



Non Medullary Thyroid Cancer & FOXE1 Gene

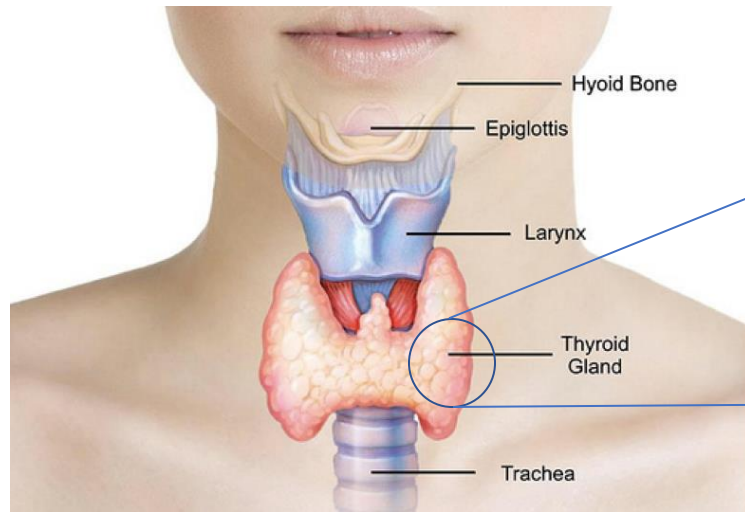
Franklin Yeo



WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

GEN 564

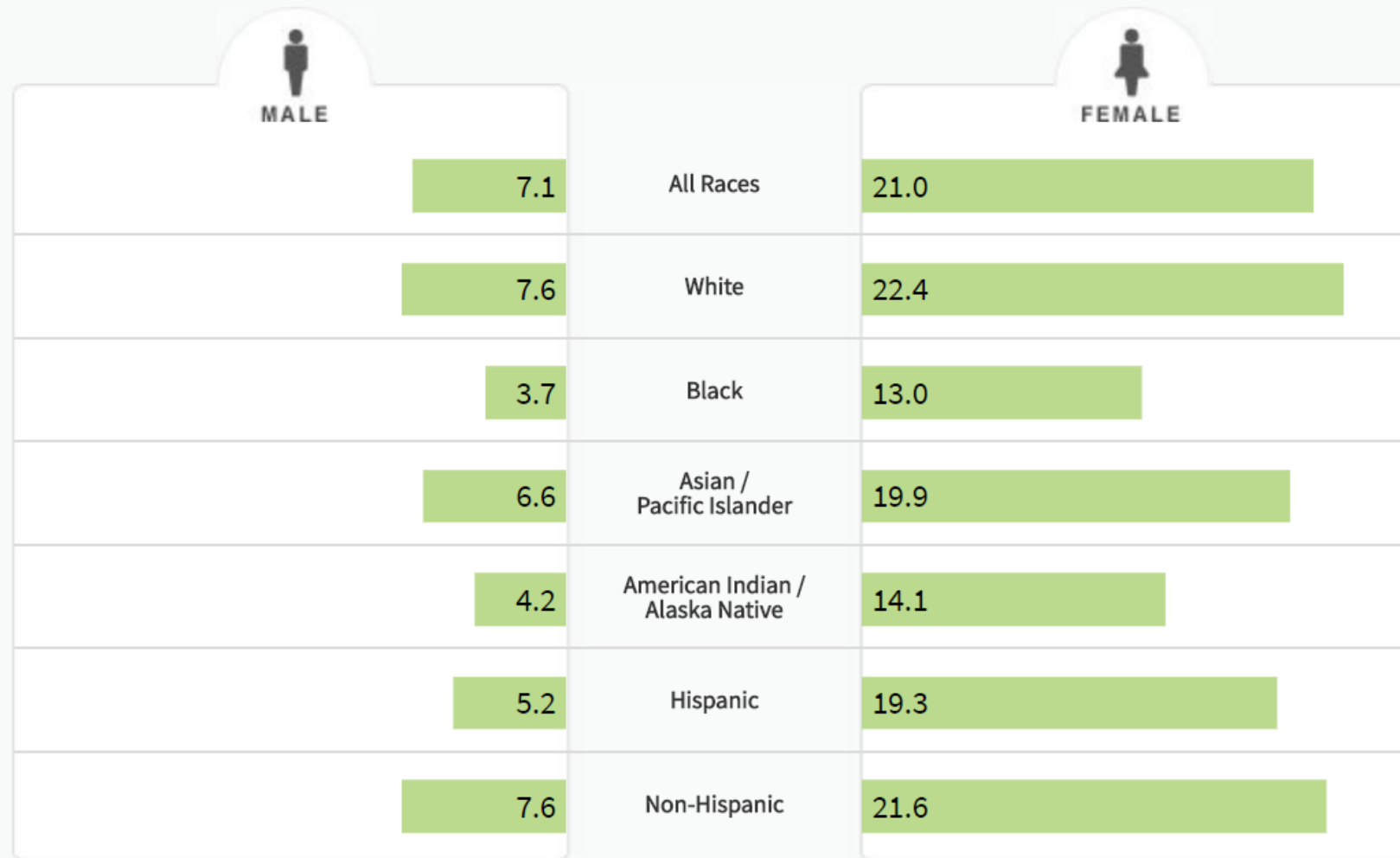
What is Non Medullary Thyroid Cancer (NMTC)?



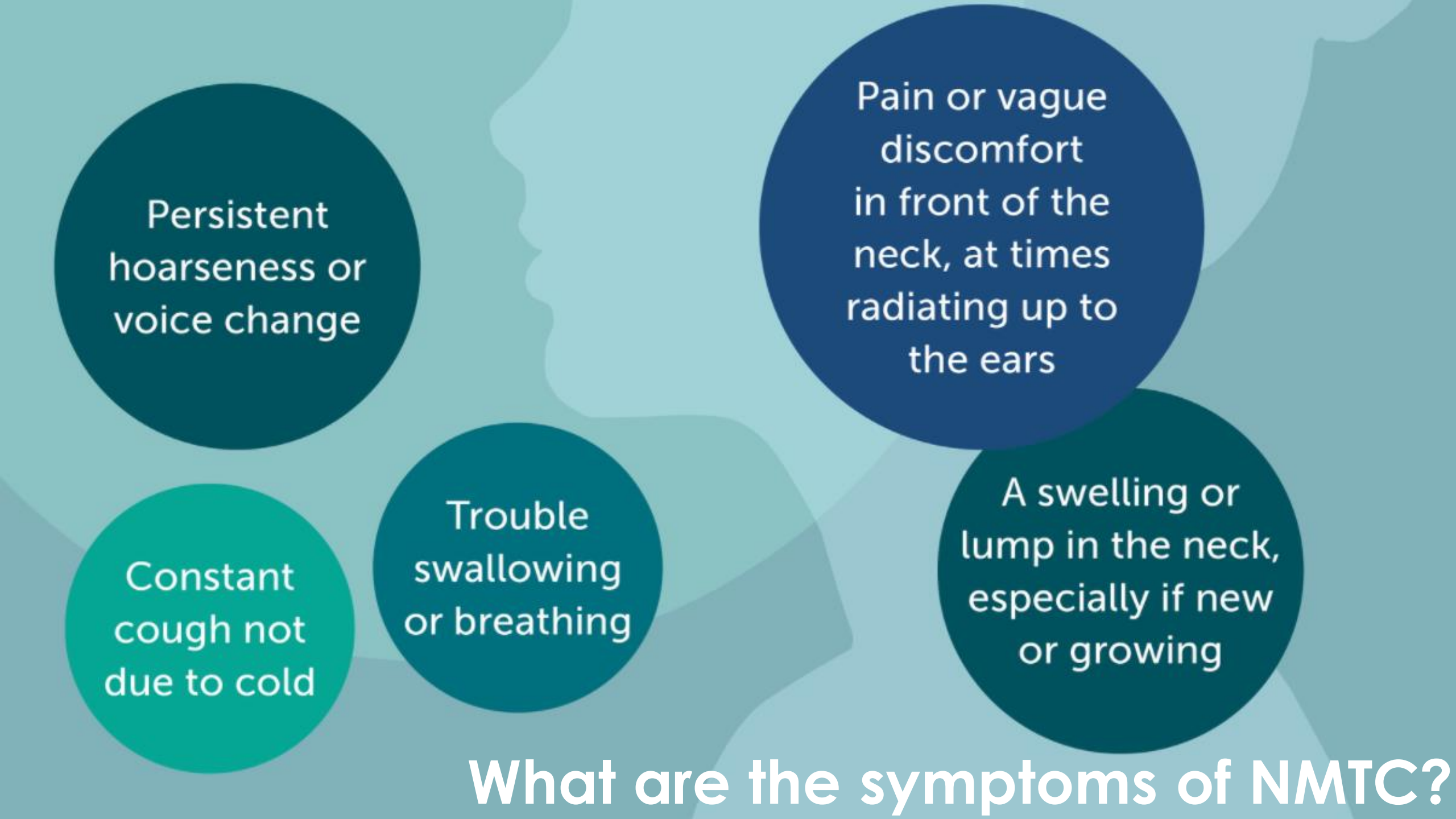
Abnormal growth of thyroid follicular cells

Who does NMTC affect?

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Thyroid Cancer



More common in those with a family history of thyroid disease

The infographic features a light blue background with a faint silhouette of a human head and neck. Five circular bubbles of varying shades of teal and blue are arranged around the silhouette. Each bubble contains a symptom of NMTC. The bubbles are: a large dark teal bubble at the top left, a medium teal bubble at the top right, a small teal bubble at the bottom left, a medium teal bubble at the bottom center, and a large dark teal bubble at the bottom right. The text is white and centered within each bubble.

Persistent
hoarseness or
voice change

Pain or vague
discomfort
in front of the
neck, at times
radiating up to
the ears

Constant
cough not
due to cold

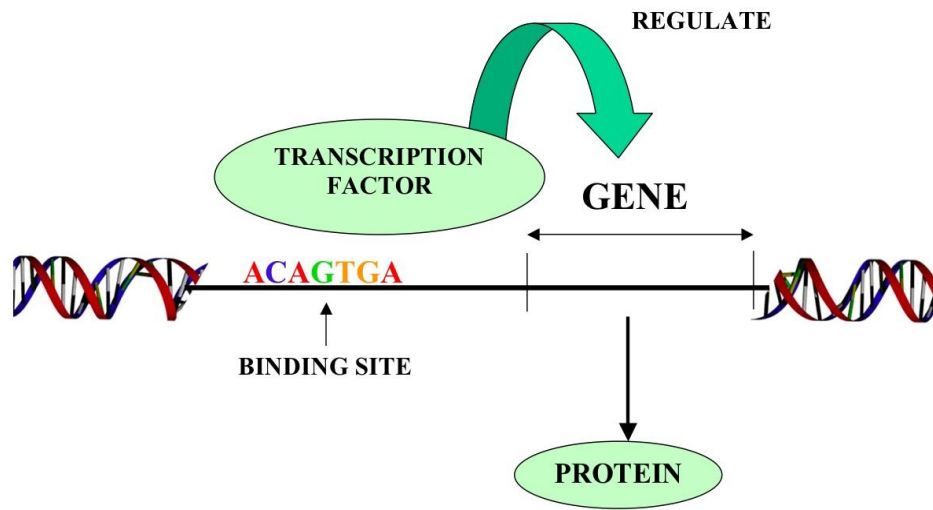
Trouble
swallowing
or breathing

A swelling or
lump in the neck,
especially if new
or growing

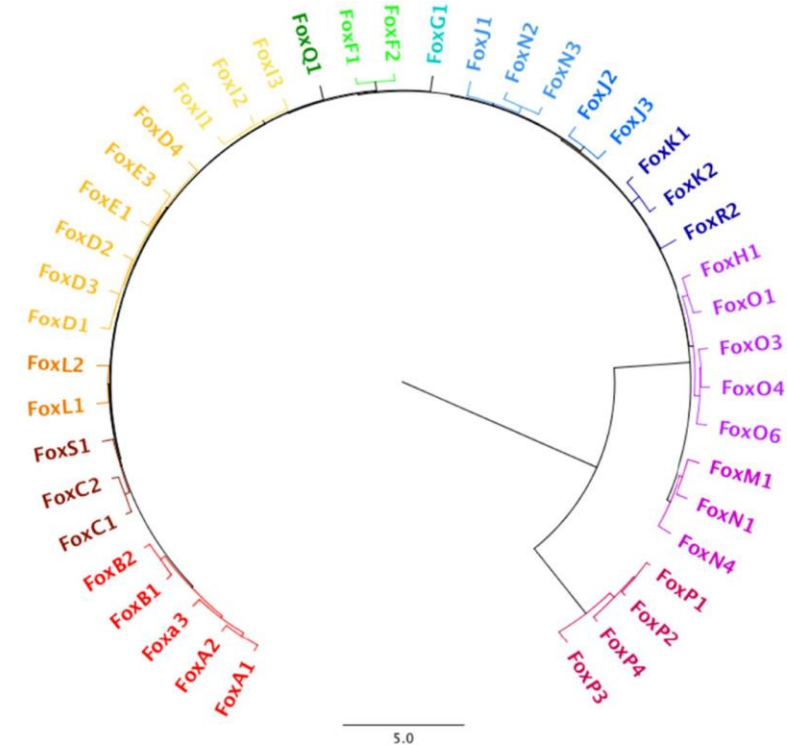
What are the symptoms of NMTC?

What is FOXE1?

Thyroid Transcription Factor



Forkhead box protein family



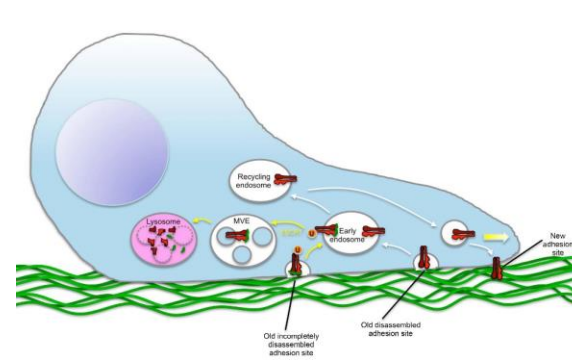
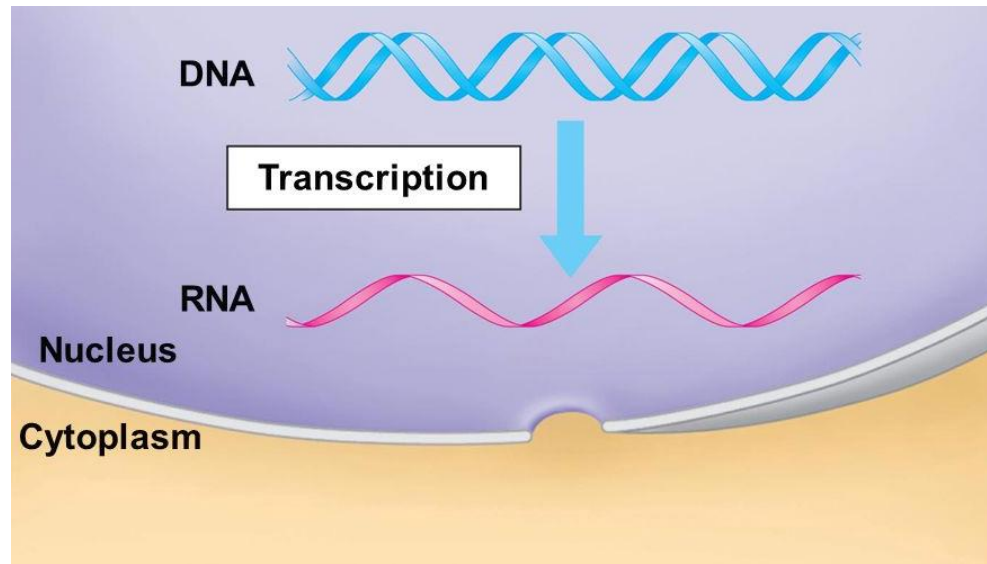
Pioneer factors: transcription factors that can bind directly to condensed chromatin and can positively/negatively affect transcription

Where and how does FOXE1 function?

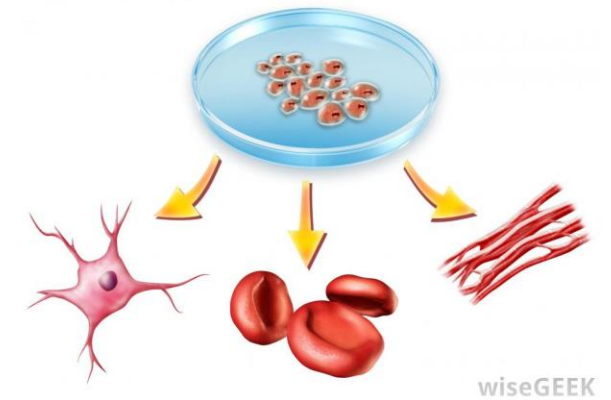
Cellular Component

Molecular Function

Biological Processes



Cell Migration



Cell Differentiation

FOXE1 is highly conserved

% Identity



FH

373 aa



FH

372 aa

97%



FH

373 aa

91%



FH

371 aa

89%



FH

370 aa

88%



FH

349 aa

55%



FH

377 aa

49%



FH

354 aa

47%



FH

354 aa

40%

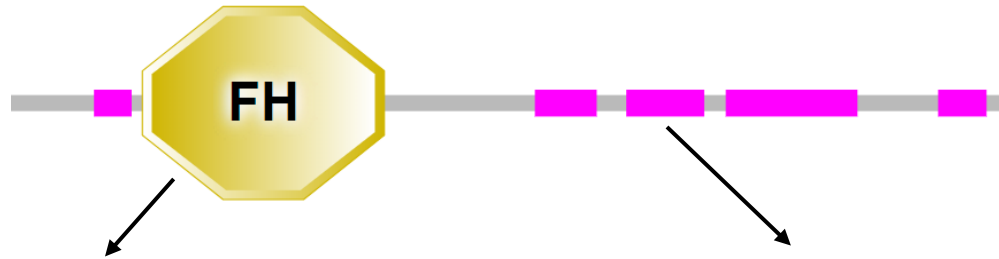


FH

323 aa

24%

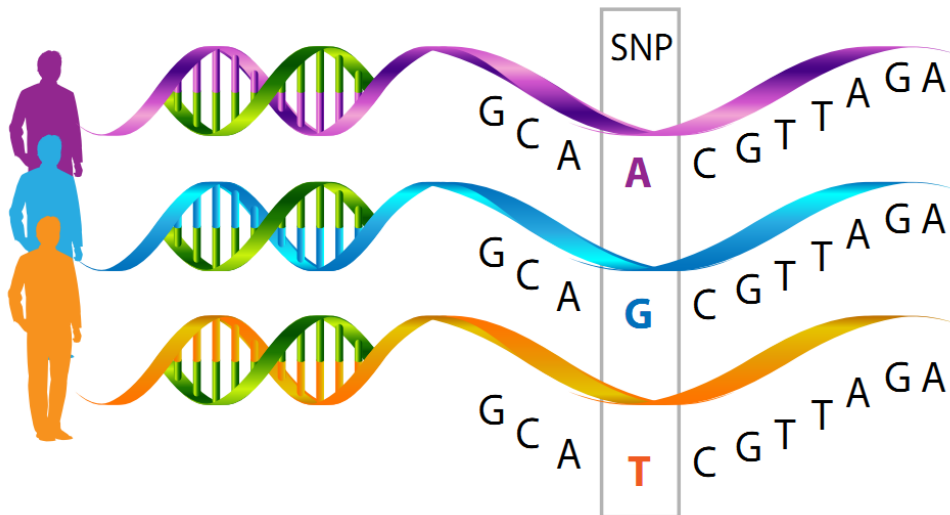
What is known about FOXE1?



Forkhead (FH) domain is responsible for sequence specific DNA binding

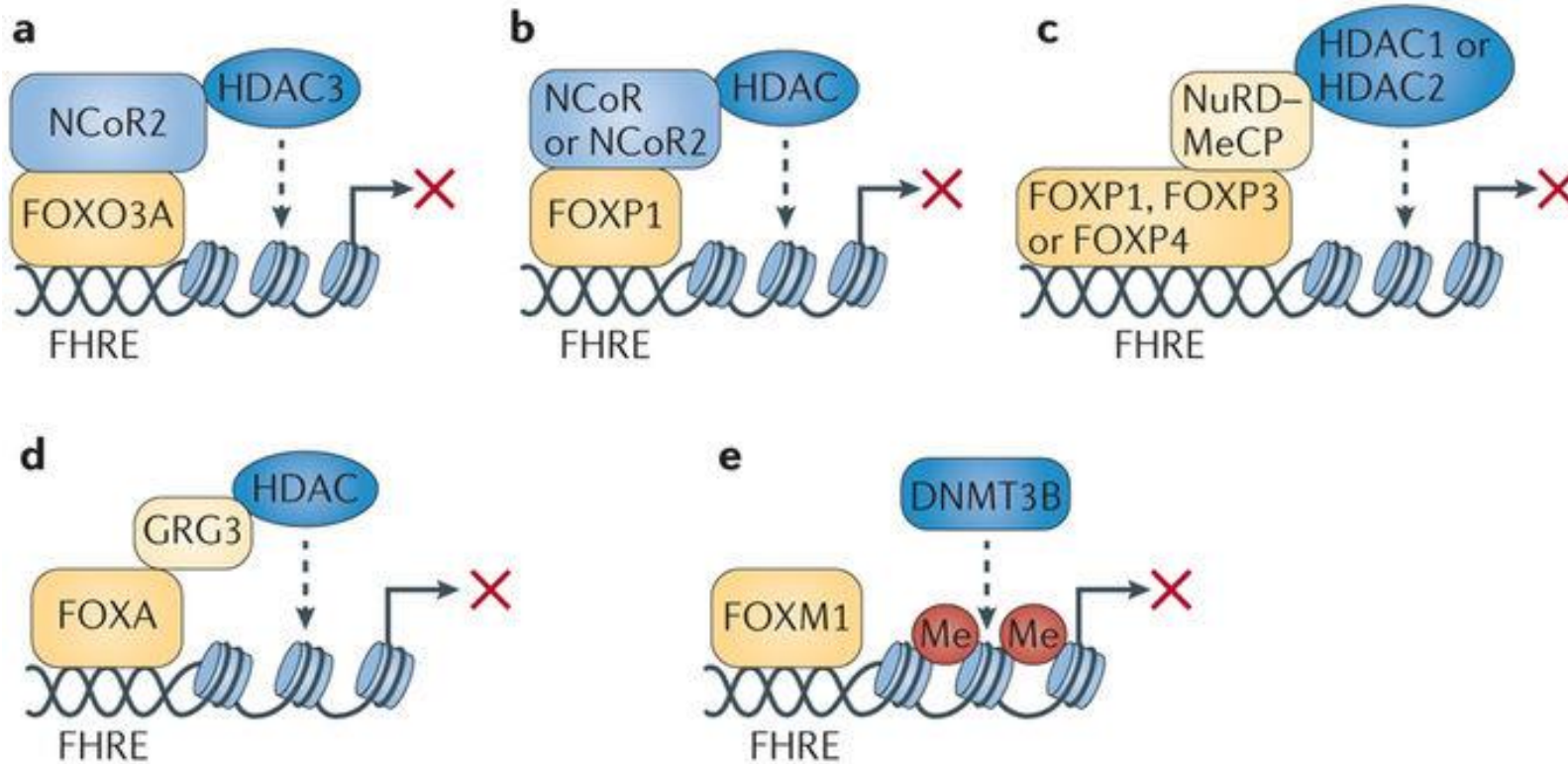
Mutations in the FH domain leads to congenital hypothyroidism

Mutations in the Low Complexity Region (LCR) results in NMTC and is associated with an increased WNT5A gene expression.



Specific Single nucleotide polymorphisms (SNP) are associated with specific subtypes of NMTC

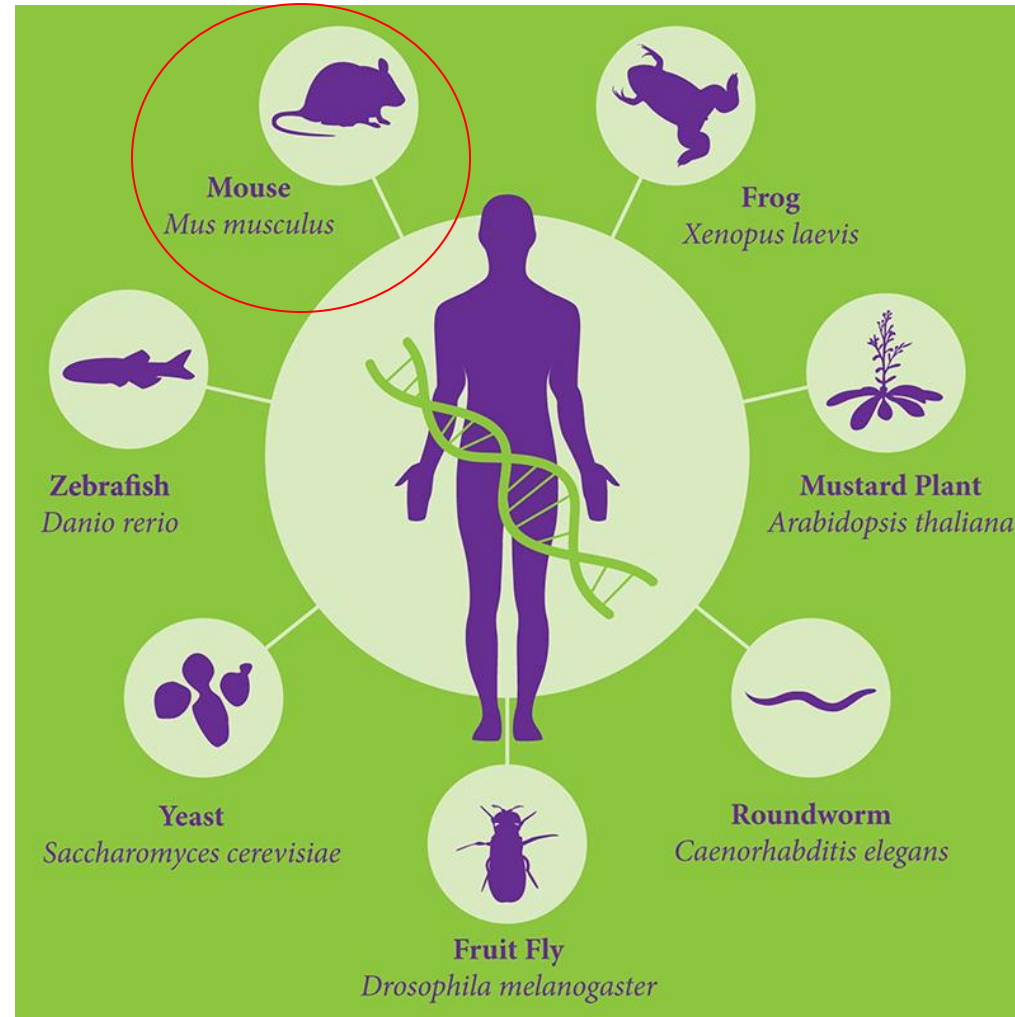
What is unknown about FOXE1?



Nature Reviews | [Cancer](#)

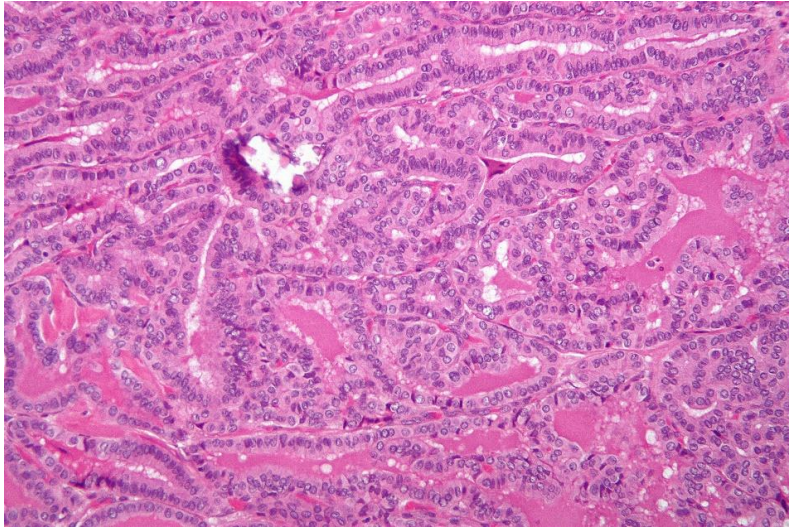
Although protein-protein interaction networks indicate how FOXE1 may regulate gene transcription, there is little understanding regarding its mechanism

What model organisms should be utilized to study FOXE1?



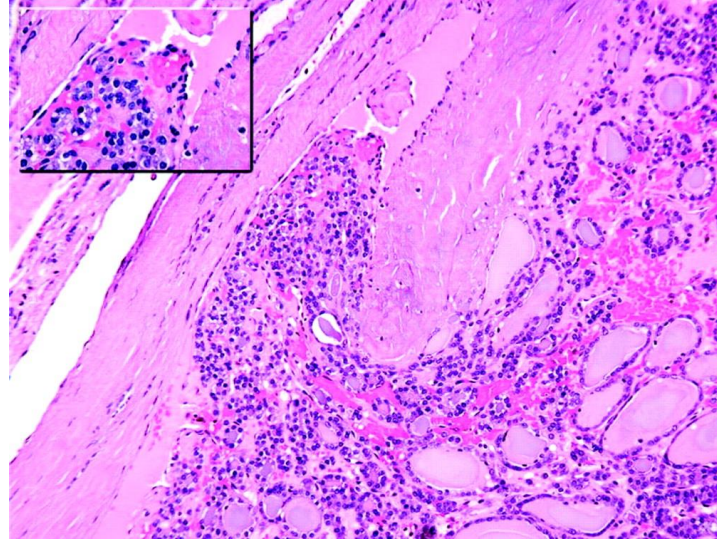
Why study mice for NMTC?

Papillary Thyroid Cancer
(PTC)



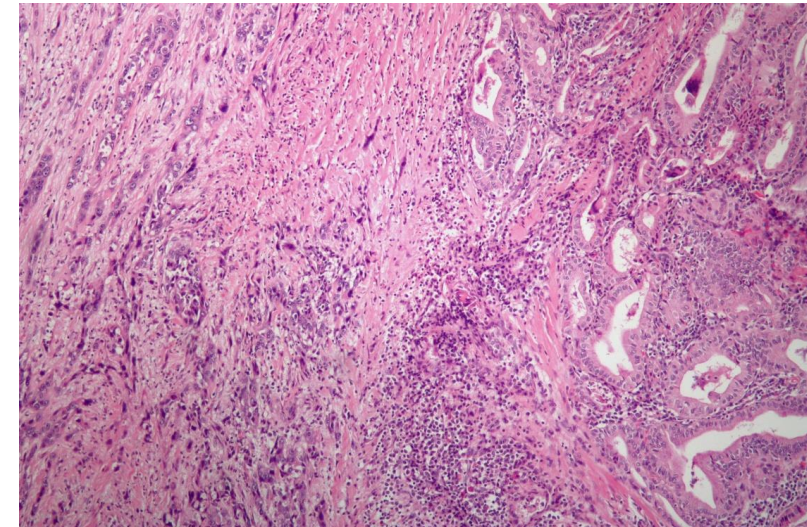
Psammoma bodies, well- formed fibrovascular cores, and ground glass appearance of nuclei observed

Follicular Thyroid Cancer
(FTC)



Capsular and vascular invasion observed

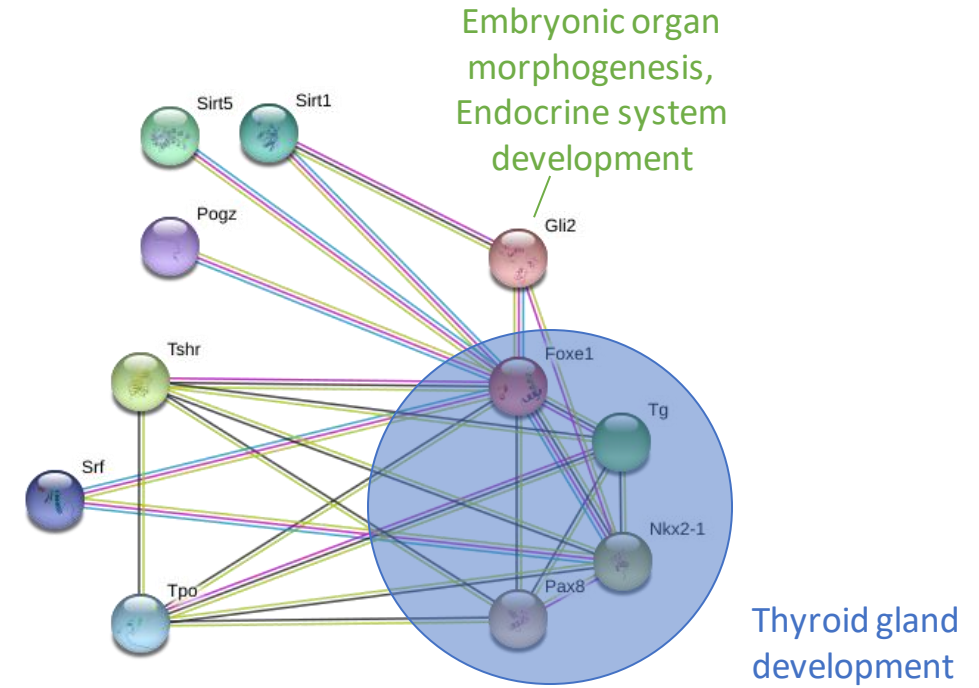
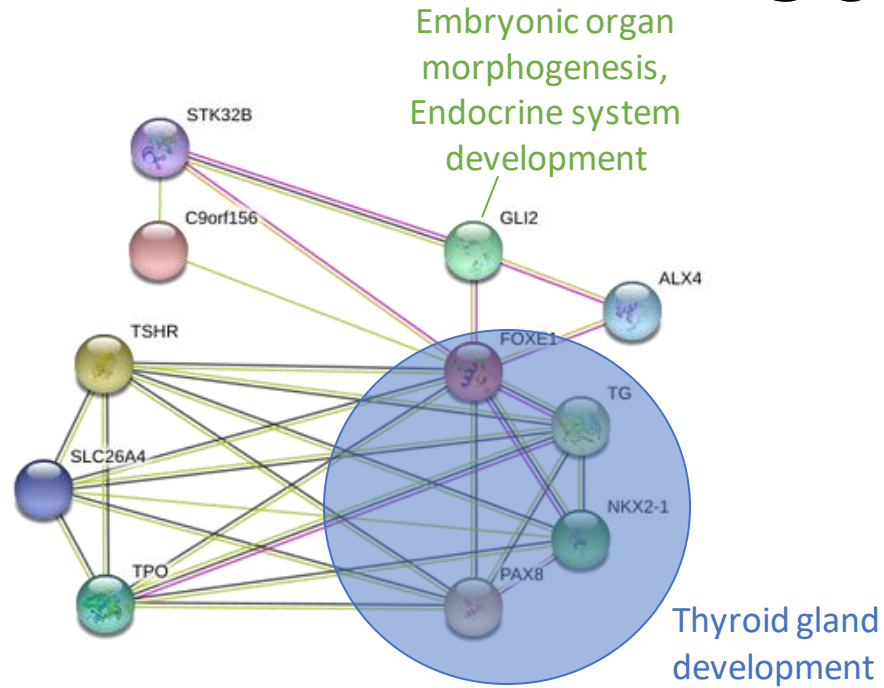
Anaplastic Thyroid Cancer
(ATC)



Poor cell differentiation observed

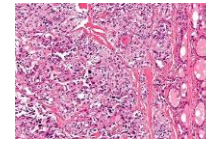
In both humans and mice, NMTC subtypes can be classified according to histopathological characteristics of the cell
(Microscopic Examination)

How do human and mouse FOXE1 interactions compare?

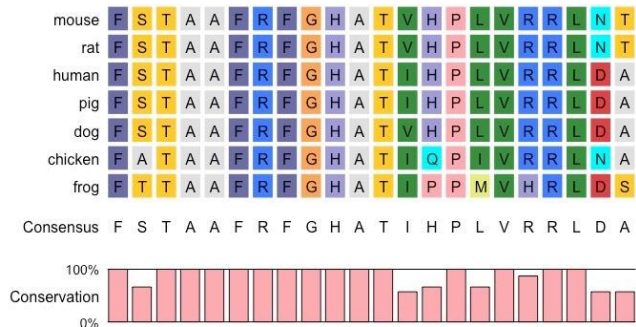


What is the primary goal?

Identify how FOXE1 is responsible for the uncontrolled growth of follicular cells within the thyroid gland

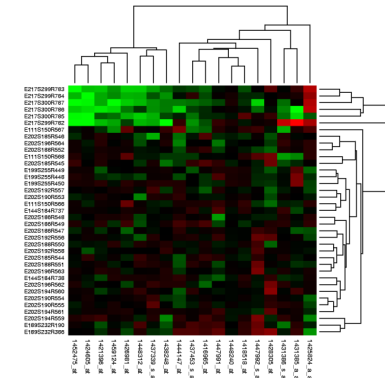


Aim 1



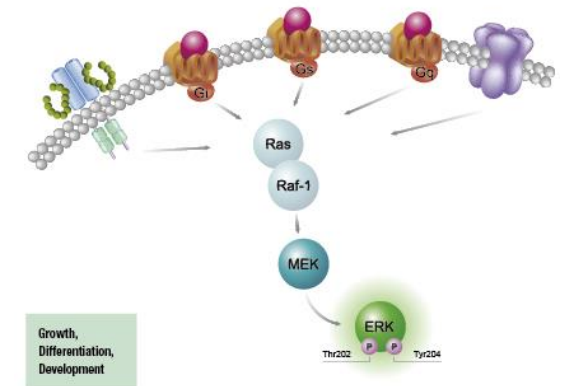
Identify conserved amino acid sequences that regulate cell growth/ proliferation

Aim 2



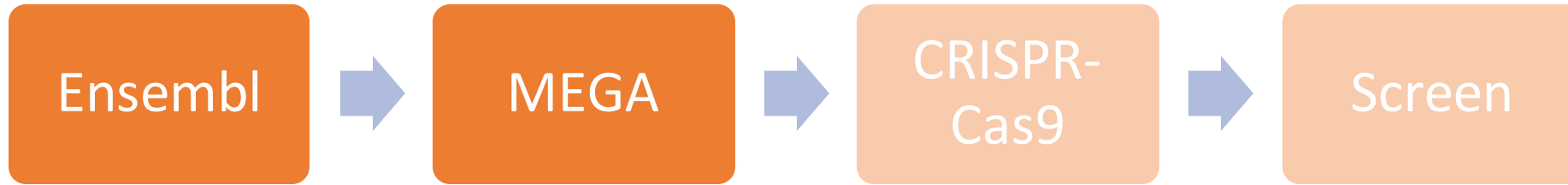
Identify genes involved in thyroid morphogenesis

Aim 3



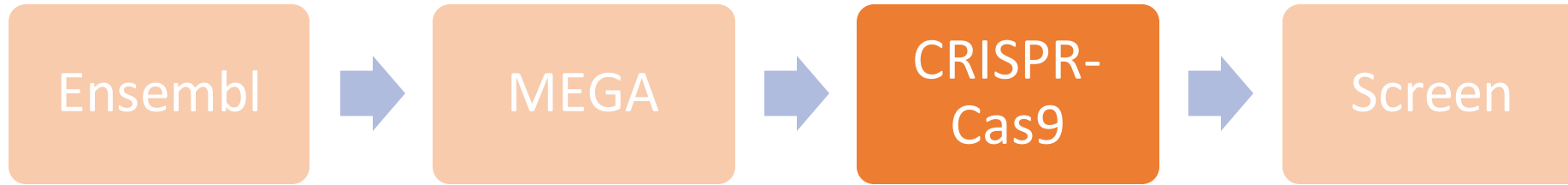
Characterize phosphorylation patterns of NMTC

Aim 1: Identify conserved amino acids sequences that regulate cell growth/ proliferation

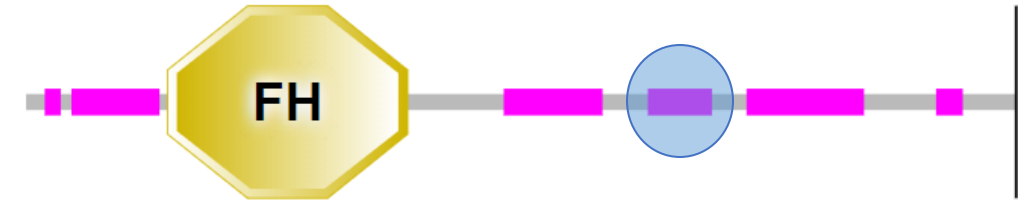


M	T	A	E	S	G	P	P	P	P	Q	P	E	V	L	A	T	V	K	E	E	R	G	E	T	A	A	G	A	G	V	P	G
L	S	R	D	I	F	Q	P	S	M	T	M	P	V	V	K	V	E	K	E	S	S	A	E	N	P	P	P	A	S	N	L	P
M	I	M	P	V	V	K	V	E	K	E	S	P	A	D	S	G	L	P	S	S	N	P	S	P	Q	T	E	D	Q	Q	P	R
M	T	A	E	S	G	P	P	P	P	Q	P	E	V	L	A	A	V	K	E	E	R	G	E	T	A	A	G	A	G	V	P	G
M	T	A	D	T	Q	Q	S	P	C	K	D	S	S	V	P	Y	N	L	H	R	S	L	A	F	S	G	K	T	M	P	V	V
M	T	A	E	S	G	P	P	P	P	P	Q	P	E	A	L	A	A	V	K	E	E	R	G	E	A	G	A	G	V	P	G	
M	T	A	E	S	G	P	P	P	P	Q	P	P	Q	P	E	A	L	A	T	V	K	E	E	R	G	E	A	G	A	G	V	P
T	M	P	V	V	K	L	E	K	D	S	L	A	E	N	P	P	P	A	S	N	L	T	Q	Q	T	E	E	Q	P	R	G	R
M	T	A	E	N	Q	Q	S	P	T	R	A	T	A	A	G	A	S	L	Q	Q	A	S	G	L	T	M	P	V	V	K	V	E
W	Q	N	S	I	R	H	N	L	T	L	N	D	C	F	V	K	I	P	R	E	P	G	H	P	G	K	G	N	Y	W	T	L
M	T	M	P	V	V	K	V	E	K	D	S	P	A	D	T	L	L	A	S	N	P	P	P	Q	T	E	E	Q	P	R	G	R
P	A	G	G	R	R	R	K	R	P	V	Q	R	G	K	P	P	Y	S	I	A	L	I	A	M	A	I	A	N	A	A	E	E
R	K	R	P	L	Q	R	G	K	P	P	Y	S	Y	I	A	L	I	A	M	A	I	A	H	A	P	D	R	K	L	T	L	G
P	P	P	P	Q	P	E	A	L	A	V	V	K	E	E	R	S	E	A	V	V	G	A	G	V	L	A	D	G	T	G	R	R
M	T	A	E	S	G	P	P	P	P	P	P	P	E	A	L	A	A	V	K	E	E	R	G	A	A	G	A	G	V	P	A	A
M	T	A	E	N	Q	R	S	P	P	K	A	S	S	A	V	V	S	V	Y	Q	S	N	N	N	F	M	P	T	E	H	G	P

Aim 1: Identify conserved amino acids sequences that regulate cell growth/ proliferation



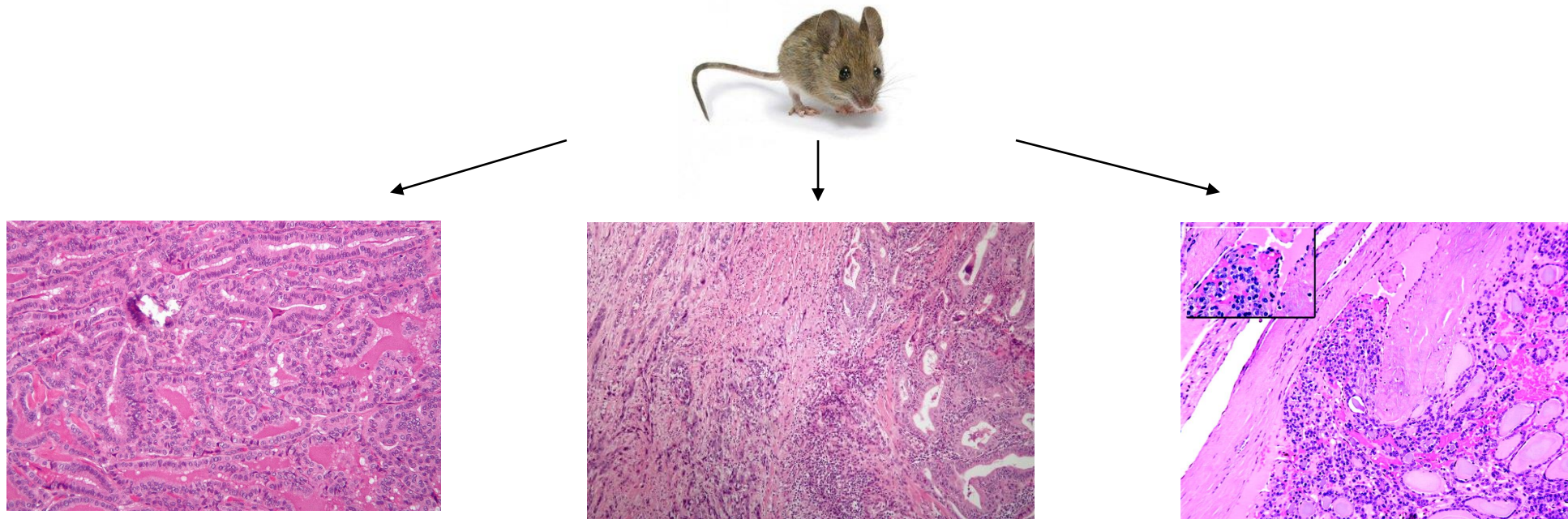
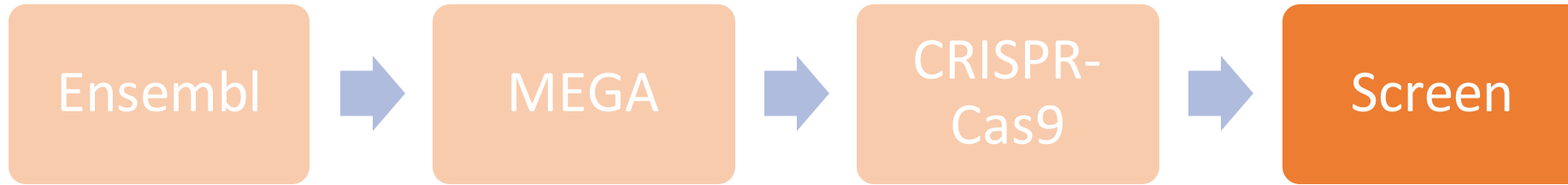
Induce NMTC subtype specific gene mutation using CRISPR



89%

94%

Aim 1: Identify conserved amino acids sequences that regulate cell growth/ proliferation



Hypothesis: Human NMTC subtype specific mutations will cause same NMTC subtypes in FOXE1 mutant mice

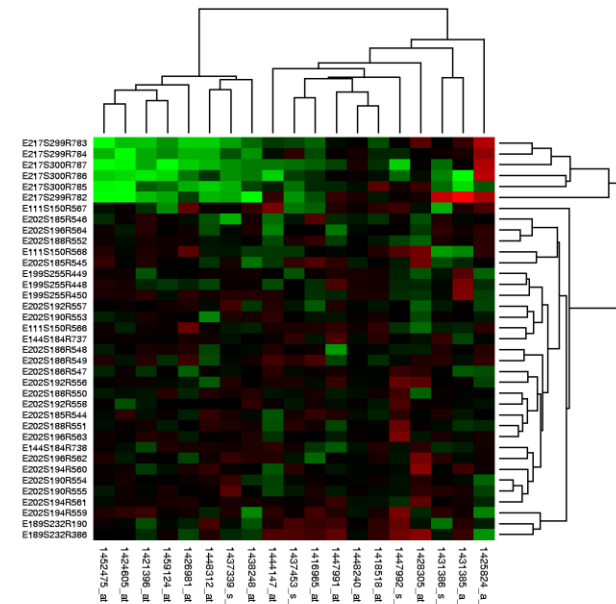
Aim 2: Identify genes involved in thyroid morphogenesis



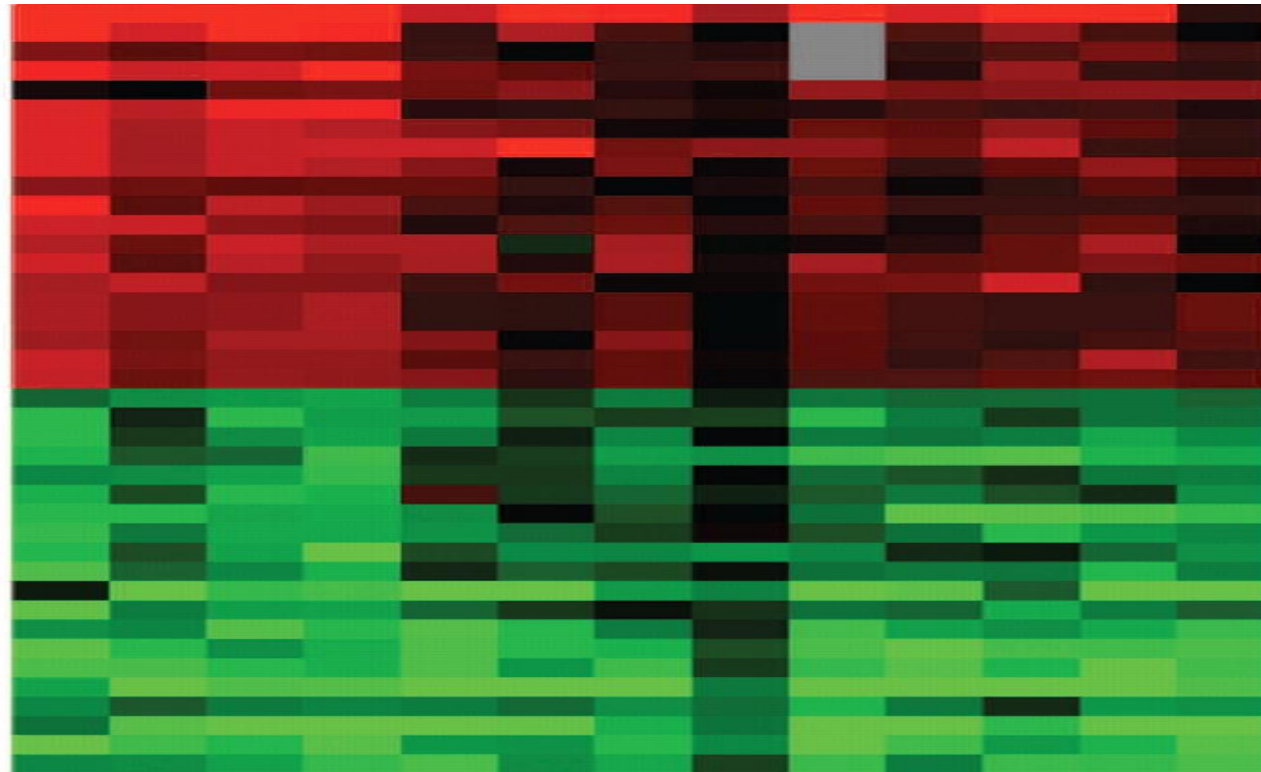
WT



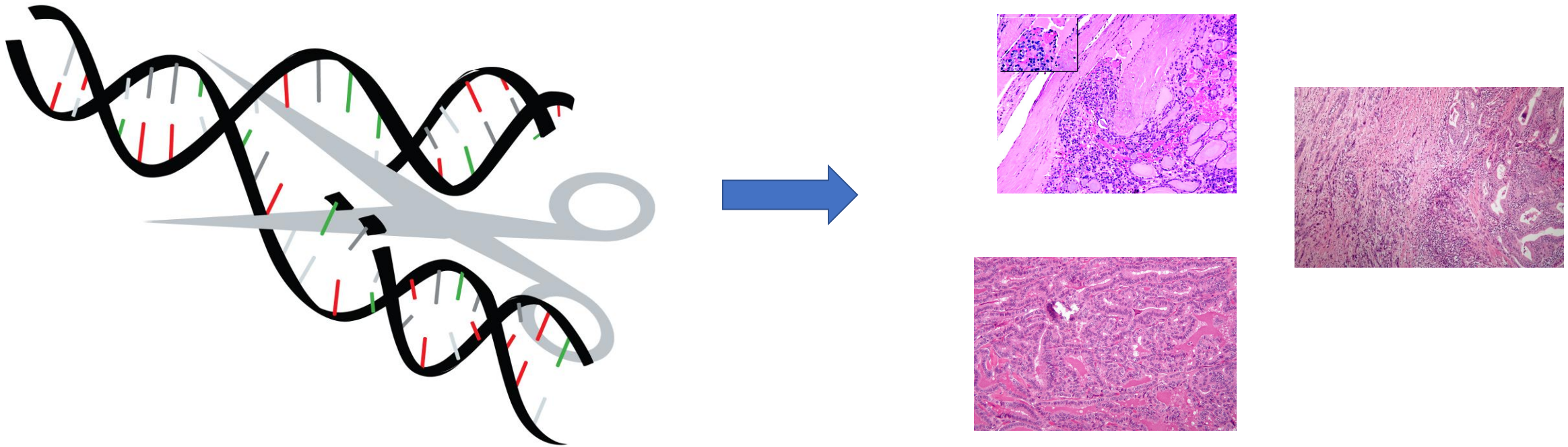
Mutant



Aim 2: Identify genes involved in thyroid morphogenesis

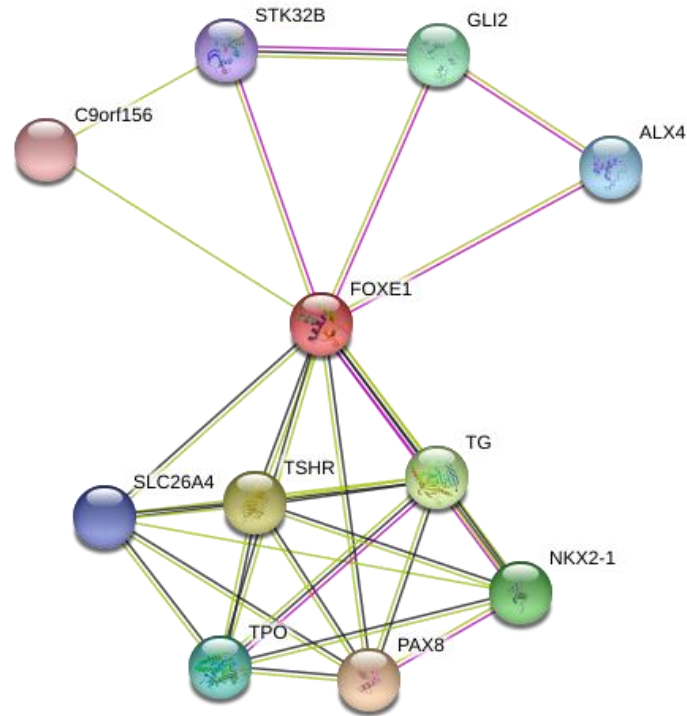


Aim 2: Identify genes involved in thyroid morphogenesis



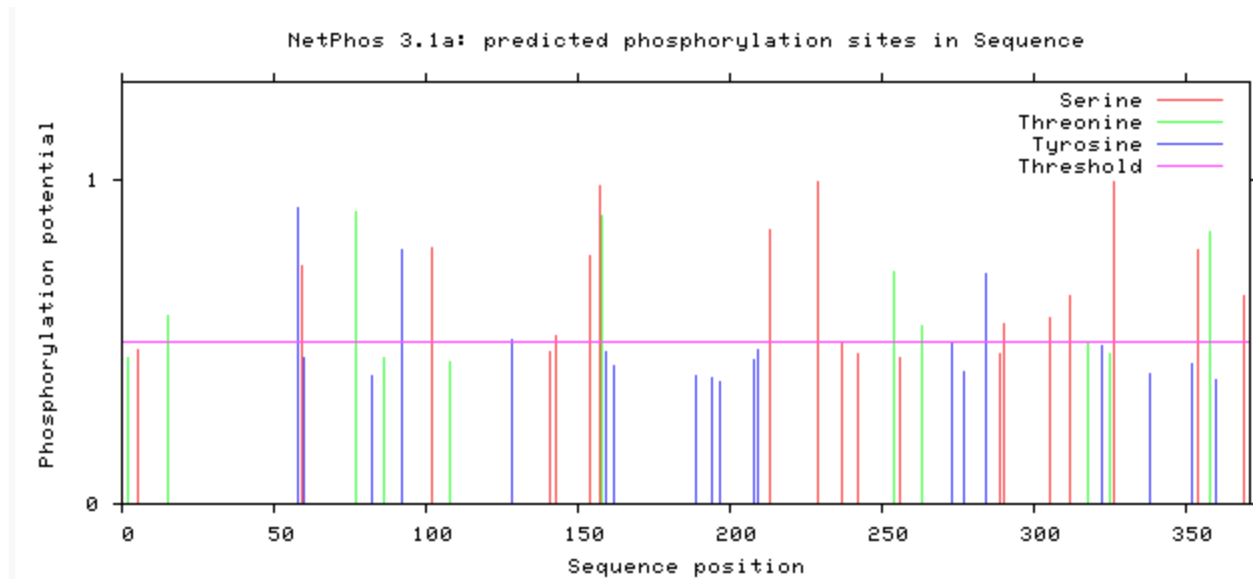
Hypothesis: Genes responsible for cellular growth regulation will be over or under expressed

Aim 3: Characterize phosphorylation patterns of NMTC



Identify proteins that interact with FOXE1

Aim 3: Characterize phosphorylation patterns of NMTC



Identify putative phosphorylation sites for FOXE1 and FOXE1 interacting proteins

Aim 3: Characterize phosphorylation patterns of NMTC

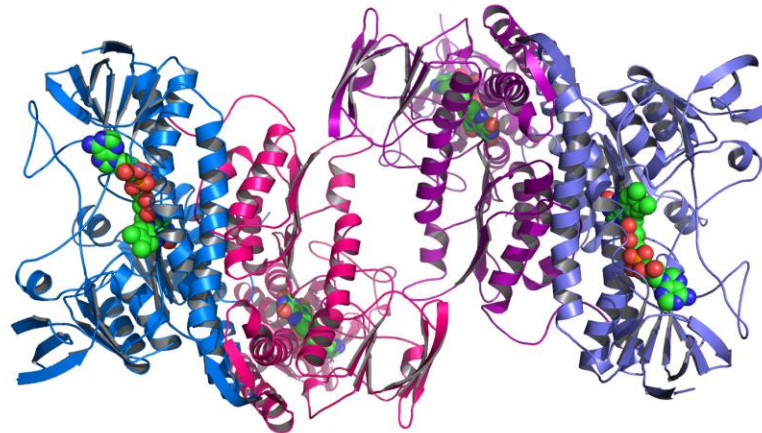
Protein-protein interactions



NETPHOS



Mass Spec.

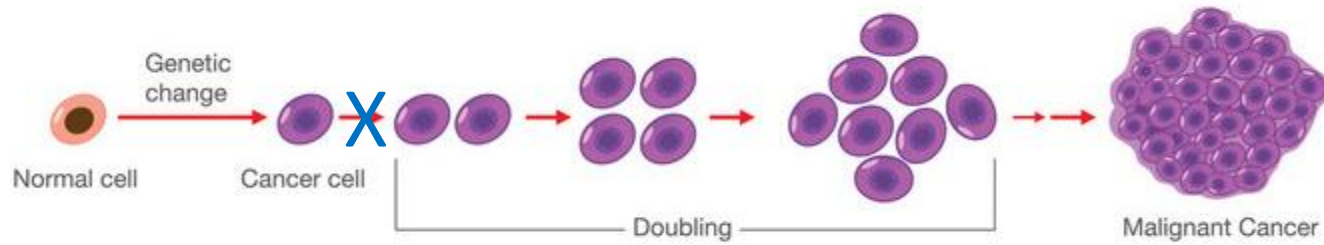


Hypothesis: FOXE1, as well as FOXE1 interacting proteins responsible for cell growth/ proliferation will be over-phosphorylated

Future Directions

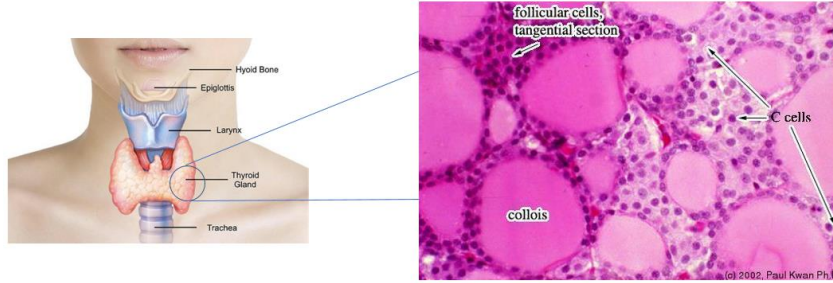


Identify regulatory roles and mechanisms of FOXE1 low complexity regions

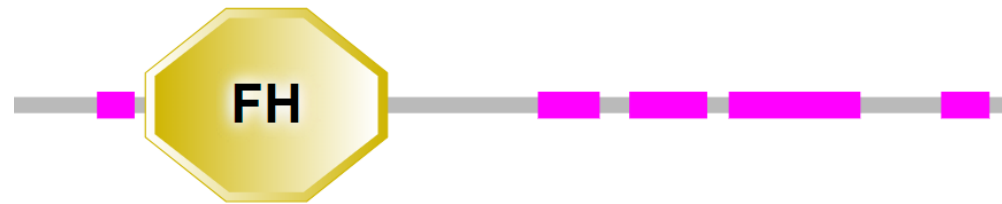


Identify ways to stop NMTC progression

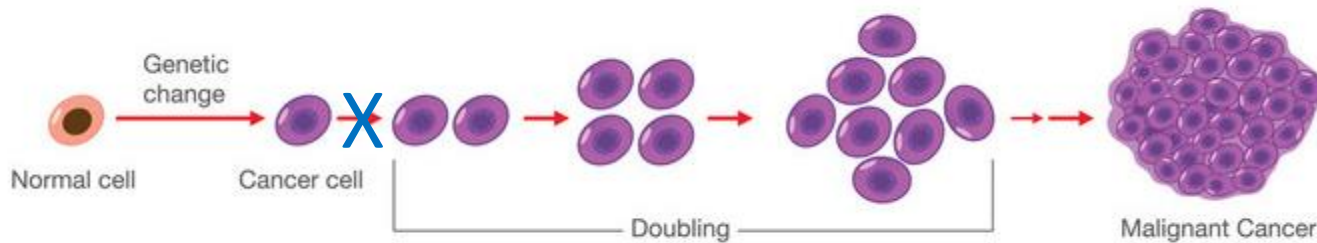
Conclusion



NMTC is the uncontrolled growth of thyroid follicular cells



Low complexity regions of FOXE1 are associated with NMTC



Understanding FOXE1's mechanism of transcription regulation may help identify ways to stop NMTC progression

References

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