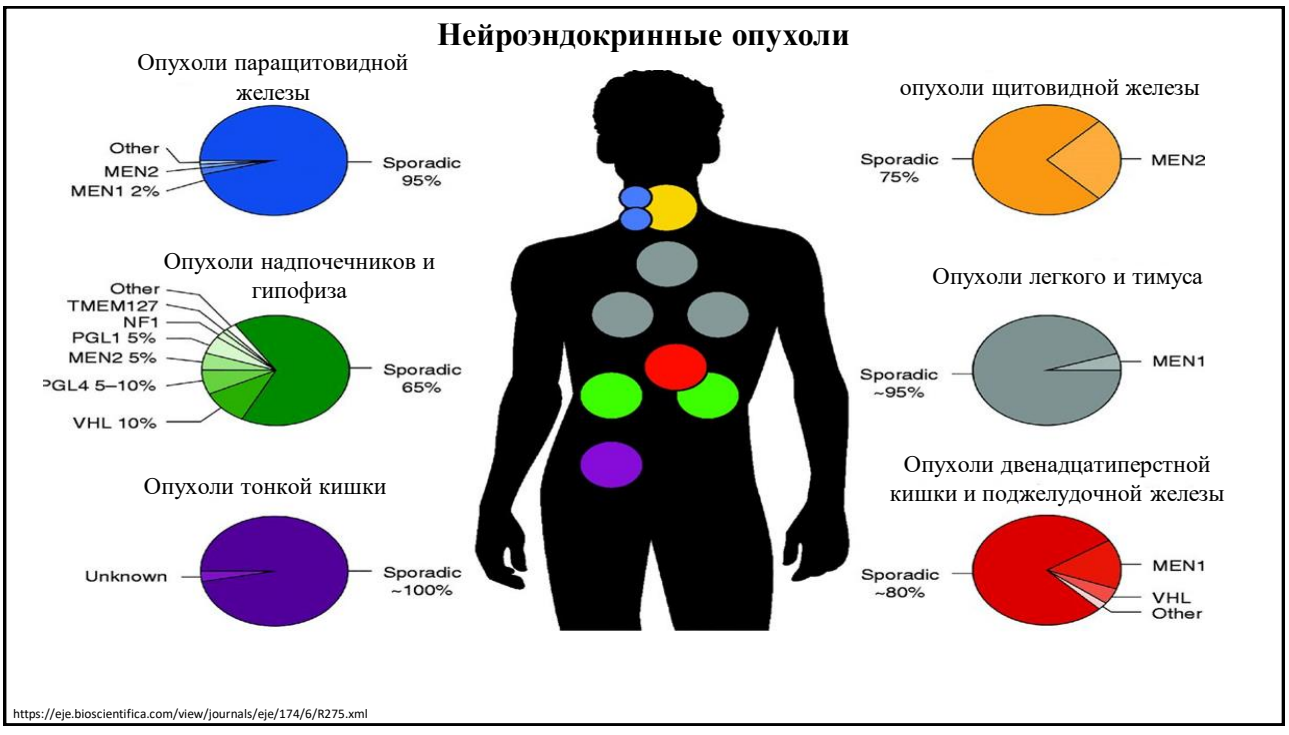
Генетические маркеры нейроэндокринных опухолей

К.м.н. Бяхова Мария Михайловна

1 ноября 2019



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Наследственные синдромы

Название	Ген	Манифестация	Другие варианты манифестации
MEN1	*MEN1*	Паращитовидная железа (> 90%), ЖКТ и поджелудочная железа(50%), передний гипофиз (30%), легкие и тимус (10%)	Адренокортикальные опухоли
MEN2A (FMTC)	*RET*	щитовидная железа (90–100%), мозговое вещество надпочечников (20–80%), паращитовидная железа (20%)	
MEN2B	*RET*	Паращитовидная железа, щитовидная железа (100%), мозговое вещество надпочечников (50%)	Марфаноподобная внешность
MEN4	*CDKN1B*	Паращитовидная железа, поджелудочная железа, гипофиз	
Neurofibromatosis type 1	*NF1*	Мозговое вещество надпочечника (1–5%), двенадцатиперстная кишка	нейрофиброматоз
von Hippel–Lindau	*VHL*	Мозговое вещество надпочечников и симпатические ганглии (15%), поджелудочная железа (10%)	Гемангиобластома, рак почки
Familial PGL 1-5	*SDHA-D*, *SDHAF2*	Симпатическая и парасимпатическая параганглия, мозговое вещество надпочечников	ГИСО, рак почки
Familial PCC and PGL syndromes	*TMEM127*, *MAX*, *FH*, *MDH2*	Мозговое вещество надпочечников, симпатические ганглии (TMEM127 30%)	
Polycytemia paranganglioma syndrome	*EPAS1*	Симпатические ганглии, мозговое вещество надпочечника, двенадцатиперстная кишка	Полицитемия
Tuberous sclerosis complexes	*TSC1*, *TSC2*	Поджелудочная железа	Гамартома
HPT-JT syndrome	*HRPT2*	Аденома паращитовидных желез (80%)	

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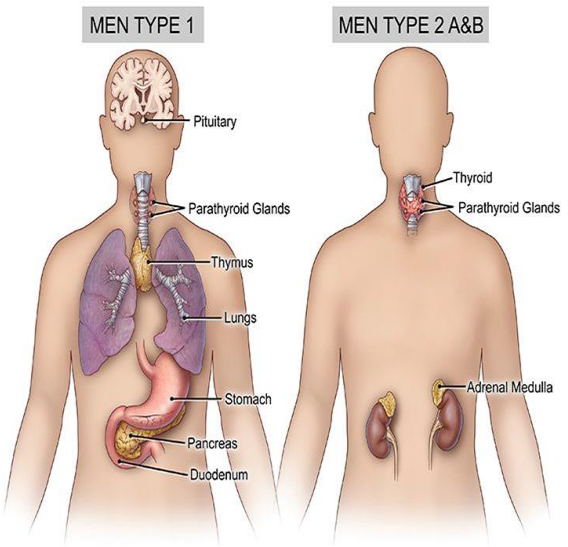
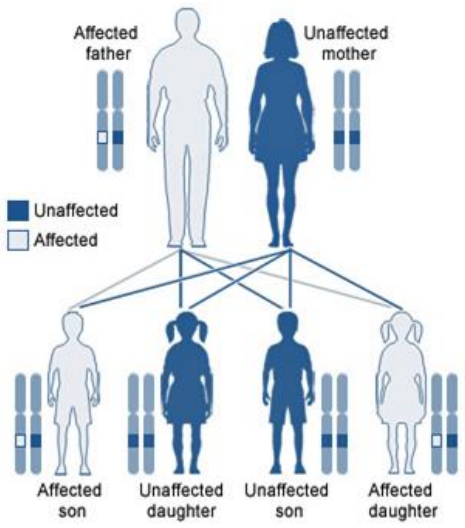
Синдром множественной эндокринной неоплазии

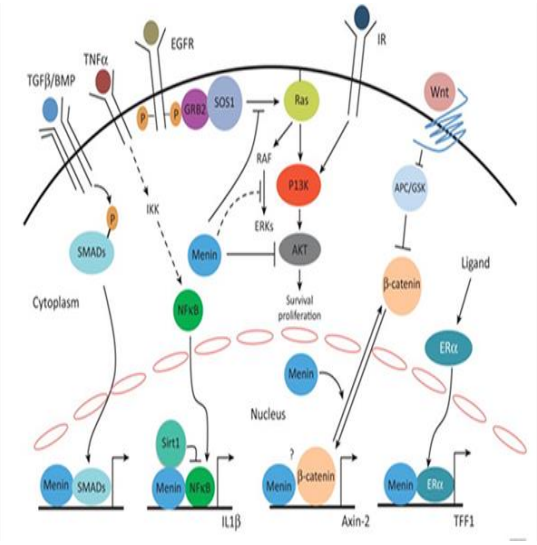


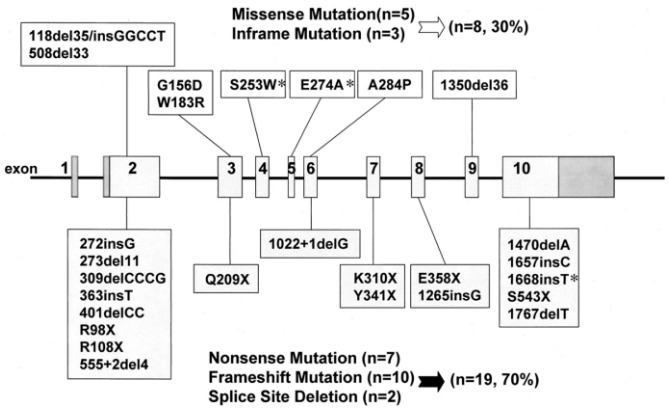


http://www.endocrinesurgery.net.au/men-syndrome-genetics/

https://www.mdanderson.org/cancer-types/multiple-endocrine-neoplasia.html

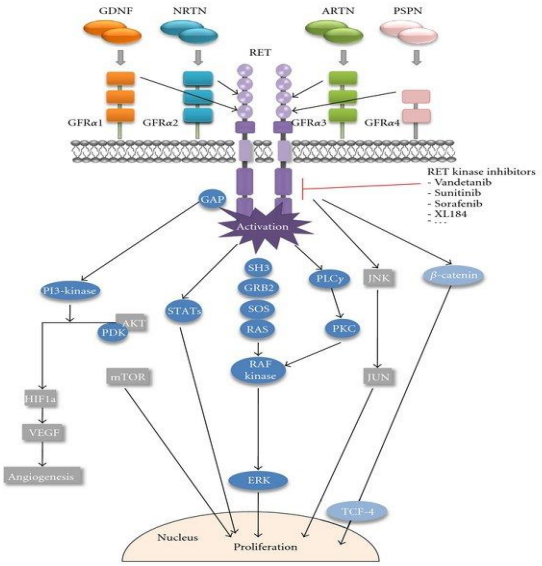
Синдром множественной эндокринной неоплазии тип 1

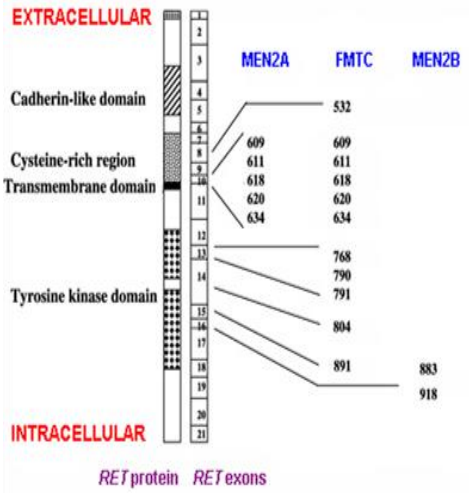




https://www.creative-biogene.com/genesearch/MEN1.html ; Shinya Uchino et al., CANCER RESEARCH Volume 60, Issue 19

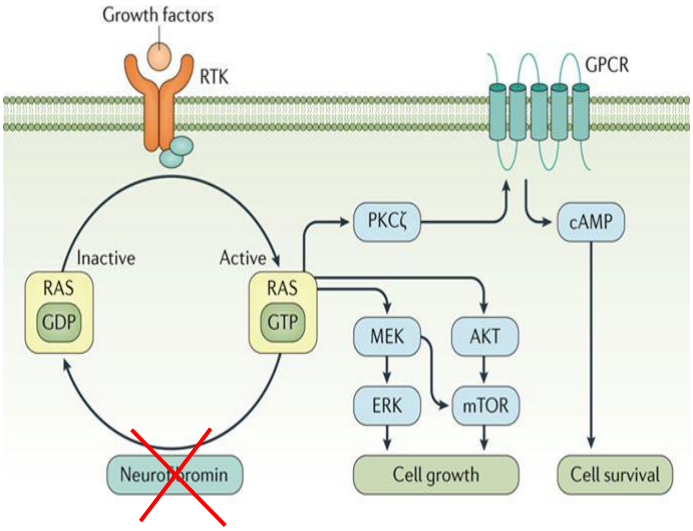
Синдром множественной эндокринной неоплазии тип 2

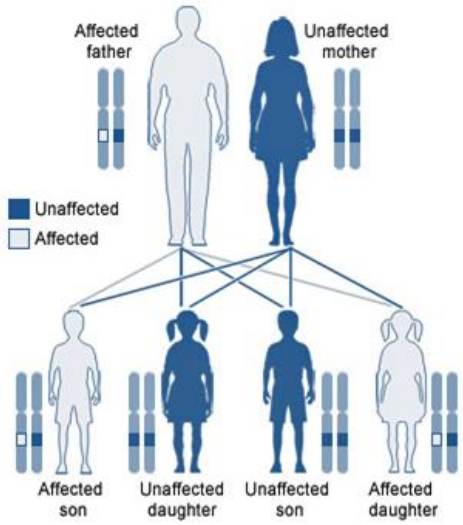




http://www.endocrinesurgery.net.au/men-syndrome-genetics/ https://www.researchgate.net/figure/Outline-of-RET-signalling-pathways_fig1_51499178

Нейрофиброматоз типа 1





https://www.nature.com/articles/nrdp20174?draft=collection

Список генов, участвующих в нейроэндокринном онкогенезе

Gene	Gene function	Chronological classification	Organ specificity
ATM	Chromatin integrity	Unknown	Pancreas
ATRX	ALT	Late	Pancreas, adrenal medulla, paraganglia
CDKN1B	Cell cycle	Unknown	Pancreas, small intestine, parathyroid, anterior pituitary
DAXX	ALT	Late	Pancreas
EPAS1	Cell signaling	Early	Paraganglia, adrenal medulla, duodenum
H-, K-RAS	Cell signaling	Early	Thyroid C-cell, adrenal medulla
FH	Metabolism	Early	Adrenal medulla, paraganglia
KTMD2	Chromatin modification	Unknown	Adrenal medulla
MAX	Cell signaling	Early	Paraganglia, adrenal medulla
MDH2	Metabolism	Unknown	Paraganglia
MEN1	Unknown	Early	Parathyroid, anterior pituitary, endocrine cells in pancreas, duodenum, gastrium, lung, thymus
NF1	Cell signaling	Early	Adrenal medulla, duodenum
RET	Cell signaling	Early	thyroid C-cell, adrenal medulla, parathyroid
SDHx	Metabolism	Early	Paraganglia, adrenal medulla
TERT promoter	Telomere maintenance	Late	Paraganglia
TMEM127	Cell signaling	Early	Paraganglia, adrenal medulla
TP53	Chromatin integrity, Cell signaling	Unknown	Endocrine pancreas, adrenal medulla
TSC1-2	Cell signaling	Unknown	Pancreas
YY1	Transcriptional regulation	Early	Pancreas

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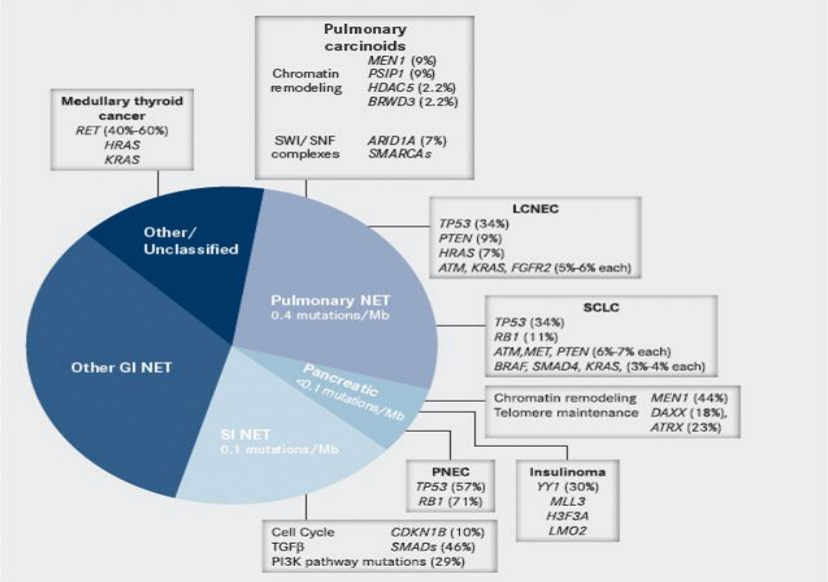
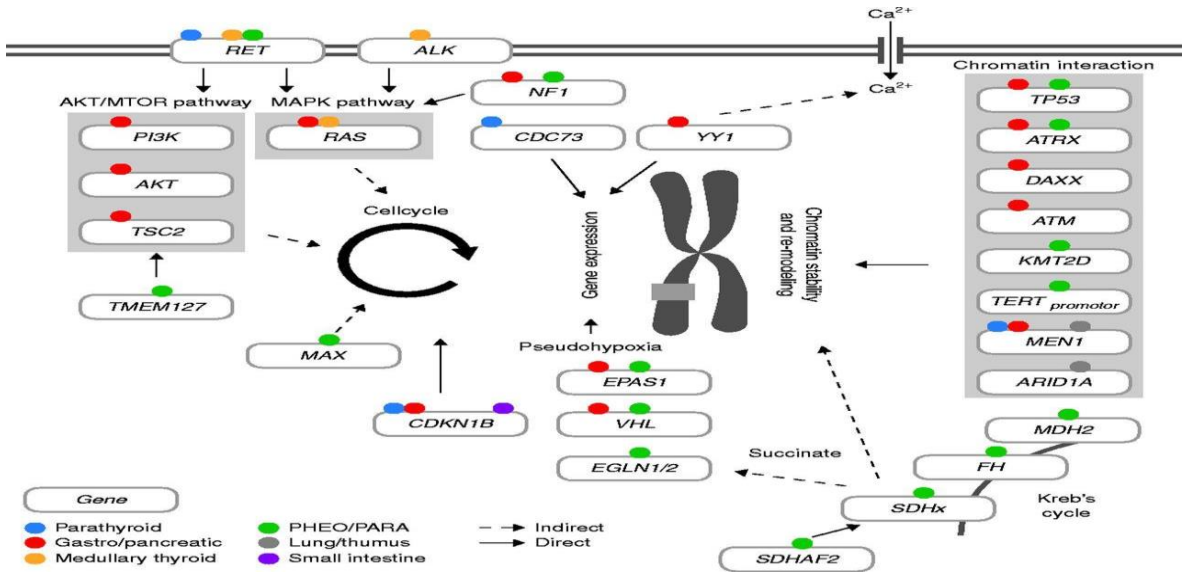
Генетические нарушения при нейроэндокринных опухолях



https://www.onc-central.com/research-spotlight/genomic-diversity-clouds-outlook-for-neuroendocrine-tumors

Сигнальные пути при нейроэндокринных опухолях



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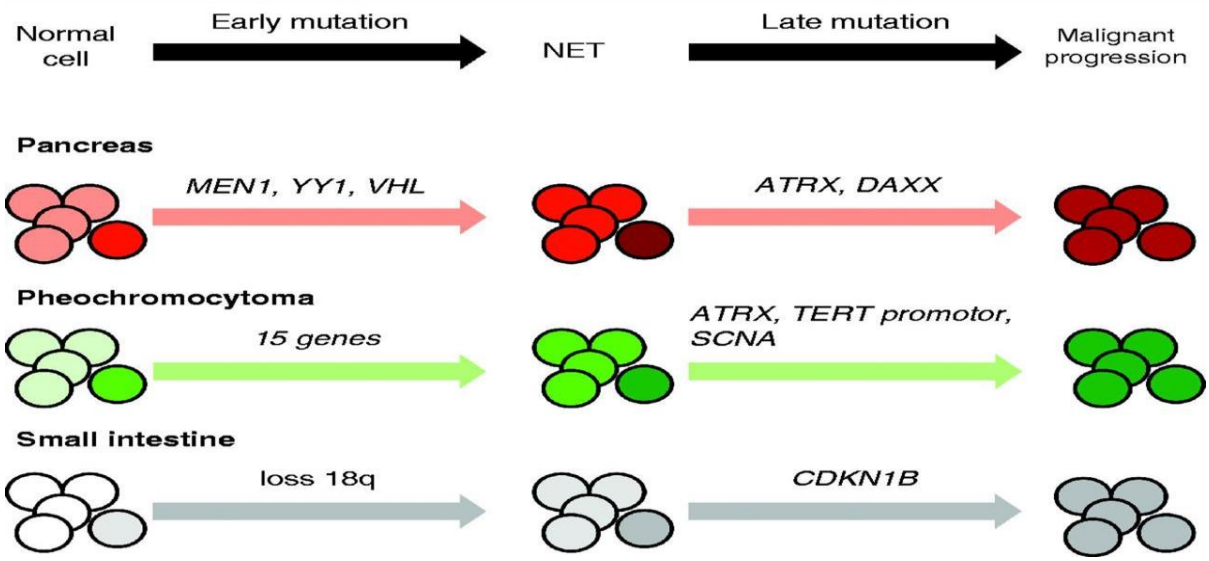
Эволюционная теория нейроэндокринных опухолей



https://eje.bioscientifica.com/view/journals/eje/174/6/R275.xml

Нейроэндокринные опухоли ЖКТ

Пищевода

Экспрессия
KIT
PDGFRA

Желудка

<u>Мутации</u>
TP53 – 50-100%
KRAS,RB1
Потеря гетерозиготности 11p13 (MEN1)

<u>Эпигенетика</u>
Гиперметилирование CDKN2A

Аппендикса

<u>Мутации</u>
Карциноид
CDH1
Карциноид из бокаловидных клеток с карциномой
ARID1A, RHOA, KDM6A, SOX9

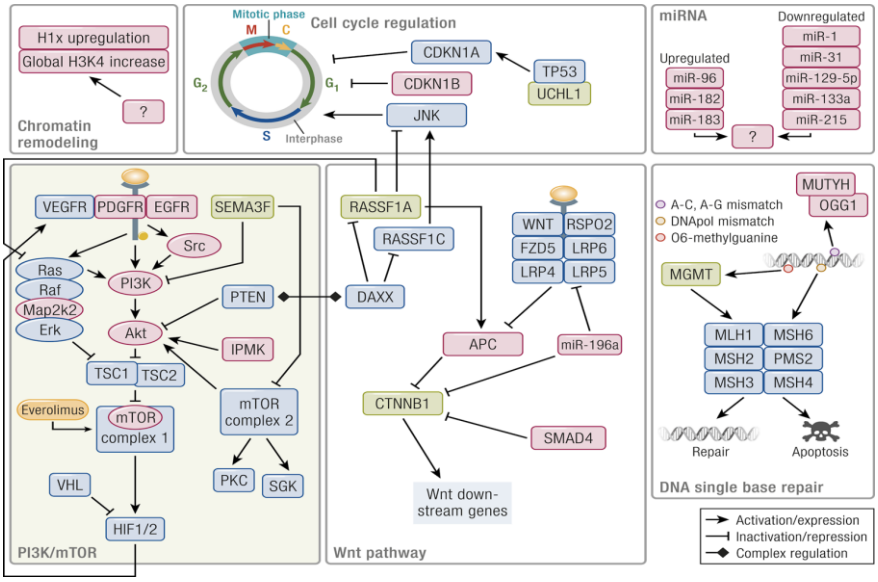
Колоректальные

<u>Мутации</u>
HSPG2
SERPINF2
SMARCA1
(метастазы в печени)

<u>Эпигенетика</u>
В 13% случаев
Метилирование промоторов генов *CDKN2A* (*p16*), *IGF2, MINT1, MINT2, MINT31*, and *MLH1*

слайд к.м.н. Аношкина К.И.

Нейроэндокринные опухоли тонкой кишки



Потеря гетерозиготности 18хр – 76%

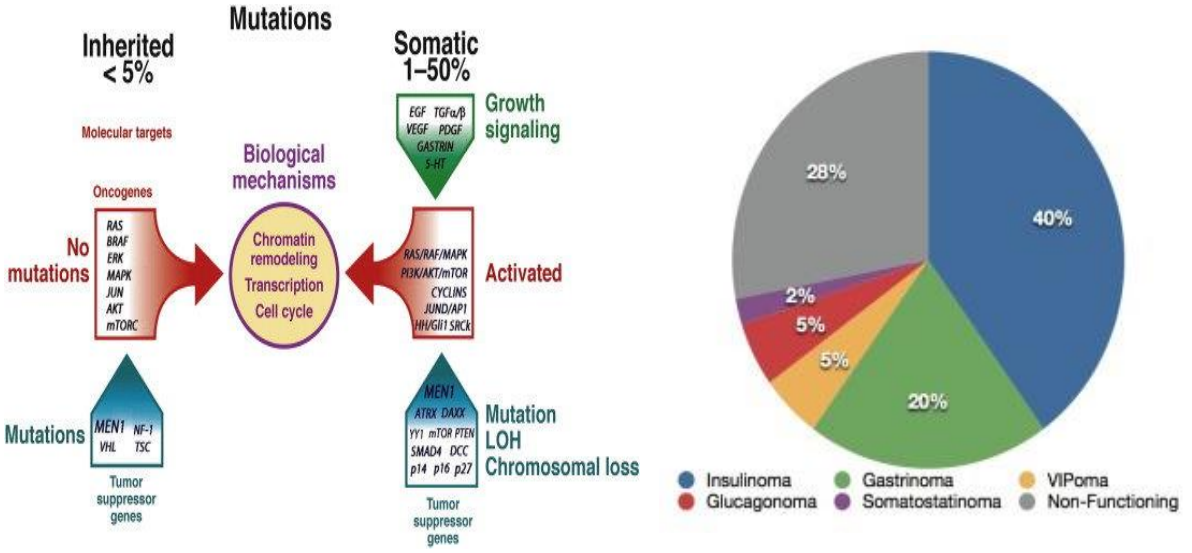
CDKN1B – 8% мутации и 14% делеции локуса

Трисомия 7 хр – 7% (только в метастазах)

APC – 23%

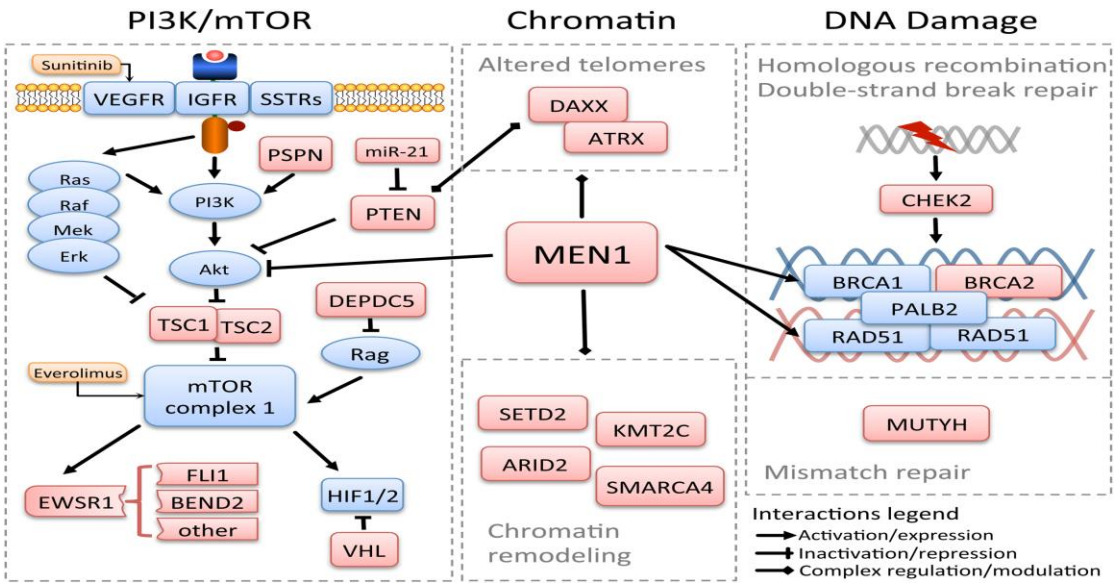
Endocrine Reviews, Volume 40, Issue 2, April 2019, Pages 506–536, https://doi.org/10.1210/er.2018-00160,. слайд к.м.н. Аношкина К.И

Нейроэндокринные опухоли поджелудочной железы



https://www.researchgate.net/figure/Inherited-mutations-have-only-been-identified-in-tumor-suppressor-genes-TSGs-and-occur_fig1_271726350; https://www.gracegawlerinstitute.com/net-cancers/

Сигнальные пути при НЭО поджелудочной железы



Andrea Mafficini et al, Journal of Endocrinology, Volume 236: Issue 3, https://doi.org/10.1530/JOE-17-0560

Нейроэндокринные опухоли легких

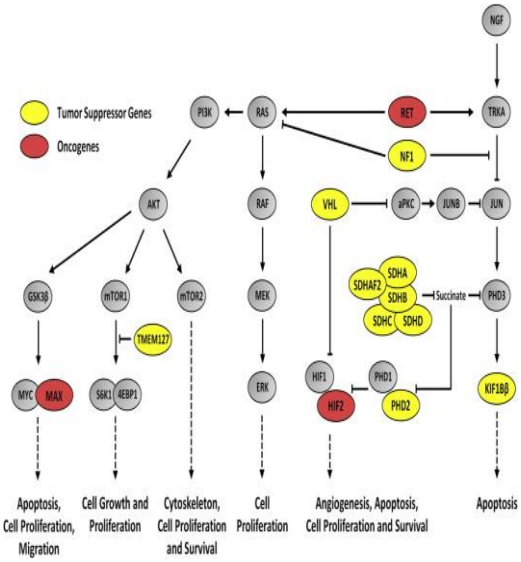
Erratum to: Derks JL, Leblay N, Lantuejoul S, Dingemans A-M, Speel, E-JM, Fernandez-Cuesta L. New insights into the molecular characteristics of pulmonary carcinoids and large cell neuroendocrine carcinomas, and the impact on their clinical management. *J Thorac Oncol.* 2018;13(6):752-766.Journal of Thoracic Oncology, Volume 13, Issue 8, August 2018, Pages 1229

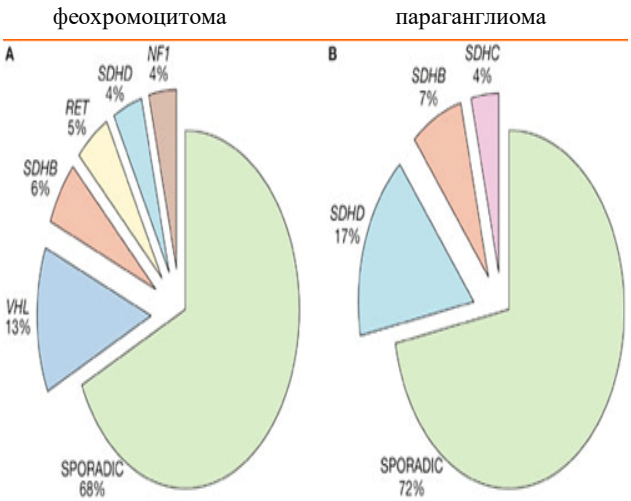
Генетические нарушения при НЭО легких

Type of molecular alteration	Carcinoid	LCNEC	SCLC[a]
Cell Cycle mutations	*TP53* (5%), *RB1* (2%), *APC* (4%)	*TP53* (81%), *RB1* (33%), *ATM* (4%)	*TP53* (92%), *RB1* (75%)
RAS/MAPK pathway	*KRAS* (3%), *EGFR*[a] (2%[b])	*STK11* (18%), *KRAS/NRAS/HRAS* (11%), *ERBB4* (6%), *BRAF*[c] (2%), *EGFR*[c] (2%)	*BRAF* (1%), *KIT* (6%)
PI3K-AKT-mTOR pathway:	*PIK3CA* (2%)	*PTEN* (5%), *PIK3CA* (3%), *NF1* (5%), *INSR* (3%), *TSC2* (2%), *RICTOR* (2%)	*PTEN* (5%)
Oxidative stress response:	—	*KEAP1* (21%)	—
Cell migration/adhesion:	—	*ADAMTS12*[a] (20%), *ADAMTS2*[a] (15%), *EPHA5*[a] (7%), *FAT1* (6%),	—
Neurogenesis/endocrine differentiation:	—	*GAS7*[a] (12%), *NTM*[a] (10%), *PCLO* (5%), *PTPRT*[a] 10%, *CSMD3*[a] (7%) *NOTCH* family: *NOTCH1* (10%), *NOTCH2* (4%), *NOTCH3* (4%), *NOTCH4* (8%)	*NOTCH* family (25%): *NOTCH1* (15%), *NOTCH2* (5%), *NOTCH* 3 (9%)
Epigenetic regulation: *Chromatin remodeling SWI/SNF complex Histone (methyl/ acetyl) transf* E3 ubiquitin-protein ligase	*MEN1* (11%), *EIF1AX*[a] (9%), *PSIP1*[a] (5%), *MLL2*[a] (3%), *MLL3*[a] (5%), *ARID1A* (6%), *ARID2* (2%), *SMARCA4* (3%), *SMARCB1* (3%), *SETD1B*[a] (5%), *HERC2*[a] (5%), *SEC31A*[a] (5%), *WDR26*[a] (5%)	*MEN1/PSIP1 (3%), ARID1A/B* (9%), *MLL1* (3%), *MLL2* (9%), *MLL3* (8%), *ATRX* (4%) *SMARCA4* (5%), *CREBBP/EP300* (7%) —	*EP300* (11%), *CREBBP* (10%)
Amplifications	—	*NKX2-1* (14%), *MYC* family: *MYC* (7%), *MYCL1* (9%) and *MYCN* (1%) *FGFR1* (3%), *SOX2* (3%), *IRS2* (3%)	*MYC* family: *MYCL1* (9%), *MYC* (6%) and *MYCN* (4%) *SOX2* (27%), *FGFR1* (8%)
Deletions	*RB1*[a] (6%), *TP53*[a] (3%)	*RB1* (9%), *CDKN2A* (6%)	*RB1* (13%), *TP73* (7%), *CREBBP* (4%), *PTEN* (4%), *RBL1* (3%)
Commonly altered pathways	Chromatin remodeling	Cell cycle control, oxidative stress response, neuroendocrine differentiation, *PI3K* and *RAS* signaling, chromatin remodeling	Cell cycle control, *PI3K* signaling, neuroendocrine differentiation
Advised routine screening	—	*BRAF* (2%),[c] *EGFR* (2%)[c]	—

Erratum to: Derks JL, Leblay N, Lantuejoul S, Dingemans A-M, Speel, E-JM, Fernandez-Cuesta L. New insights into the molecular characteristics of pulmonary carcinoids and large cell neuroendocrine carcinomas, and the impact on their clinical management. *J Thorac Oncol*. 2018;13(6):752-766.Journal of Thoracic Oncology, Volume 13, Issue 8, August 2018, Pages 1229

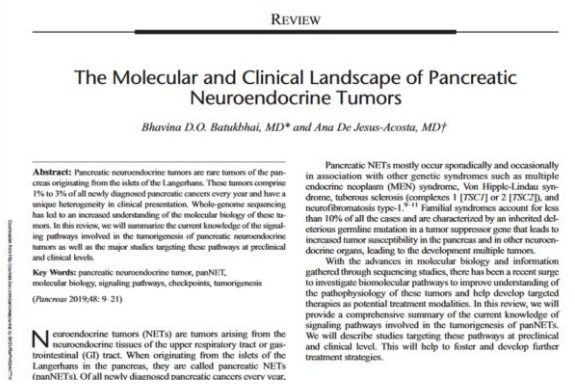
Генетические нарушения при феохромоцитоме и параганглиоме





https://www.sciencedirect.com/science/article/pii/S0090429514000405; https://www.medscape.com/viewarticle/571408_3

Таргетная терапия НЭО



REVIEW

The Molecular and Clinical Landscape of Pancreatic Neuroendocrine Tumors

Bhavina D.O. Batukbhai, MD and Ana De Jesus-Acosta, MD†*

Abstract: Pancreatic neuroendocrine tumors are rare tumors of the pancreas originating from the islets of the Langerhans. These tumors comprise 1% to 3% of all newly diagnosed pancreatic cancers every year and have a unique heterogeneity in clinical presentation. Whole-genome sequencing has led to an increased understanding of the molecular biology of these tumors. In this review, we will summarize the current knowledge of the signaling pathways involved in the tumorigenesis of pancreatic neuroendocrine tumors as well as the major studies targeting these pathways at preclinical and clinical levels.

Key Words: pancreatic neuroendocrine tumor, panNET, molecular biology, signaling pathways, checkpoints, tumorigenesis

(*Pancreas* 2019;48: 9–21)

Neuroendocrine tumors (NETs) are tumors arising from the neuroendocrine tissues of the upper respiratory tract or gastrointestinal (GI) tract. When originating from the islets of the Langerhans in the pancreas, they are called pancreatic NETs (panNETs). Of all newly diagnosed pancreatic cancers every year.

Pancreatic NETs mostly occur sporadically and occasionally in association with other genetic syndromes such as multiple endocrine neoplasm (MEN) syndrome, Von Hipple-Lindau syndrome, tuberous sclerosis (complexes 1 [*TSC1*] or 2 [*TSC2*]), and neurofibromatosis type-1.[9–11] Familial syndromes account for less than 10% of all the cases and are characterized by an inherited deleterious germline mutation in a tumor suppressor gene that leads to increased tumor susceptibility in the pancreas and in other neuroendocrine organs, leading to the development multiple tumors.

With the advances in molecular biology and information gathered through sequencing studies, there has been a recent surge to investigate biomolecular pathways to improve understanding of the pathophysiology of these tumors and help develop targeted therapies as potential treatment modalities. In this review, we will provide a comprehensive summary of the current knowledge of signaling pathways involved in the tumorigenesis of panNETs. We will describe studies targeting these pathways at preclinical and clinical level. This will help to foster and develop further treatment strategies.

Pathway	Drug	Intended Target	Phase
PI3K/AKT/mTOR	Erlotinib and rapamycin	mTOR	Preclinical
PI3K/AKT/mTOR	Perifosine	AKT	Preclinical
PI3K/AKT/mTOR	LY294002	PI3K	Preclinical
PI3K/AKT/mTOR	MK-2206	AKT	Preclinical
PI3K/AKT/mTOR	BEZ235	PI3K, mTORC1/2	Preclinical
PI3K/AKT/mTOR	MK-2206	AKT	Phase I
PI3K/AKT/mTOR	Everolimus vs everolimus + LAR octreotide	mTOR	Phase II
PI3K/AKT/mTOR	Temsirolimus	mTOR	Phase II
PI3K/AKT/mTOR, VEGF	Temsirolimus + bevacizumab	mTOR and VEGF	Phase II
PI3K/AKT/mTOR	Everolimus + LAR octreotide vs placebo + LAR octreotide	mTOR	Phase III
PI3K/AKT/mTOR	Everolimus vs placebo	mTOR	Phase III
VEGF pathway	Sunitinib	VEGF	Preclinical
VEGF pathway	Sunitinib	VEGF	Phase II
VEGF pathway	Bevacizumab	VEGF	Phase II
VEGF pathway	Sorafenib	VEGF	Phase II
VEGF pathway	Pozapanib	VEGF	Phase II
VEGF pathway	Sunitinib	VEGF	Phase III
VEGF pathway, MET	PF-04217903	VEGF, c-MET	Preclinical
VEGF pathway, MET	Cabozantinib	VEGF, c-MET	Phase II
Immune checkpoint	Pembrolizumab	PDL-1	Phase Ib

Batukbhai, B. D. O., & De Jesus-Acosta, A. (2019). *The Molecular and Clinical Landscape of Pancreatic Neuroendocrine Tumors. Pancreas, 48(1), 9–21.* doi:10.1097/mpa.0000000000001189

СПАСИБО ЗА ВНИМАНИЕ!