Another case of proximal muscle weakness

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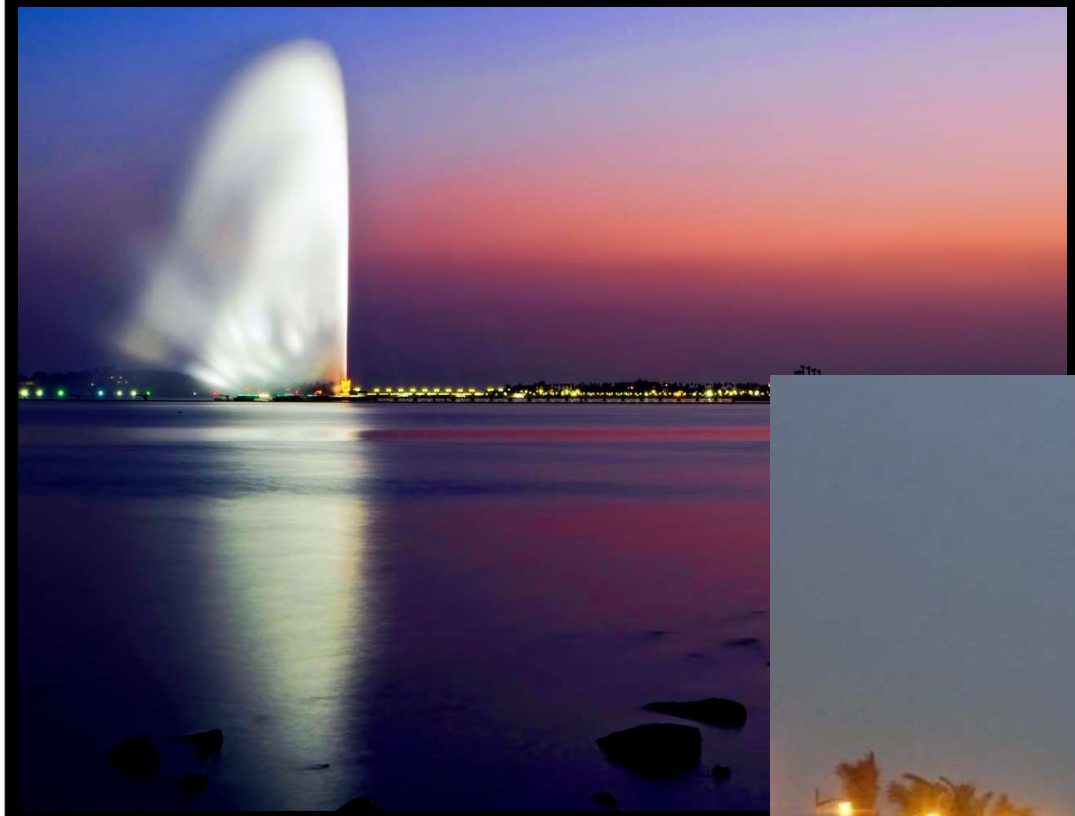
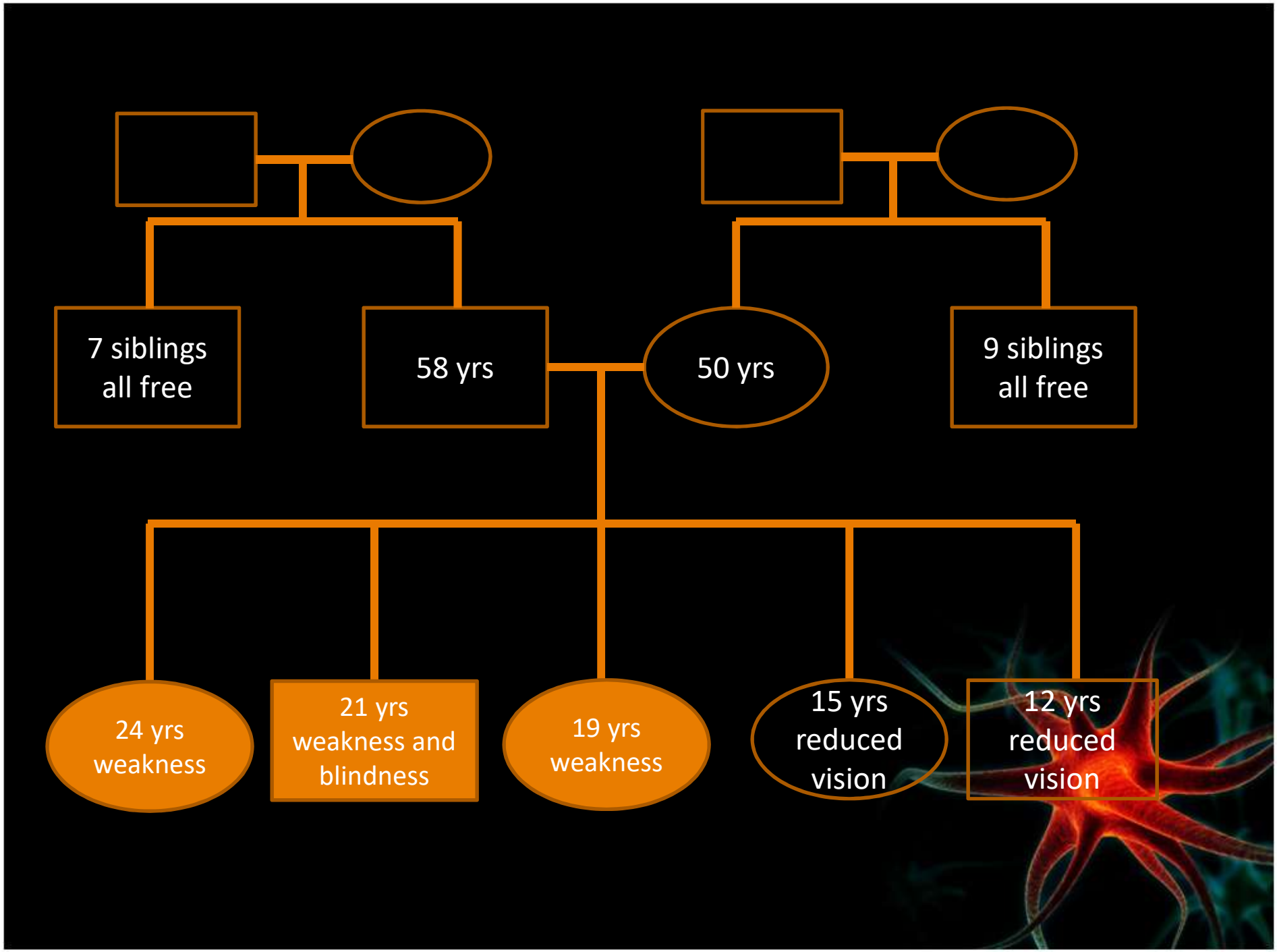
Jeddah Fountain: the tallest



History

- 19 year old woman
- C/O: Gradually progressive generalized weakness for 3 to 4 years
- Difficulty
  - standing from chairs and climbing stairs
    - now she cannot stand up from floor
  - Placing things over the shoulder level
- Trips over her feet occasionally
- Need to repeat her self to be understood
- No sensory symptoms
- No Dysphagia, no diplopia, no seizures and no cognitive dysfunction.

- Family History:
- First degree consanguinity.


7 siblings
all free
58 yrs
50 yrs
9 siblings
all free
24 yrs
weakness
21 yrs
weakness and
blindness
19 yrs
weakness
15 yrs
reduced
vision
12 yrs
reduced
vision

Examination

- Oculi 5-
- Buccal 4
- NF 5
- NE 5
- Tone: normal, no fasciculation or atrophy

- Reflexes:
- Bilateral Biceps, triceps and brachioradialis: 3.
- Bilateral Knees jerks: 3.
- Bilateral ankles jerks: 3.

- Planter response: upgoing plantar bilaterally

	Right	Left
Detoid	4-	4-
Biceps	4	4
Triceps	4-	4-
WE	4	4-
EDC	4-	4-
FDI	4-	4-
FRP	4-	4-

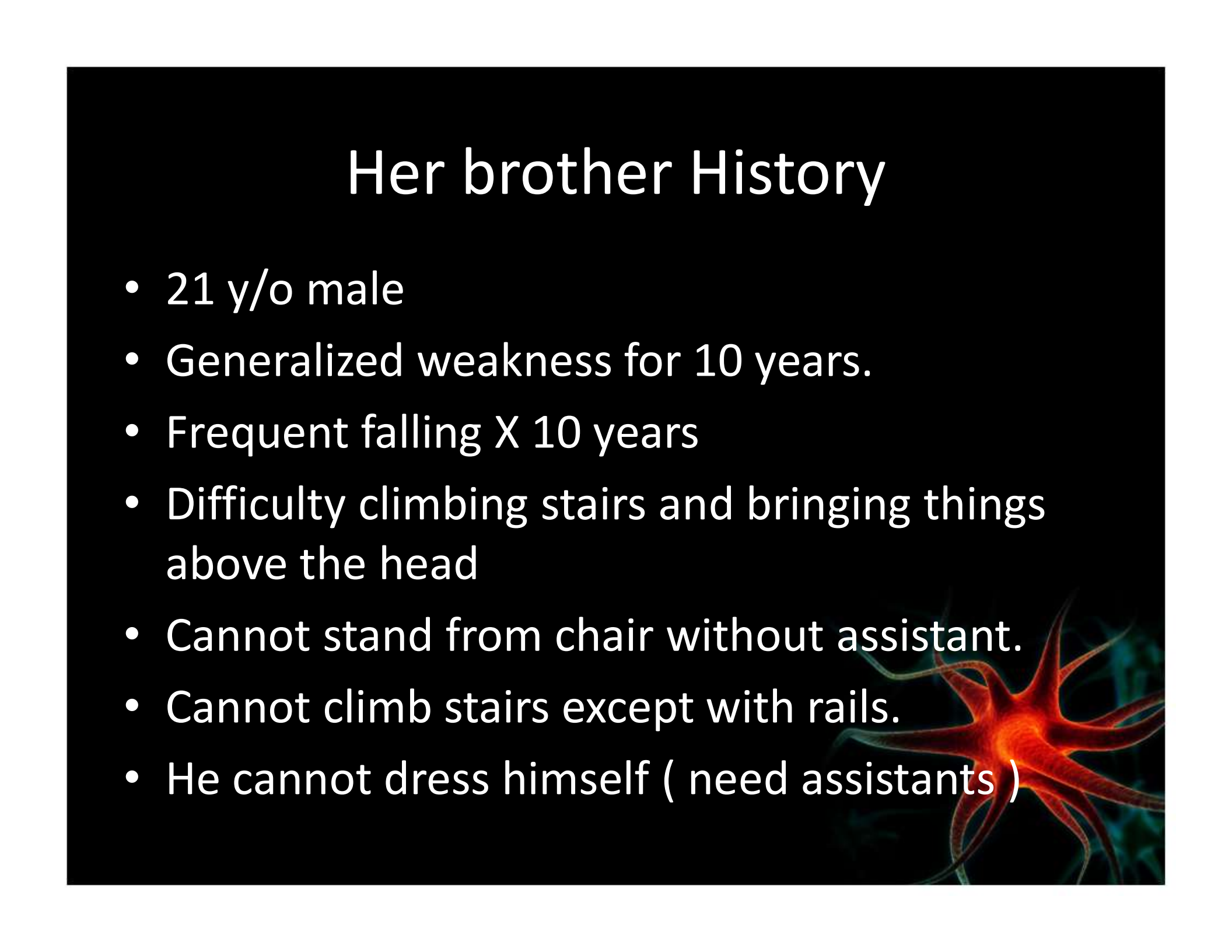
Hip Flex	**3**	**3**
Knee Flex	4	4
Knee Ext	5	5
Ankle DF	4-	4-
Ankle PF	5	5

- Pinprick:
  - Fore head 100%
  - Big toe: Right 100 % Left 100 %
  - Ankle: Right 100 % Left 100 %
  - below knees: Right 40 % Left 40 %

- Gait: waddling

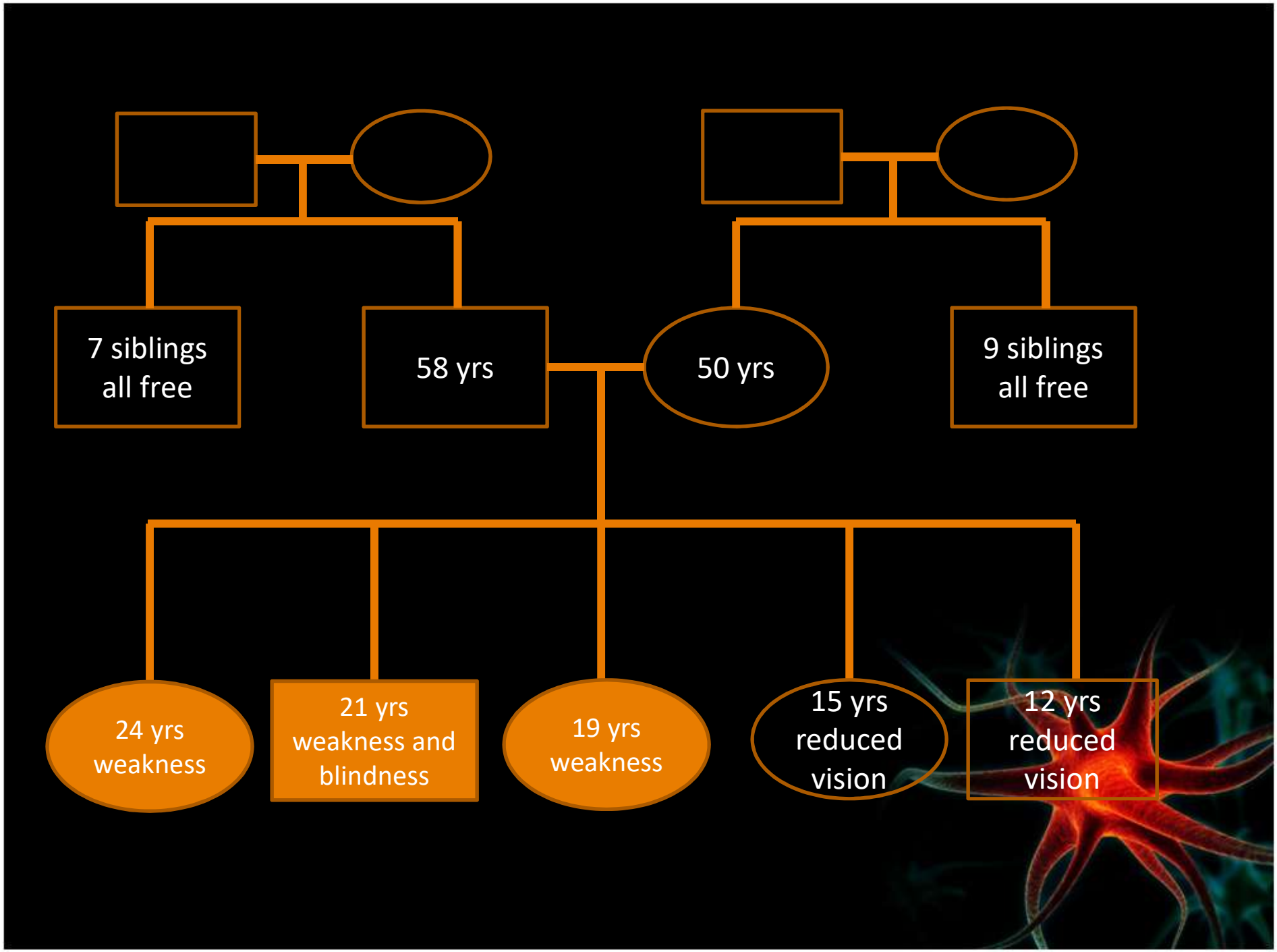
Her brother History

- 21 y/o male
- Generalized weakness for 10 years.
- Frequent falling X 10 years
- Difficulty climbing stairs and bringing things above the head
- Cannot stand from chair without assistant.
- Cannot climb stairs except with rails.
- He cannot dress himself (need assistants)



- Mild slurred speech
- No dysphagia
- Blurred vision and diagnosed with retinal diseases
- No seizures , double vision
- No cognitive dysfunction,
- Law student at KAU.

- Family History:
- First degree consanguinity.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weakness
15 yrs
reduced
vision
12 yrs
reduced
vision

Examination

- Oculi 4
- Buccal 4

- Tone:
- upper limb: normal
- lower limb: increase
- No fasciculation or atrophy

- Reflexes:
- Bilateral Biceps, triceps and brachioradialis: 0.
- Bilateral Knees jerks: 4.
- Bilateral ankles jerks: 3.

- Planter response: upgoing plantar bilaterally

	Right	Left
Detoid	3	3
Biceps	3	3
Triceps	3+	3+
WE	-3	-3
EDC	-3	-3
FDI	3	3
FRP	3	3

Hip Flex	**2**	**2**
Knee Flex	4	4
Knee Ext	5	5
Ankle DF	3	3
Ankle PF	5	5

Exam…cont

- Pinprick:
  - Fore head 90%
  - Median distribution: Right 60 % Left 60 %
  - Ulnar distribution: Right 60 % Left 60 %
  - Big toe: Right 40 % Left 40 %
  - below knees: Right 60% Left 60 %
- Vibration:
  - hand: 7.5 RS bilaterally
  - big toe: 5.5 bilaterally
- Proprioception: normal

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

Differential diagnosis

- Mitochondrial myopathies (POLG Kearns Sayre, MELAS, MERFF)
- Leukodystrophy (Refsum's disease, … etc)
- Hereditary motor and sensory neuropathy particularly type V.

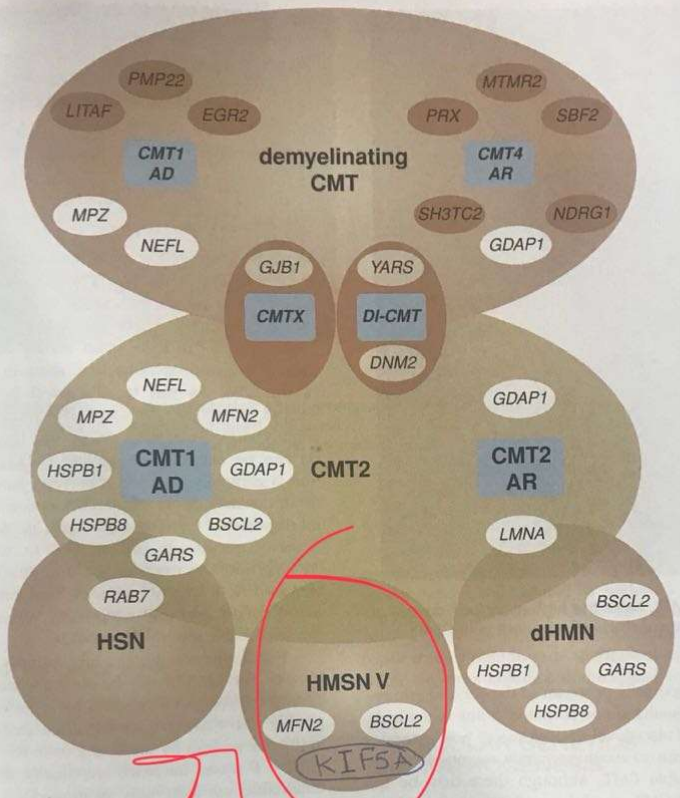
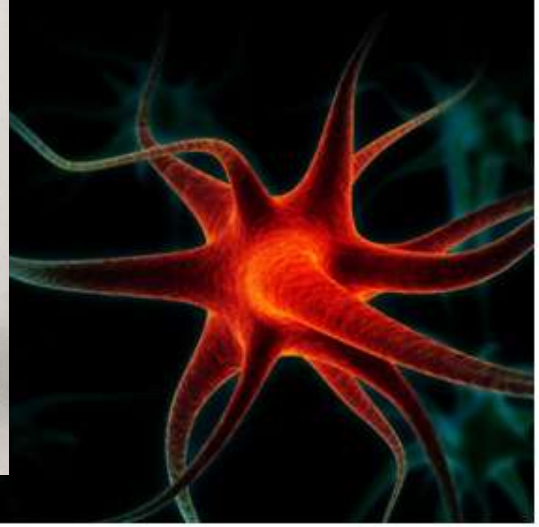


Figure 9–1. The various types of Charcot–Marie–Tooth disease and their areas of overlap. Identified causative genes are also shown. Diseases: CMT, Charcot–Marie–Tooth disease (CMT1, demyelinating, autosomal dominant; CMT2, axonal, autosomal dominant or recessive; CMT4, demyelinating, autosomal recessive; CMTX, X-linked; DI-CMT, dominant intermediate); dHMN, distal hereditary motor neuropathies; HSN, hereditary sensory neuropathies; HMSN V, hereditary motor and sensory neuropathy V (CMT with pyramidal involvement). Inheritance: AD, autosomal dominant; AR, autosomal recessive. Genes: BSCL2, Berardinelli–Seip congenital lipodystrophy type 2; DNM2, dynamin 2; EGR2, early-growth response 2; GARS, glycyl-tRNA synthetase; GDAP1, ganglioside-induced differentiation-associated protein 1; GJB1, gap junction B1/connexin-32; HSPB1 (or HSP27), heat-shock 27-kDa protein 1; HSPB8 (or HSP22), heat-shock 22-kDa protein 8; LITAF, lipopolysaccharide-induced tumor necrosis factor-alpha factor; LMNA, lamin A/C nuclear envelope protein; MFN2, mitofusin 2; MTMR2, myotubularin-related protein 2; SBF2, SET binding factor 2; SH3TC2, SH3 domain and tetratricopeptide repeat domain 2; NDRG1, N-myc downstream-regulated gene 1; NEFL, neurofilament light chain; MPZ, myelin protein zero; PMP-22, peripheral myelin protein-22; PRX, periaxin; RAB7, small GTPase late endosomal protein RAB7; YARS, tyrosyl-tRNA synthetase. (With permission from Pareyson D. Axonal Charcot–Marie–Tooth disease: The fog is only slowly lifting. Neurology 2007;68:1649–1650, Fig. 1, p. 1650.)



The girl's Motor NCS

MNCS								
Nerve	Lat	Amp					CV	F-M Lat
	ms	Amp (mV)	Area (ms*mV)	Area (%)	Duration (ms)	Dur (%)	m/s	ms
Axillaris Motor Right								
Erb's - Deltoid	--	--	--		--			
Medianus Motor Right								
Wrist - APB	--	--	--		--			
Elbow-Wrist	--	--	--	--	--	--	--	
Peroneal TA Motor Right								
Distal FH - Tib. ant	2.87	1.81	5.9		6.3			
Prox FH-Distal FH	4.50	1.62	4.1	-30.5	6.3	0	61.3	
Peroneus Motor Right								
Ankle - EDB	5.01	**0.95**	4.1		7.6			
Distal FH-Ankle	12.0	0.36	1.70	-58.5	7.2	-5.3	42.9	
Prox FH-Distal FH	44.9	0.24	0.35	-79.4	4.5	-37.5	--	
Radial Motor Right								
Forearm - EIP	--	--	--		--			
Tibialis Motor Right								
Med. mal - Abd hal	5.34	**4.0**	9.2		5.6			43.7
Pop Fossa-Med. mal	12.9	1.22	1.86	-79.8	6.8	21.4	51.6	
Ulnaris Motor Right								
Wrist - ADM	--	--	--		--			
Bl. elbow-Wrist	--	--	--	--	--	--	--	

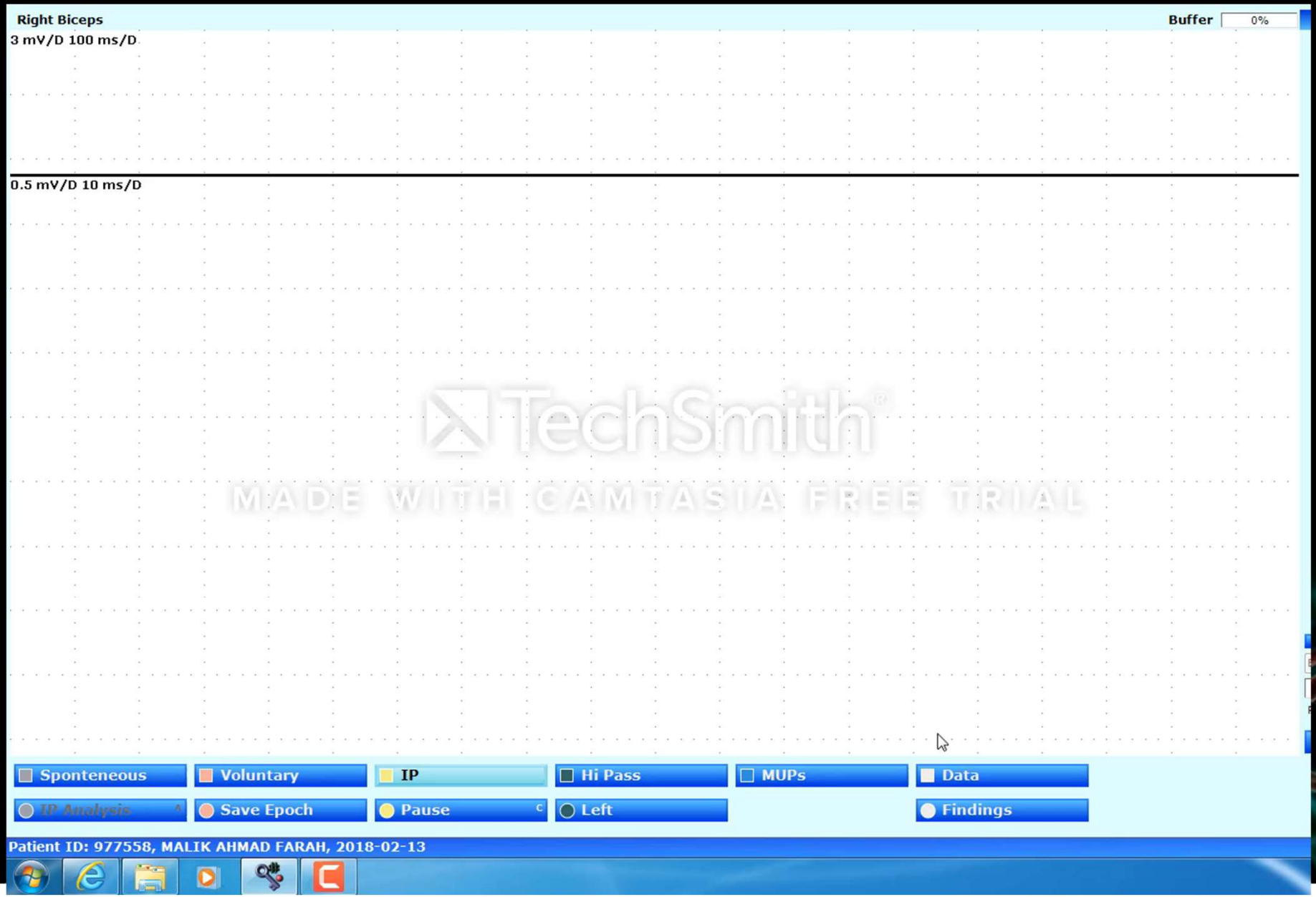
The boy's motor NCS

MNCS								
Nerve	Lat	Amp					CV	F-M Lat
	ms	Amp (mV)	Area (ms*mV)	Area (%)	Duration (ms)	Dur (%)	m/s	ms
Axillaris Motor Right								
Axilla - Deltoid	3.50	2.8	16.7		9.4			
Medianus Motor Right								
Wrist - APB	**8.97**	**0.32**	--		--			
Peroneus Motor Right								
Ankle - EDB	5.31	**0.99**	1.97		3.7			22.2
Distal FH-Ankle	10.1	1.17	3.0	52.3	4.2	13.5	60.5	
Prox FH-Distal FH	11.4	1.28	3.3	10.0	4.2	0	76.9	
Tibialis Motor Right								
Med. mal - Abd hal	5.80	**1.86**	2.5		3.1			39.2
Pop Fossa-Med. mal	12.5	0.70	2.2	-12.0	6.6	113	59.7	
Ulnaris Motor Right								
Wrist - ADM	**4.52**	**0.58**	0.87		4.2			

Sensory NCS

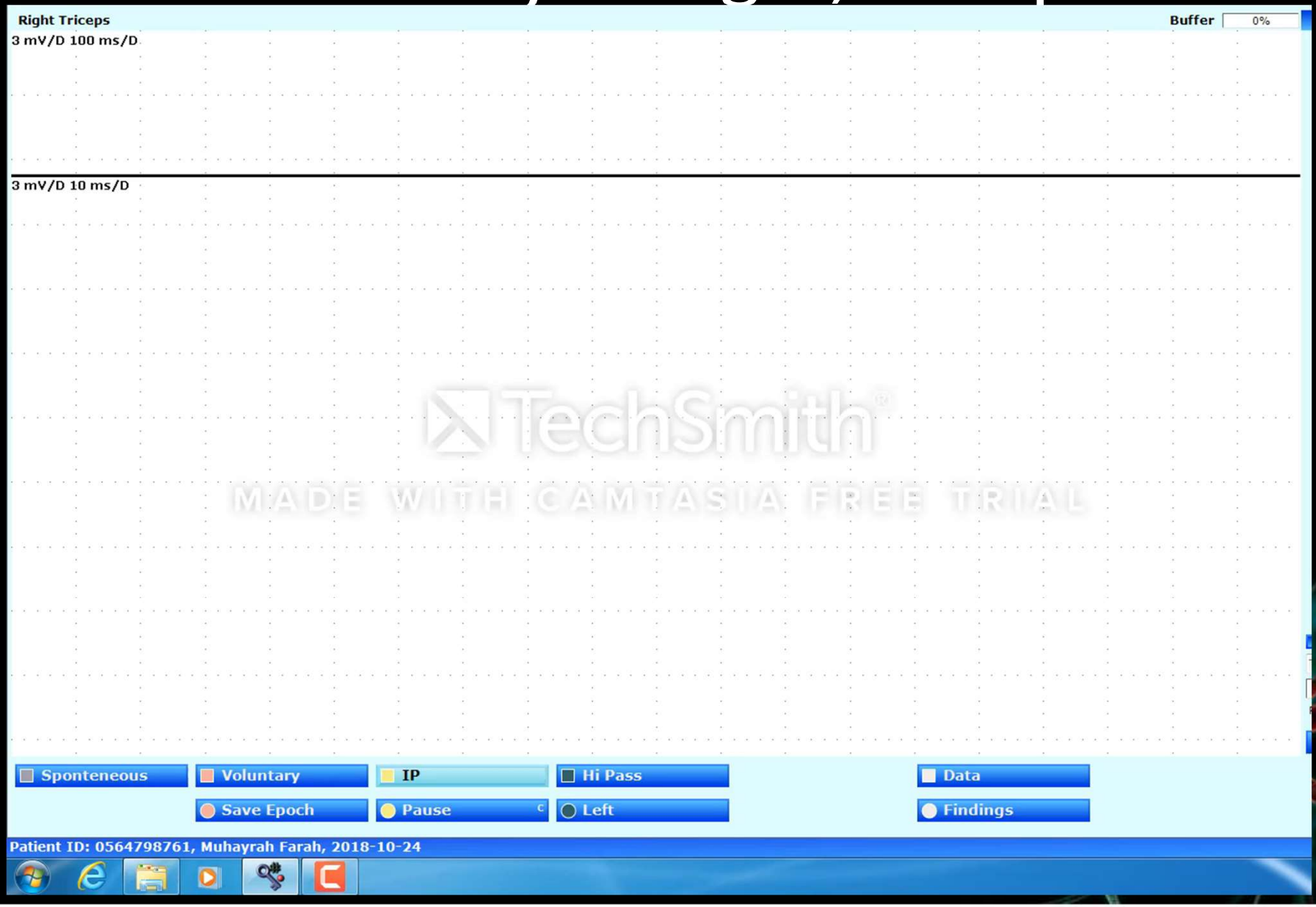
- Normal in the girl
- Absent sural in the boy

EMG: 21 yrs boy, biceps



EMG: 21 yrs boy, vastus

EMG: 9 years girl, triceps



19 years girl

Muscle	Fib	PSW	Fasc	CRD	Amp	Dur	Poly	IP	Recruit	Firing
Right Semitendinosus	No	0	0	0	Normal	Normal	+	Normal	Reduced	3+
Right Vastus lat	No	0	1+	0	+	+	Normal	-	Reduced	2+
Right Tibialis anterior	No	1+	1+	0	Normal	Normal	+	---	Reduced	3+
Right FDI	No	0	0	0						
Right Triceps	No	0	1+	0	+++	Normal	+	--	Reduced	2+
Right Biceps	No	0	0	2+	++	Normal	++	--	Reduced	2+

21 year old boy

Muscle	Fib	PSW	Fasc	Amp	Dur	Poly	Stabil	IP	Recruit	Firing
Right Tibialis anterior	3+	3+	0	Normal	Normal	Normal	Normal	Normal	Late	2+
Right Iliopsoas	No	0	0	++	++	Normal	Normal	Normal	Late	2+
Right Vastus lat	No	0	0	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Right FDI	No	0	0							
Right Triceps	2+	2+	0	+	+	Normal	Normal	Normal	Late	3+
Right Biceps	No	0	0	Normal	+	Normal	Normal	Normal	Late	3+

Other testing results

- CK: normal in both patients
- MRI brain and whole spine was normal

Impression

- This study is consistent with clinical diagnosis of inherited motor neuronopathy with upper motor neuron signs and that include

1. Hereditary motor and sensory neuropathy type V (MFN2, KIF5A, BSCL2).
2. Mitochondrial disease e.g. POLG1 mutation
3. Leukodystrophy (Refsum's, .. etc).
4. SMA

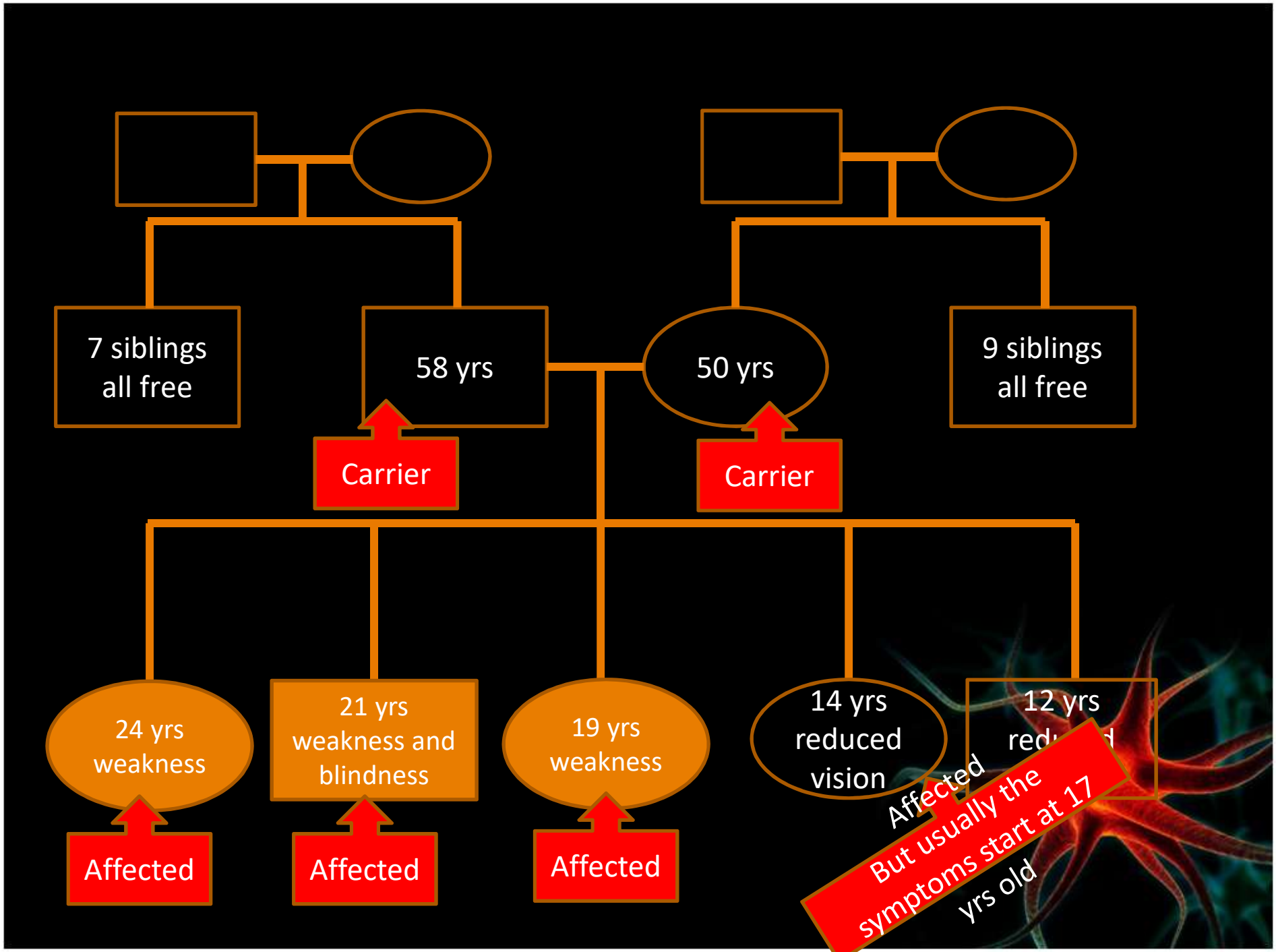
SMA testing

- No exon 7 or 8 deletion.

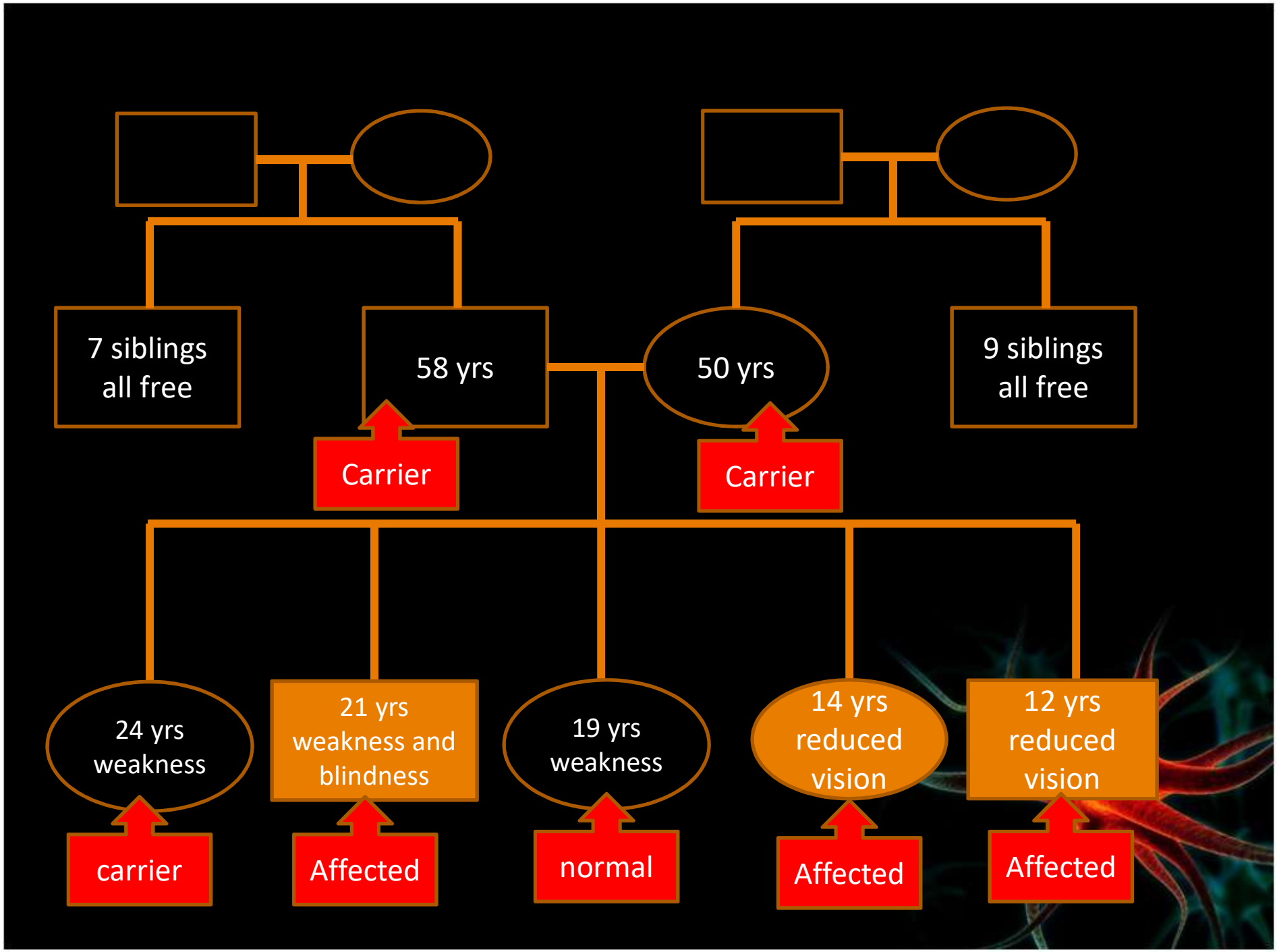
Diagnostic test

- Whole exom sequencing was choosing to target our broad differential diagnosis

- WES for the boy showed:
- SYNE1 gene homozygous mutation
- Known to case autosomal recessive spinocerebellar ataxia type 8, with one report of motor neuronopathy.


7 siblings all free
58 yrs
50 yrs
9 siblings all free
Carrier
Carrier
24 yrs weakness
21 yrs weakness and blindness
19 yrs weakness
14 yrs reduced vision
12 yrs
Affected
Affected
Affected
Affected
But usually the symptoms start at 17
yrs old

- WES also revealed that the boy has:
  - Homozygous mutation in gene: C8ORF37
- Known to cause:
  - Cone rod dystrophy 16 (AR)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19 yrs
weakness
14 yrs
reduced
vision
12 yrs
reduced
vision
carrier
Affected
normal
Affected
Affected

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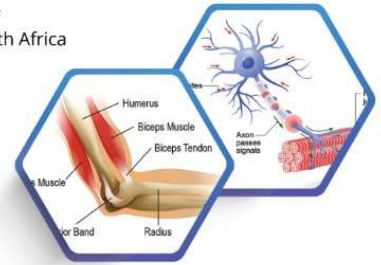

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much