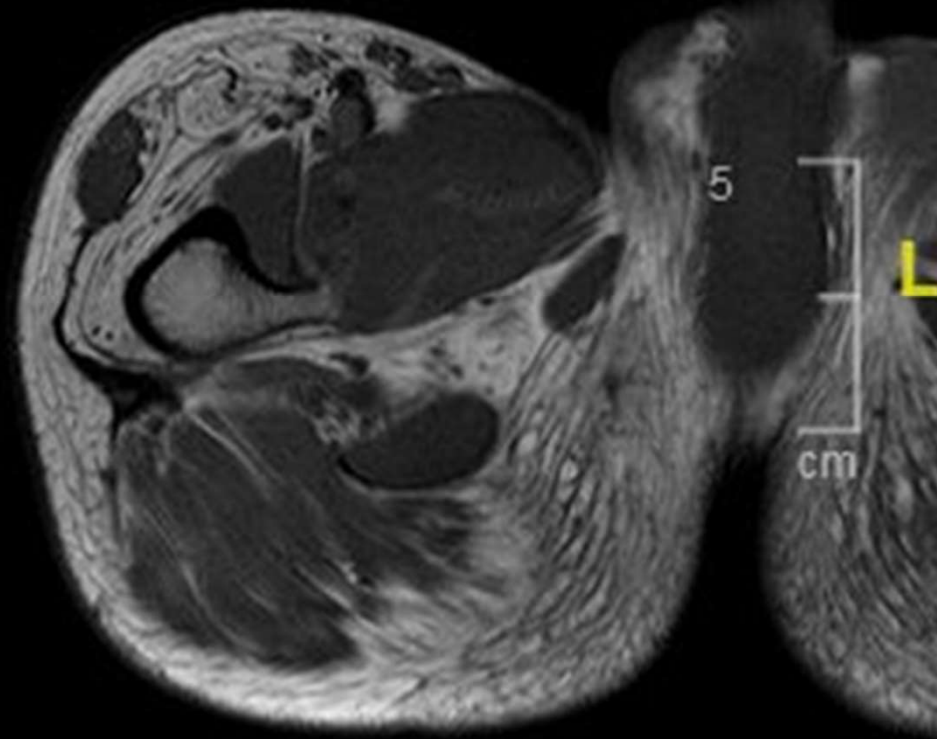
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:36/90

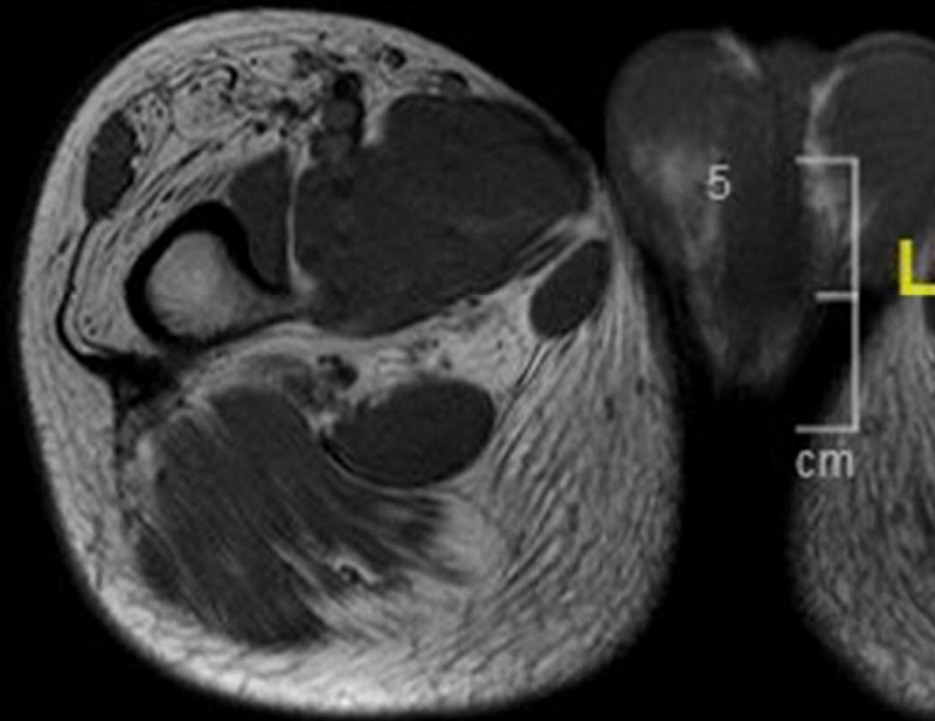
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:37/90

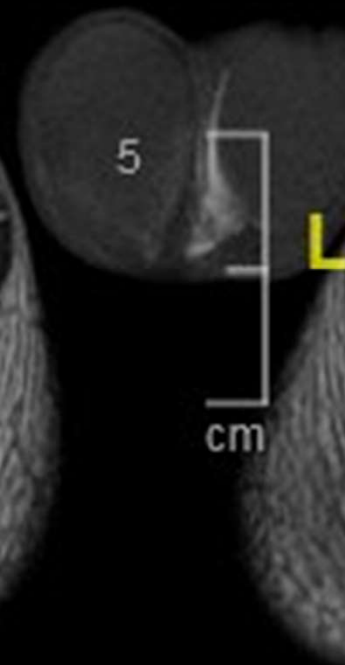
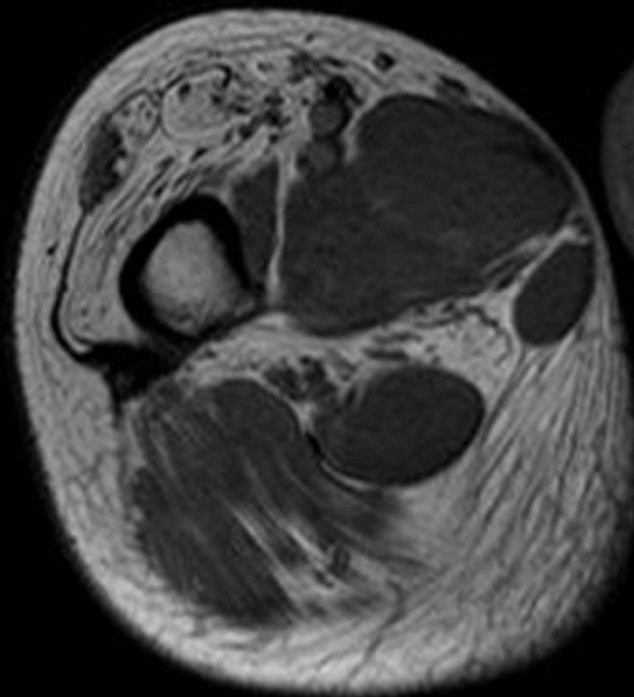
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



PF

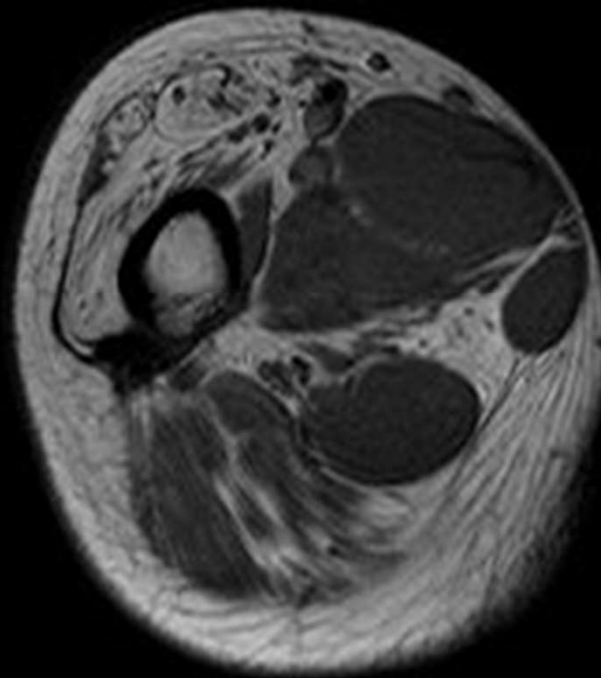
WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:38/90

COMPARISON

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

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:39/90

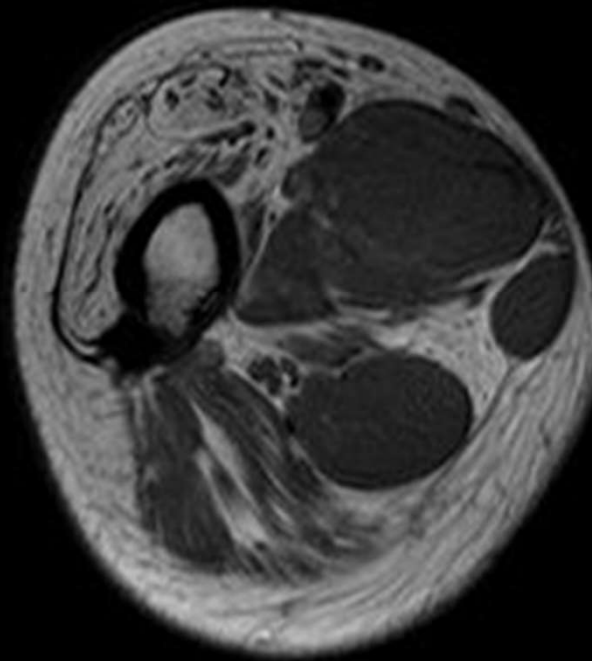
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

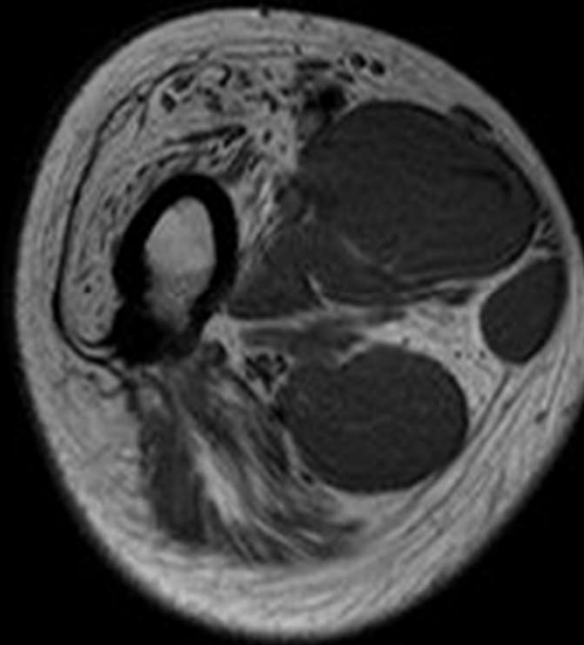
WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:40/90

COMPARISON

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

R



5



cm

L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:41/90

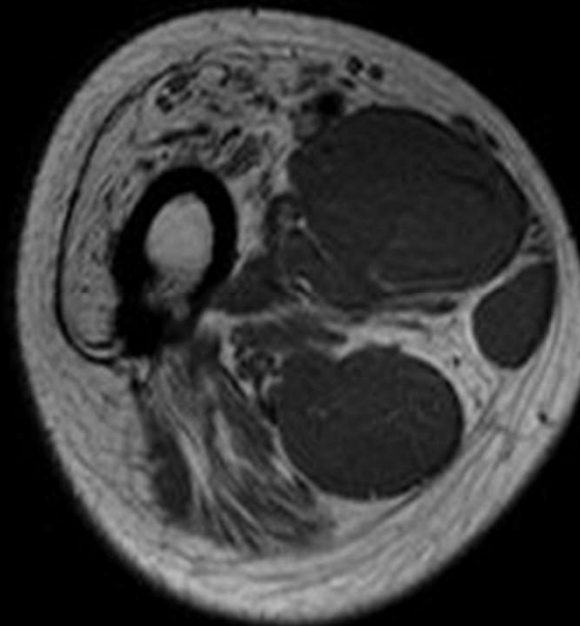
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

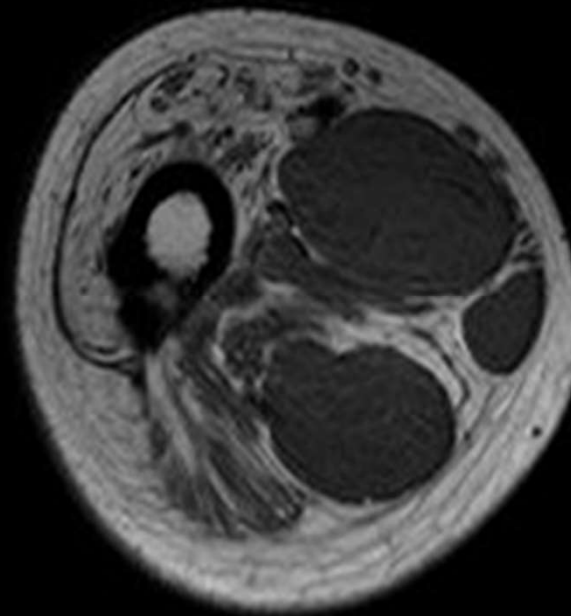
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

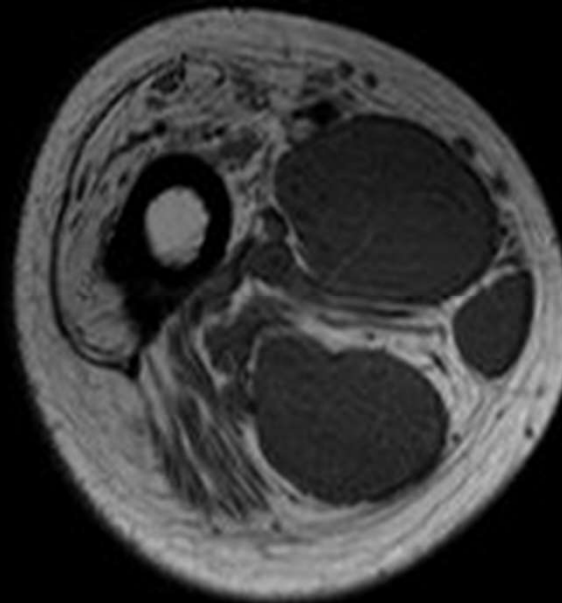
WL:381 - WW:676

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

COMPARISON

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

R



5



L

PF

WL:381 - WW:676

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

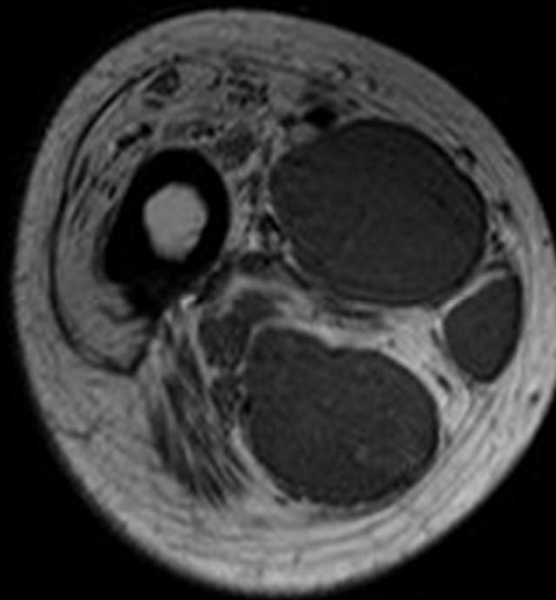
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

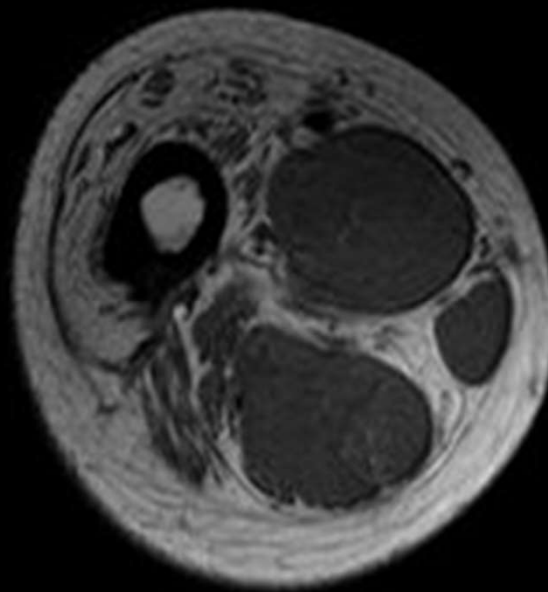
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

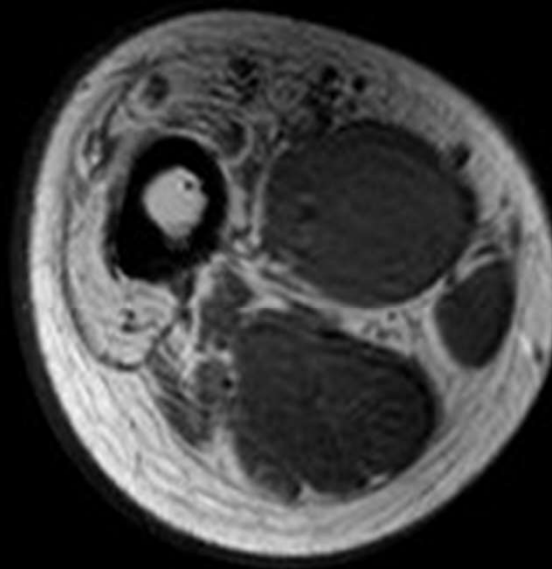
WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:46/90

COMPARISON

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

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:47/90

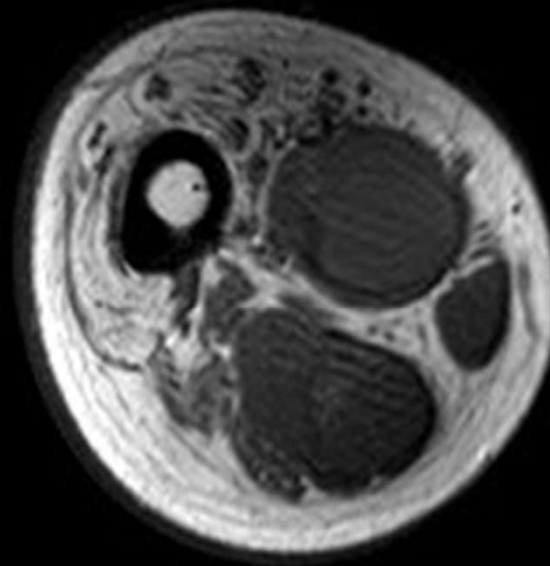
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

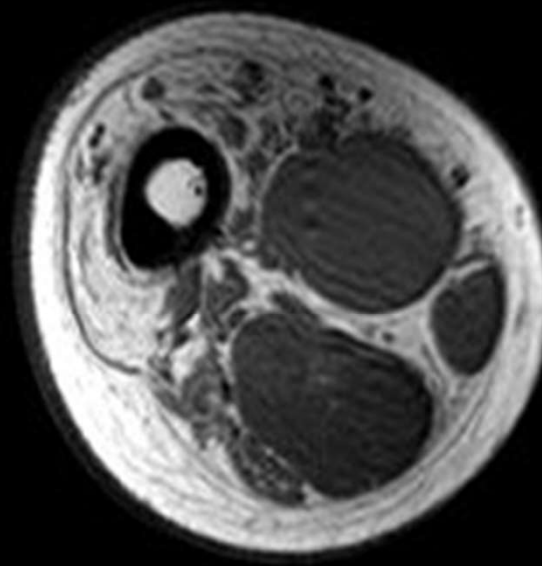
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

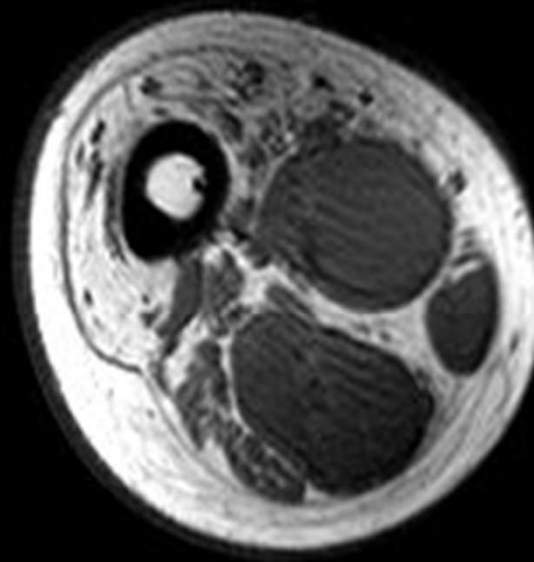
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

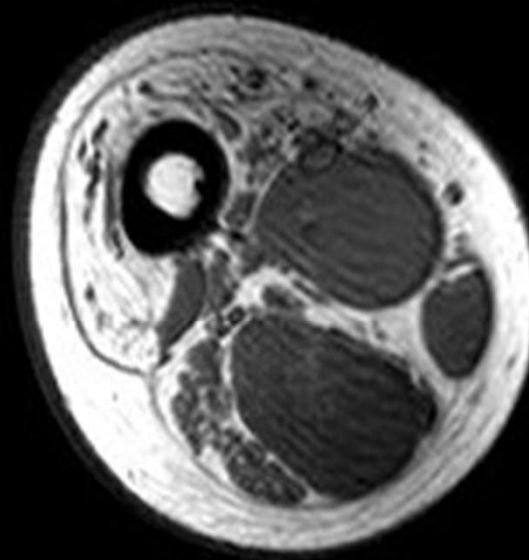
WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:50/90

COMPARISON

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

R



5

L

cm

PF

WL:381 - WW:676

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

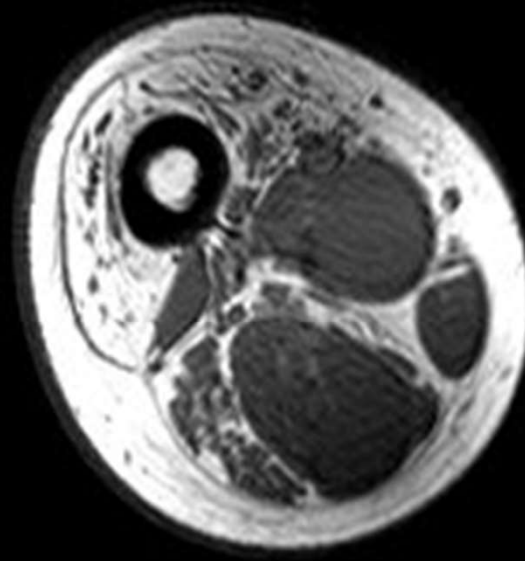
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

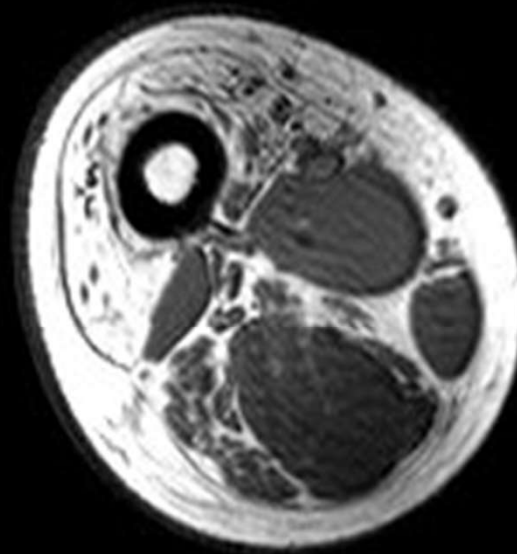
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:53/90

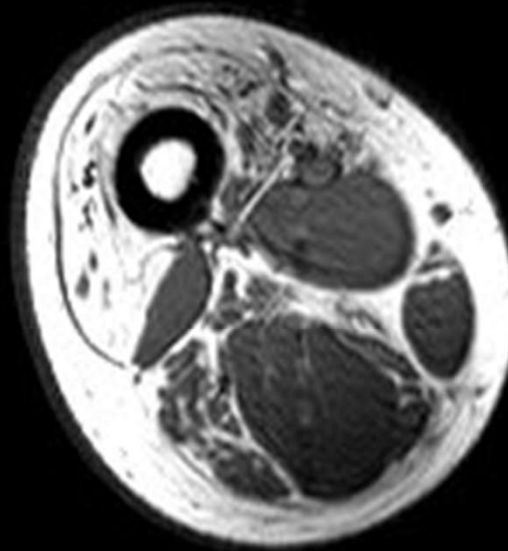
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:54/90

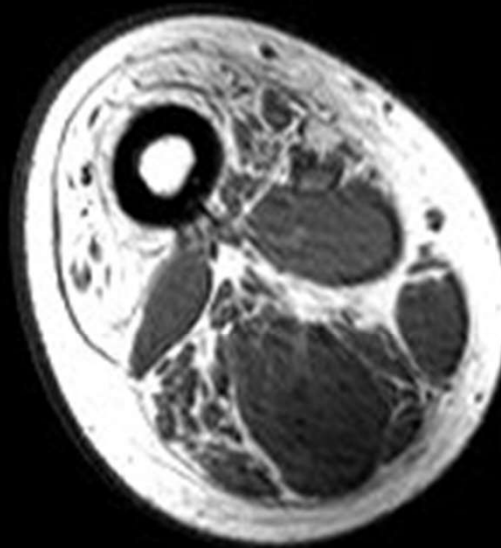
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

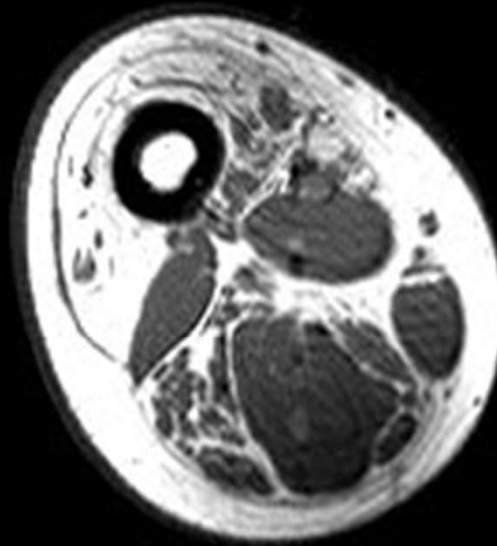
WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:55/90

COMPARISON

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

R



5



L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:56/90

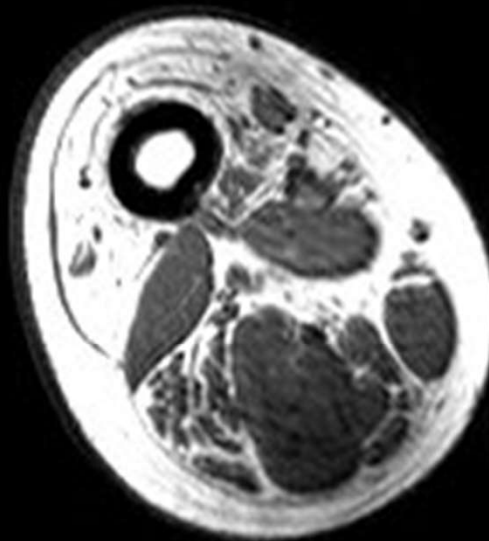
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

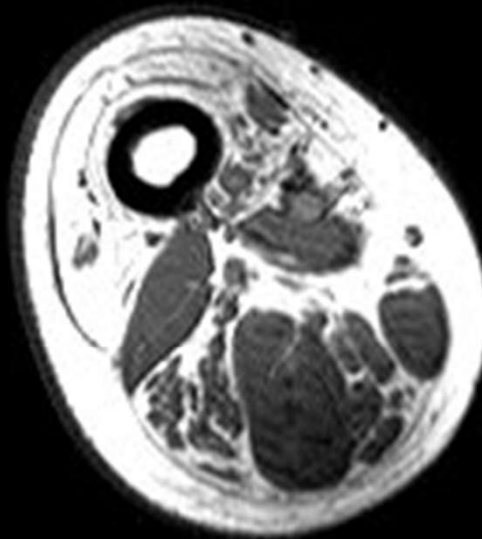
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

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

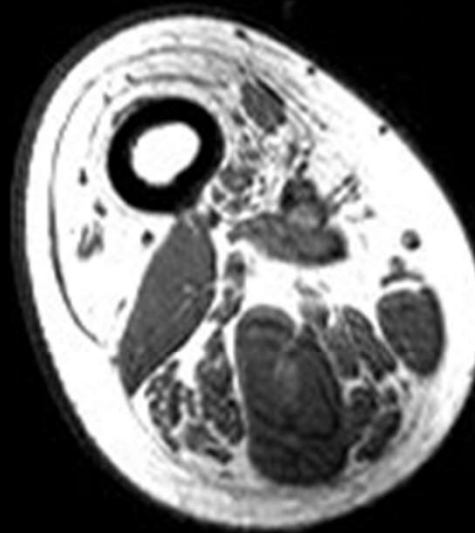
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

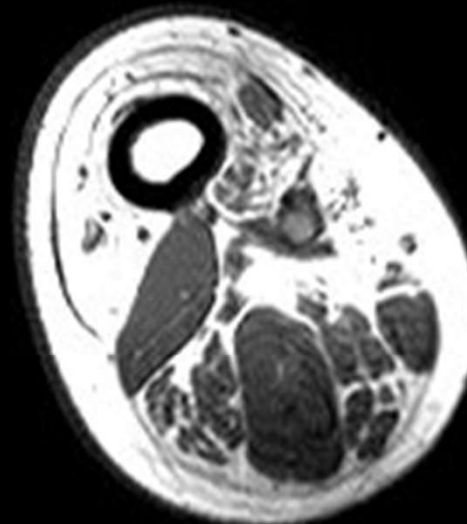
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:60/90

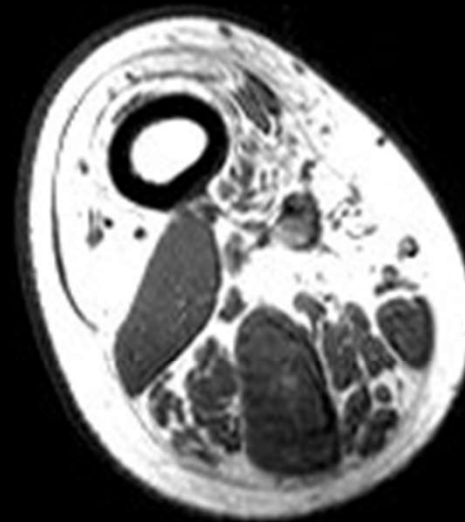
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

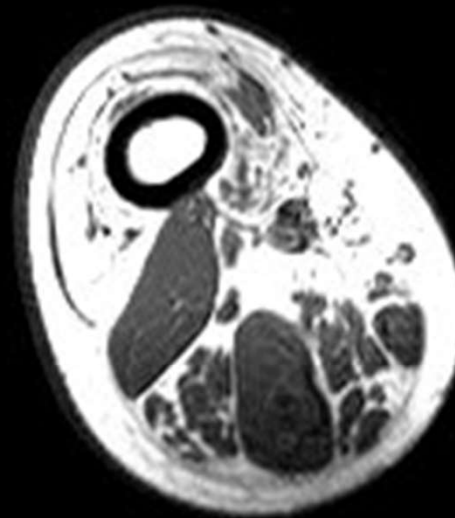
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:62/90

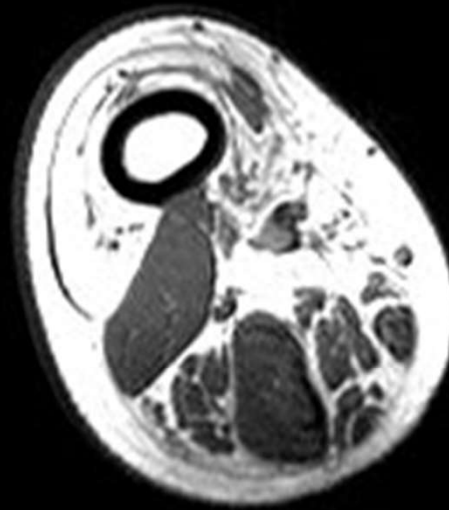
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

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

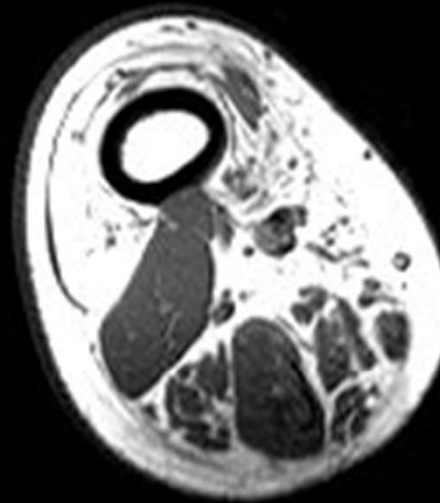
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:64/90

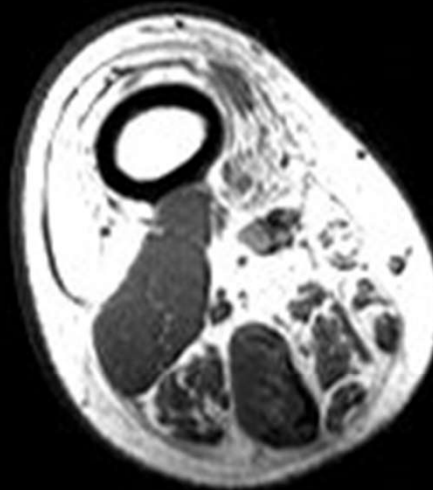
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

cm

PF

WL:381 - WW:676

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

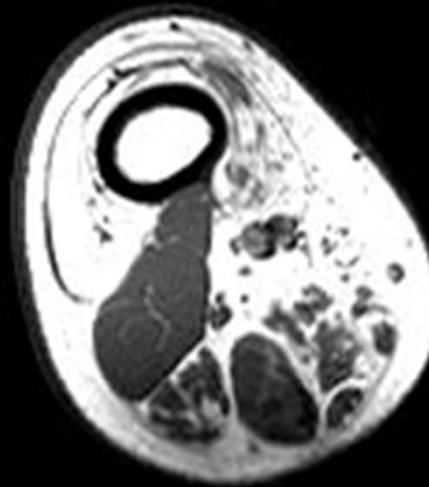
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:66/90

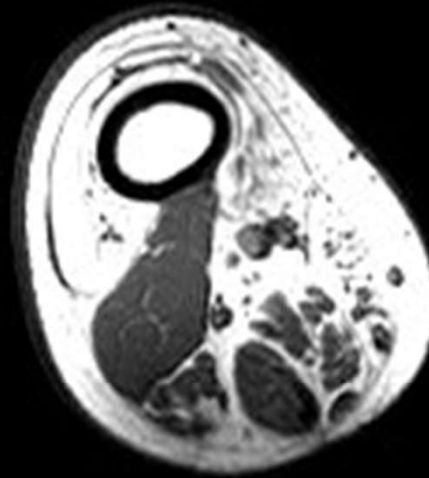
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

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

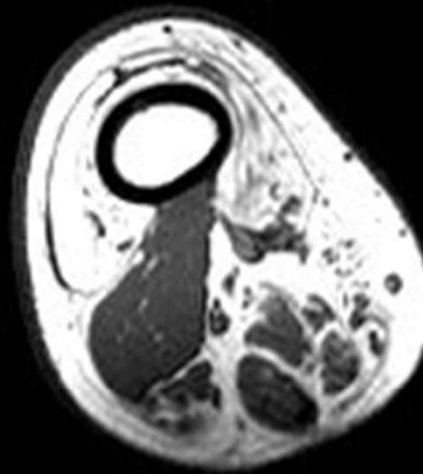
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

cm

PF

WL:381 - WW:676

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

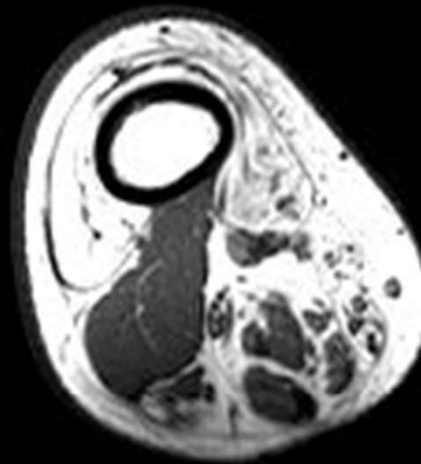
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

cm

PF

WL:381 - WW:676

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

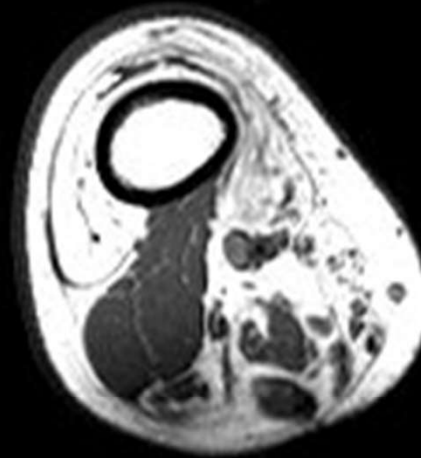
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:70/90

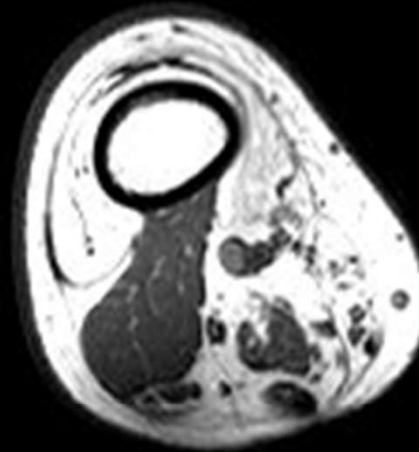
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

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

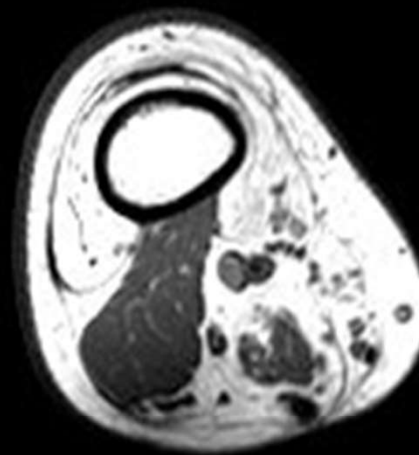
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

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

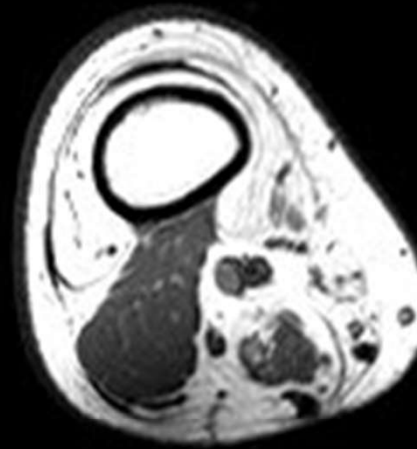
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:73/90

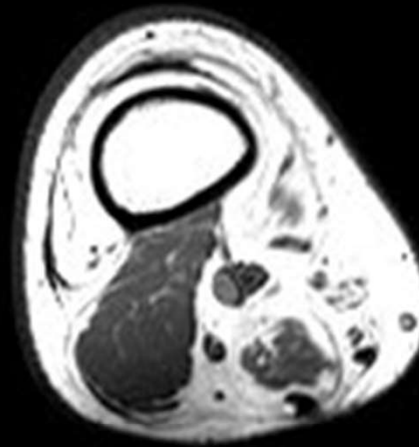
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5



L

PF

WL:381 - WW:676

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

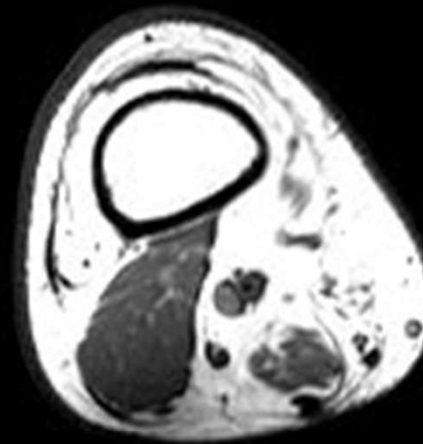
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:75/90

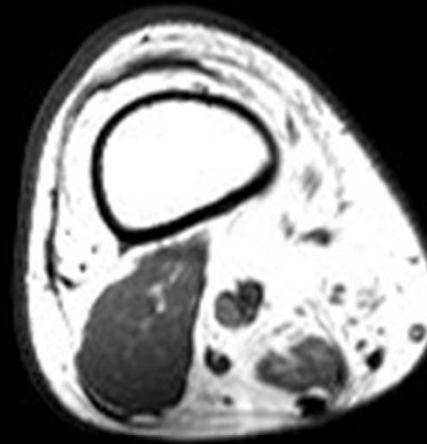
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:76/90

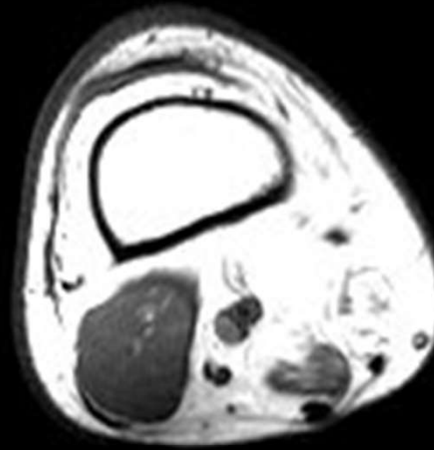
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

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

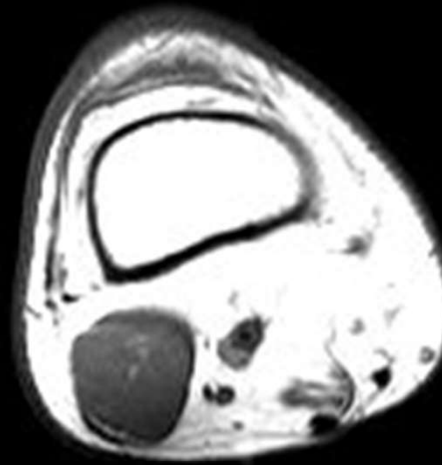
COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:78/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54

R



5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:79/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



R

5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:80/90

COMPARISON

Westwood Rad

13-Feb-2017

14:48:54



R

5

L

cm

PF

WL:381 - WW:676

MR FEMUR WO CONTRAST RIGHT
Rt_t1_tse_tra pelvis-thigh_COMPOSED_-9
Se:21
Im:81/90

COMPARISON

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



R

5

L


cm

PF

WL:381 - WW:676



MRI of the right leg

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

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

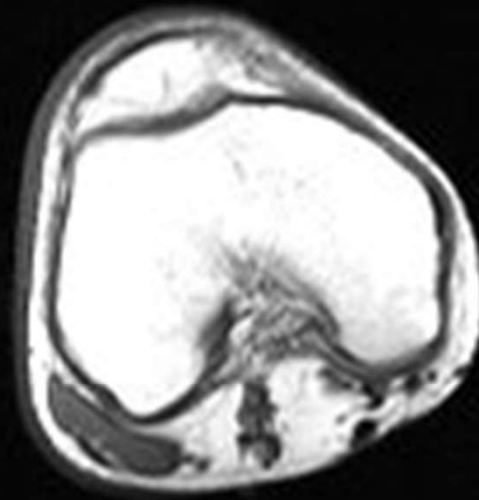
Se:22

13-Feb-2017

Im:9/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

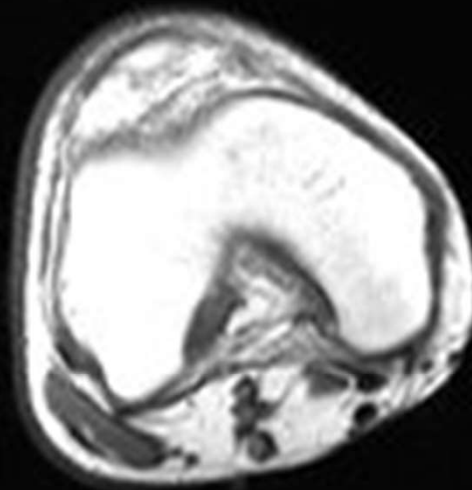
Se:22

13-Feb-2017

Im:10/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

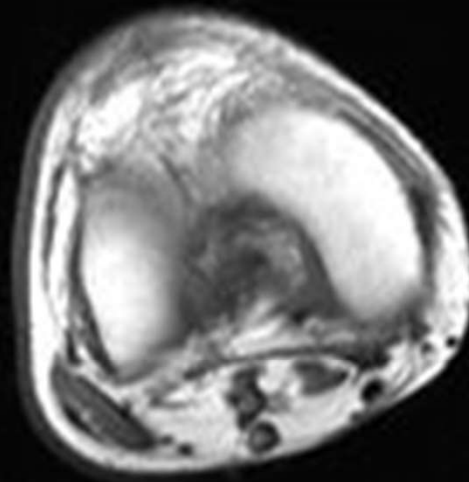
Se:22

13-Feb-2017

Im:11/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

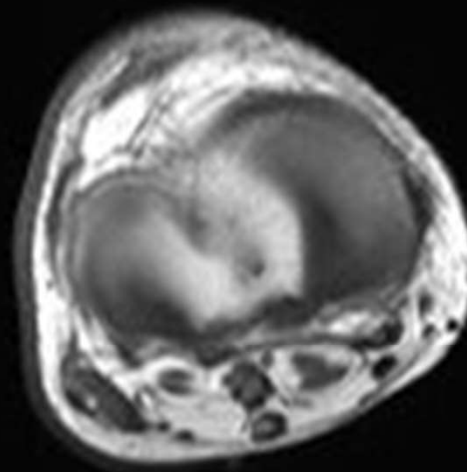
Se:22

13-Feb-2017

Im:12/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

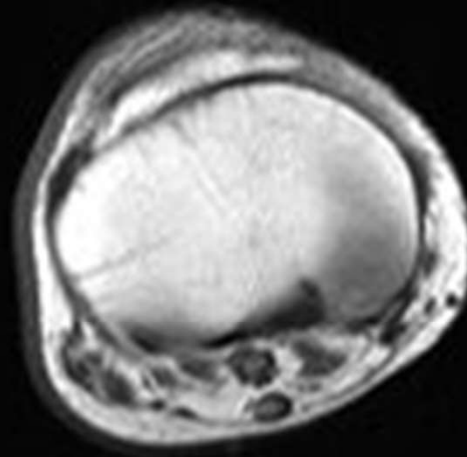
Se:22

13-Feb-2017

Im:13/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

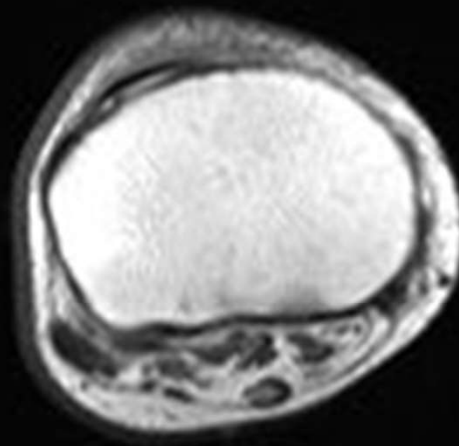
Se:22

13-Feb-2017

Im:14/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

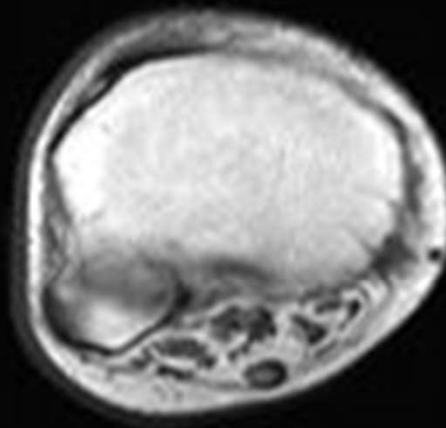
Se:22

13-Feb-2017

Im:15/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

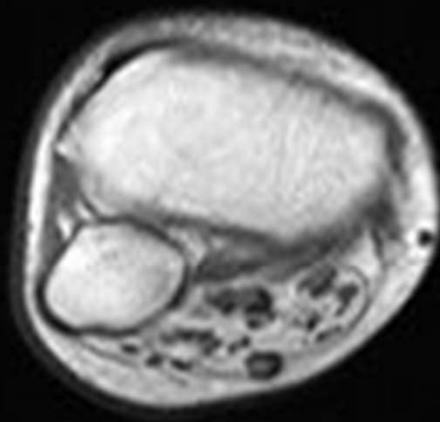
Se:22

13-Feb-2017

Im:18/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

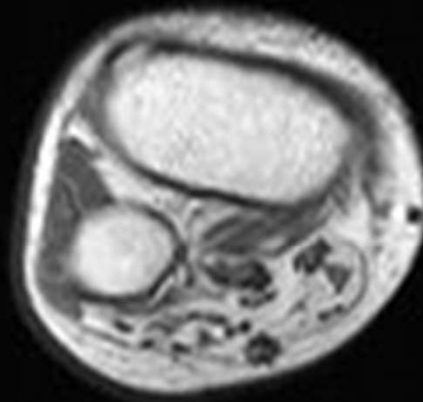
Se:22

13-Feb-2017

Im:17/88

14:52:20

R



5



cm

L

P

① WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

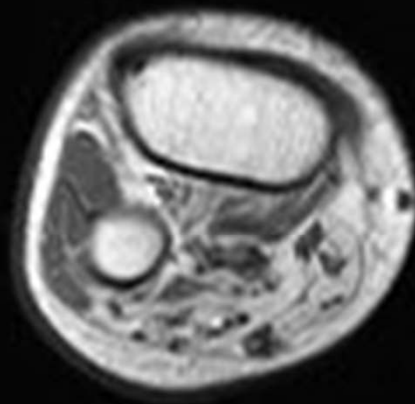
Se:22

13-Feb-2017

Im:18/88

14:52:20

R



5



L

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

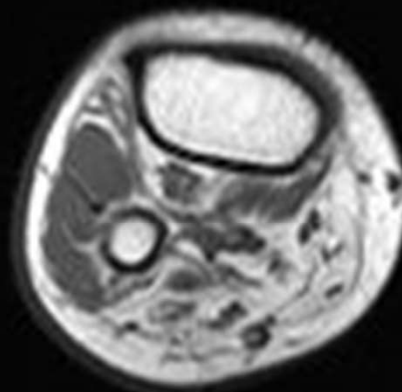
Se:22

13-Feb-2017

Im:19/88

14:52:20

R



5



L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

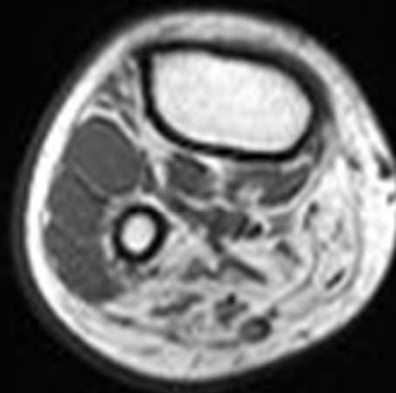
Se:22

13-Feb-2017

Im:20/88

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

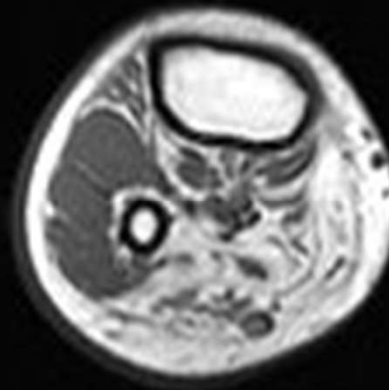
Se:22

13-Feb-2017

Im:21/88

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

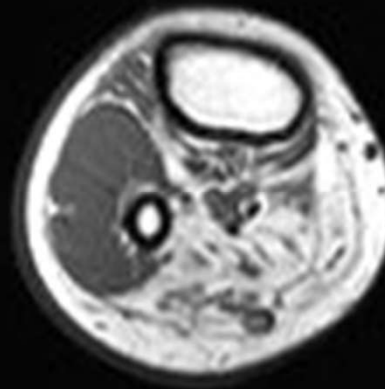
Se:22

13-Feb-2017

Im:22/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

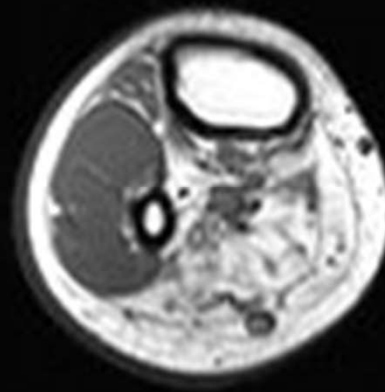
Se:22

13-Feb-2017

Im:23/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

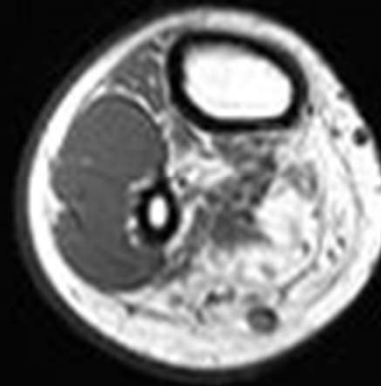
Se:22

13-Feb-2017

Im:24/88

14:52:20

R



5



L

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

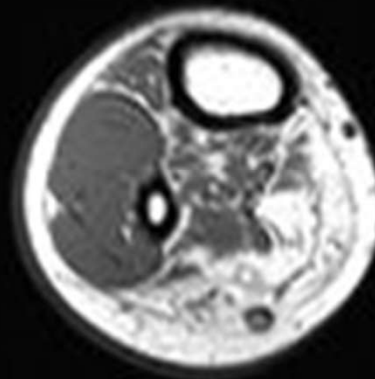
Se:22

13-Feb-2017

Im:25/88

14:52:20

R



5



L

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

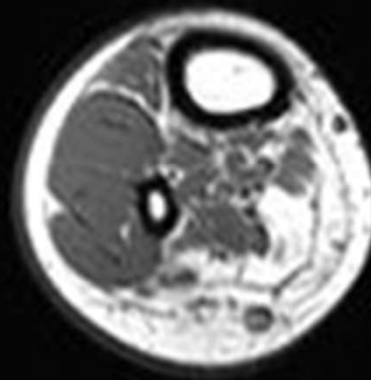
Se:22

13-Feb-2017

Im:28/88

14:52:20

R



5



L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

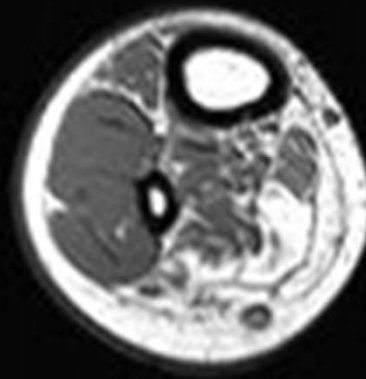
Se:22

13-Feb-2017

Im:27/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

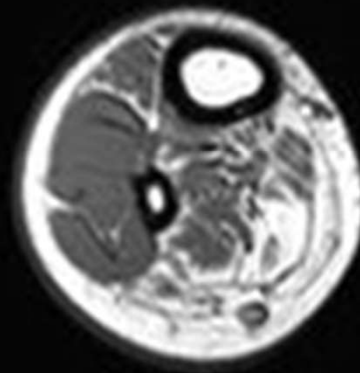
Se:22

13-Feb-2017

Im:28/88

14:52:20

R



5



L

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

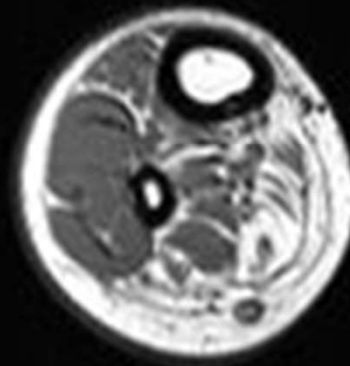
Se:22

13-Feb-2017

Im:29/88

14:52:20

R



5



L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

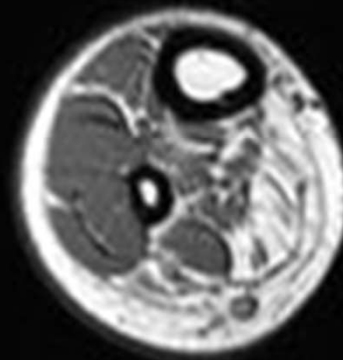
Se:22

13-Feb-2017

Im:30/88

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:31/88

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:32/88

14:52:20

R



5

L

cm

P

WL:542 - WW:1119

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

Primary

Rt_t1_tse_tra calves_COMPOSED_-11 Westwood Rad

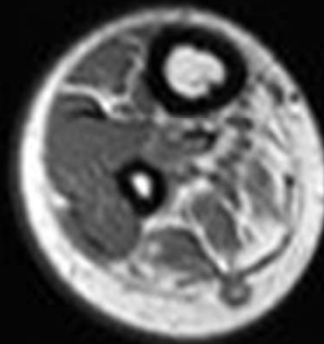
Se:22

13-Feb-2017

Im:33/88

14:52:20

R



5

L

cm

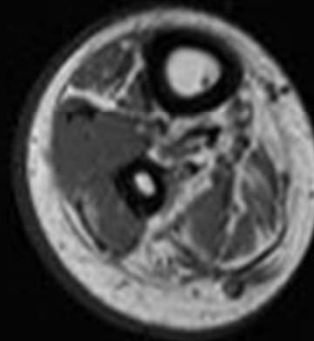
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:34/88

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

R



5



L

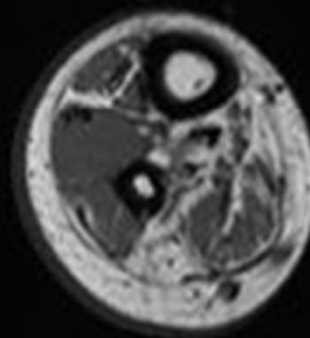
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:35/88

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

R



5



L

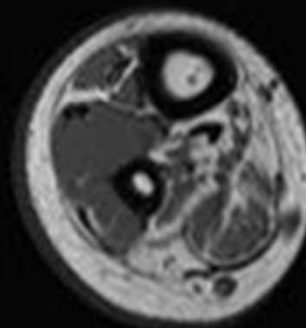
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:36/86

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

R



5



L

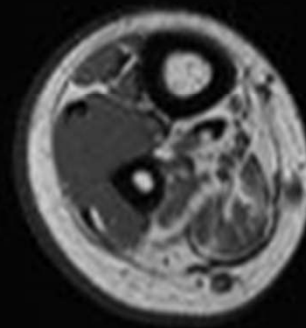
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:37/88

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

R



5



L

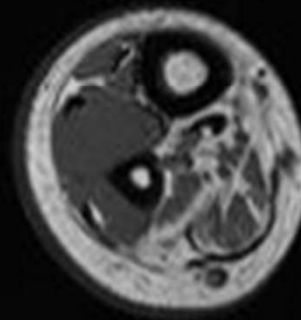
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:38/88

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

R



5



L

cm

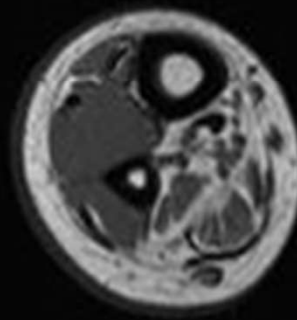
P

WL:542 - WW:1119

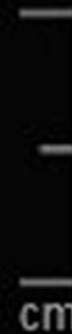
MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:39/88

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

R



5



L

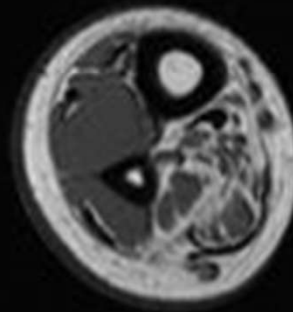
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:40/88

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

R



5



L

cm

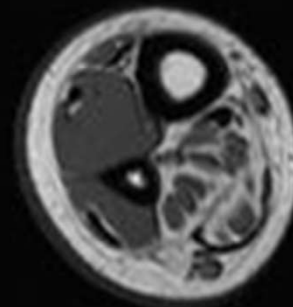
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:41/88

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

R



5



L

cm

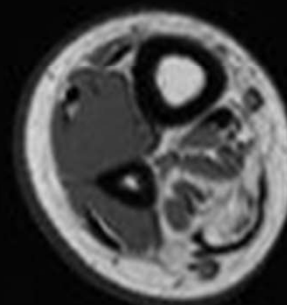
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:42/88

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

R



5



L

cm

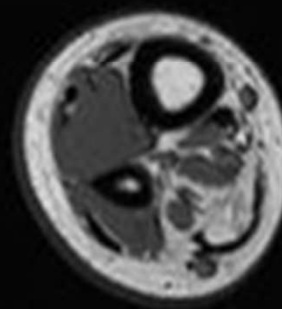
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:43/86

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

R



5



L

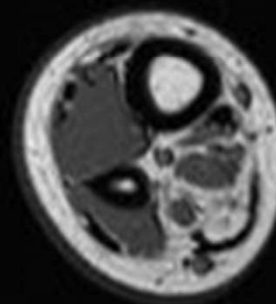
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:44/88

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

R



5

L

cm

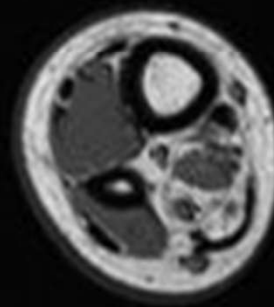
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:45/86

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

R



5



L

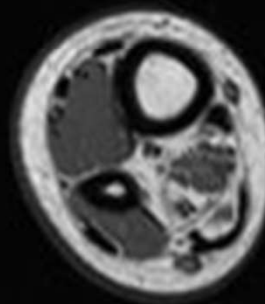
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:46/86

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

R



5



L

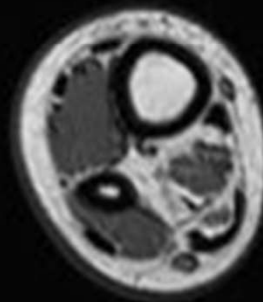
P

WL:542 - WW:1119

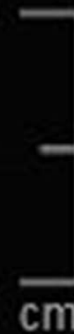
MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:47/86

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

R



5



L

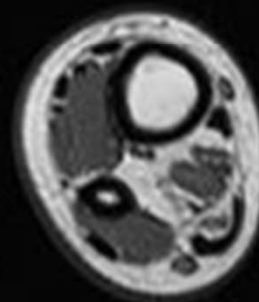
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:48/88

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

R



5



L

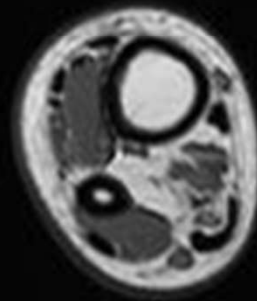
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:49/86

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

R



5



L

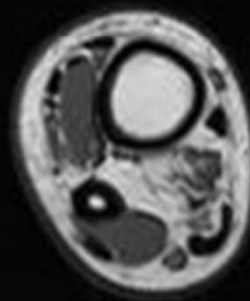
P

WL:542 - WW:1119

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

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

R



5



L

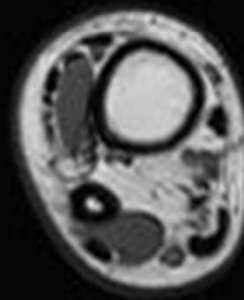
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:51/88

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

R



5



L

cm

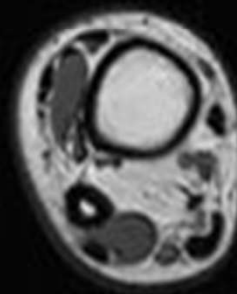
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:52/86

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

R



5



L

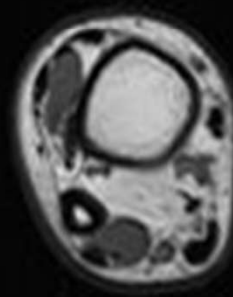
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:53/88

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

R



5



L

cm

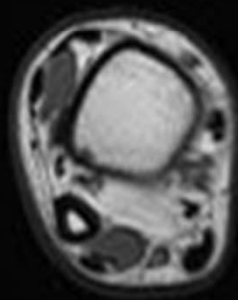
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:54/88

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

R



5



L

cm

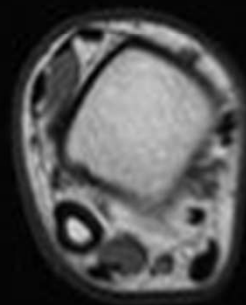
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:55/88

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

R



5



L

cm

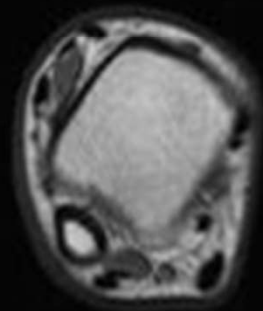
P

WL:542 - WW:1119

MR TIB-FIB WO CONTRAST RIG^A
Rt_t1_tse_tra calves_COMPOSED_-11
Se:22
Im:56/86

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

R



5



cm

L

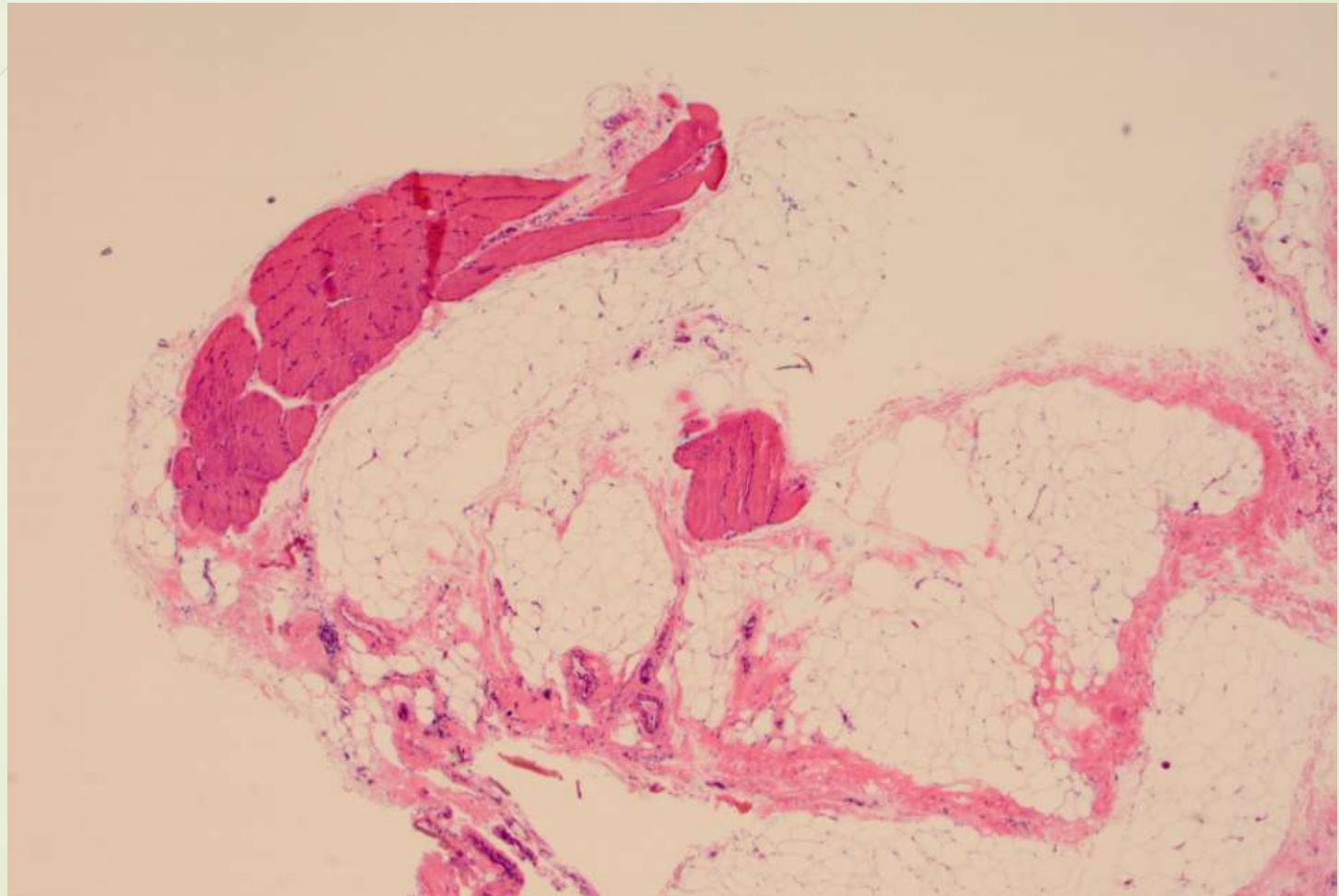
P

WL:542 - WW:1119

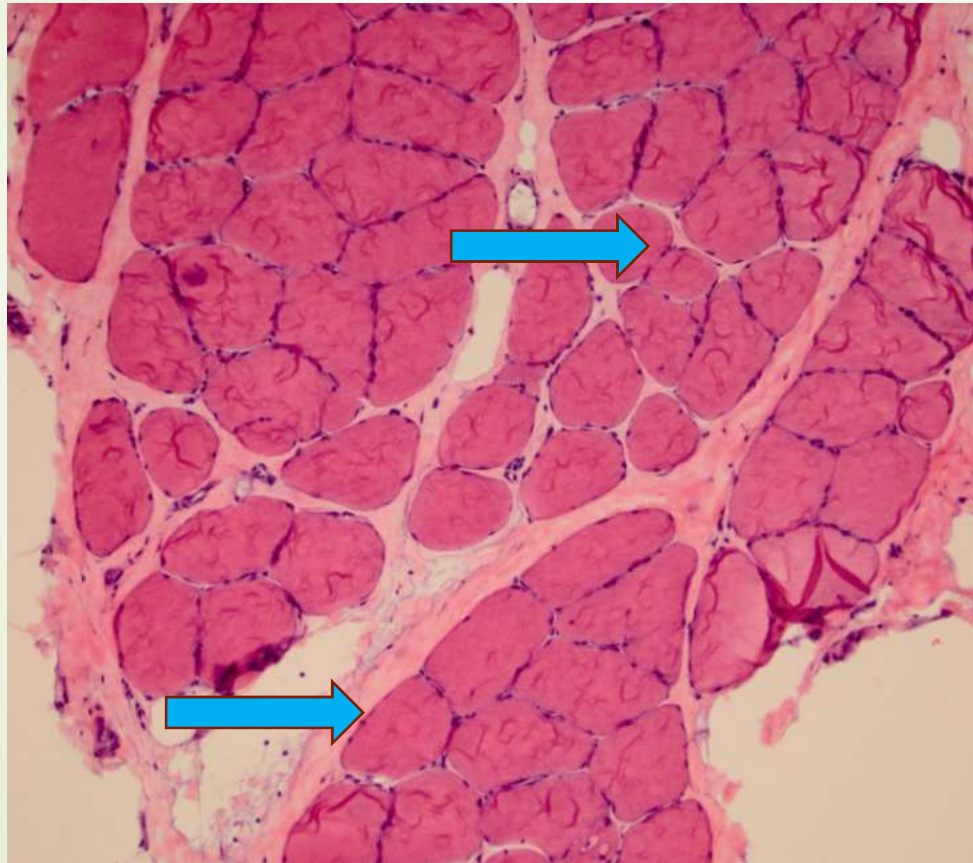
The three brothers: same phenotype



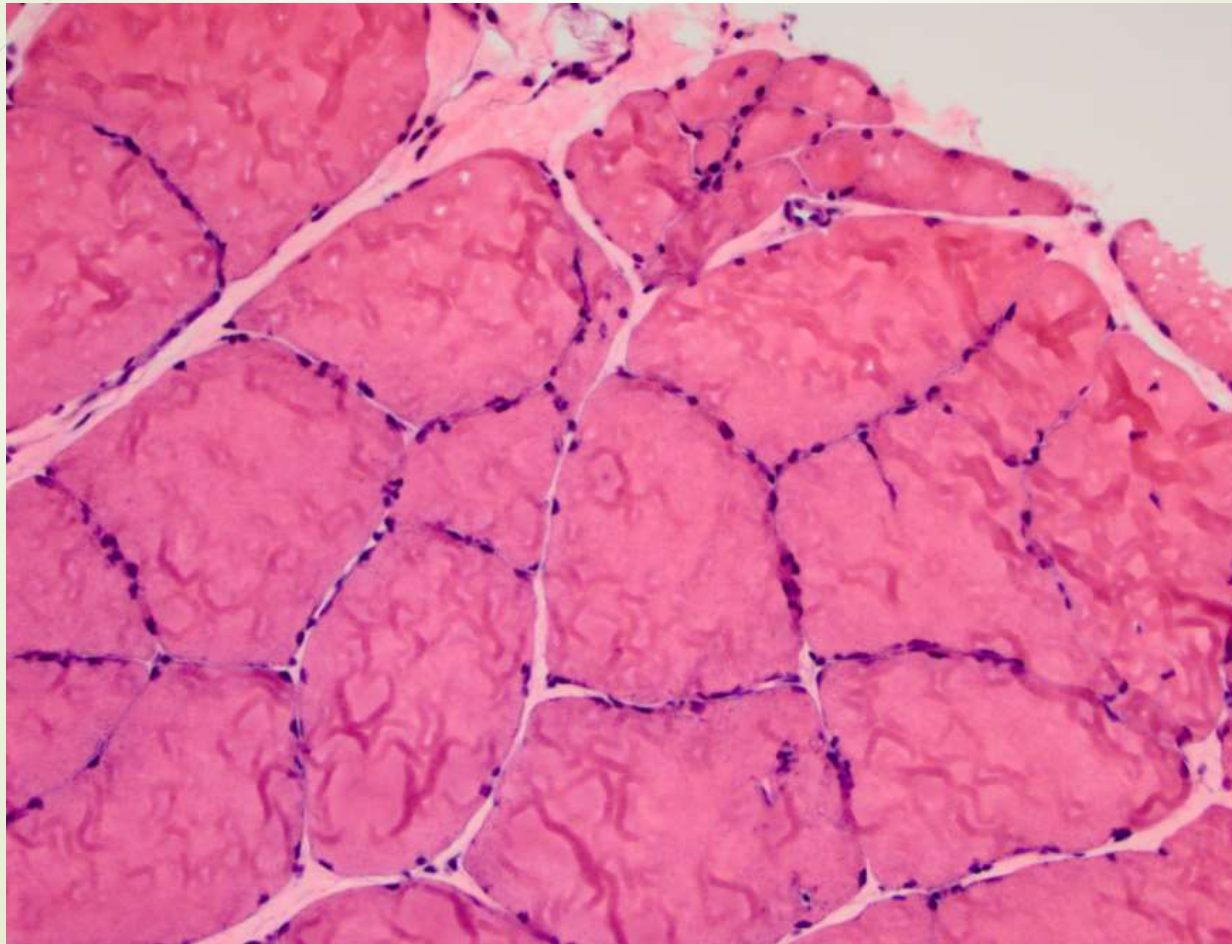
Biopsy: tibialis anterior



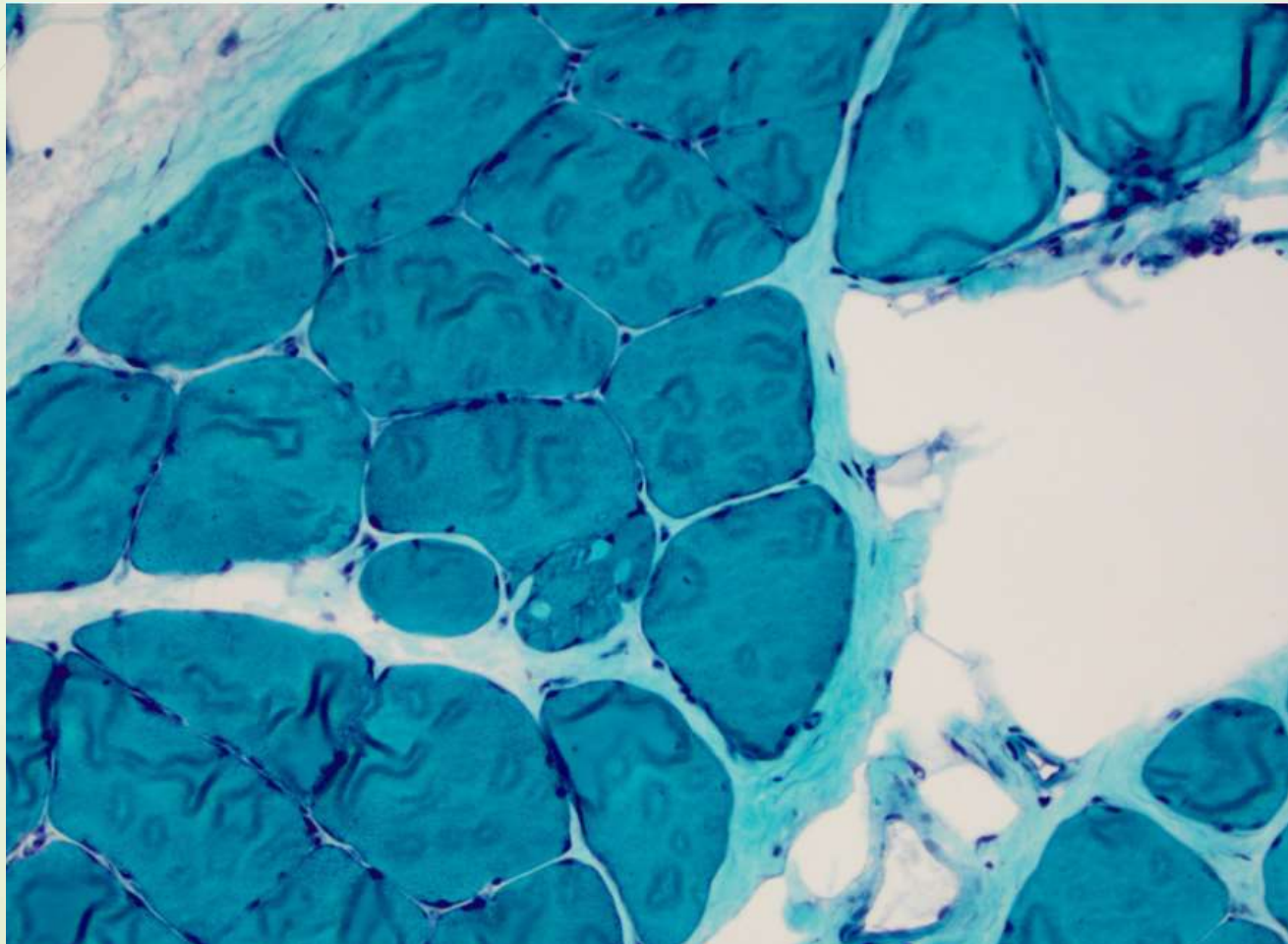
H/E



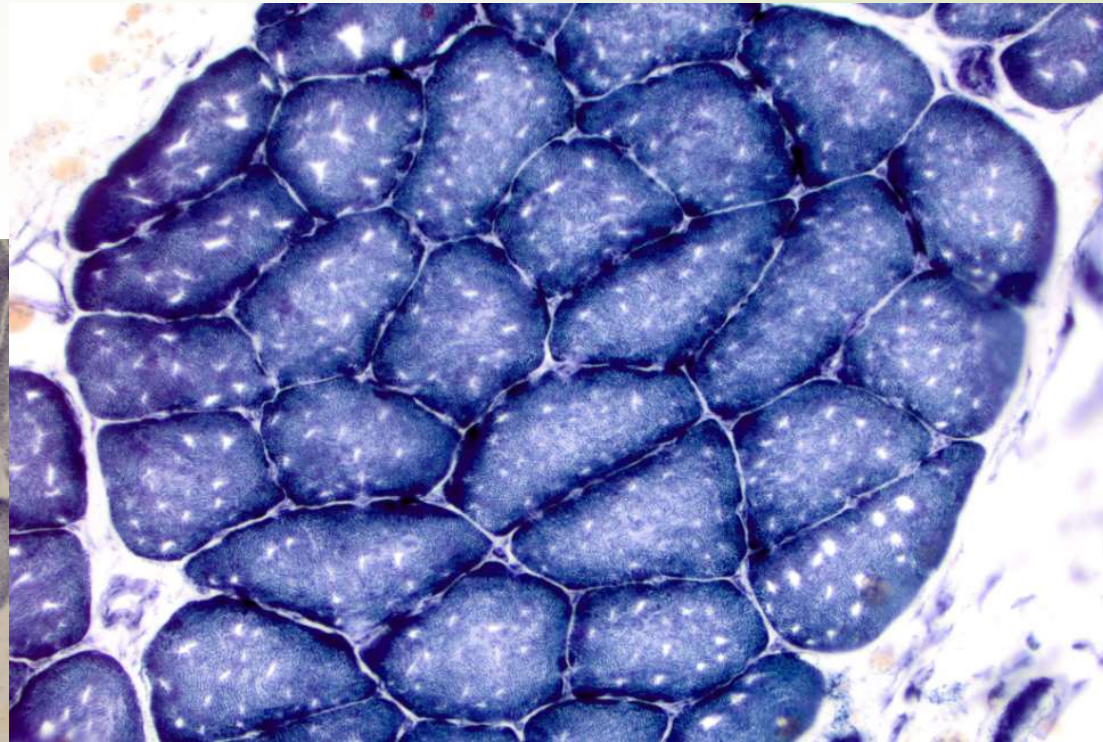
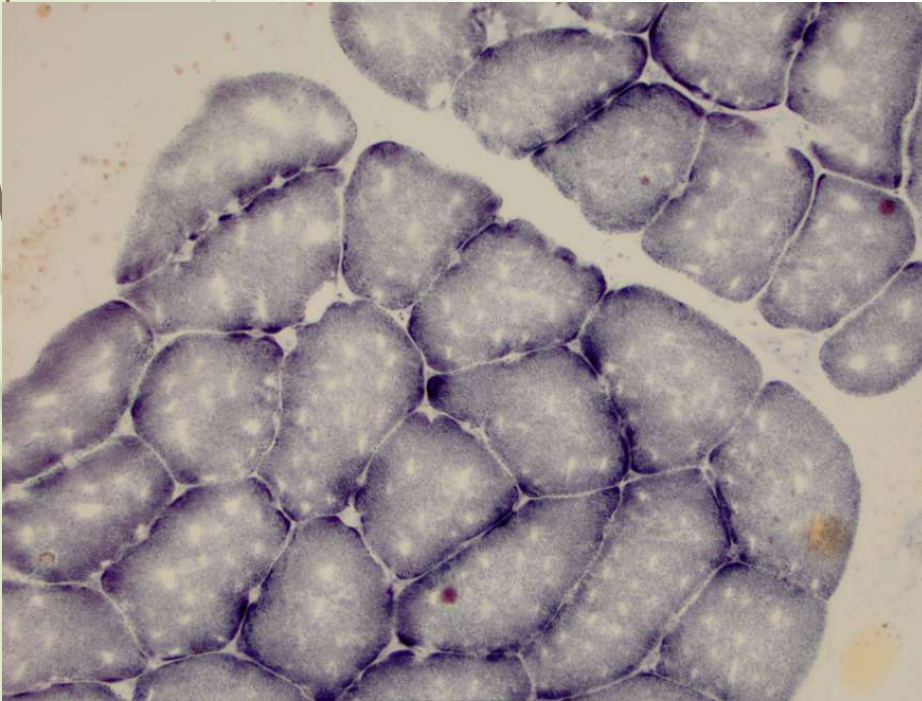
H/E



Gömöri trichrome

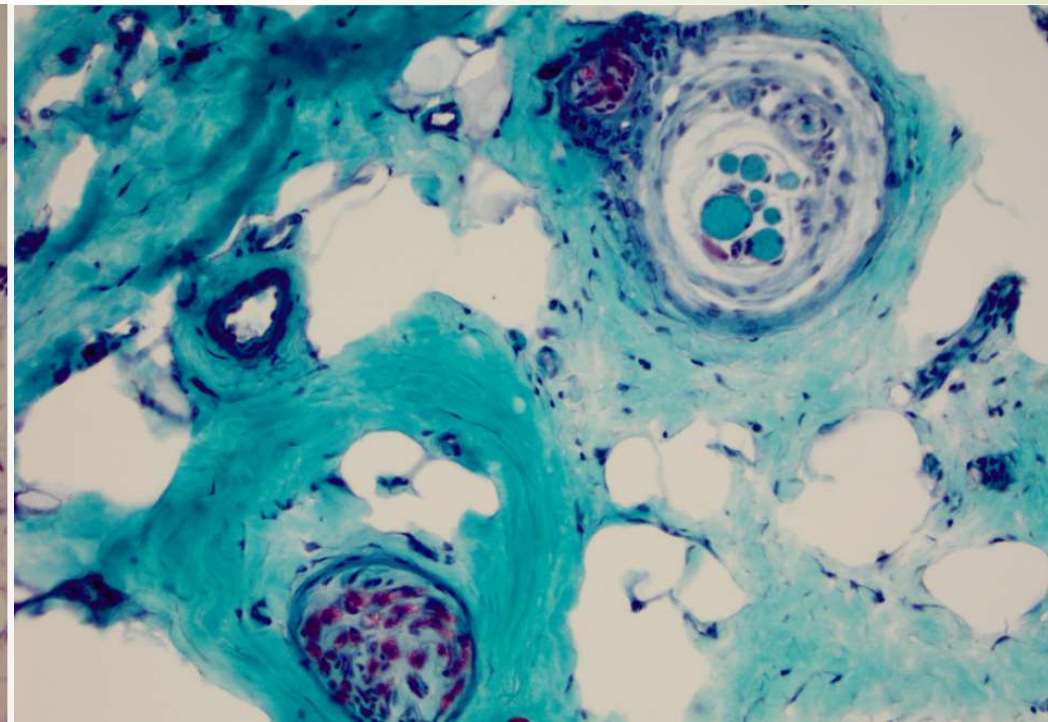
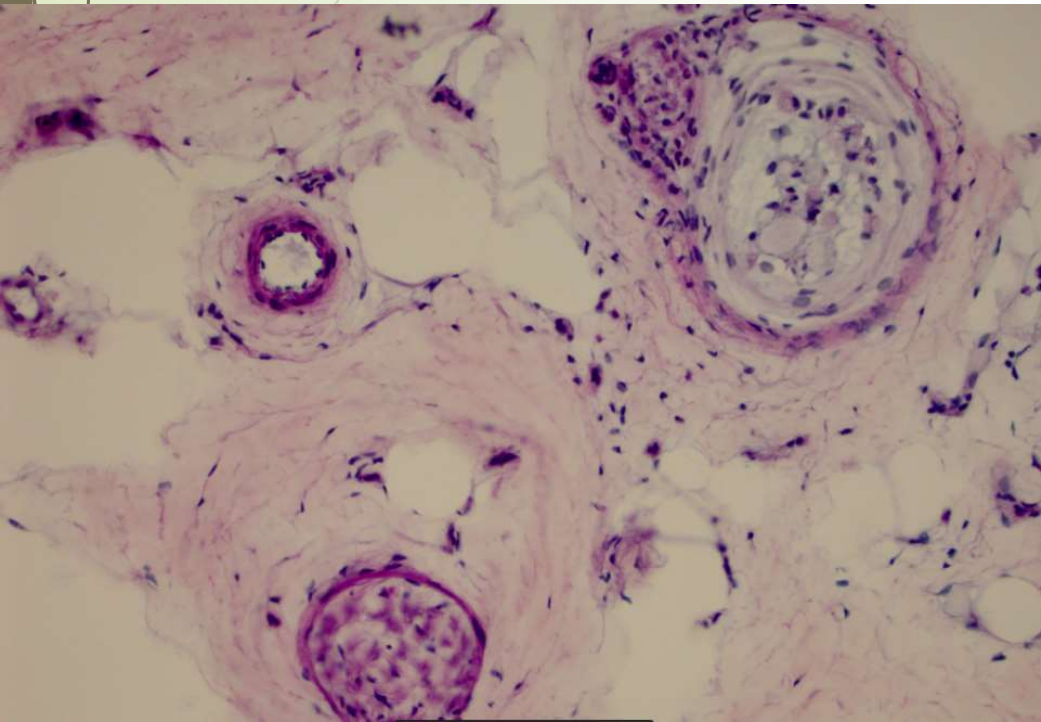


SDH/NADH stain

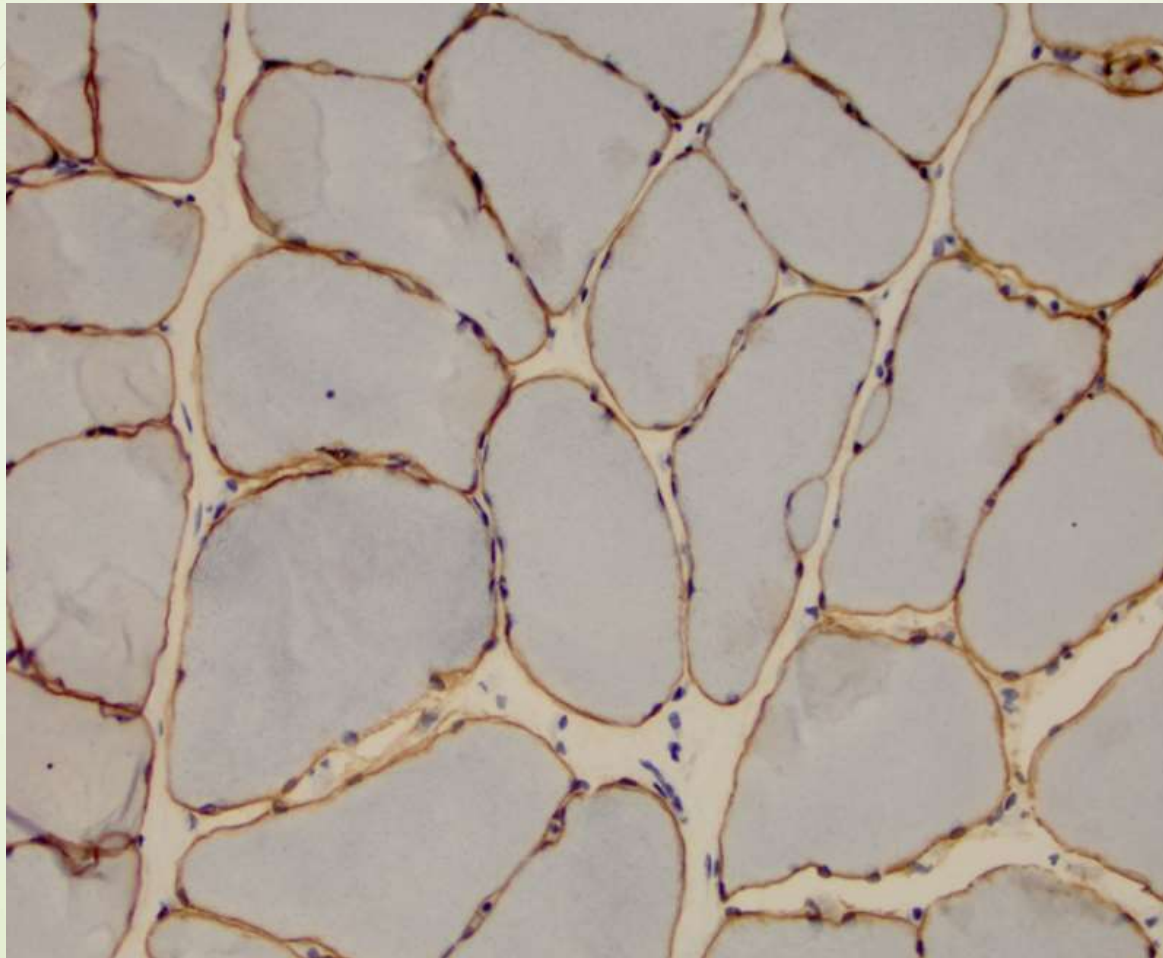


ATPase 9.2, 4.6, 4.2- exclusive type 1 fiber only

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

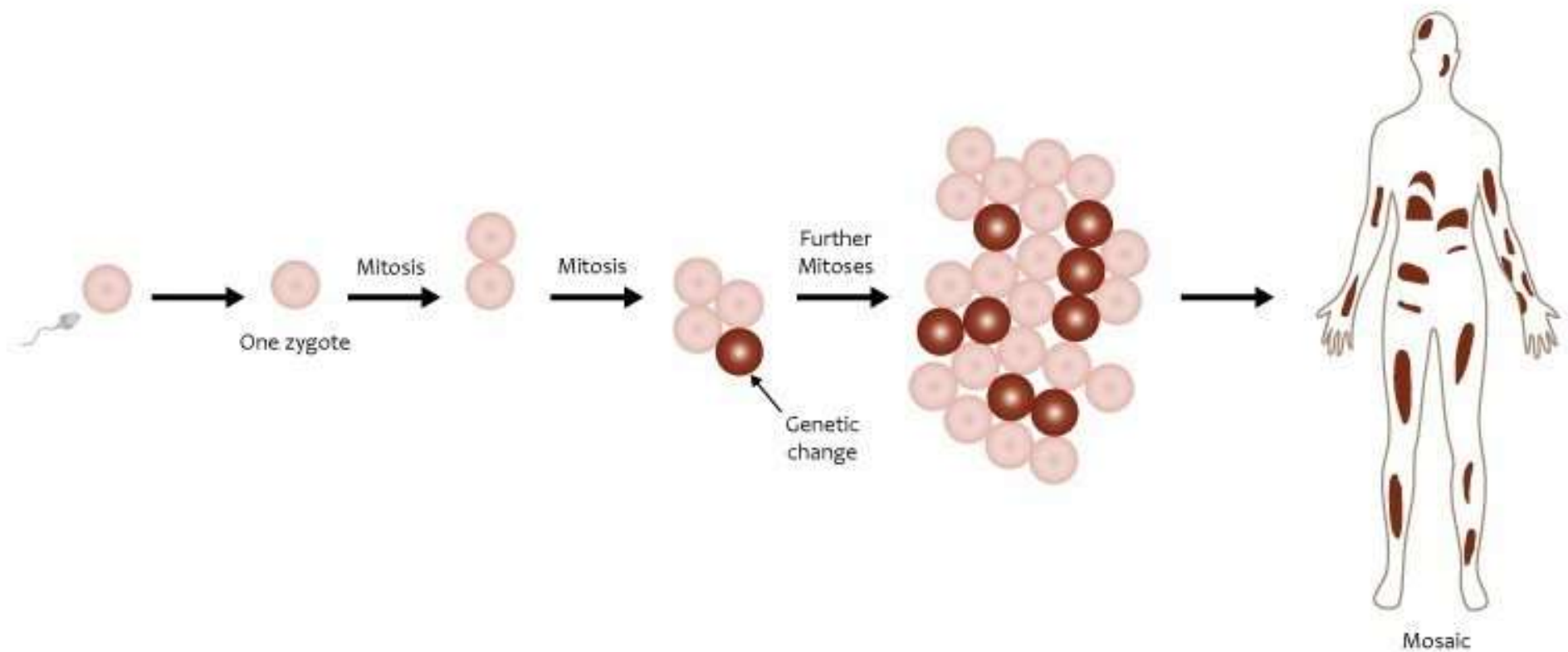
- **DYNC1H1 gene (AD Lower extremity predominant SMA)**
 - variant c.2327C>T (p.Pro776Leu)
 - Twin brothers also tested positive for this mutation
 - Father is also tested positive for this mutation
 - It appears that it is inherited from Father who does not have phenotype

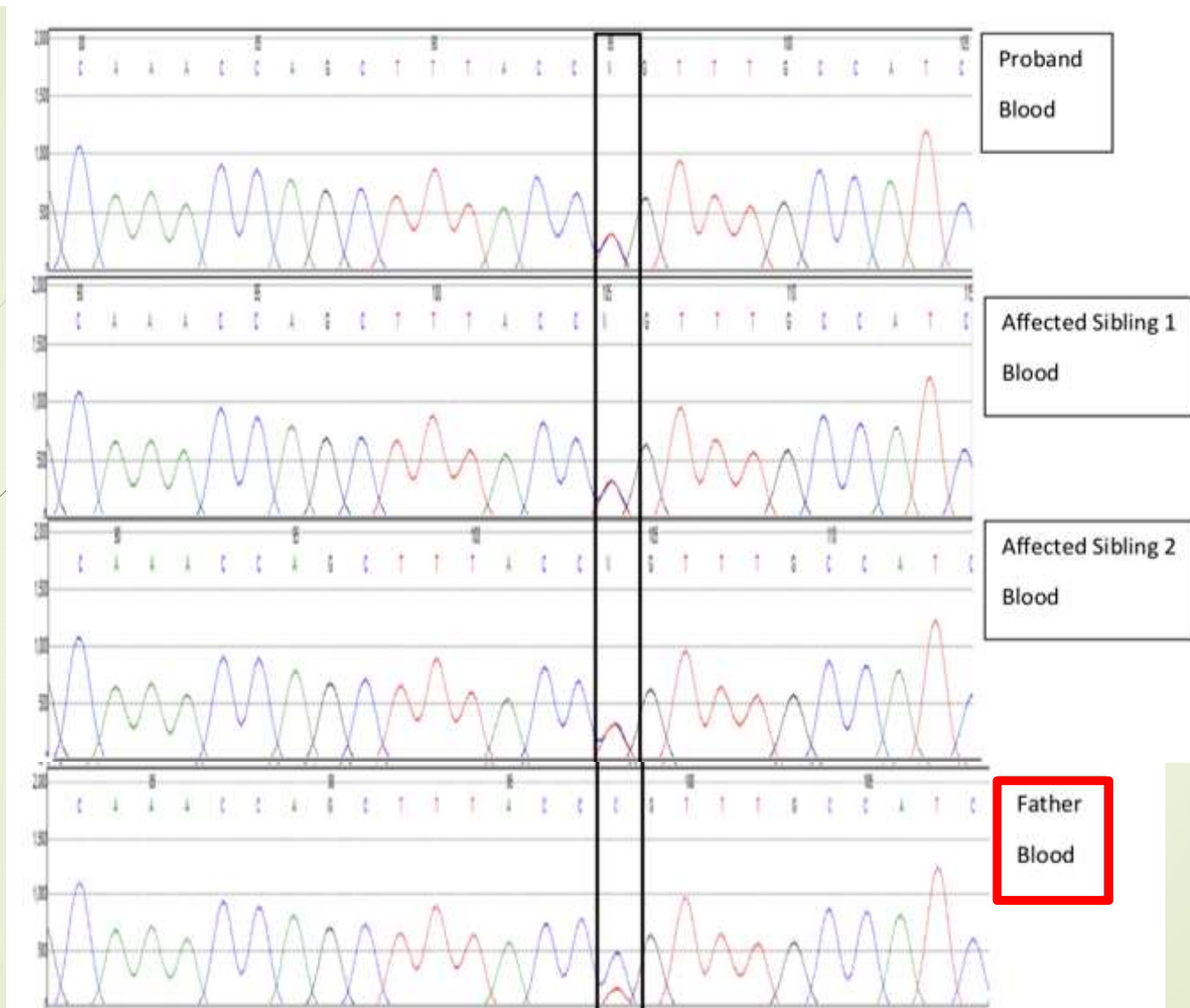



Whole Genome Sequencing: allele imbalance observed

- ▶ 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

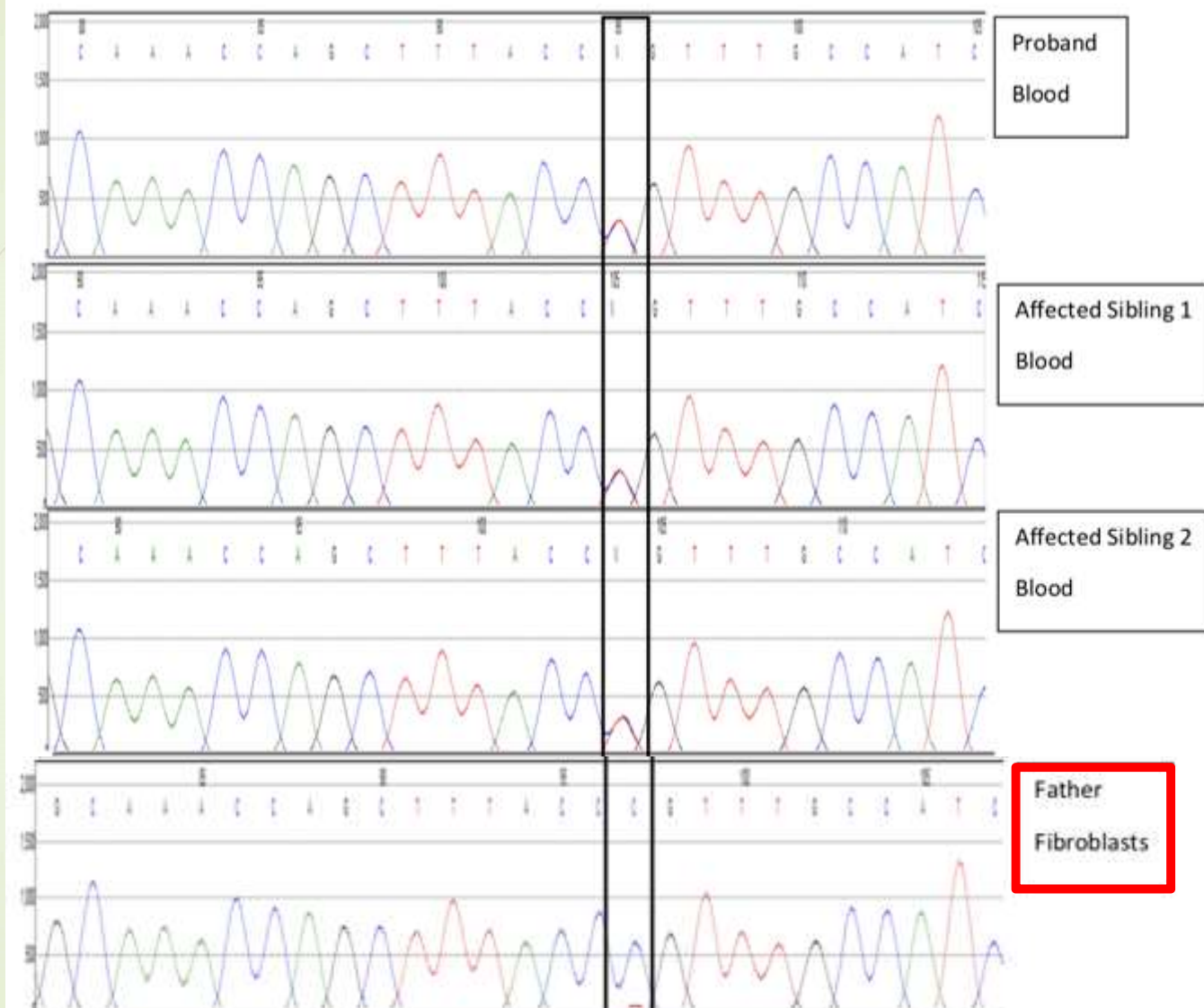






Confirmation with second tissue analysis: fibroblast

- 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



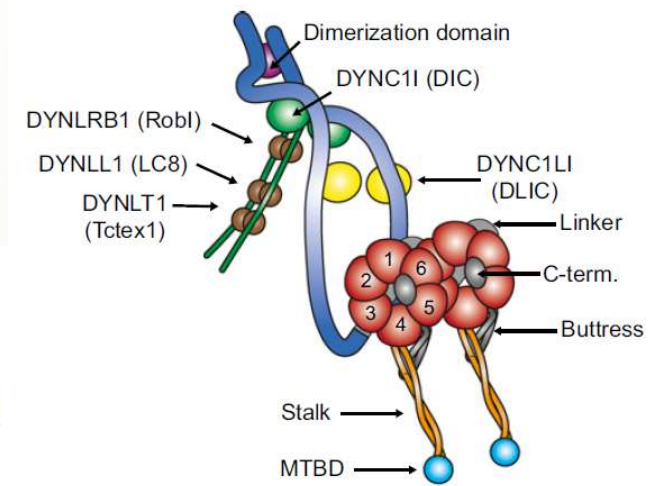


Final diagnosis: SMA-LED due to DYNC1H1 mutation

- **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

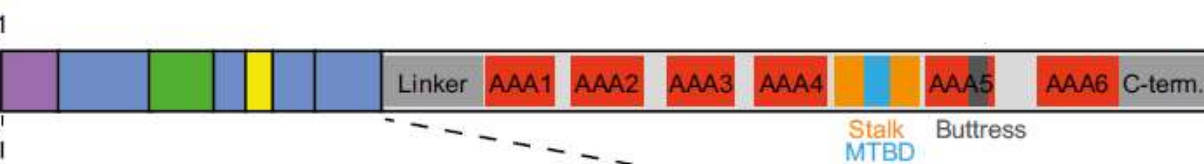
- Dynein-Dynactin complex consists of 2 heavy chain, one intermediate chain, and three light chains
- The heavy chain contains a motor domain which translocate the protein complex across microtubules



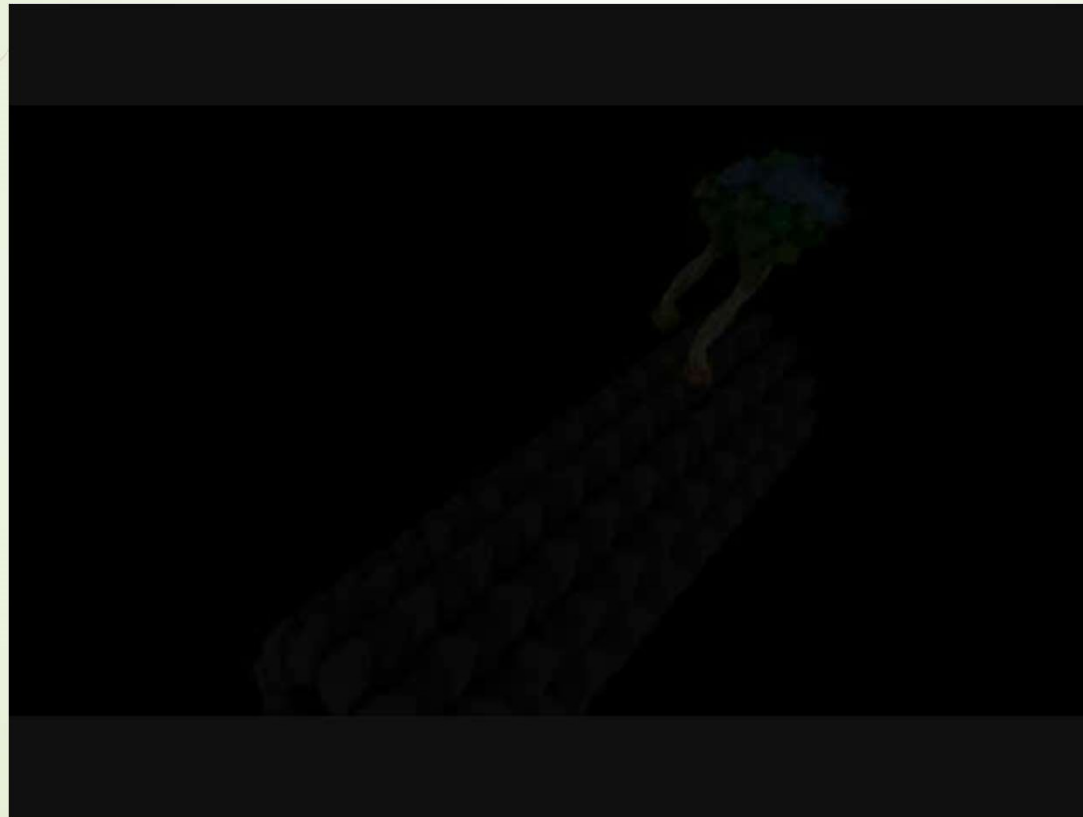
DYNC1H1 mutations associated with neurological diseases compromise processivity of dynein-dynactin- cargo adaptor complexes
 Ha Thi Hoanga, Max A. Schlagerb,1, Andrew P. Carterb, and Simon L. Bullocka,2

Tail

Motor



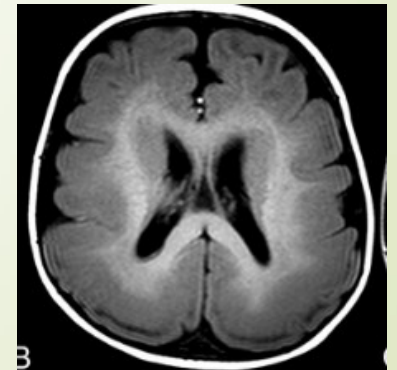
Dynein-Dynactin complex



Animation created by Janet Iwasa, Harvard Medical School

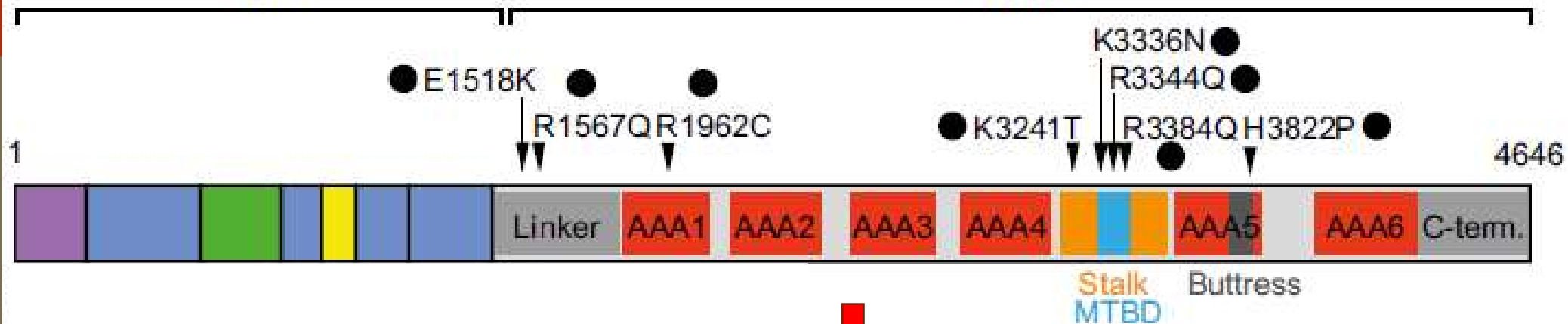
Clinical significance of DYNC1H1 mutation

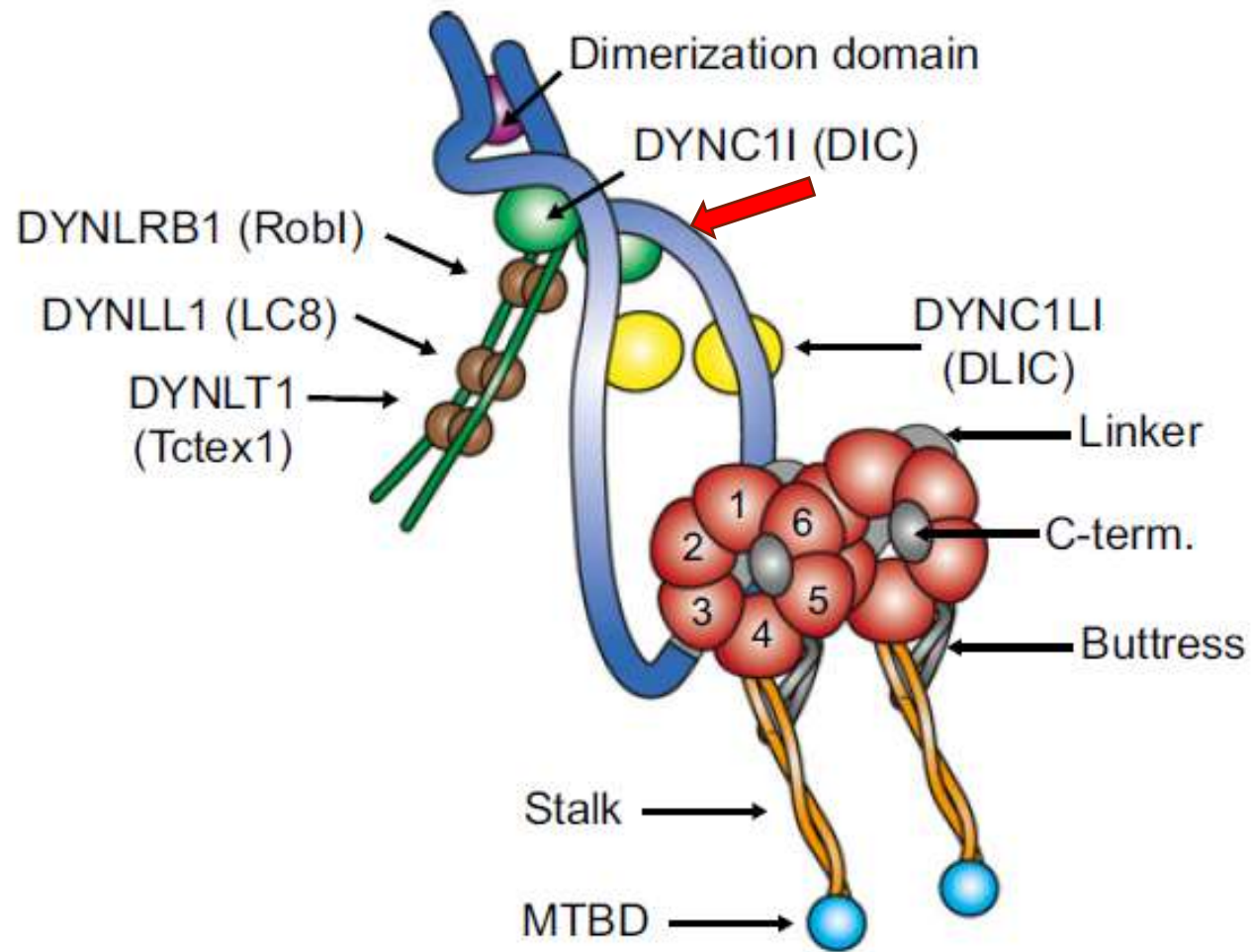
- Spinal muscular atrophy-Lower Extremity predominant (SMA-LED)
 - Muscle weakness in the legs
- Malformation of Cortical Development (MCD)
 - Due to defective neuronal proliferation or migration
 - Associated with severe intellectual disability and epilepsy



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