Mahidol University
Faculty of Medicine Siriraj Hospital

SIENDO
Faculty of Medicine Siriraj Hospital

Interhospital Conference Case 1

24th March 2023

F1 SAHARAT LEELANUWATKUL
F2 PRAPA PAKDEEMEECHAI
ASST. PROF. PAWEENA CHUNHAROJRITH

Patient identification

ผู้ป่วยหญิงไทยคู่	อายุ 57 ปี
ภูมิลำเนา	จังหวัดสมุทรปราการ
อาชีพ	ครู

Chief complaint: ปวดศีรษะมากขึ้น 1 เดือนก่อนมา รพ.

Underlying diseases

> Hypertension for 7 years

- ล่าสุด on losartan (50) 1/2x1 po pc
- Baseline BP 130-140/85 mmHg

History (protocol)

1 เดือนก่อนมา รพ. ปวดศีรษะข้างซ้าย ไม่มีร้าว ปวดตลอดเวลา มีอาการคลื่นไส้เป็น ๆ หาย ๆ มองเห็นชัดเจน ไม่มีแขนขาอ่อนแรง ไม่มีชา ไป รพ. เอกชน วินิจฉัย ปลายประสาทอักเสบ ได้ prednisolone(5) 4x2 po pc, norgesic, ultracet, lorazepam อาการไม่ดีขึ้น

1 วันก่อนมา รพ. ปวดศีรษะด้านซ้ายมาก Pain score 10/10 อาเจียน 5 ครั้ง ไม่มีแขนขาอ่อนแรง ไม่มีชา ไม่มีตามัว

Physical examination (protocol)

V/S: BT 37 °C, BP 113/72 mmHg, PR 78 bpm, RR 18/min, BW 50 kg, HT 156 cm,

GA: A middle aged woman, alert and cooperative, not pale, no jaundice

HEENT: Right anterior mass moves with swallowing, size 1 cm, firm consistency, not tender

CVS: JVP 3 cm above sternal angle, PMI at 5^{th} ICS left MCL, no heaving, normal S1,S2, no murmur

RS: Normal breath sounds, no adventitious sounds

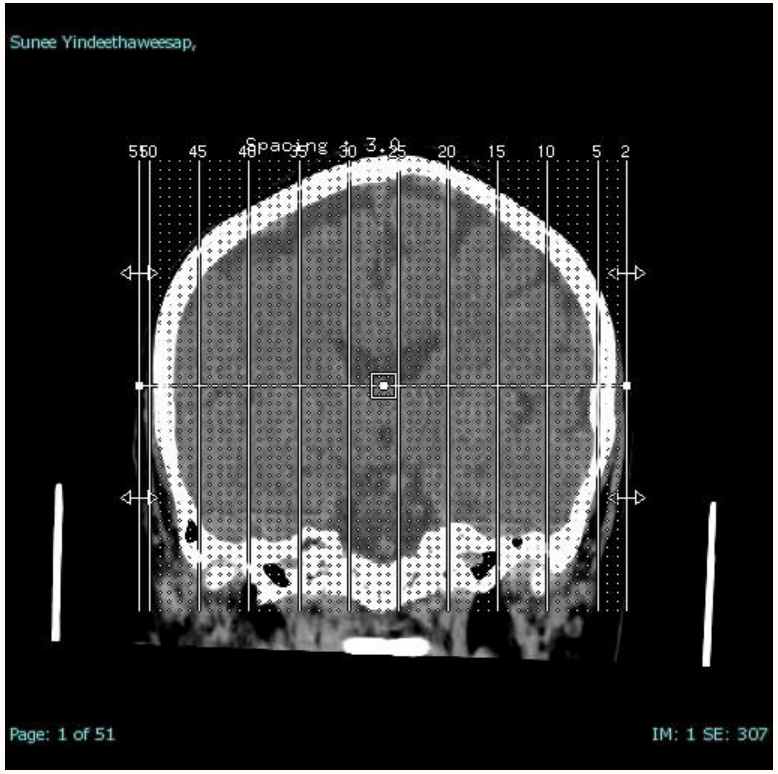
Abd: No distension, soft, not tender

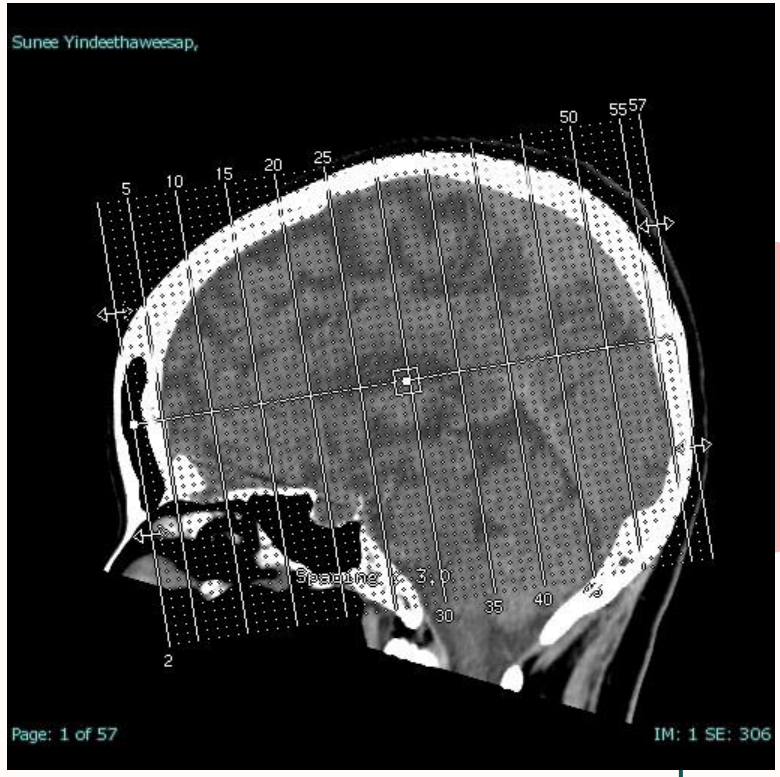
NS: E4V5M6, pupil 2 mm BRTL BE, full EOM, normal visual field by confrontation test, motor grade V all, sensory intact

Present illness

- **Work up:** CT brain NC 30/5/64

CT brain NC 30/5/64





History and Physical examination

History

Present illness

1 เดือนก่อนมา รพ. ปวดศีรษะข้างซ้าย ไม่มีร้าว ปวดตลอดเวลา มีอาการคลื่นไส้เป็น ๆ หาย ๆ มองเห็นชัดเจน ไม่มีแขนขาอ่อนแรง ไม่มีชา ไป รพ. เอกชน วินิจฉัย ปลายประสาทอักเสบ ได้ prednisolone(5) 4x2 po pc, norgesic, ultracet, lorazepam อาการไม่ดีขึ้น

1 วันก่อนมา รพ. ปวดศีรษะด้านซ้ายมาก Pain score 10/10 อาเจียน 5 ครั้ง ไม่มีแขนขาอ่อนแรง ไม่มีชา ไม่มีตามัว

Present illness

- ไม่มีคนทักว่าหน้าเปลี่ยน/ปากหนา/มือเท้าใหญ่ขึ้น
- ไม่มีหน้ากลมแดง/ผิวแตกลายสีม่วง/หรือเป็นจ้ำเลือดง่าย
- ไม่มีน้ำนมไหลผิดปกติ
- ไม่มีขี้ร้อนขี้หนาว/ใจสั่น/มือสั่น/ตะคริว/ผิวแห้ง
- ไม่มีวูบหน้ามืดขณะเปลี่ยนท่าทาง
- ไม่มีอาการตามัว/ลานสายตาแคบลง/หรือเห็นภาพซ้อน ไม่มีแขนขาอ่อนแรง
- ไม่มีน้ำใสไหลออกจากจมูก
- ดื่มน้ำวันละ 500-600 ml ปัสสาวะกลางวัน 3 รอบ กลางคืน 1 รอบ
- ประจำเดือนหมดอายุ 48 ปี

Family history

- ปฏิเสธประวัติโรคไทรอยด์ มะเร็งต่อมไทรอยด์ โรคต่อมพาราไทรอยด์ เนื้องอกที่ต่อมใต้สมอง หรือต่อมหมวกไตในครอบครัว
- ปฏิเสธประวัติบิดา มารดา กระดูกสะโพกหัก
- ปฏิเสธประวัติคนในครอบครัวมีนิ่วไต
- มีบุตรสาว 2 คนอายุ 22 ปีและ 24 ปี แข็งแรงดี
- มีพี่น้อง 5 คน เป็นบุตรคนที่ 4
- น้องสาวเคยเจาะพบแคลเซียมในเลือดสูงเล็กน้อย (Ca 10.2 เมื่อปี 2563) และมีประวัติผ่าตัดถุงน้ำที่ต่อมไทมัส

Present illness

- ไม่มีประวัติปวดตามกระดูก/กระดูกหัก
- ไม่มีประวัติปวดท้องใต้ลิ้นปี่/ปวดท้องทะลุหลัง/หรือได้รับการวินิจฉัยตับอ่อนอักเสบมาก่อน
- ไม่มีช่วงที่สับสน/มึนงง ตื่นรู้ตัวดีตลอด
- ไม่มีปัสสาวะเป็นเลือด หรือมีก้อนกรวดปน
- ไม่มีท้องผูก ถ่ายอุจจาระปกติ กินได้ปกติ
- ไม่ได้สังเกตว่ามีก้อนที่คอมาก่อน
- ไม่มีอาการกลืนติด/กลืนลำบาก
- ไม่เคยได้รับการฉายรังสีที่บริเวณคอ
- ไม่เคยใช้ยากลุ่ม Lithium, HCTZ

Physical examinations

Physical examinations

V/S: BT 37 °C, BP 113/72 mmHg, PR 78 bpm, RR 18/min, BW 50 kg, HT 156 cm

GA: A middle aged woman, alert and cooperative, not pale, no jaundice, **no cushingoid appearance, no acromegalic features**

Skin and nail: No dry or coarse or moist skin, no purplish striae, **no facial angiofibroma, no collagenoma, no lipoma**

HEENT: No loss of lateral 1/3 of eyebrows, no band keratopathy, no thyroid gland enlargement, **right anterior neck mass moves with swallowing, size 1 cm, firm consistency, not tender**

CVS, RS, Abd: as protocol

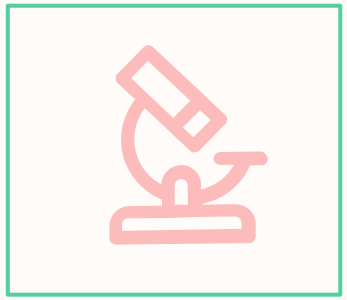
NS: E4V5M6, pupil 2 mm BRTL BE, full EOM, normal visual field by confrontation test, motor grade V all, sensory intact, CN grossly intact, Normal tone, motor power grade V all extremities, sensory intact, DTR 2+ all

Problem list

Problem list

A 57-year-old woman known case hypertension presented with

1. Severe headache for 1 month
2. Right anterior neck mass
3. Family history of hypercalcemia and thymic lesion in first degree relative
4. Widening of sella region from CT brain



Approach & Investigation

Investigation (protocol)

Hb 13.7 g/dL, Hct 42.8%, WBC 5,520 /μL, PMN 61.1%, L 32.8 %, Plt 347,000 /μL

BUN 13.6 mg/dL, Cr 0.52 mg/dL

Na 139 mmol/L, K 4.1 mmol/L, Cl 103 mmol/L, HCO_3 22 mmol/L

Investigation

01

02

03

04

05

06

07

08

09

Blood chemistry

- **Total Calcium 11.8 mg/dL**
- **Albumin 4.7 g/dL**
- **Phosphate 2.9 mg/dL**
- **PTH 97.3 pg/mL**
- **Vitamin D 12.4 mg/dL**
- Cr 0.52 mg/dL
- ALP 67 U/L

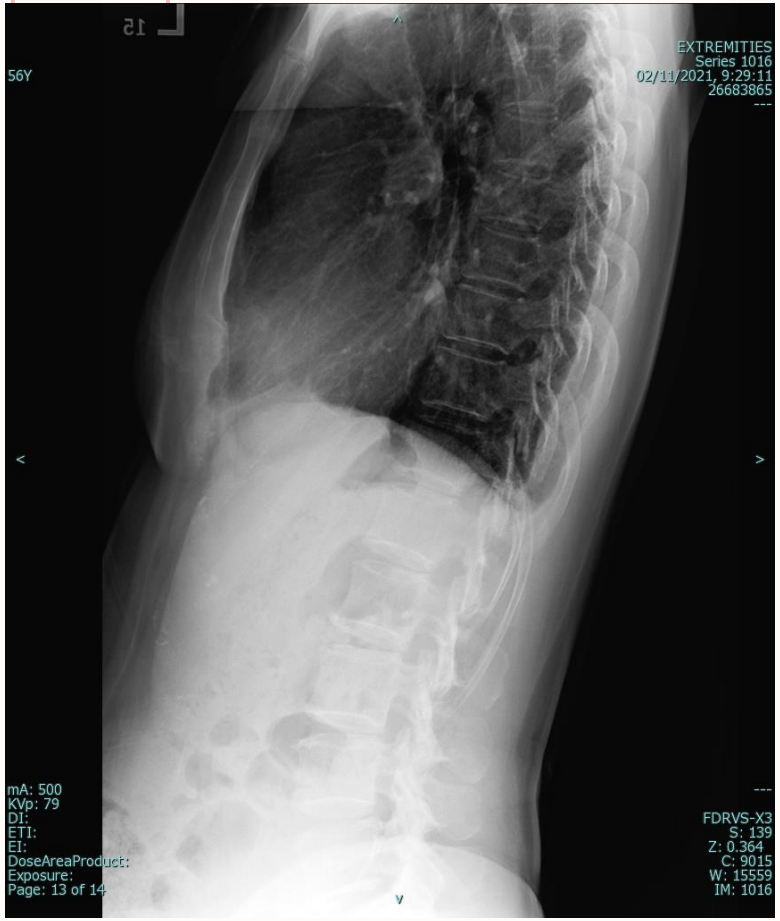
Hormonal assessment 18/11/64

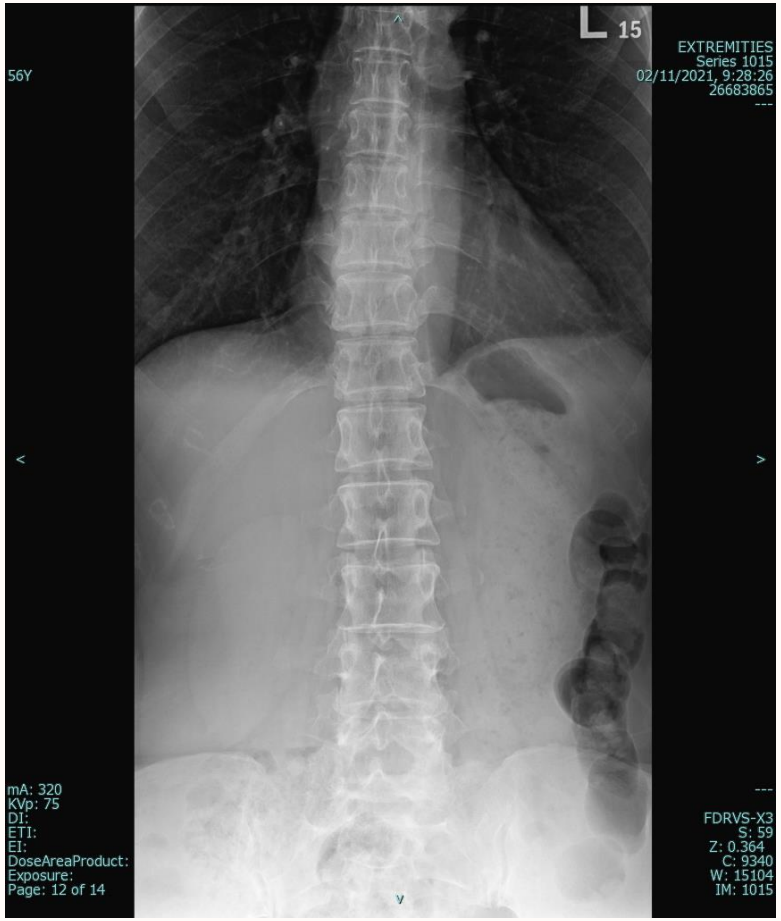
- 8AM cortisol 13.5 µg/dL
- FT4 1.54 ng/dL (0.93-1.71), TSH 1.07 µIU/mL (0.27-4.2)
- FSH 99.40 mIU/mL
- Prolactin 14.10 ng/mL
- IGF-1 173.00 ng/mL (42.3-214)

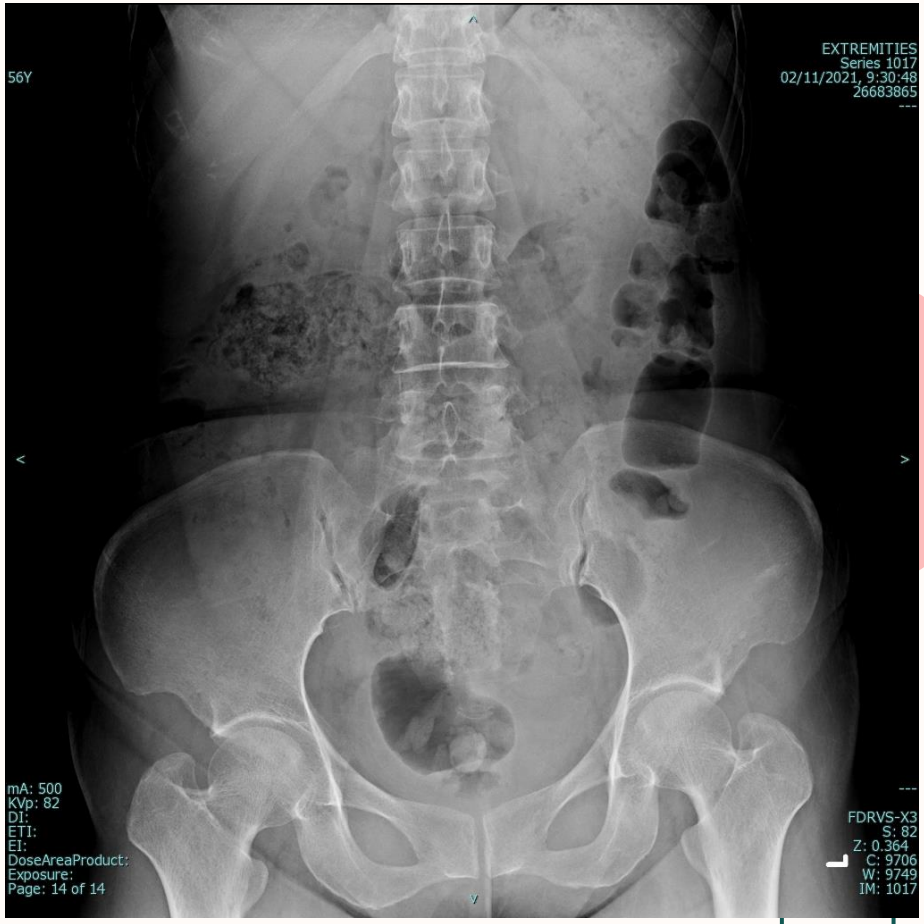
Ultrasound thyroid and FNA 3/8/64

- **Rt thyroid lobe:**
  - Indistinct mass with internal coarse heterogeneous microcalcification 1.3 x 1.2 cm
    - FNA: **Atypia of undetermined significance** (AUS), the smears contain sheets and clusters of epithelial cells showing round to oval enlarged nuclei. No colloid is appreciated.
- **Lt thyroid lobe:**
  - Indistinct mass with peripheral microcalcification 0.7 cm
    - FNA: **Unsatisfactory** for evaluation due to insufficiency of well preserved follicular cells.

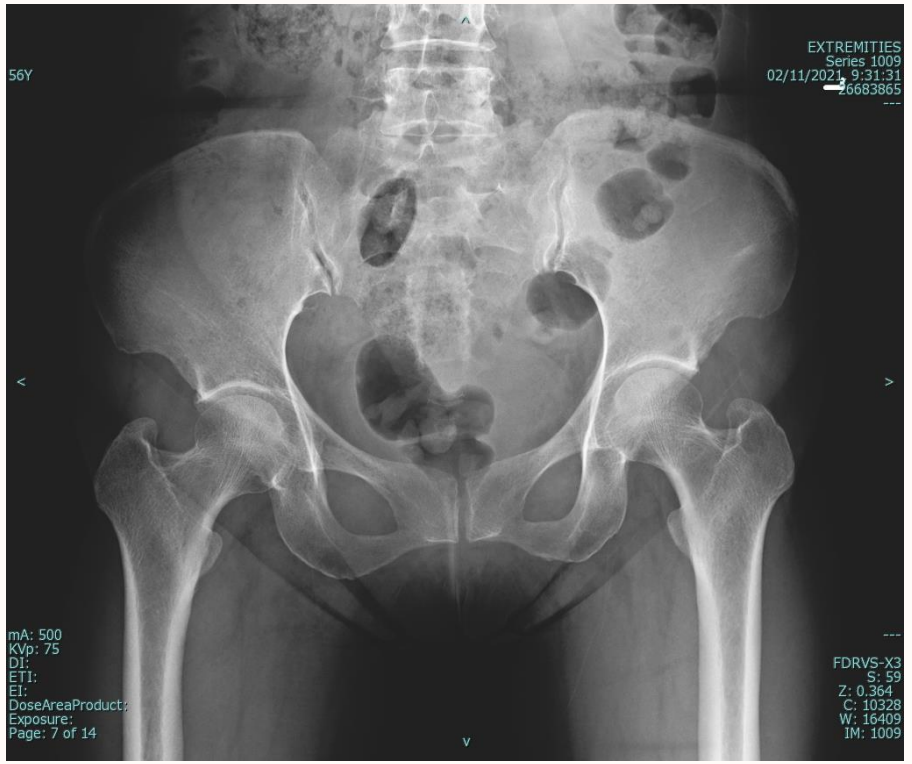
Bone survey 2/11/64

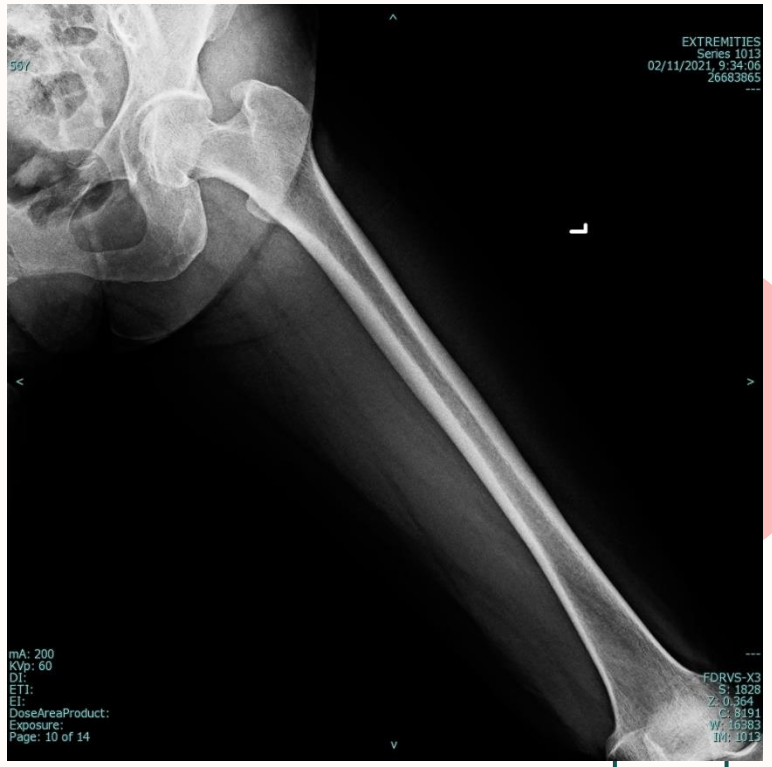






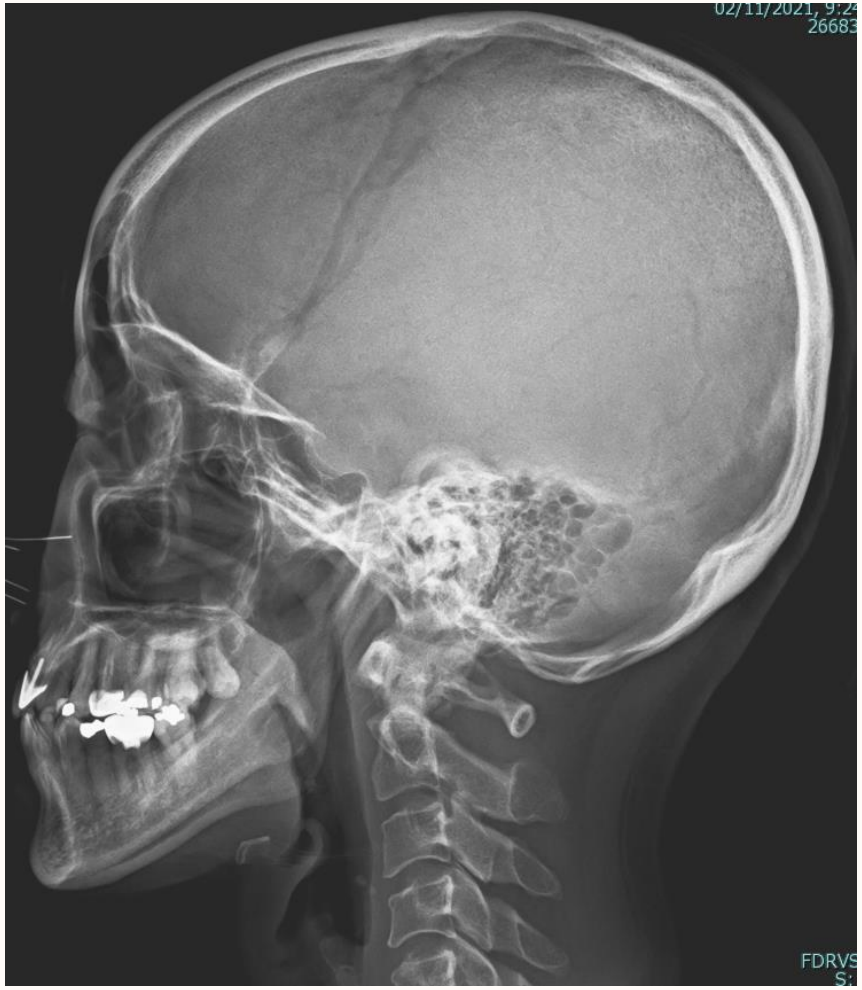
Bone survey 2/11/64





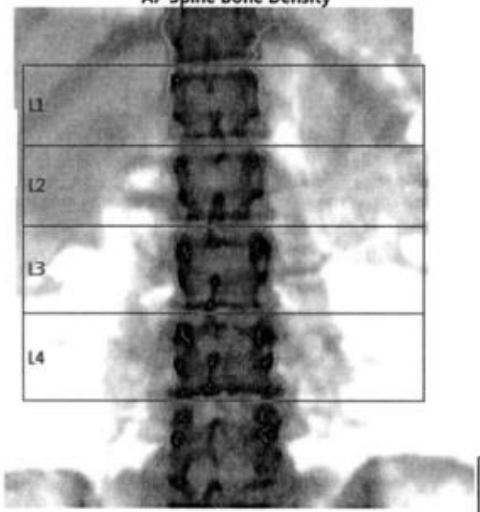
Bone survey 2/11/64

Bone survey 2/11/64



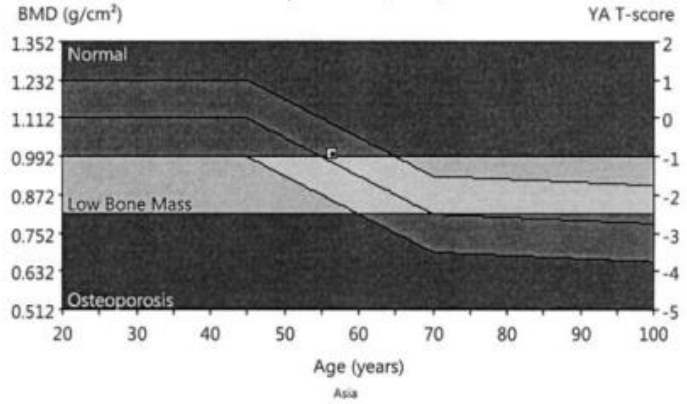
Bone mineral density 16/7/64

AP Spine Bone Density



COMMENTS:

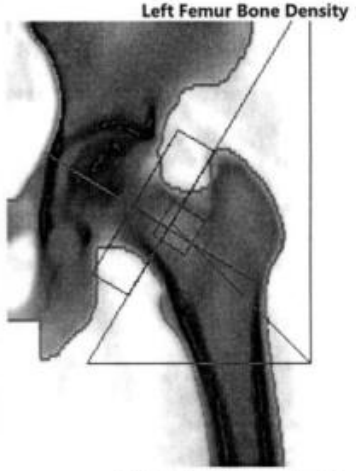
AP Spine: L1-L4 (BMD)



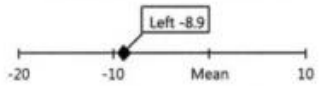
Densitometry: Asia

Region	BMD (g/cm²)	YA (%)	YA T-score	AM (%)	AM Z-score
L1	0.932	89	-1.0	102	0.2
L2	0.898	81	-1.8	92	-0.7
L3	1.041	92	-0.8	104	0.3
L4	1.104	98	-0.2	110	0.8
L1-L2	0.914	85	-1.4	97	-0.2
L1-L3	0.961	87	-1.2	100	0.0
L1-L4	1.003	90	-0.9	103	0.2
L2-L3	0.973	87	-1.3	98	-0.1
L2-L4	1.023	91	-0.9	103	0.3

Left Femur Bone Density

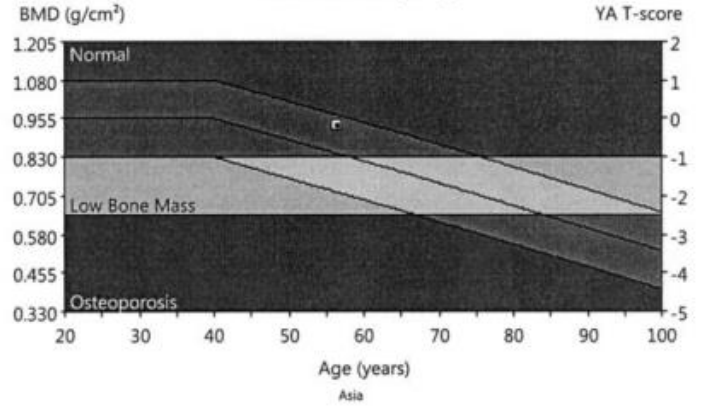


Hip Axis Length Comparison (mm)



Left=92.7 mm Mean=101.6 mm

Left Femur: Total (BMD)

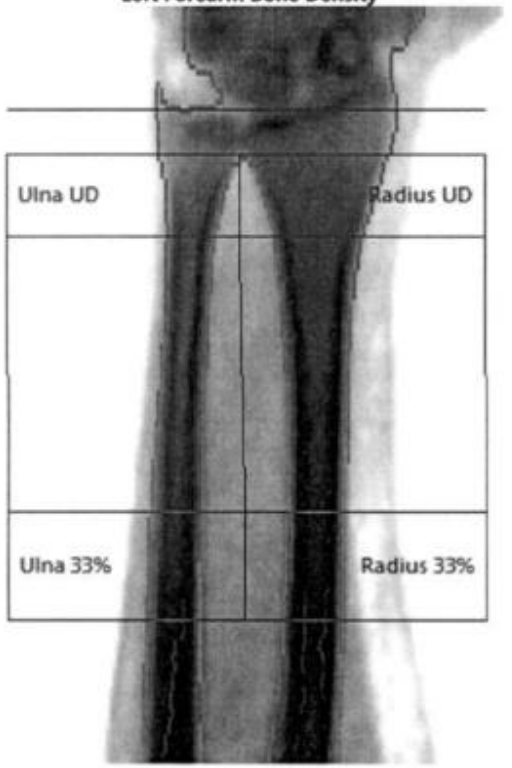


Densitometry: Asia

Region	BMD (g/cm²)	YA (%)	YA T-score	AM (%)	AM Z-score
Neck	0.911	100	0.0	118	1.2
Upper Neck	0.790	-	-	-	-
Lower Neck	1.026	-	-	-	-
Wards	0.647	74	-1.7	98	-0.1
Troch	0.767	102	0.1	112	0.7
Shaft	1.112	-	-	-	-
Total	0.936	98	-0.2	111	0.7

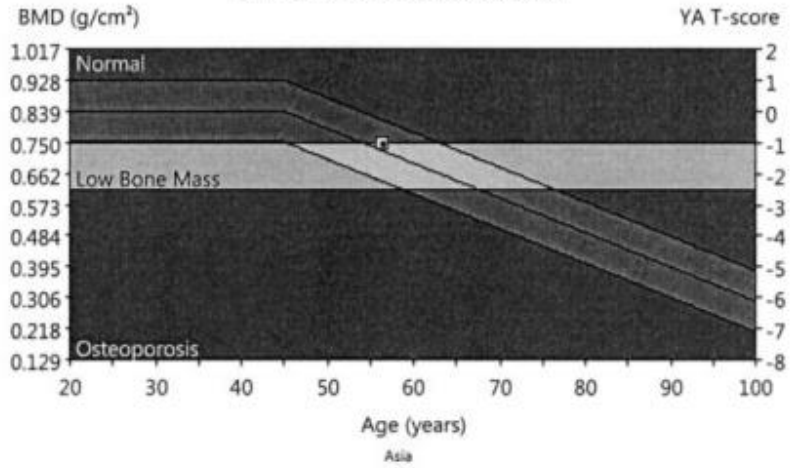
Bone mineral density 16/7/64

Left Forearm Bone Density



COMMENTS:

Left Forearm: Radius 33% (BMD)

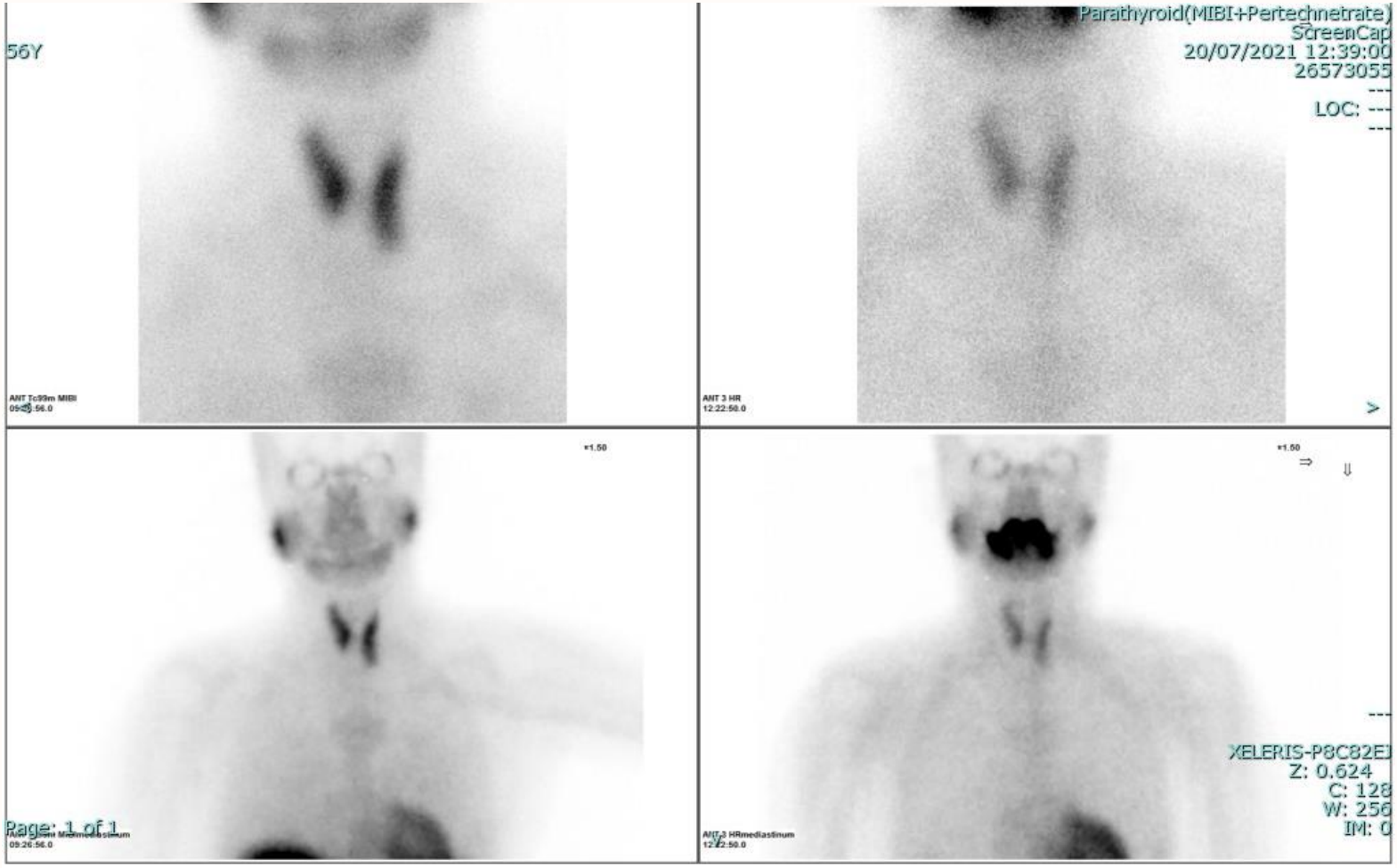


Densitometry: Asia

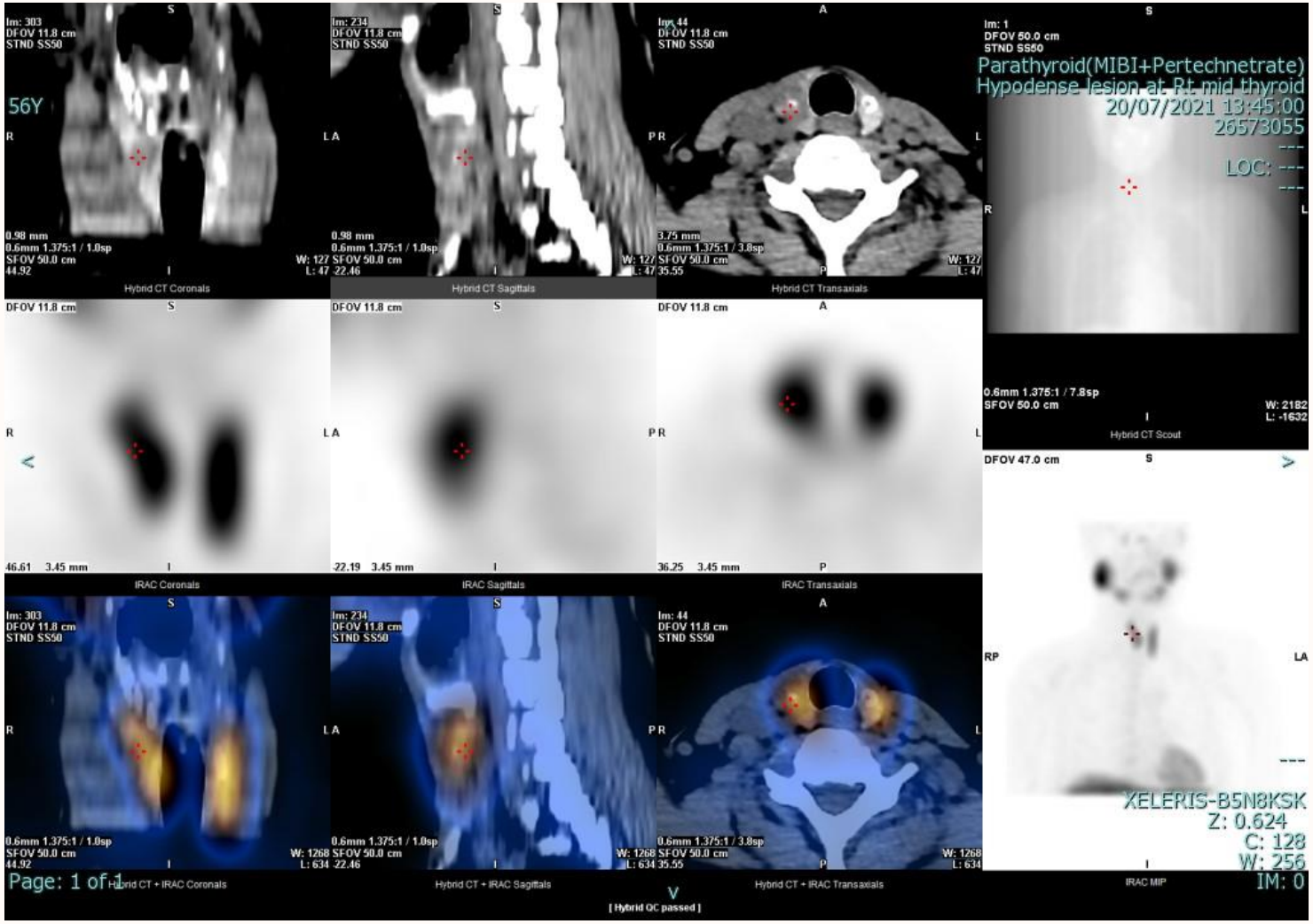
Region	BMD (g/cm²)	YA (%)	YA T-score	AM (%)	AM Z-score
Radius UD	0.417	94	-0.6	108	0.7
Ulna UD	0.320	-	-	-	-
Radius 33%	0.750	89	-1.0	103	0.3
Ulna 33%	0.663	-	-	-	-
Both UD	0.384	-	-	-	-
Both 33%	0.708	-	-	-	-
Radius Total	0.593	91	-0.9	104	0.4
Ulna Total	0.522	-	-	-	-
Both Total	0.564	-	-	-	-

Parathyroid scan 20/7/64

Parathyroid scan 20/7/64



Parathyroid scan 20/7/64



Parathyroid scan 20/7/64

- **Tc-99m pertechnetate** scan reveals inhomogeneous radiotracer uptake of thyroid gland with **focally decreased radiotracer uptake at lateral aspect of mid rt thyroid lobe.**
- **Tc-99m MIBI** scan reveals additional visualization of radiotracer uptake at lateral aspect of mid rt thyroid lobe.
- After **subtraction, there is also focal radiotracer remaining at lateral aspect of mid rt thyroid lobe**, which is possible hyperfunctioning parathyroid tissue.
- **The 3-hour delayed** Tc-99m MIBI images show **rapid washout of radioactivity from the lesion at lateral aspect of rt thyroid** lobe, as compared with the thyroid uptake.
- No other abnormal radiotracer to suggest ectopic parathyroid tissue is detected.
- **The SPECT/ low dose CT** of the neck shows MIBI **uptake in both lobes of thyroid gland associated with well-defined hypodensity lesion, 1.3x1.1 cm with internal calcification in rt thyroid lobe**, which could be either intrathyroidal parathyroid adenoma or thyroid nodule.

>> **Impression: possibly either intrathyroidal parathyroid adenoma or thyroid nodule at lateral aspect of mid right thyroid gland, size about 1.3x1.1 cm with internal calcification.** No evidence of ectopic parathyroid tissue.

24-hour urine calcium

	3-11-64
Serum calcium (mg/dlL	10.9
Urine calcium (mg/dL)	5.5
Urine creatinine (mg/dL)	25.9
Urine volume (mL)	3900
Urine Cr (mg/kg/d)	20.2

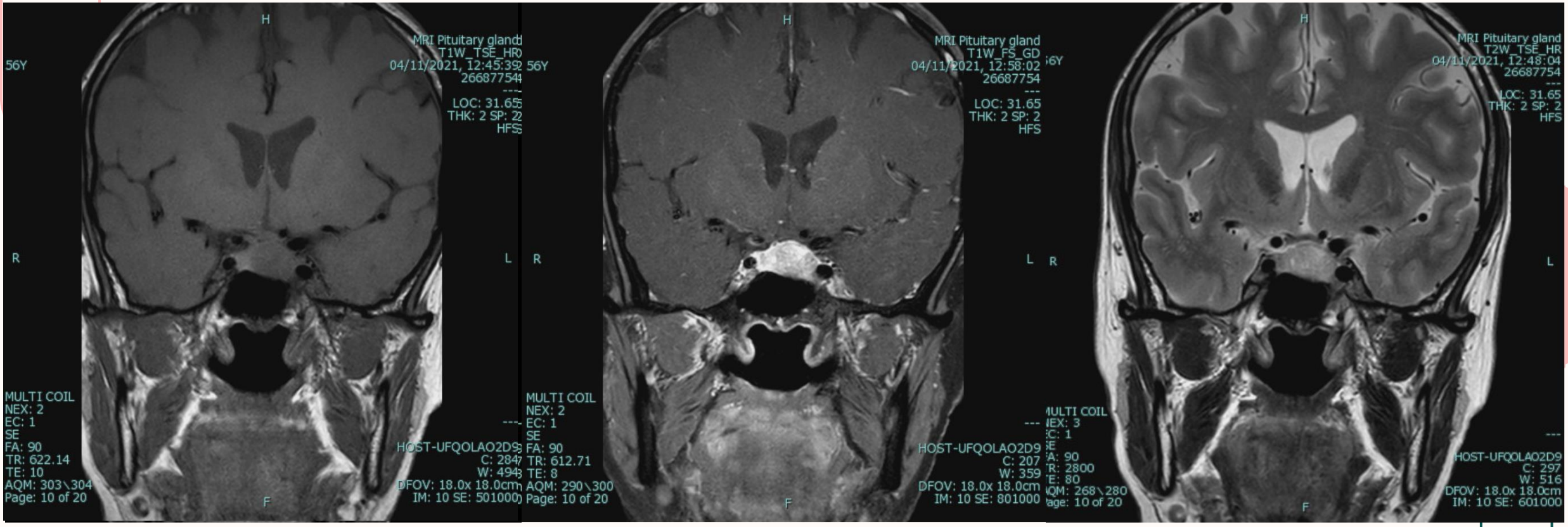
>> Urine calcium = 214.5 mg/day

Urine calcium/creatinine ratio (UCCR)

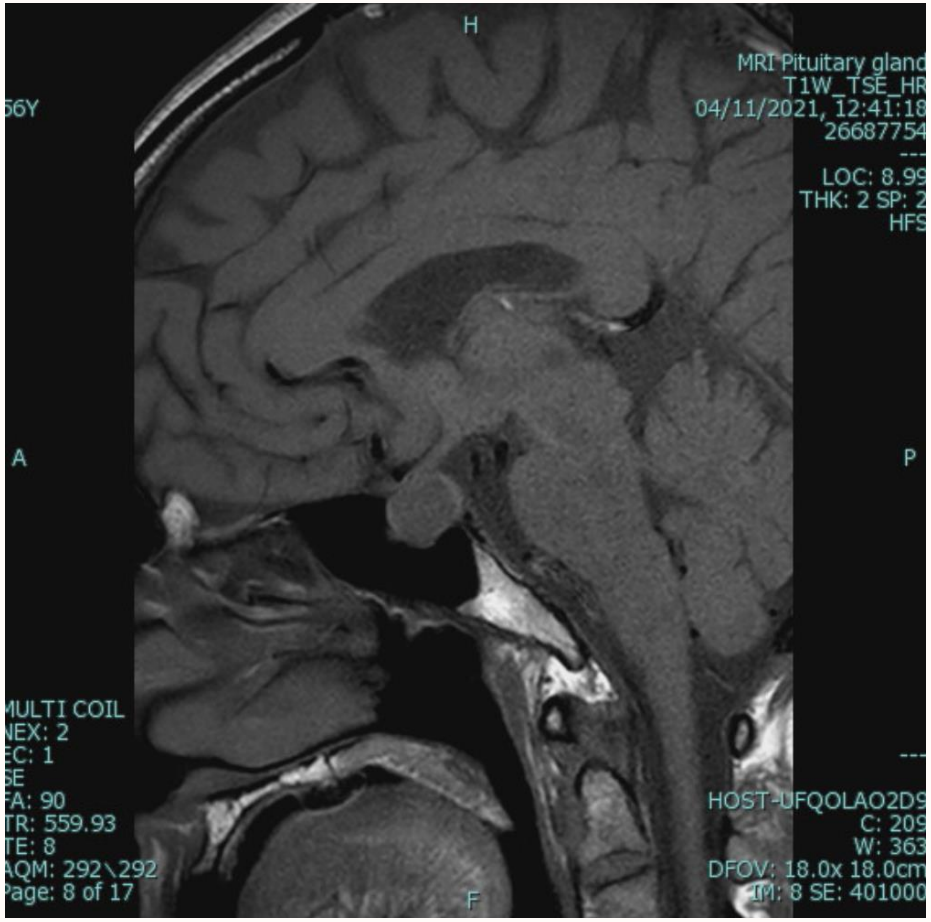
	3-11-64
Serum calcium (mg/dL)	10.9
Serum creatinine (mg/dL)	0.57
Urine calcium (mg/dL)	5.5
Urine creatinine (mg/dL)	25.9
UCCR	**0.0111**

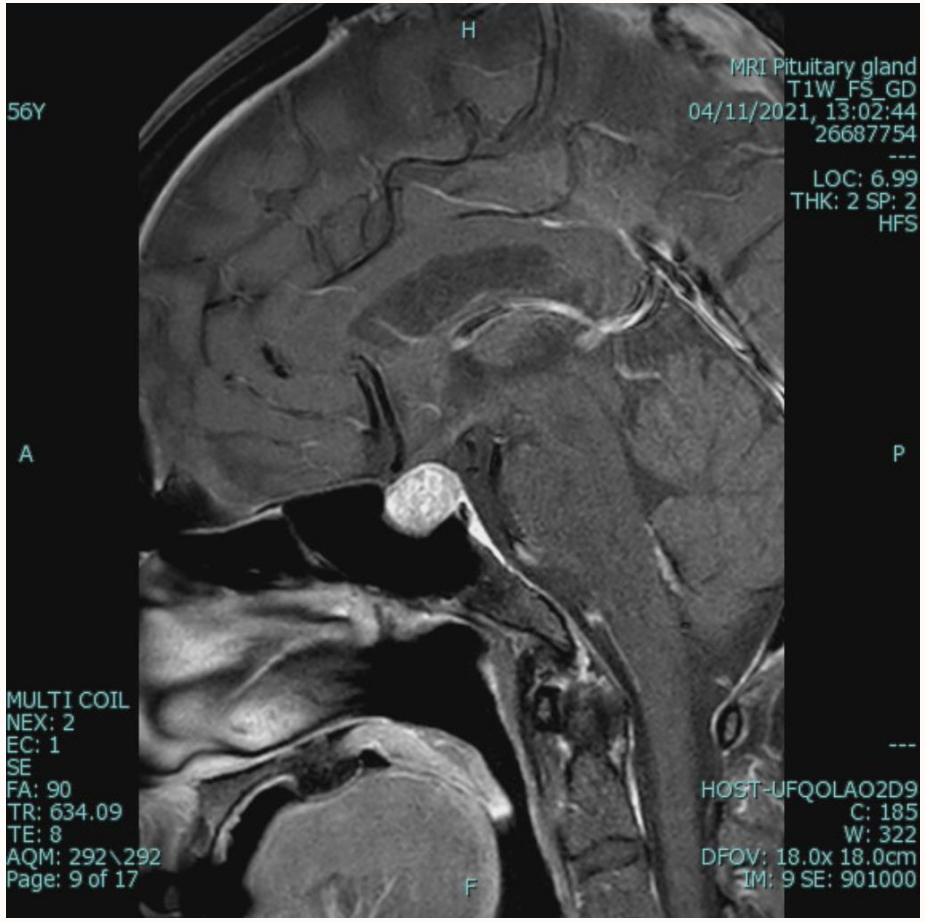
$$\text{UCCR} = \frac{\text{Urine Calcium (mg/dL) x Serum Creatinine (mg/dL)}}{\text{Serum Calcium (mg/dL) x Urine Creatinine (mg/dL)}}$$

MRI pituitary 4/11/64



MRI pituitary 4/11/64





Problem list

Problem list

1. Asymptomatic PTH dependent hypercalcemia
2. Bilateral thyroid nodule
3. Clinically nonfunctioning pituitary macroadenoma
4. Family history of hypercalcemia in first degree relative
5. Vitamin D deficiency

Problem list

1. Asymptomatic PTH dependent hypercalcemia
2. Bilateral thyroid nodule
3. Clinically nonfunctioning pituitary macroadenoma
4. Family history of hypercalcemia in first degree relative
5. Vitamin D deficiency
6. UCCR 0.0111

Discussion and Management

Discussion and Management

Problem 1: Asymptomatic PTH dependent hypercalcemia

Family history of hypercalcemia in first degree relative

Vit D deficiency

- สงสัย Primary hyperparathyroidism DDx MEN1
- แต่เนื่องจากมีประวัติครอบครัวที่สงสัย hypercalcemia ร่วมกับผู้ป่วยมีปัญหาเรื่อง vit D deficiency

  >> replace vitamin D2 (20000) 2 caps weekly

  >> repeat serum Ca, PTH, and urine Ca

Blood chemistry

	26-6-64	11-9-64	3-11-64
Serum Ca (mg/dL)	**11.8**	**11.7**	**10.9**
Serum PO4 (mg/dL)	2.9	2.6	2.5
Serum Cr (mg/dL)	0.52	0.67	0.57
Albumin (g/dL)	4.7	4.7	4.2
PTH (pg/mL)	**97.3**		64.10
25OH vit D (ng/mL)	**12.4**		**21.8**
Urine Ca (mg/dL)			5.5
UCCR			**0.0111**

Familial hypocalciuric hypercalcemia ???

Start Vit D2 (20000) 2 caps weekly

Discussion and Management

Problem 1: Asymptomatic PTH dependent hypercalcemia

Family history of hypercalcemia in first degree relative

Vit D deficiency

UCCR 0.0111

- สงสัย **Familial hypocalciuric hypercalcemia (FHH)**

  >> replace vitamin D2 (20000) 2 caps weekly

  >> repeat urine Ca

- Review PTH scan: นึกถึง thyroid nodule > parathyroid adenoma

High Ca

Normal PO4

Minimal increase PTH

Family history

UCCR 0.0111

No end organ damage

Blood chemistry

	26-6-64	11-9-64	3-11-64	9-11-64
Serum Ca (mg/dL)	**11.8**	**11.7**	**10.9**	**11.6**
Serum PO4 (mg/dL)	2.9	2.6	2.5	3.0
Serum Cr (mg/dL)	0.52	0.67	0.57	- (0.57)
Albumin (g/dL)	4.7	4.7	4.2	4.6
PTH (pg/mL)	**97.3**		64.10	
25OH vit D (ng/mL)	**12.4**		**21.8**	
Urine Ca (mg/dl)			5.5	8.3
UCCR			**0.0111**	**0.0106**

Start Vit D2 (20000) 2 caps weekly

FHH ?

Discussion and Management

Problem 1: Asymptomatic PTH dependent hypercalcemia

Family history of hypercalcemia in first degree relative

Vit D deficiency

UCCR 0.0111

- สงสัย Familial hypocalciuric hypercalcemia (FHH)

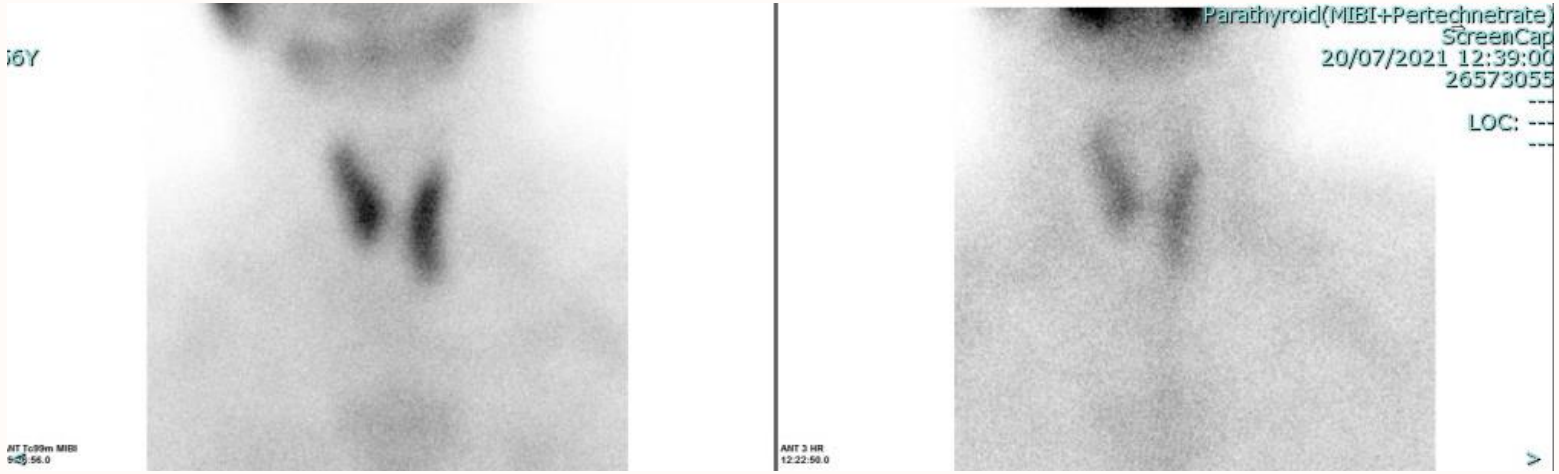
  >> replace vitamin D2 (20000) 2 caps weekly

  >> repeat urine Ca

- **Review PTH scan**

Parathyroid scan 20/7/64

Parathyroid scan 20/7/64



Discussion and Management

Problem 1: Asymptomatic PTH dependent hypercalcemia

Family history of hypercalcemia in first degree relative

Vit D deficiency

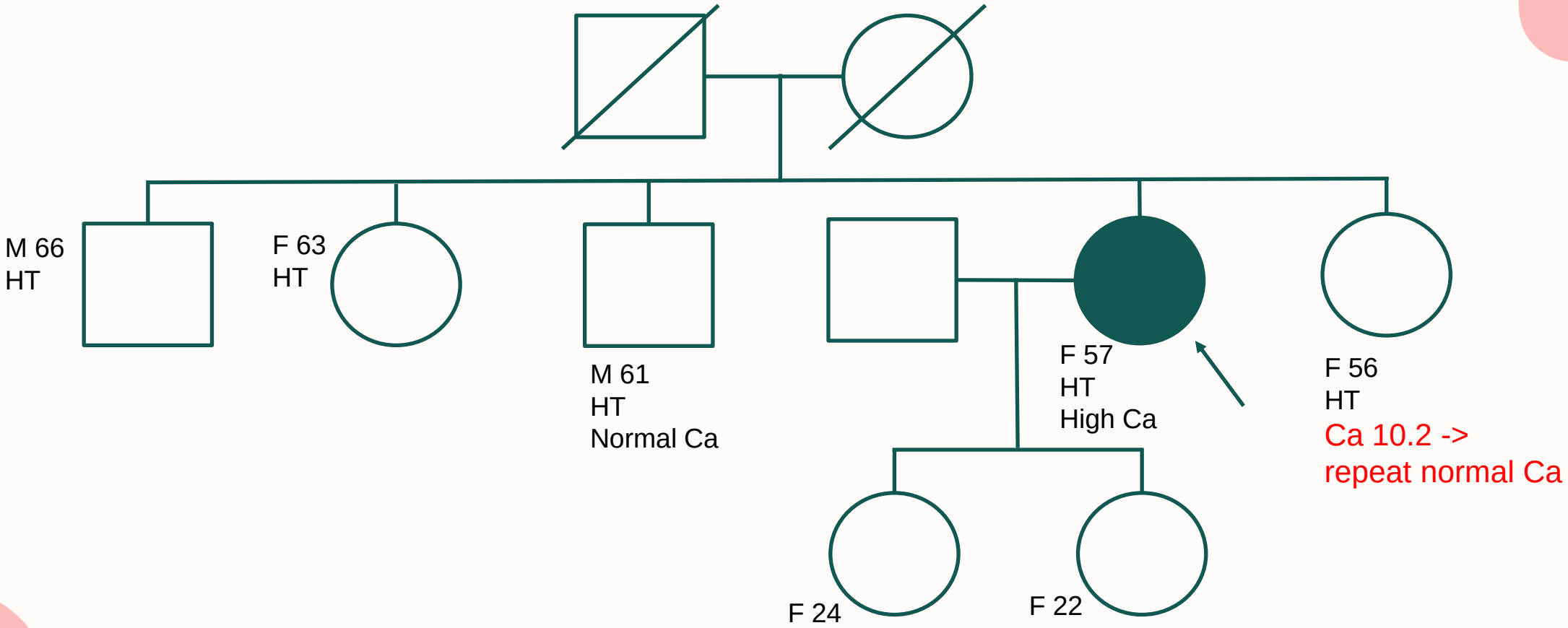
UCCR 0.0111

- สงสัย Familial hypocalciuric hypercalcemia (FHH)

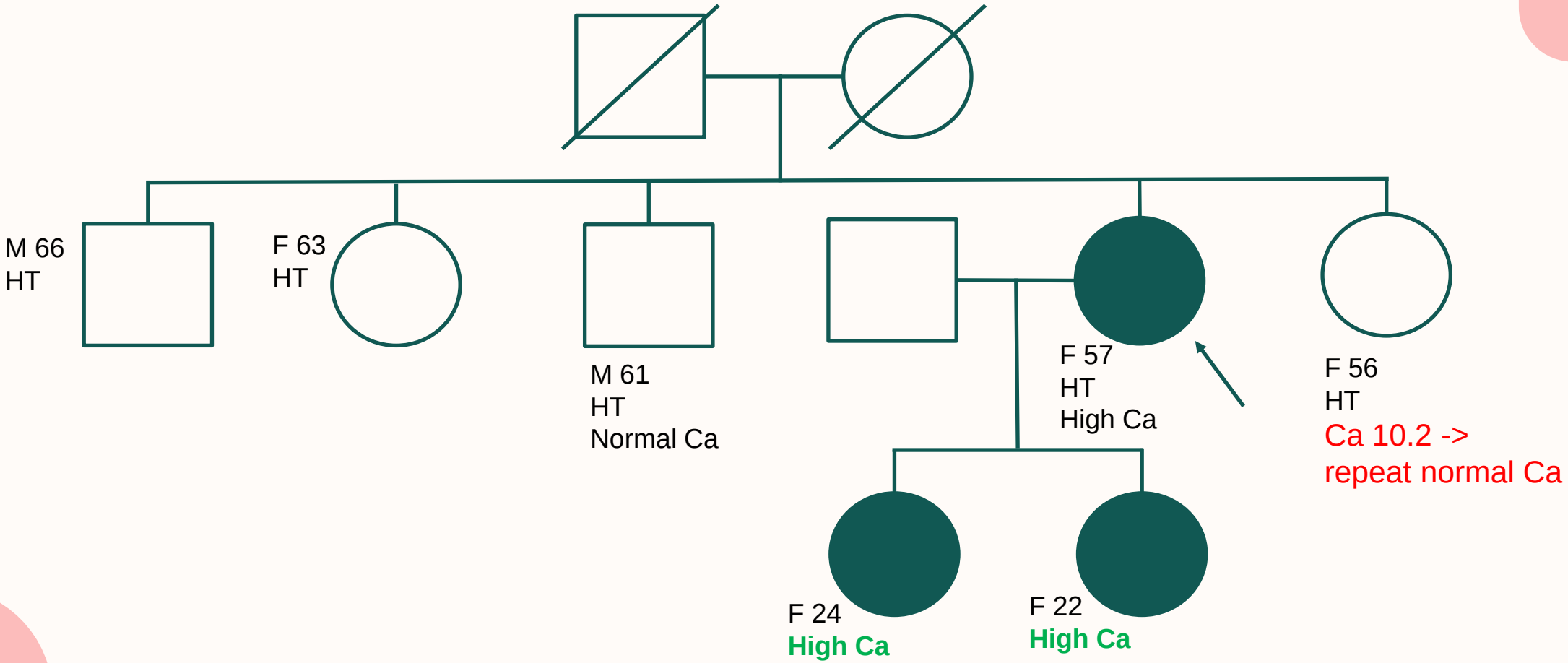
  >> replace vitamin D2 (20000) 2 caps weekly

  >> repeat urine Ca
- Review PTH scan: นึกถึง thyroid nodule > parathyroid adenoma
- **ส่ง genetic for FHH**

Pedigree

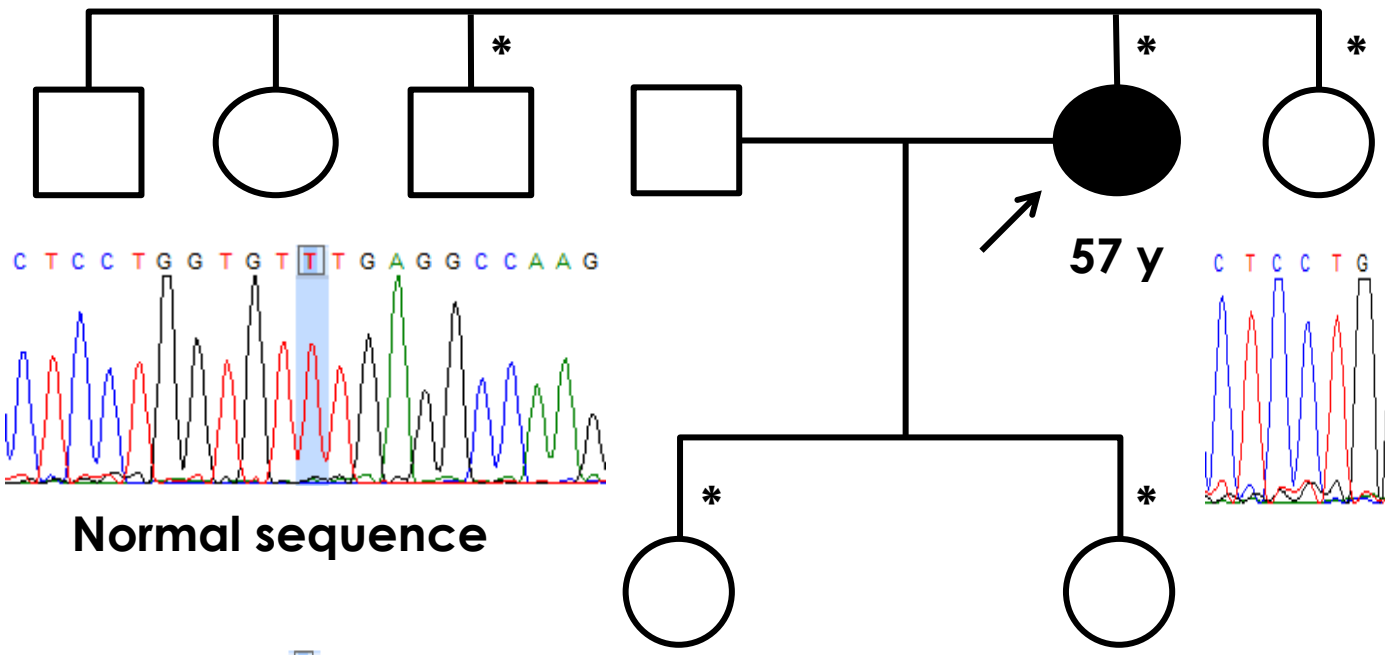

M 66
HT
F 63
HT
M 61
HT
Normal Ca
F 57
HT
High Ca
F 56
HT
Ca 10.2 ->
repeat normal Ca
F 24
F 22

Pedigree


M 66
HT
F 63
HT
M 61
HT
Normal Ca
F 57
HT
High Ca
F 56
HT
Ca 10.2 ->
repeat normal Ca
F 24
High Ca
F 22
High Ca

Mutation

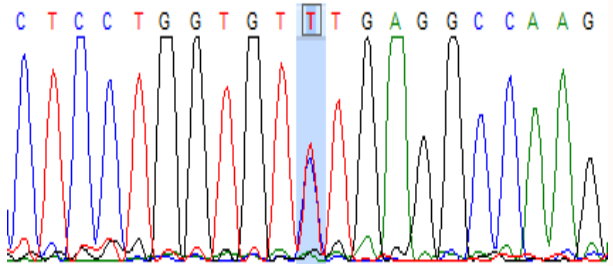
Pedigree

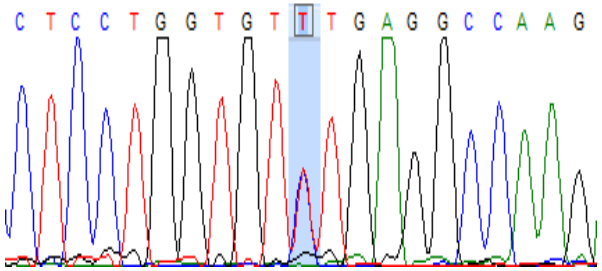


c.2147T>C
p.Phe716Ser
Heterozygous
Exon 7

57 y

Normal sequence

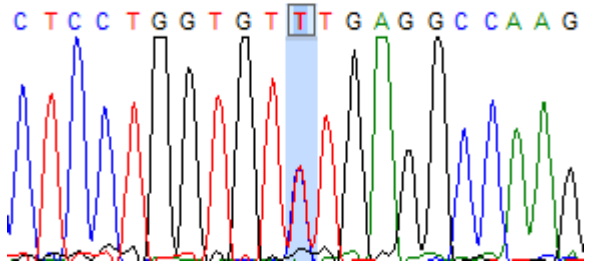




Same mutation

24 y
High Ca

22 y
High Ca



Same mutation

Interhospital Conference

24 March 2023

Assoc.Prof. Boonchai Boonyawat M.D.
Division of Medical Genetics
Department of Pediatrics
Phramongkutklao Hospital/College of Medicine

Familial Hypocalciuric Hypercalcemia (FHH)

FHH Type I (50%)

* autosomal dominant
* **calcium sensing receptor *(CASR)*** inactivating mutation

3q13.3-q21.1 (7 exon)

FHH Type 2 (10%)

* autosomal dominant
* **G-protein subunit alpha 11 *(GNA11)*** mutation

19p13.3 (7 exon)

FHH Type 3 (20%)

* autosomal dominant
* **adaptor related protein complex 2 subunit sigma 1 *(AP2S1)*** mutation

19q13.3 (6 exon)

Unknown genes (20%)

Molecular Genetic Testing

Single Gene Testing

: Distinctive clinical features clearly point to a specific gene

: Minimal locus heterogeneity

: Limitation of NGS technology to detect

e.g. trinucleotide repeat
epigenetic abnormalities

"Phenotype First"

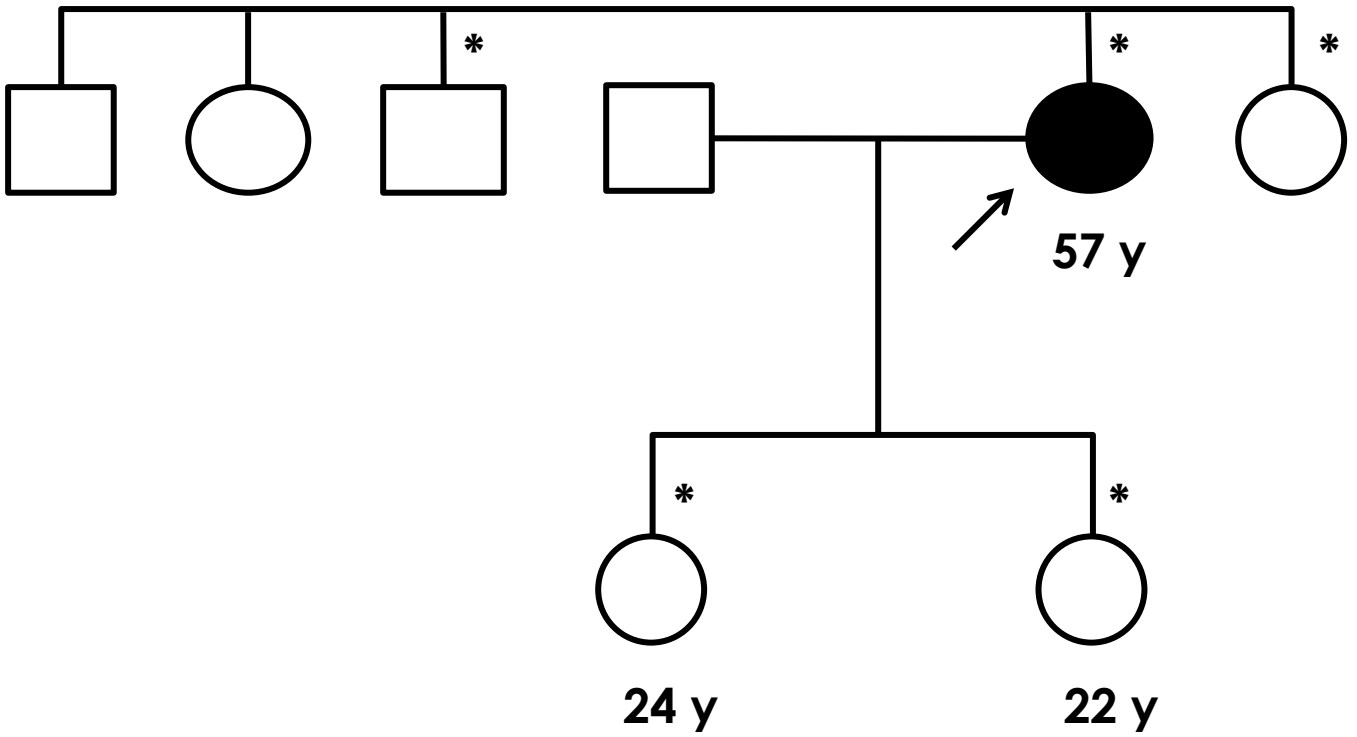
Molecular Genetic Testing

"Phenotype First"

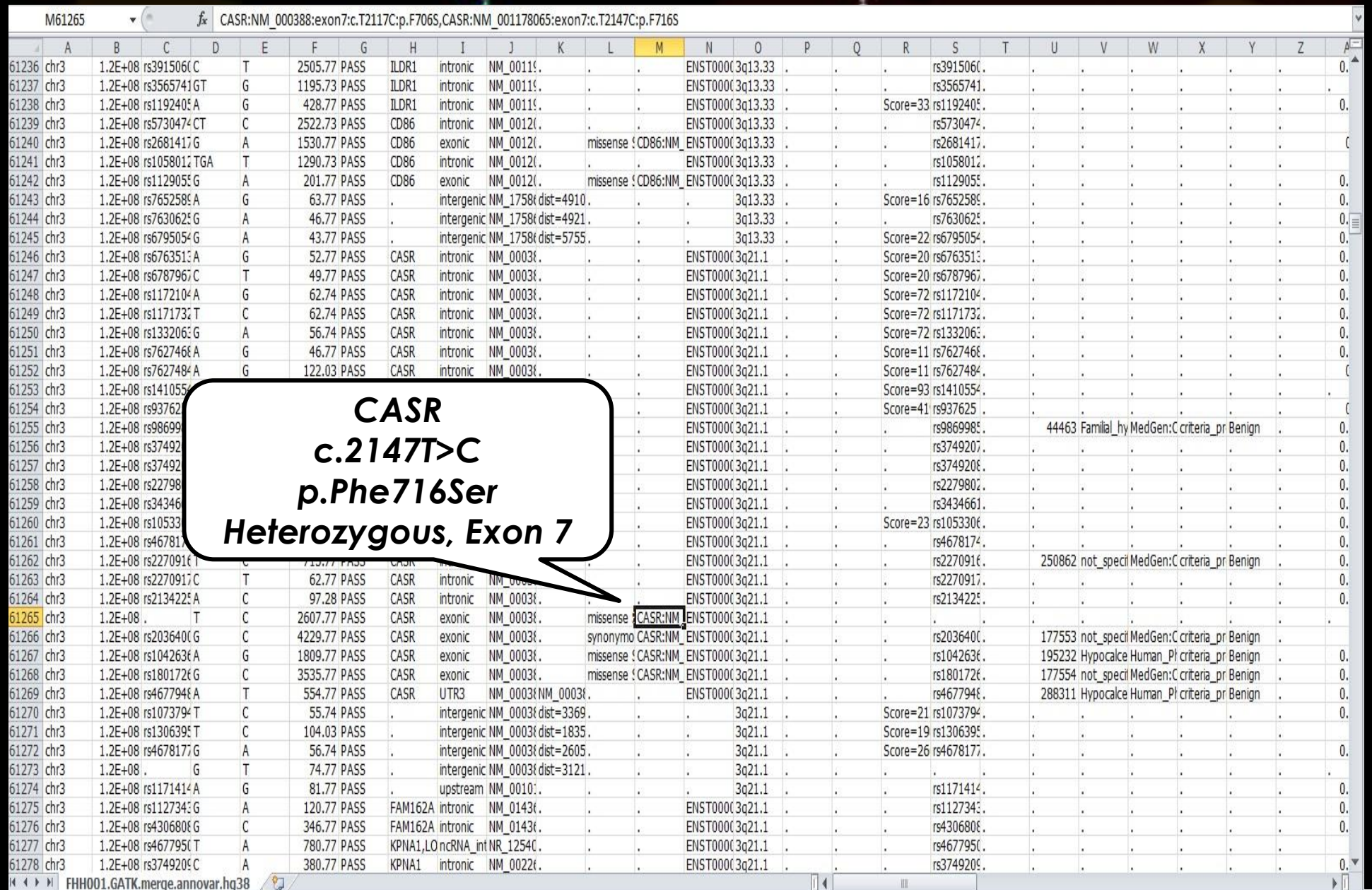
"Genotype First"

Case

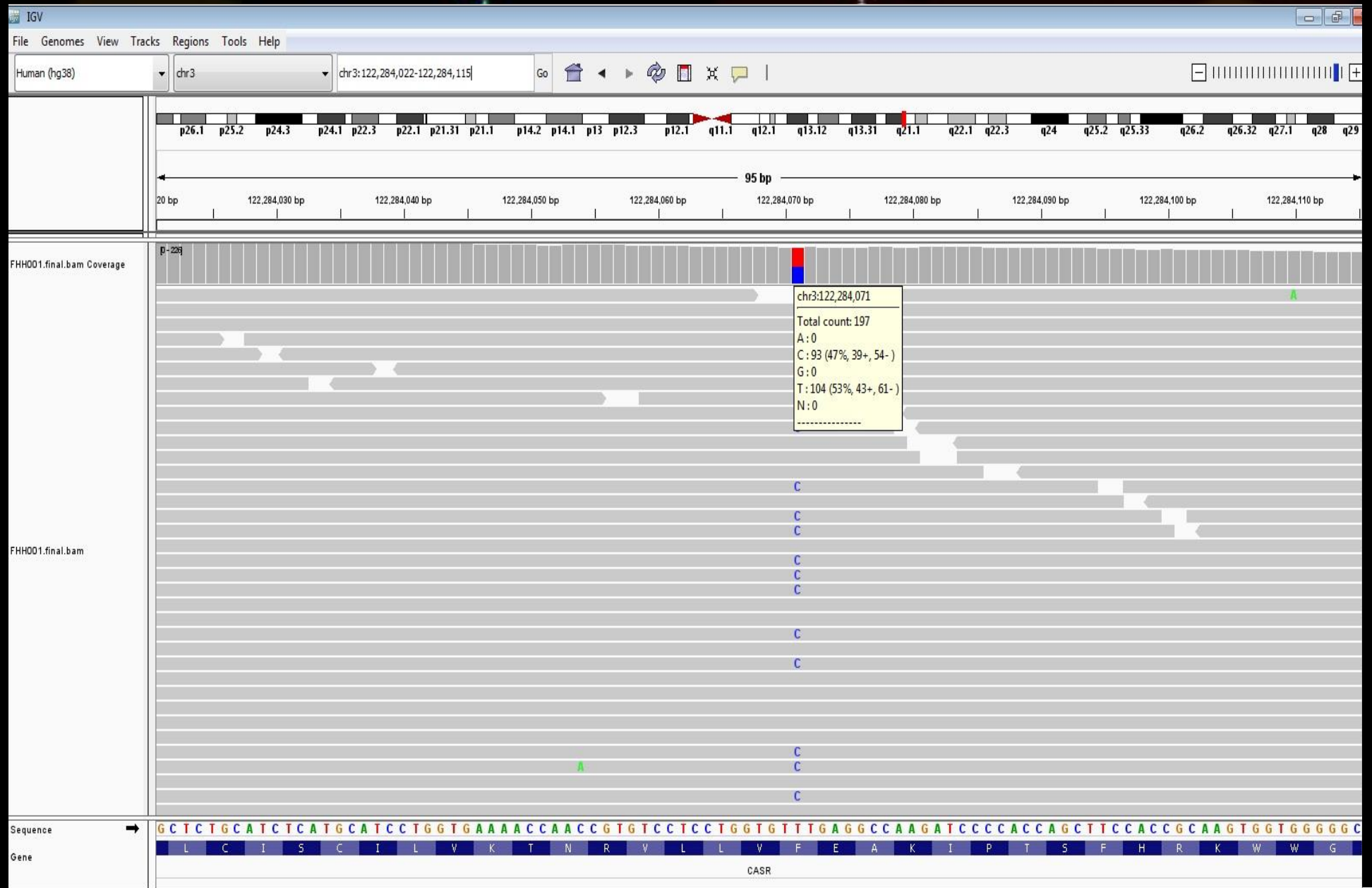
Pedigree



Case

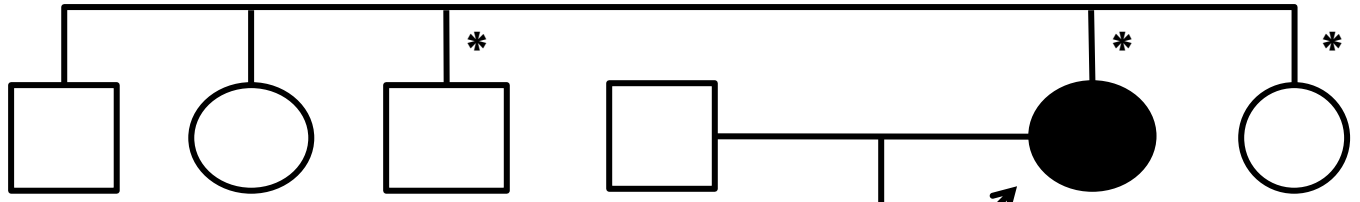


Case

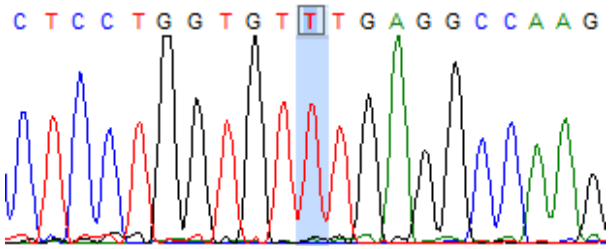

IGV
File Genomes View Tracks Regions Tools Help
Human (hg38)
chr3
chr3:122,284,022-122,284,115
Go
95 bp
FHH001.final.bam Coverage
FHH001.final.bam
chr3:122,284,071
Total count: 197
A : 0
C : 93 (47%, 39+, 54-)
G : 0
T : 104 (53%, 43+, 61-)
N : 0
Sequence
Gene
CASR

Case

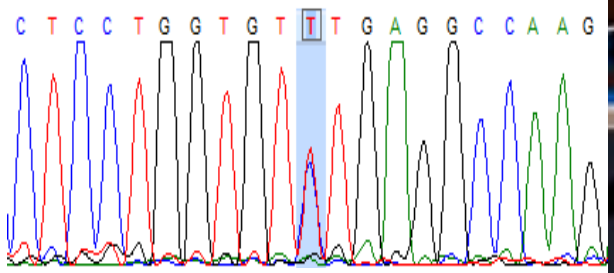
Pedigree

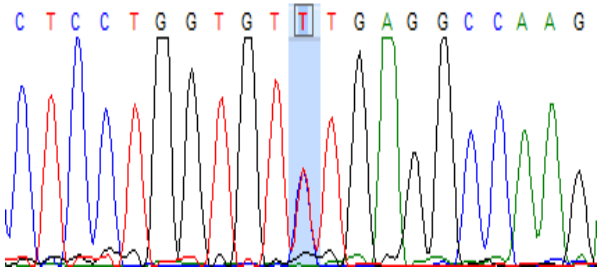


c.2147T>C
p.Phe716Ser
Heterozygous
Exon 7

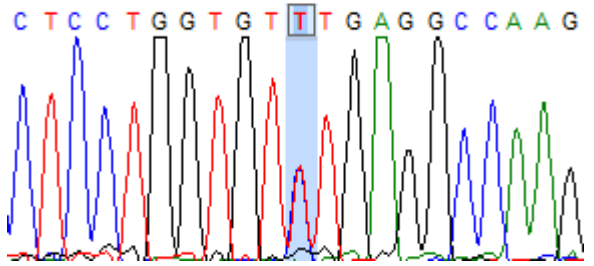


Normal sequence





Same mutation



Same mutation

Case

Variant Classificaition	**c.2147T>C (p.Phe716Ser) in exon 7 of *CASR* gene**
Mutation & Population Databases : Human Gene Mutation Database (HGMD) **:** National Center for Biotechnology Information (NCBI): dbSNP and ClinVar : Exome Aggregation Consortium (ExAC) and 1000 Genomes Project	**Not identified (PM2)**
Computation (In silico) analysis **e.g. : Mutation Taster** **: Polyphen 2** **: SIFT**	**(PP3)** **Disease causing** **Probably damaging** **Damaging**
Familial Segregation	**Positive (PP1)**
Missense variant in a gene that has a low rate of benign variation in which missense variants are a common mechanism of disease	**Yes (PP2)**
ACMG Classification (2015)	**Likely Pathogenic (PM2, PP1, PP2, PP3)**

Case

What is the next step?

: Extended family studies

: Function studies if available

Discussion and Management

Problem 2: Bilateral thyroid nodule (Rt-AUS, Lt-Unsat)

- Repeat ultrasound thyroid and FNA 23/8/65
  - **Rt thyroid lobe:**

    M1: 1.1 x 1 cm irregular shape, taller than wide hypoechoic nodule with internal microcalcification

    FNA: **Atypia of undetermined (AUS)**
  - **Lt thyroid lobe:**

    M2: 0.8 cm dense calcified nodule at mid pole

    FNA: **Unsatisfactory for evaluation**

Total thyroidectomy with NIM 10/11/65

Patho:

- **Papillary thyroid carcinoma**
- Angiolymphatic invasion: present
- Perineural invasion: present
- Extrathyroidal extension: **microscopic perithyroidal extension** only
- Margin positive at anterior capsule

>> **I-131 ablation**

Discussion and Management

Problem 3: Clinically nonfunctioning pituitary macroadenoma

- **Hormonal assessment:**

  IGF-1 173.0 ng/mL (42.3-214)

  8AM cortisol 13.5 µg/dL

  FT4 1.70 ng/dL (0.93-1.71) , TSH 1.24 µIU/mL (0.27-4.2)

  FSH 99.40 mIU/mL (menopause)

  Prolactin 14.10 ng/mL

  Na 139 mmol/L

- Consult eye (18/11/64): VA Lt 6/9.5-1, Rt 6/12, normal VF
- F/U MRI pituitary 23/6/65: No significant change in size of pituitary macroadenoma (1.6x1.2x1.2 cm)
- Consult eye (9/8/65): VA Lt 6/7.5-1, Rt 6/12, normal VF

Diagnosis

1. Familial hypocalciuric hypercalcemia (new mutation)
2. Papillary thyroid cancer
3. Clinically nonfunctioning pituitary macroadenoma

SIENDO
Faculty of Medicine Siriraj Hospital

Thank you