



北京大学  
PEKING UNIVERSITY



# ABCA12基因致鱼鳞病的生物信息分析

G11 , G13&G18

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# 鱼鳞病

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## 定义及分类

鱼鳞病是一组遗传性角化障碍性皮肤病，主要表现为皮肤干燥。伴有鱼鳞状脱屑。本病多在儿童时发病，主要表现为四肢伸侧或躯干部皮肤干燥、粗糙，伴有菱形或多角形鳞屑，外观如鱼鳞状或蛇皮状。寒冷干燥季节加重，温暖潮湿季节缓解。易复发。多系遗传因素致表皮细胞增殖和分化异常，导致细胞增殖增加和（或）细胞脱落减少。





## 定义及分类

- 1.寻常型鱼鳞病**：为具有不全外显率的常染色体显性遗传病。目前认为是mRNA的不稳定，转录后控制机制缺陷所致。
- 2.性联隐性鱼鳞病**：为X染色体连锁隐性遗传。类固醇硫酸酯酶基因（STS）缺失或突变，造成硫酸胆固醇积聚，角质层细胞结合紧密不能正常脱落，形成鳞屑。
- 3.板层状鱼鳞病**：系常染色体隐性遗传。基因定位多个位点，包括2q33-35、19p12-q12、定位于14q11TGM1基因发生突变、缺失或插入，至细胞粘连和细胞被膜蛋白交联缺陷。
- 4.表皮松解性角化过度鱼鳞病**：为常染色体显性遗传病。致病基因与角蛋白1（K1）和角蛋白10（K10）基因突变有关，导致角蛋白的合成或降解缺陷，影响基底层角质形成细胞内张力微丝的正常排列与功能，进而造成角化异常及表皮松解。
- 5.先天性非大疱性鱼鳞病样红皮病**：为常染色体隐性遗传，由多个基因如脂氧合酶12（R）（ALOX12B）基因、油脂氧化酶3（ALOXE3）基因的突变引起。
- 6.迂回性线状鱼鳞病**：为常染色体隐性遗传病，是由染色体5p32上的丝氨酸蛋白酶抑制剂Kazal5型（SPINK5）基因突变造成。



# ABCA12分析

ABCA12是鱼鳞病的一个致病基因。ABCA12全称为ATP-binding cassette sub-family 12，由ABCA12基因编码。ABCA12属于ATP-binding cassette family，该家族的蛋白主要在细胞膜上转运分子。在一些皮肤类型中表达活跃。我们此次以实际患者为例，对其进行了基因序列测定，发现其该基因的21和47号外显子分别发生了一个突变。

Feature key	Position(s)	Description	Actions	Graphical view	Length
Natural variant <sup>1</sup> (VAR_067076)	387	S → N in ABCA12. <a href="#">1 Publication</a> Corresponds to variant dbSNP:rs746315995	Ensembl.		1
Natural variant <sup>1</sup> (VAR_067078)	1179	G → R in ABCA12. <a href="#">1 Publication</a> Corresponds to variant dbSNP:rs267606622	Ensembl, ClinVar.		1
Natural variant <sup>1</sup> (VAR_019598)	1380	N → S in ABCA12. <a href="#">1 Publication</a> Corresponds to variant dbSNP:rs28940269	Ensembl, ClinVar.		1
Natural variant <sup>1</sup> (VAR_019599)	1381	G → E in ABCA12. <a href="#">1 Publication</a> Corresponds to variant dbSNP:rs28940268	Ensembl, ClinVar.		1
Natural variant <sup>1</sup> (VAR_067080)	1494	I → T in ABCA12; skin phenotype consistent with non-bullous congenital ichthyosiform erythroderma. <a href="#">1 Publication</a>			1
Natural variant <sup>1</sup> (VAR_019600)	1514	R → H in ABCA12. <a href="#">2 Publications</a> Corresponds to variant dbSNP:rs28940270	Ensembl, ClinVar.		1
Natural variant <sup>1</sup> (VAR_019601)	1539	E → K in ABCA12. <a href="#">1 Publication</a> Corresponds to variant dbSNP:rs28940271	Ensembl, ClinVar.		1
Natural variant <sup>1</sup> (VAR_067081)	1559	G → V in ABCA12; skin phenotype consistent with non-bullous congenital ichthyosiform erythroderma. <a href="#">1 Publication</a>			1
Natural variant <sup>1</sup> (VAR_019602)	1651	G → S in ABCA12. <a href="#">1 Publication</a> Corresponds to variant dbSNP:rs28940568	Ensembl, ClinVar.		1
Natural variant <sup>1</sup> (VAR_067082)	1798	P → L in ABCA12; skin phenotype consistent with non-bullous congenital ichthyosiform erythroderma. <a href="#">1 Publication</a> Corresponds to variant dbSNP:rs181314573	Ensembl.		1
Natural variant <sup>1</sup> (VAR_067083)	1980	T → K in ABCA12; skin phenotype consistent with non-bullous congenital ichthyosiform erythroderma. <a href="#">1 Publication</a>			1

这些氨基酸位点的突变引起遗传性严重程度的隐性突变造成先天性鱼鳞病患儿出生时皮肤的鳞屑是极厚的鱼鳞病皮肤未愈合鱼鳞病模型疾病样板状态正童鳞病患者通常受到严重的影响包裹有半膜状的眼睑膜耳廓发育迟缓和情绪大疱性鱼鳞病样皮肤病见盆在身斑痕鳞屑够存累及面部活鬃蹄儿期酌患侧部会鳞屑较重的在腿侧鱼鳞病样躯干、面部和头皮则较细小。



# ABCA12分析——测序

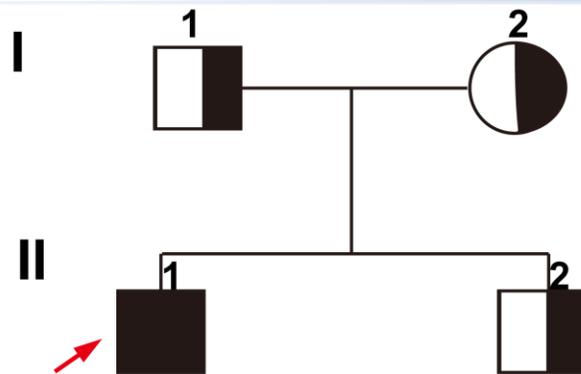
Ensembl网站下载序列

Intron 1-2  
ENSE000009659  
Intron 2-3  
ENSE000009659  
Intron 3-4  
ENSE000010384

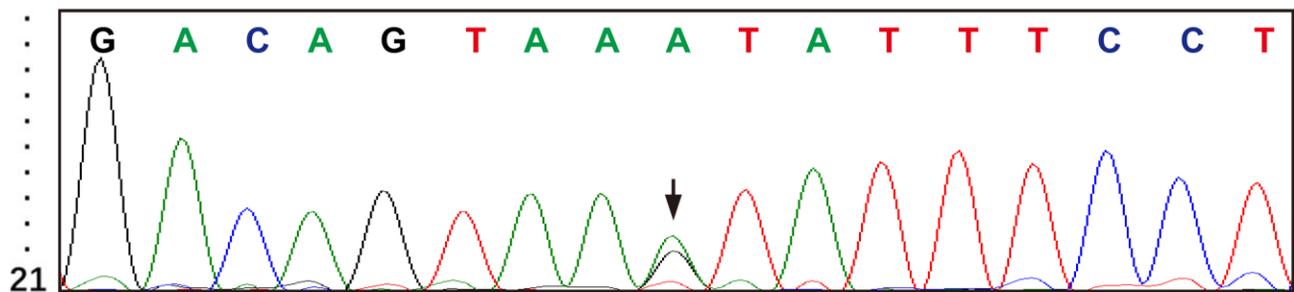
Primer-BLAST设计引物

Primer-BLAST  
Design primers for your

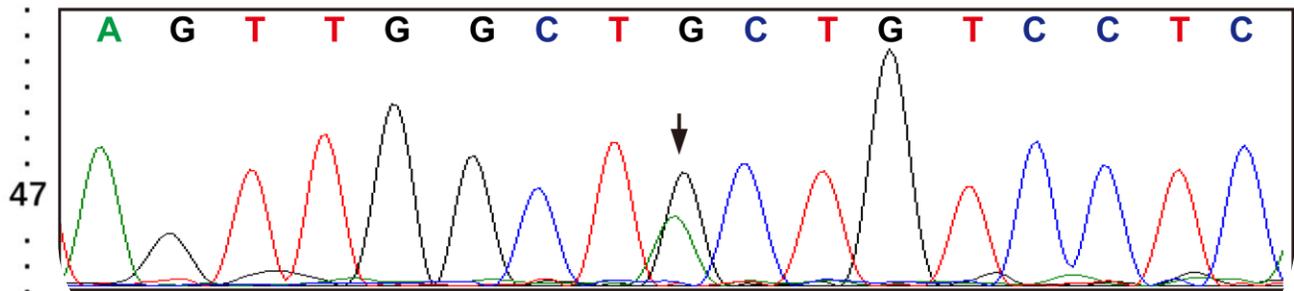
测序及家系分析



Exon  
1  
2  
3  
4+5  
6  
7



Exon 21 c.2759A>G, p.N920S



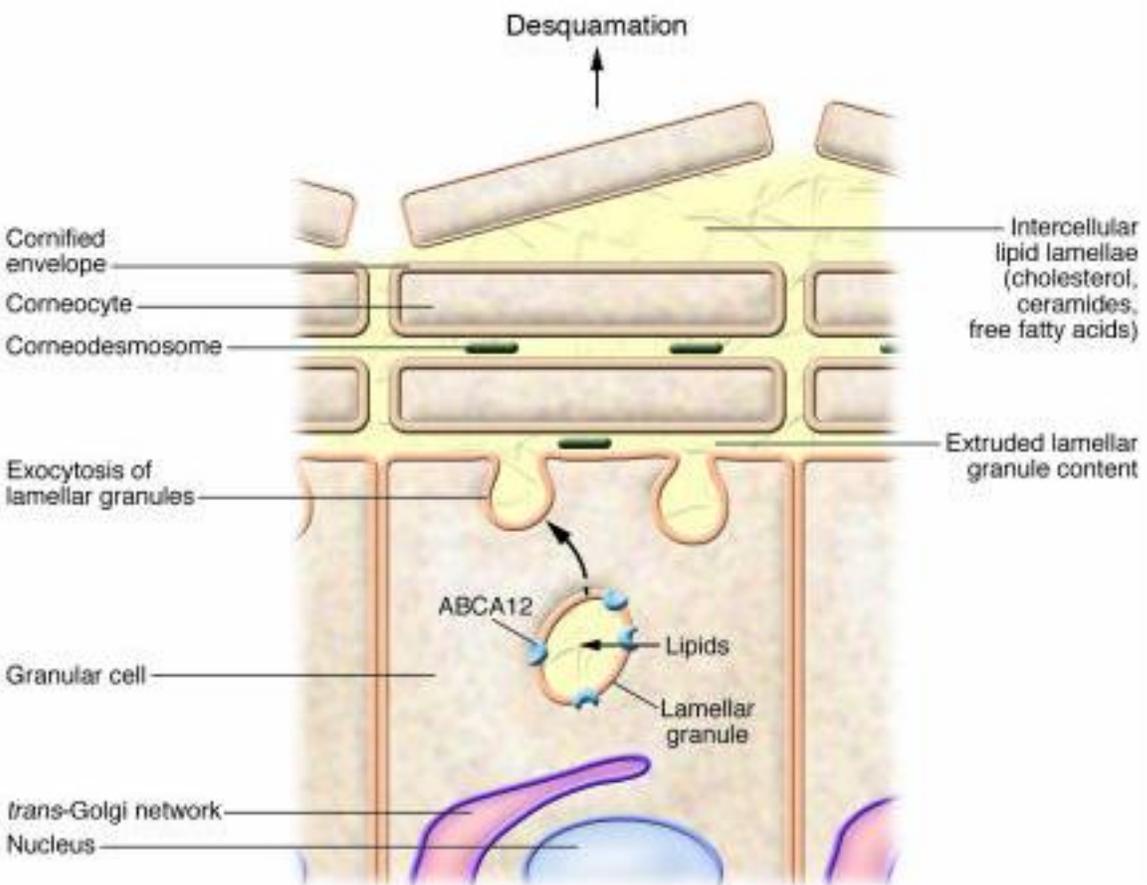
Exon 47 c.7004A>G, p.Y2335C

子  
To  
150  
535

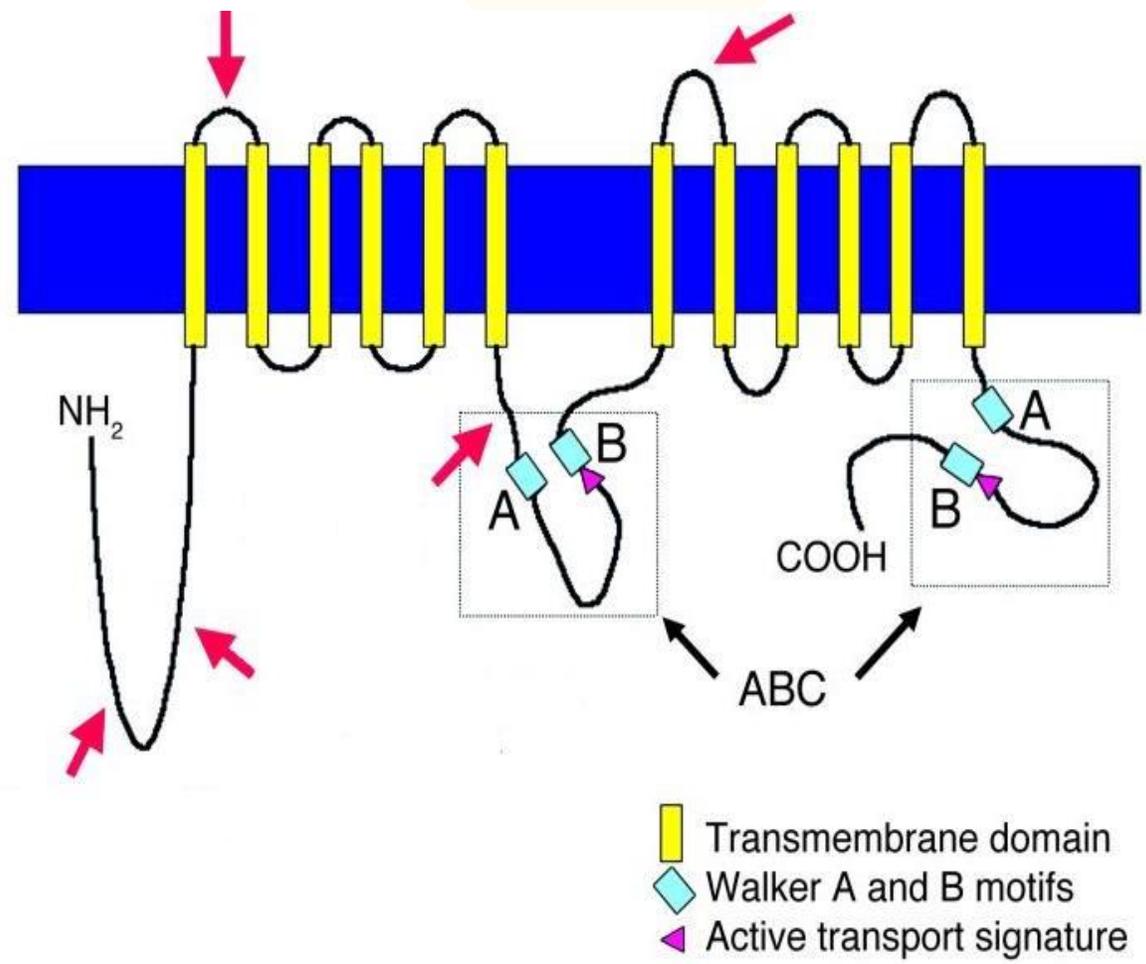


# ABCA12分析——蛋白

功能



蛋白domain





# ABCA12分析——相互作用

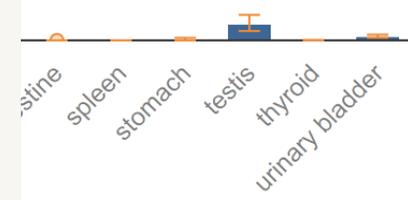
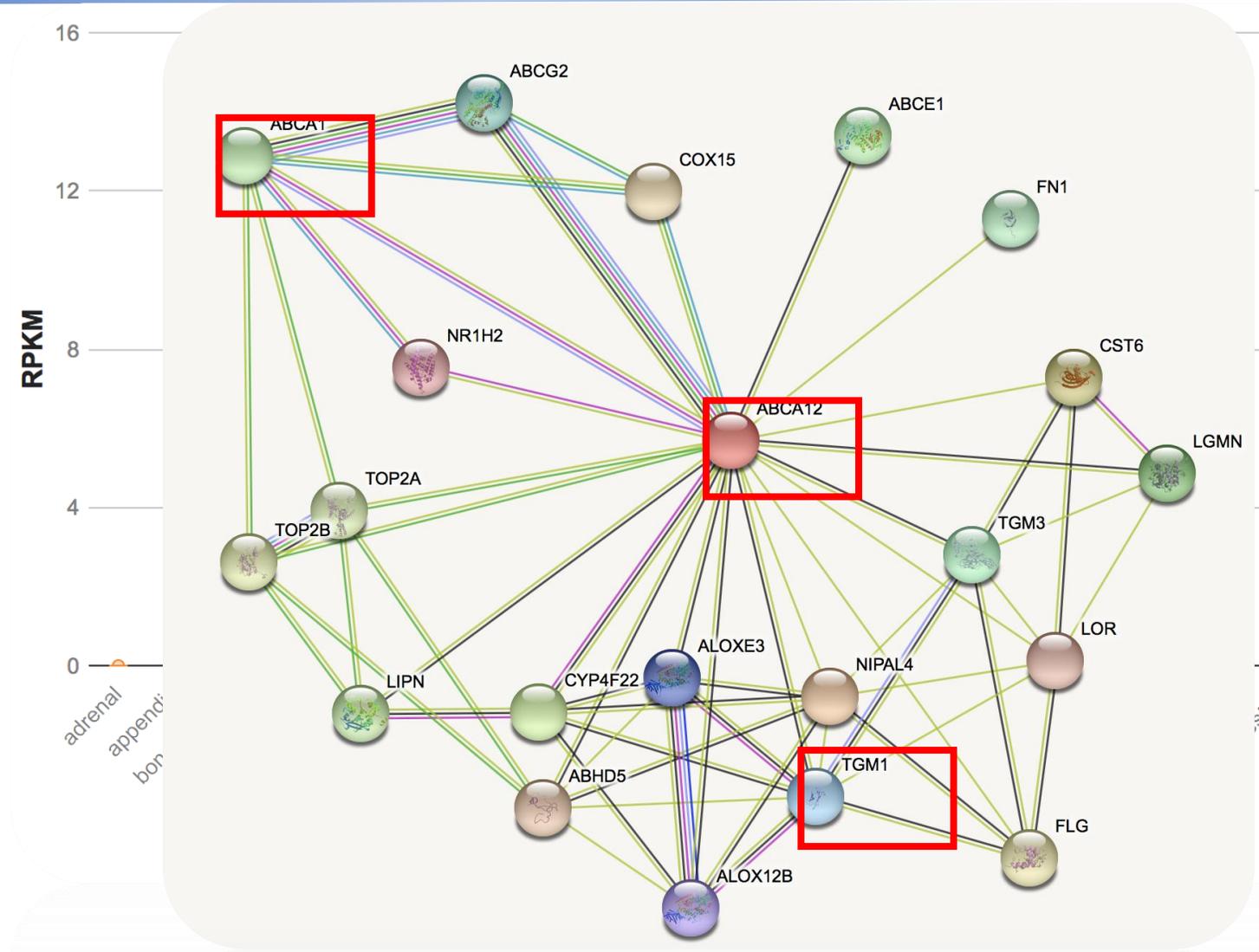
保守性分析  
-UCSC



表达谱分析  
-NCBI

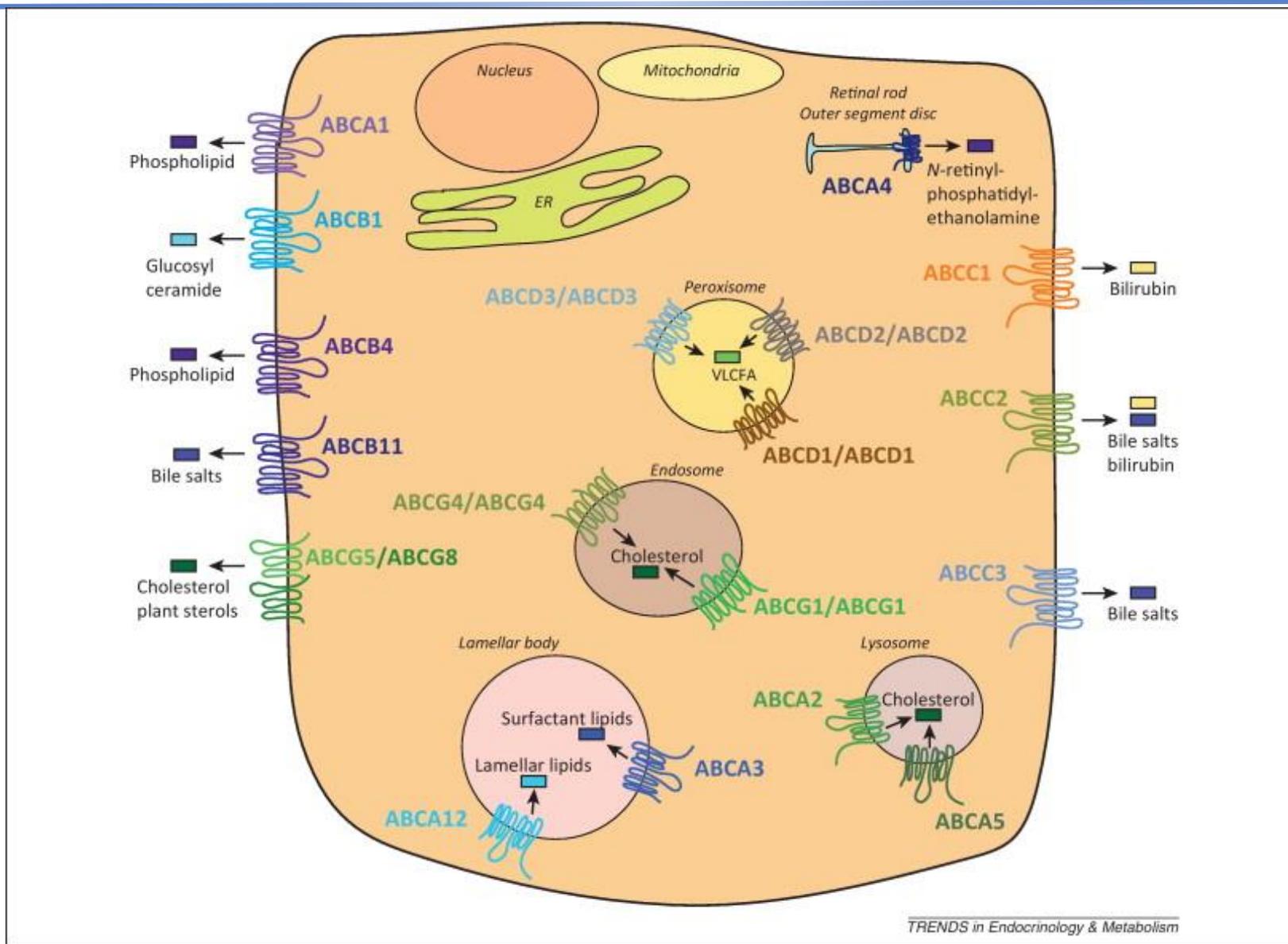


互作蛋白分析  
-String





# ABCA12分析——家族蛋白及功能





# 生物信息分析



结构预测



功能预测



家族序列对比



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## RaptorX: a Web Portal for Protein Structure and Function Prediction

This web portal for protein structure and function prediction is developed by Xu group, excelling at secondary, tertiary and contact prediction for protein sequences without close homologs in the Protein Data Bank (PDB). Given a protein sequence, RaptorX predicts its secondary and tertiary structures as well as contact map, solvent accessibility, disordered regions and binding sites. RaptorX assigns confidence scores to indicate the quality of prediction results. RaptorX-Binding predicts the binding sites of a protein sequence, based upon the predicted 3D model by RaptorX. More details can be found [HERE](#).

Currently the following servers are running. [Instructions](#).

**RaptorX Structure Prediction:** template-based tertiary structure prediction. For only secondary structure prediction, please use RaptorX-Property, which is much faster. This server is **ranked 1st** in the past 3 months in the fully-automated blind test CAMEO. See [here](#) for a ranking list of the publicly-released structure prediction servers.

[Submit][Find jobs by: [ID or sequence](#),[Email](#)][[Example](#)][Refs: [1](#),[2](#),[3](#),[4](#)]

**RaptorX Property Prediction:** protein structure property prediction without using templates, including secondary structure, solvent accessibility, and disordered regions. RaptorX-Property was **ranked 1st in secondary structure prediction** in a third-party evaluation work [published in Briefings in Bioinformatics](#).

[Submit][Find jobs by:[ID or sequence](#),[Email](#)][[Example](#)][Refs:[1](#),[2](#),[3](#),[4](#)][[Software Download](#)]

### Login to your account

Once you submit one job with your email, an account is automatically created for you. Fill in your email address below to see the status of all your jobs.

Email:

### Server Status

82 jobs pending  
302 jobs done in the last 24 hours  
5486 jobs done in the last 30 days

#server users: 40140  
#processed jobs: 247640

[74479](#) Visits since [September 27, 2015](#)



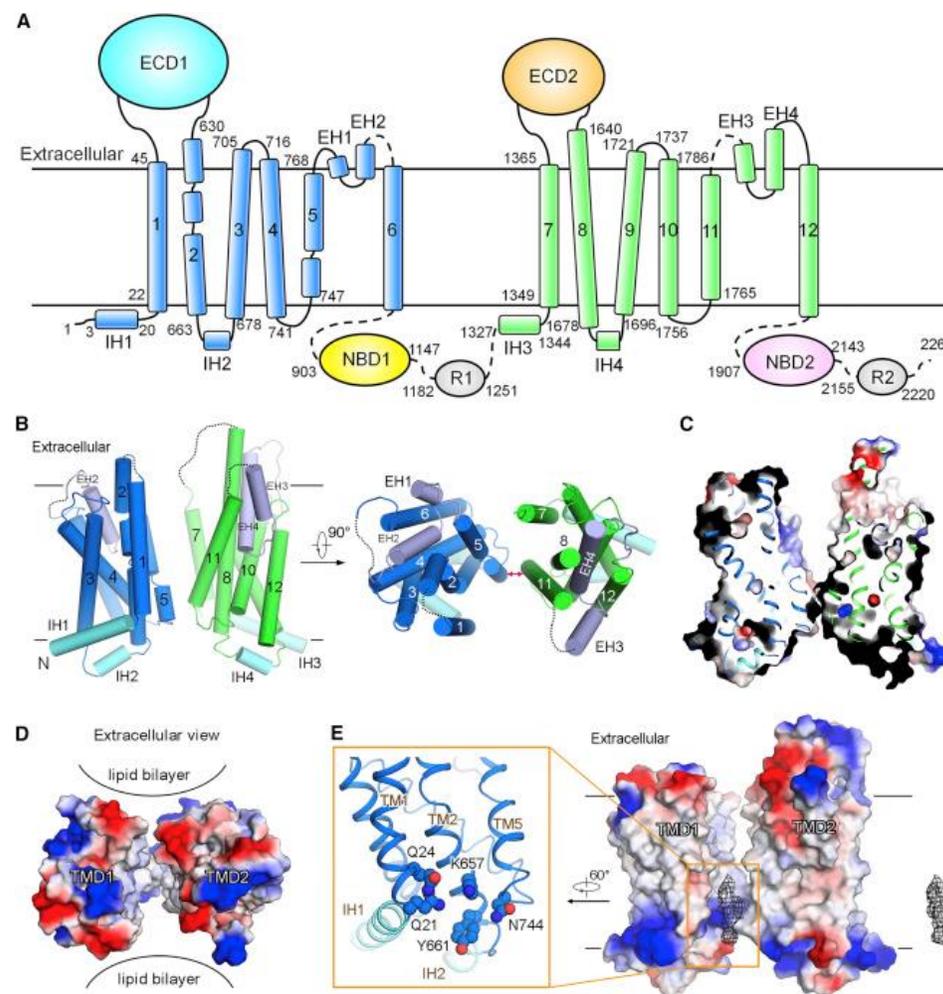
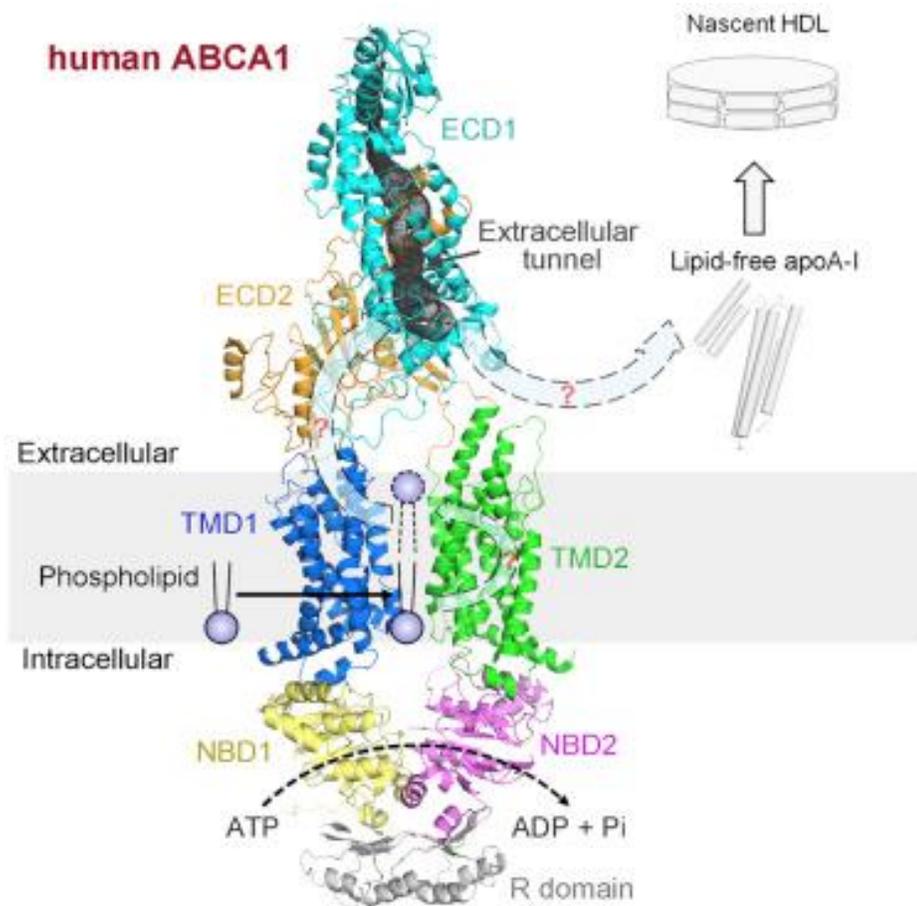
RaptorX Structure Prediction

RaptorX Property Prediction

RaptorX Contact Prediction

RaptorX Binding Prediction

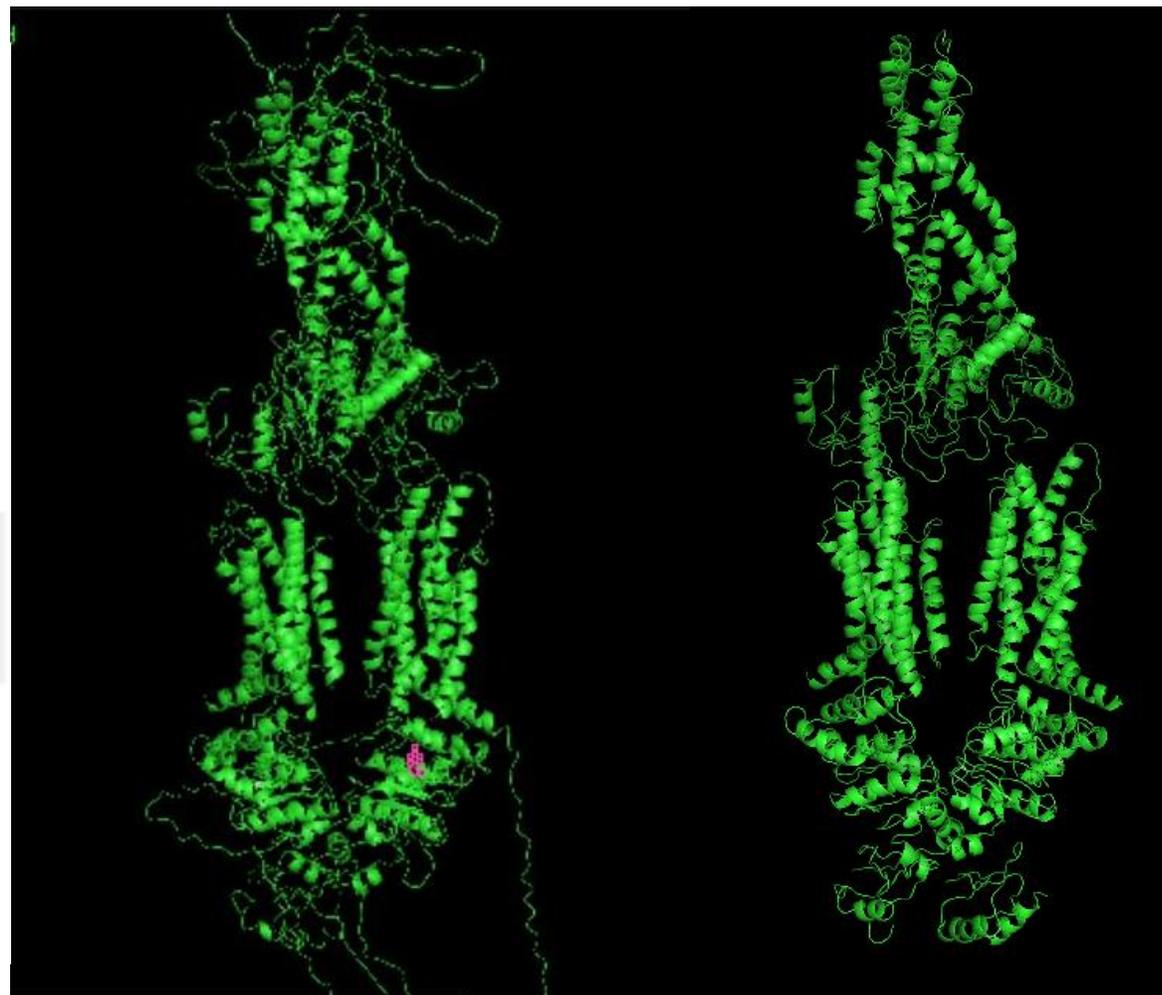
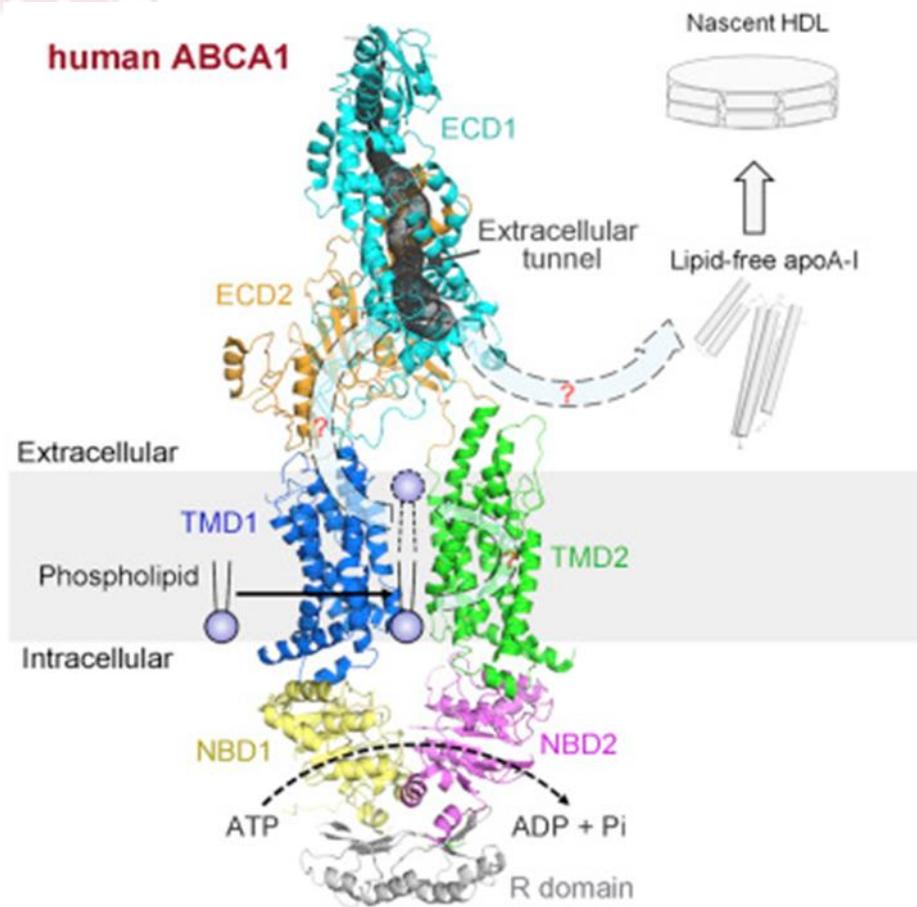
RaptorX Structure Alignment





## ABCA12 and ABCA1 seq alignment

LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
2808	3301.5	820/2808 (29.2%)	1289/2808 (45.9%)	760/2808 (27.1%)



ECD

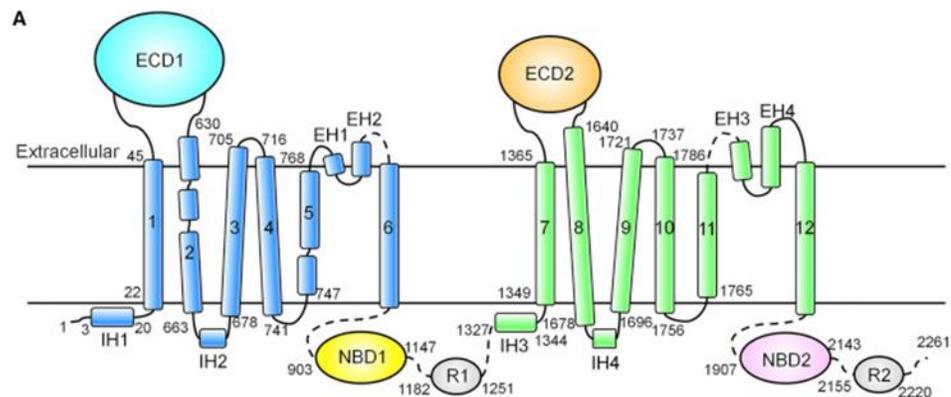
TMD

NBD

Qian, *et al. Cell* 2017

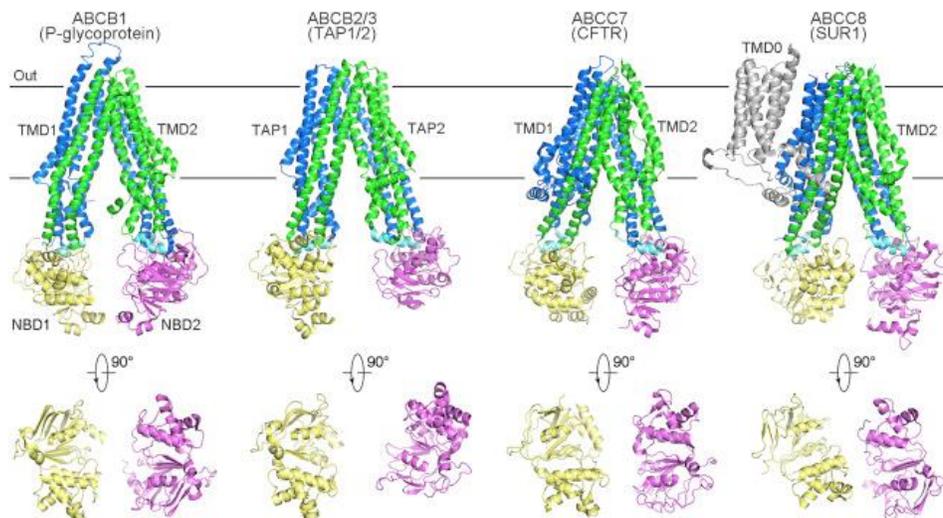
RaptorX

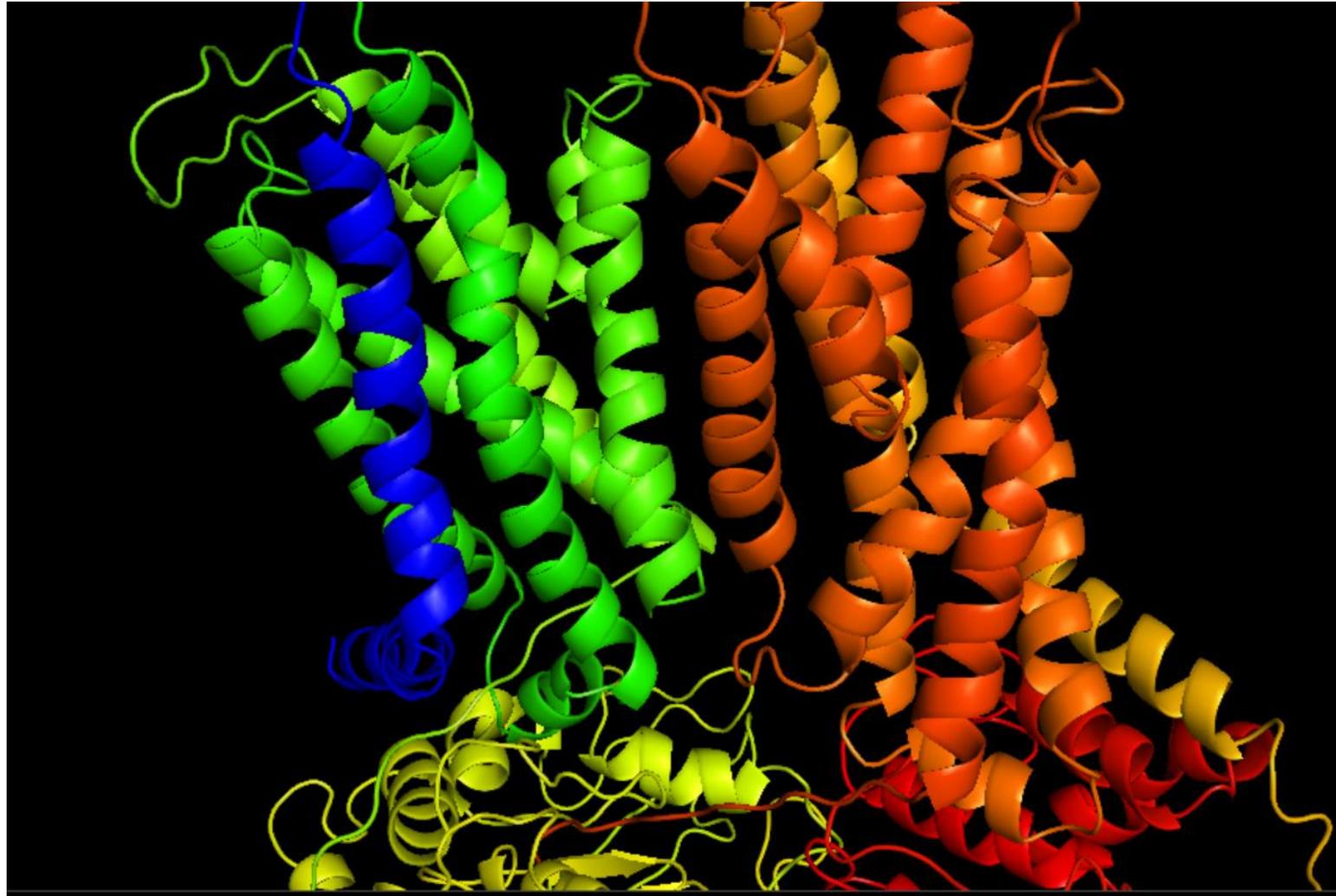
Phyre



2 TMDs

6 transmembrane helices



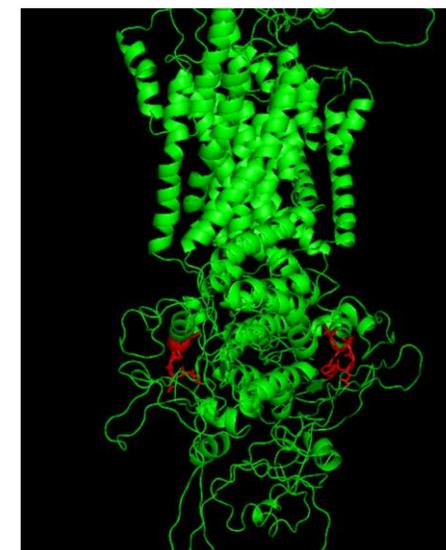
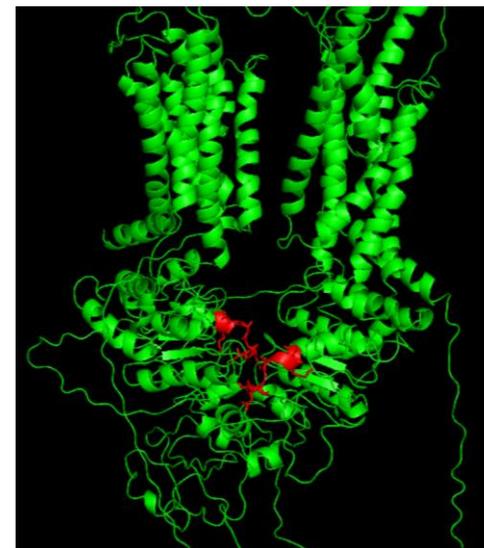
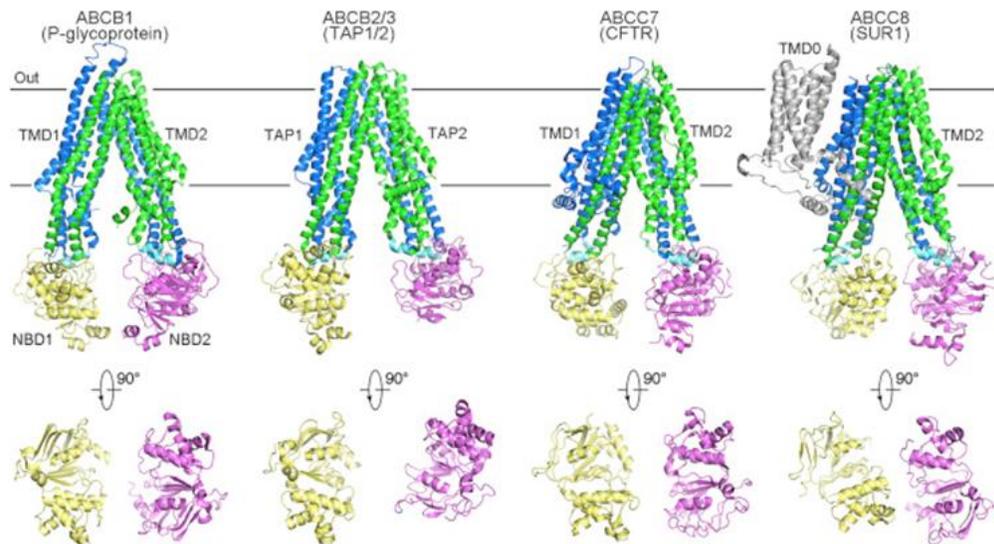




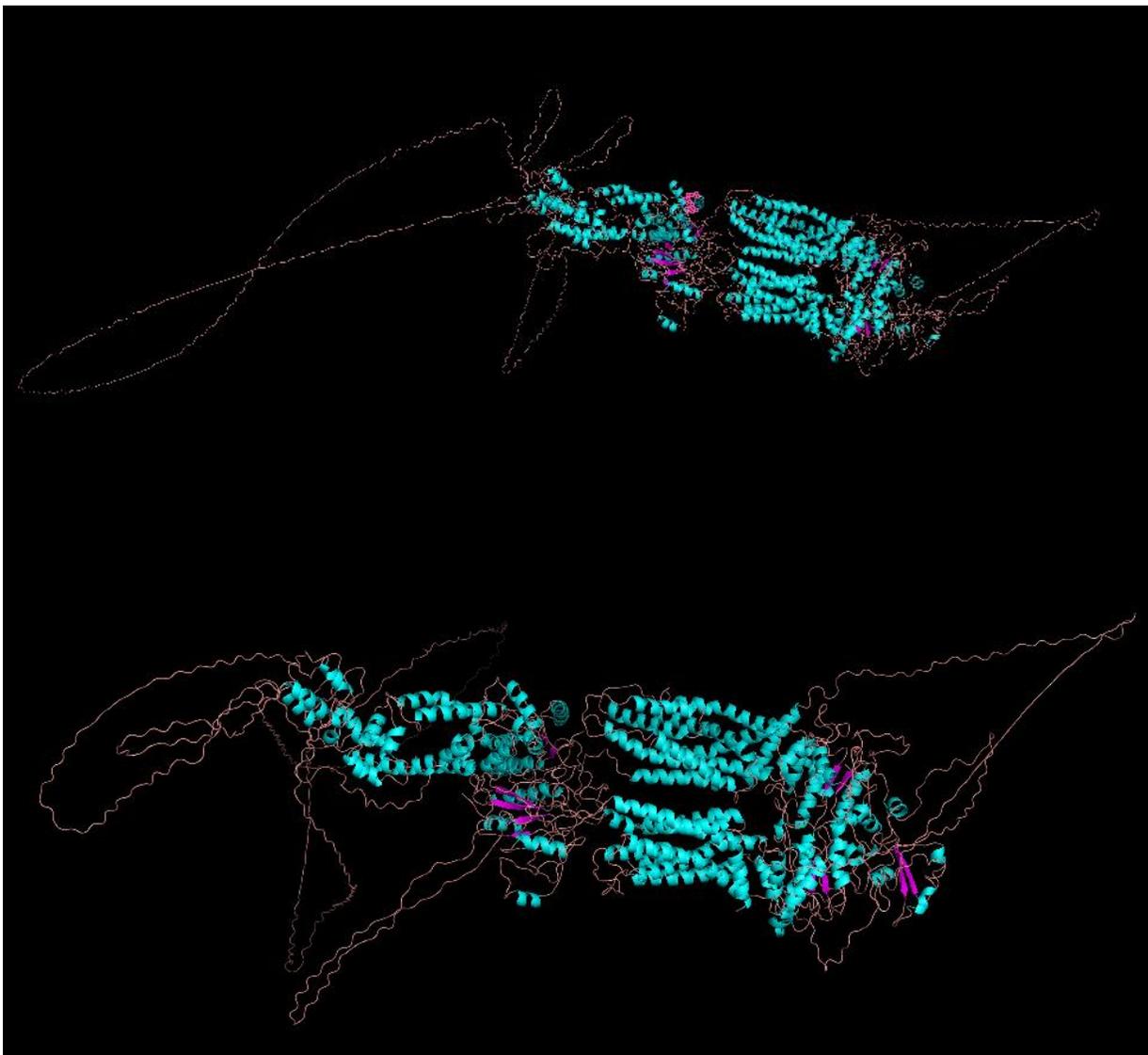
ABCA12 has two nucleotide-binding sites:

1378-1375 GPNGAGKT

2290-2297 GVNGAGKT



Qian, *et al. Cell* 2017

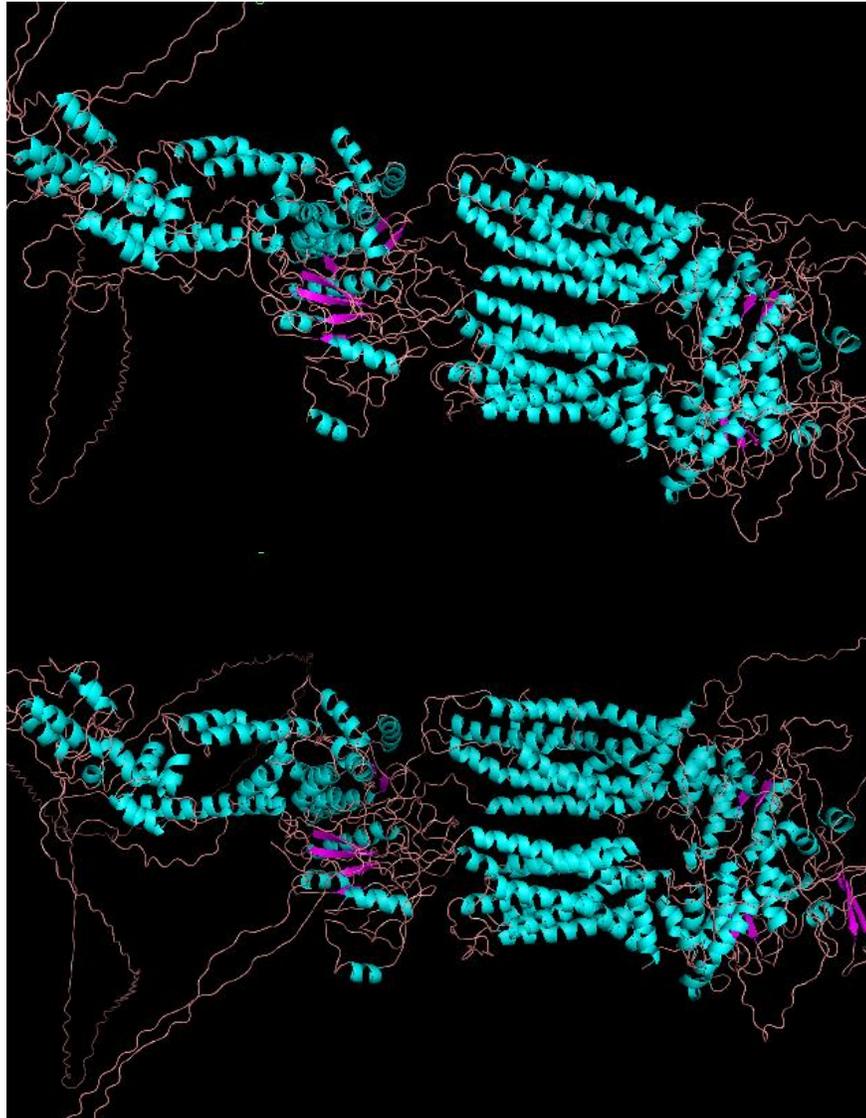


Normal

Two mutation:

N920S

Y2335C



Normal

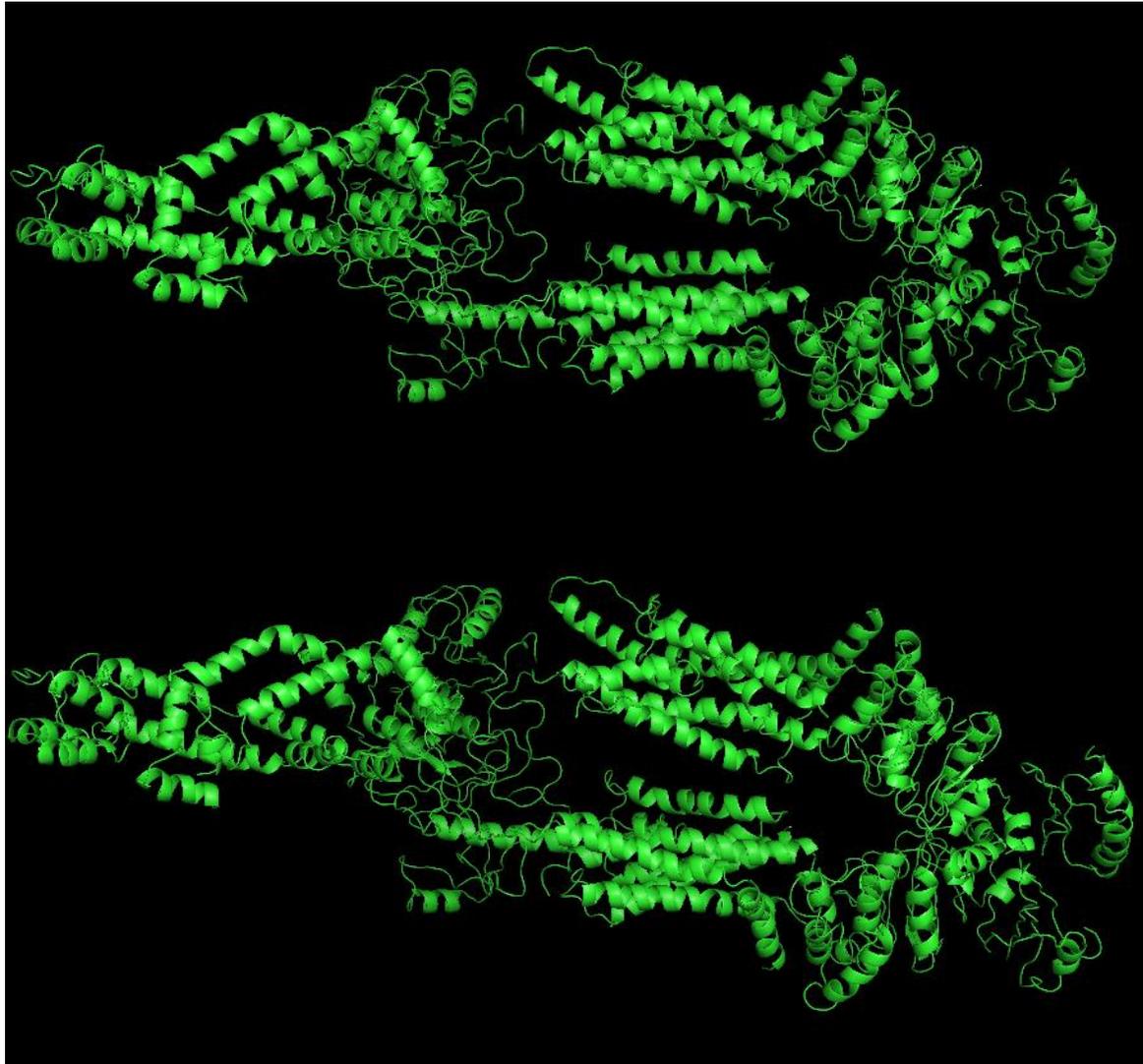
Two mutation:

N920S

Y2335C



# 生物信息分析——结构预测 ABCA12 mutant structure prediction by Phyre2

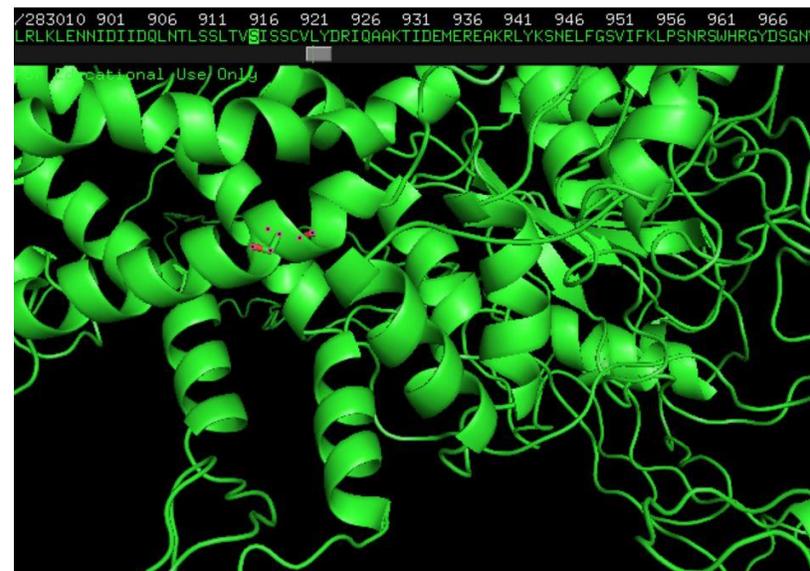
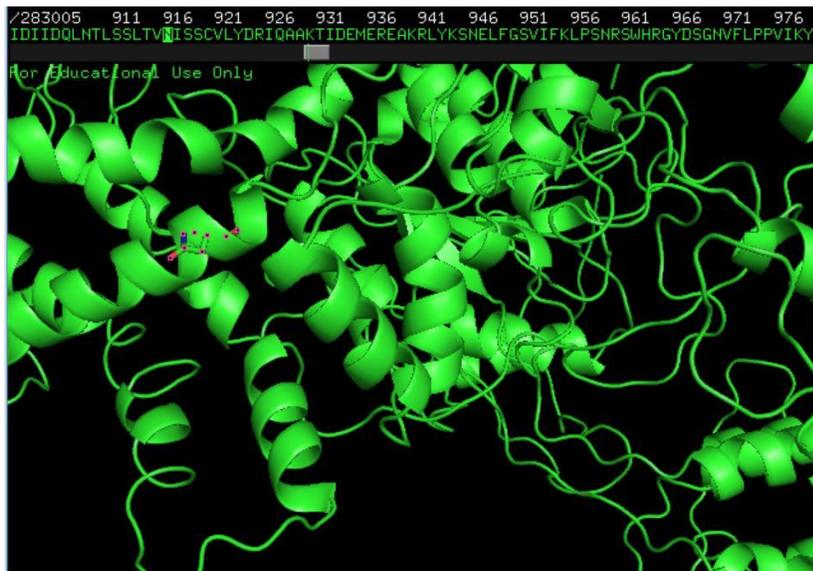


Normal

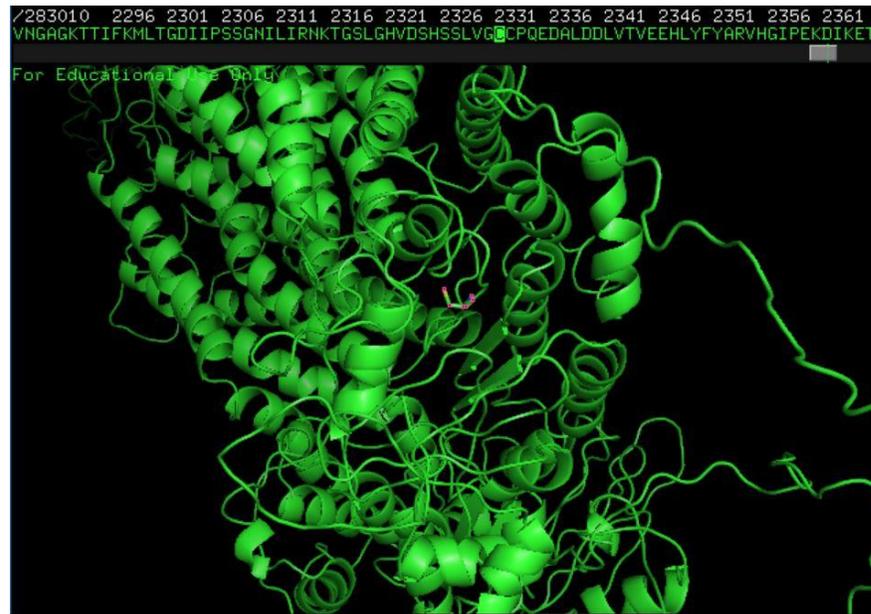
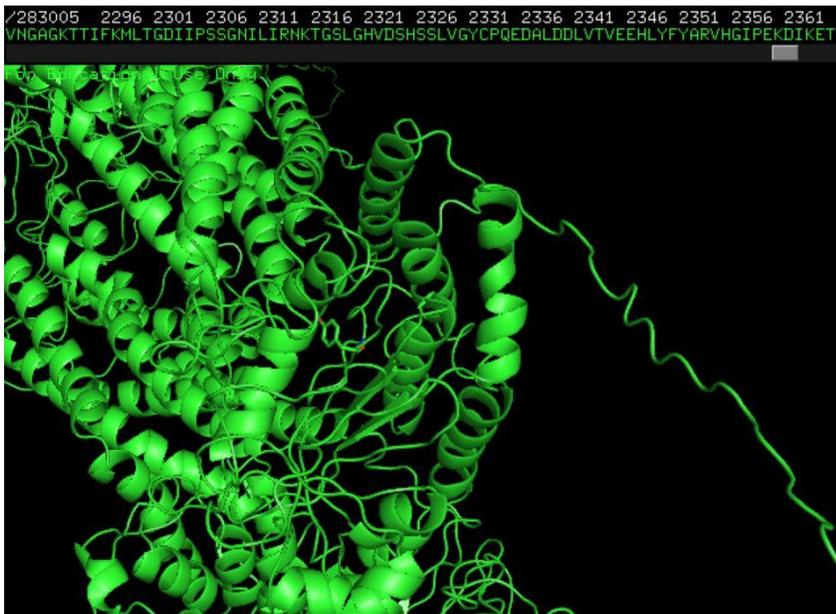
Two mutation:

N920S

Y2335C



N920S mutation  
extracellular domain ( ECD )



Y2335C mutation  
transmembrane domain ( TMD )



# 生物信息分析——家族序列比对

# ABCA家族蛋白多序列比对

Protein Sequences

Species/Abb	Group Name	Sequence
1. ABCA1		IY S V A V I I K G I V Y E K E A R L K E T M R I M G L D N S I L W F S W F I S S L I P L L V
2. ABCA2		V Y S V A M T I Q H I V A E K E H R L K E V M K T M G L N N A V H W V A W F I T G F V Q L S I
3. ABCA3		T Y T A L T I A R A V V Q E K E R R L K E Y M R M G L S V L H W S A W F I L T G F V Q L S I
4. ABCA4		I Y S V S M T V K S I V L E K E L R L K E T L K N Q G V S N A V I W C T W F L D S F S I M S M
5. ABCA5		S P F G Y F L A I H I V A E K E K K I K E F L K I M G L H D T A F W L S W V L L Y T S L I F L
6. ABCA6		S P L V Y F I S L N V T K E R - K K S K N L M K M M G L Q D S A F W L S W G L I Y A G F I F I
7. ABCA7		I Y S V T L T V K A V V R E K E T R L R D T M R A M G L S R A V L W L Q W F L S C L G P F L L
8. ABCA8		S S F I Y Y A S V N V T R E R - K R M K A L M T M M G L R D S A F W L S W G L L Y A G F I F I
9. ABCA9		S T F I Y Y V S V N V T Q E R - Q Y I T S L M T M M G L R E S A F W L S W G L M Y A G F I L I
10. ABCA10		S S F I Y F A S L N V A R E R - G K F K K L M T V M G L R E S A F W L S W G L T Y I C F I F I
11. ABCA12		V V F I A A F V K K L V Y E K D L R L H E Y M K M M G V N S C S H F F A W L I E S V G F L L V

Species/Abb	Group Name	Sequence
1. ABCA1		--K I F A S L L S P V A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P
2. ABCA2		F E K C I A S L M S T T A F G L G S K Y F A L Y E V A E R V D I W H F F S Q S P V E E D F N L L L A V T M L M V D A V V G I L T W Y I E A V F P G M G L P R P W Y F P
3. ABCA3		--K L C S C L L S N V A M G A D L K F E A K E M G I Q W R D L L S P V V D E D F C F G V M G L L L L S V L G L L Y W Y E A V F P G F G V P P R P W Y F F
4. ABCA4		--K K A V S L L S P V A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P
5. ABCA5		--M L F S P F C H C T V I G I A E V M H L E D F N E G A F S N L T ---A G P P Y L I I T I M L T L M S I F Y V L L A V Y L D V I P G E P G L R R S S L Y F
6. ABCA6		--W I L N I G S P P A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P
7. ABCA7		--R V A A S L L S P V A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P
8. ABCA8		--W I L S L L S P P A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P
9. ABCA9		--W T L C L L S P P A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P
10. ABCA1		--W V L S L L S P P A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P
11. ABCA1		--K V F M S L L S P P A F G C E Y F A L F E E G I G V Q W D L F E S P V E E D G F N L T T S V S M M L F D T F L G V M T W Y I E A V F P G Y G I P R P W Y F P

Species/Abb	Group Name	Sequence
1. ABCA1		N F Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G K D I R E M S T I R N L G V C P O H N V L D M L T V E E H I W F Y A R L K G - - L
2. ABCA2		N Y E N G V S F L G H N G A G K T T I S M T G L F P P T S G A Y I L - - G H D I R E M S T I R N L G V C P O H N V L D M L T V E E H L W F Y A R L K G - - M
3. ABCA3		N Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G Y E I S G D M V I R K S L G C P O H N V L D M L T V A E H L Y F A D L K G - - L
4. ABCA4		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G R D I E T S L A V R R S L G C P O H N V L H H L T V A E H M L F A S L K G - - K
5. ABCA5		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G H D V R S S M A A I R P H L G V C P O H N V L D M L T V E H V W F Y G R L K G - - I
6. ABCA6		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G H D V R S S M A A I R P H L G V C P O H N V L D M L T V E H V W F Y G R L K G - - I
7. ABCA7		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G H D V R S S M A A I R P H L G V C P O H N V L D M L T V E H V W F Y G R L K G - - I
8. ABCA8		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G H D V R S S M A A I R P H L G V C P O H N V L D M L T V E H V W F Y G R L K G - - I
9. ABCA9		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G H D V R S S M A A I R P H L G V C P O H N V L D M L T V E H V W F Y G R L K G - - I
10. ABCA1		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G H D V R S S M A A I R P H L G V C P O H N V L D M L T V E H V W F Y G R L K G - - I
11. ABCA1		H Y E G H T I L L G N G A G K T T I S M T G L F P P T S G A Y I L - - G H D V R S S M A A I R P H L G V C P O H N V L D M L T V E H V W F Y G R L K G - - I

Species/Abb	Group Name	Sequence
1. ABCA1		V I L D E P T A G V D P Y S R R G I W E L L L K Y R Q G R T I I L S T H H M D E A D V L G D R T A I I S H G K L C C G S S L F L K N Q L G T G Y Y L I
2. ABCA2		I I L D E P T A G V D P Y A R R A I W D L I L K Y K P G R T I I L S T H H M D E A D L L G D R T A I I S H G K L C C G S S L F L K N Q L G T G Y Y L I
3. ABCA3		L I L D E P T A G V D P Y S R R G I W E L L L K Y R Q G R T I I L S T H H M D E A D L L G D R T A I I A M K E L C C G S S L F L K K Q G A G Y H M I
4. ABCA4		V I L D E P T A G V D P Y S R R S I W D L L L K Y R S G R T I I M S T H H M D E A D I L D R T A I I A G R L Y C S G T P L F L K N C F G T G L Y L I
5. ABCA5		V I L D E P T A G M D P S R R H I W N L L K Y R K A N R V I F S T H H M D E A D I L A D R K A V I S G M L K C G S S M F L K S W G I G Y R L S
6. ABCA6		L L L D E P T A G L D P S R R G I W D L L R R A R A D V I L F S T G S M D E A D I L A D R K V I M S N G R L K C A G S S M F L K R R W G I G Y H L S
7. ABCA7		V I L D E P T A G V D P A S R R G I W E L L L K Y R E G R T I I L S T H H L D E A D E L L G D R V A V V A G R L C C G S S L F L R R H L S G Y Y L I
8. ABCA8		- L L D E P T A G L D P S R R H Q V W N L L K E R K T D R V I L F S T G F M D E A D I L A D R K V F L S G K L K C A G S S L F L K K K W G I G Y H L S
9. ABCA9		L L L D E P T A G L D P S R R H I W N L L K E G K S D R V I L F S T G F I D E A D I L A D R K V F I S N G L K C A G S S L F L K K K G I G Y H L S
10. ABCA1		L L L D E P T A G L D P S R R H V W S L L K E H K V D R L I L F S T G F M D E A D I L A D R K V F I S N G L K C A G S S L F L K K K G I G Y H L S
11. ABCA1		V I L D E P T A G V D P S R R S I W D V I S K K T A R T I I L S T H H L D E A E V L S D R T A F L E G G L R C C G S P F Y L K E A F G G Y H L S

使用clustal W对ABCA蛋白家族进行多序列比对：  
可以看到，第一个保守位点在1123处才出现，且越往后保守位点越多越密集，所以可以推断，ABCA家族所共有的功能位点处于序列较后部，前段变异性大，预示着不同分子间不同的分子生物学功能。

Protein Sequences

Species/Abb	Group Name	Sequence
1. ABCA1		R K H V S E A R L V E D I G H E L T Y V L P - Y E A A K E G A F V E L F H E I D D R L S D L G I S S Y G I S E T T L E E I F L K V
2. ABCA2		R K H V A S C L L V S D T S T E L S Y I L P - S E A A K K G A F E R L F Q H L E R S L D A L H L S S F G L M D T T L E E V F L K V
3. ABCA3		H H H V P N A T E S S A G A E L S F I L P - R E S T H R - - F E G L F A K L E K K Q K E L G I A S F G A S I T M E E V F L R V
4. ABCA4		L H H V P E A K L V E C I G O E L I F L L P - N K F K H R A Y A S L F R E L E E T L A D L G L S S F G I S D T P L E E I F L K V
5. ABCA5		K Q H I P G A T L L Q N D Q L V Y S L P - - - F K D M D K F S G L F S A L D S H S - N L G V I S Y G V S M T T L E V F L K L
6. ABCA6		T H H I P D A K K T E N K E K L V Y T L P - - - L E R T N T F P D L F S D L D K C S - D G G V T G Y D I S M D S T L E V F M K L
7. ABCA7		Q H W P G A R V E E L P H E L V L V L P - Y T G A H D G S F A T L F R E L D T R L A E L R T G Y G I S I D S T L E E I F L K V
8. ABCA8		K Q H I P D A K K T E N K E K L I Y T L P - - - L E R T N T K F P E L Y K D L D S Y P - D L G I E N Y G V S M T T L N E V F L K L
9. ABCA9		K Q H I S D A K T T E S E E K L V Y I L P - - - L E R T N T K F P E L Y R D L D R C S - N G G I E D Y G V S I T T L N E V F L K L
10. ABCA1		K Q H I P D A K K T T E S E E K L V Y S L P - - - L E K T N K F P D L Y S D L D K C S - D G G I R N Y A V S I T L N E V F L N L
11. ABCA1		Q S H L P E A Y K E D I G G E L V Y V L P P F S T K V S G A Y L S L R A L D N G M G D L N I G C Y G I S D T V L E V F L N L

Protein Sequences

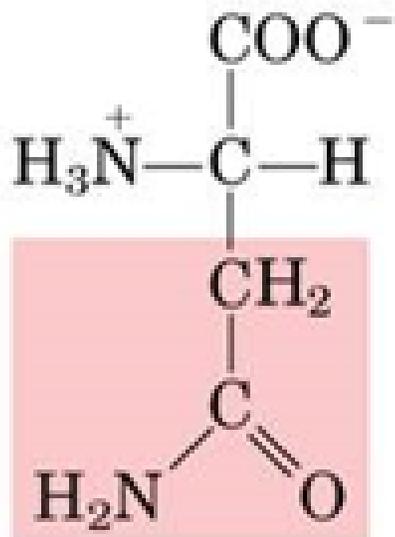
Species/Abb	Group Name	Sequence
1. ABCA1		--P A V D R I C V G I P P G E C F G L L G V N G A G K S S T F K M L T G D T T V T R G D A F L N K N S - - - L S N I H E V H O N N G Y C P O F D A I T E L L T G R E H V E
2. ABCA2		R I L A V D R L C L G V R P G E C F G L L G V N G A G K S T S F K M L T G D E S T T G G E A F V N G H S - - - V L K E L L D V G S L G Y C P O C D A I F D E L T A R E H L O
3. ABCA3		--L L A V D R L C L A V G R P G E C F G L L G V N G A G K T T T F K M L T G E E S L T S G D A F V G G H R - - - I S S D V G K V R O R I G Y C P O F D A I L D H M T G R E H L Y
4. ABCA4		--P A V D R L C V R V R P G E C F G L L G V N G A G K T T T F K M L T G D T T V T S G D A T V A G K S - - - I L T N I S E V H O N N G Y C P O F D A I D E L L T G R E H L Y
5. ABCA5		K K V A R N I S F C V K K G E I L G L L G N G A G K S T I I N I L V G D I E P T S G V F L G D Y S S E T S - E D D S L K C M G Y C P O I N P L P D T L T R E H F E
6. ABCA6		K K I A R N I S F C V G V G E I L G L L G N G A G K S S S I R M L S G I T K P T A G E V L K G - - - - - C S S V L G H L G Y C P O E N V L W P M L T R E H L E
7. ABCA7		--P A V D R L C L G I P P G E C F G L L G V N G A G K T S T F R M V T G D I L A S R G E A V L A G H S - - - V A R P S A A H L S M G Y C P O S D A I F E L L T G R E H L E
8. ABCA8		K K I A R N V S F C V R K K G E V L G L L G H N G A G K S T S I K M I T G C K P T A G V L L K G S - - - - - G G G A L E F L G Y C P O E N A L W P L T V R Q H L E
9. ABCA9		K K I A R N V S F C V K K G E V L L G L L G H N G A G K S T S I K M I T G C K P T A G V I L K G S - - - - - G G G P L G F L G Y C P O E N A L W P L T V R Q H L E
10. ABCA1		K K I A R N V S F C V K K G E V L L G L L G H N G A G K S T S I K M I T G C K P T A G V V V L G S R A S V R Q H D H S L K F L G Y C P O E N S L R P K L T M E H L E
11. ABCA1		K I I A V N I S I G I P A G E C F G L L G V N G A G K T I T F K M L T G D I P S S G I L I R N K N S - - - S L G H V D S H S S L V Y C P O E A L D G L V T V E E H L Y

Protein Sequences

Species/Abb	Group Name	Sequence
1. ABCA1		G V G S E A I R K L S L V K Y G E K Y A G N Y S G N K R K L S T A M A L I G C P R V V F L D E P T T G M D P K A R R F L W N C A L S V V Y K E - G R S V V L T S H S M E E
2. ABCA2		A R V V K W A L E K L E T P Y A D K P A G T Y S G G N K R K L S T A I A L I G Y P A F I F L D E P T T G M D P K A R R F L W N L L D L I K T - G R S V V L T S H S M E E
3. ABCA3		C A C V E N T L R G L L E P H A N K L V R T Y S G G N K R K L S T E T A L I G E P A V I F L D E P T T G M D P V A R R L L W D I V A R A R E S - G K A I I T T S H S M E E
4. ABCA4		K E V A N S R I S K S L G T V Y A D C L A G T Y S G G N K R K L S T A I A L I G C P R V L V L D E P T T G M D P A R R M L L W N V I V S I I R E - G R A V L T S H S M E E
5. ABCA5		K E V I S R I H A L D K E H L Q K V K K L P A G I K R K L C F A L S M L G N P I T L L D E P T T G M D P K A K H W M R A I T A F K N R R A A L T T H Y M E E
6. ABCA6		R L A I A R L Y S A F K H E L L Q K V P K L T A G I T R K I C F V L S L L G S N P I V L L D E P T T G M D P T G M D W G A I R A F K N T E R G V L L T H S L A E
7. ABCA7		A G T A S G L A R L S W A Y D R P A T Y S G G N K R K L A T A L A L Y G D P A V V F L D E P T T G M D P S A R R F L W N L S L A V V R E - G R S V M L T S H S M E E
8. ABCA8		E V A I R R L V D A L K D D L K S P V K T L S E G I K R K L C F V L S I L G N P E V V L D E P T T G M D P E S G G Q M W G A I R A T F R N T E R G A L L T H Y M A E
9. ABCA9		M I A I T R R L V D A L K D D L K A P V K T L S E G I K R K L C F V L S I L G N P E V V L D E P T T G M D P E S G G Q M W G I A I R A T F R N T E R G A L L T H Y M A E
10. ABCA1		A L S I S R L V E A L K G E L L K A P V K T L S E G I K R K L C F V L S I L G N P E V V L D E P T T G M D P E S G G Q M W G I A I R A T F R N T E R G A L L T H Y M A E
11. ABCA1		K E T V H K L L R R L H M P F K D R A T S M C S Y C K R K L S T A L A L I G K P E I L L D E P T S G G D P K S K R H L W K I I S E E V N - K C S V I L T S H S M E E

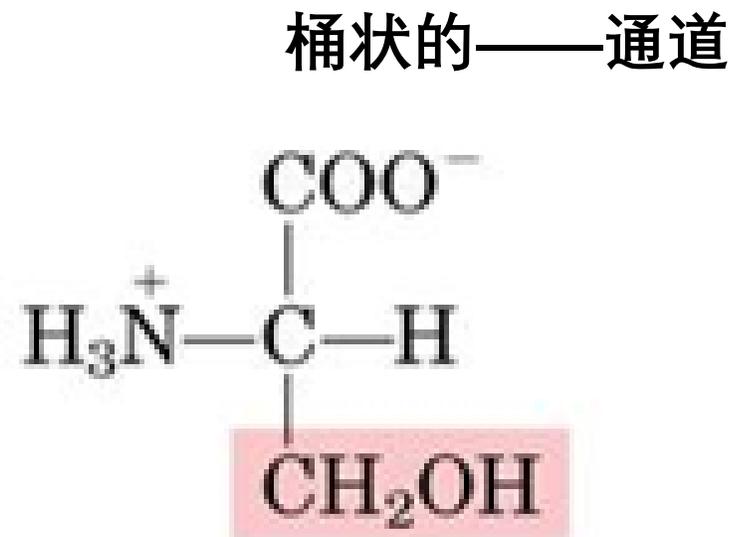


# 生物信息分析——功能预测



Asparagine

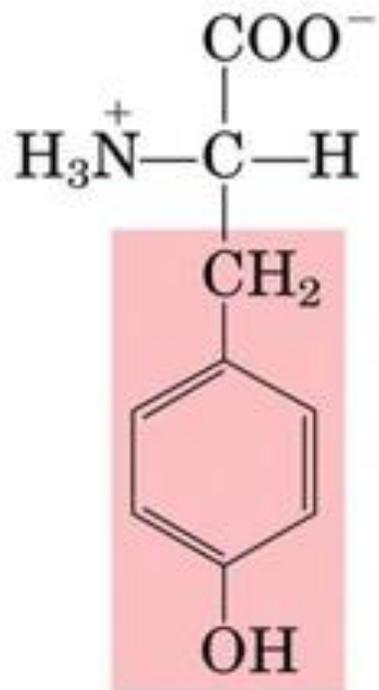
N920S mutation  
extracellular domain ( ECD )



Serine



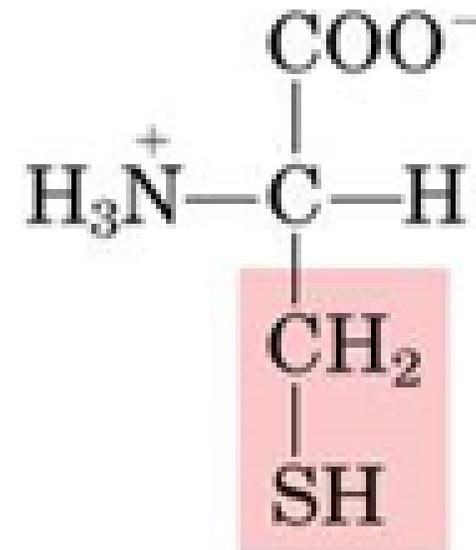
# 生物信息分析——功能预测



Tyrosine

Y2335C mutation  
transmembrane domain ( TMD )

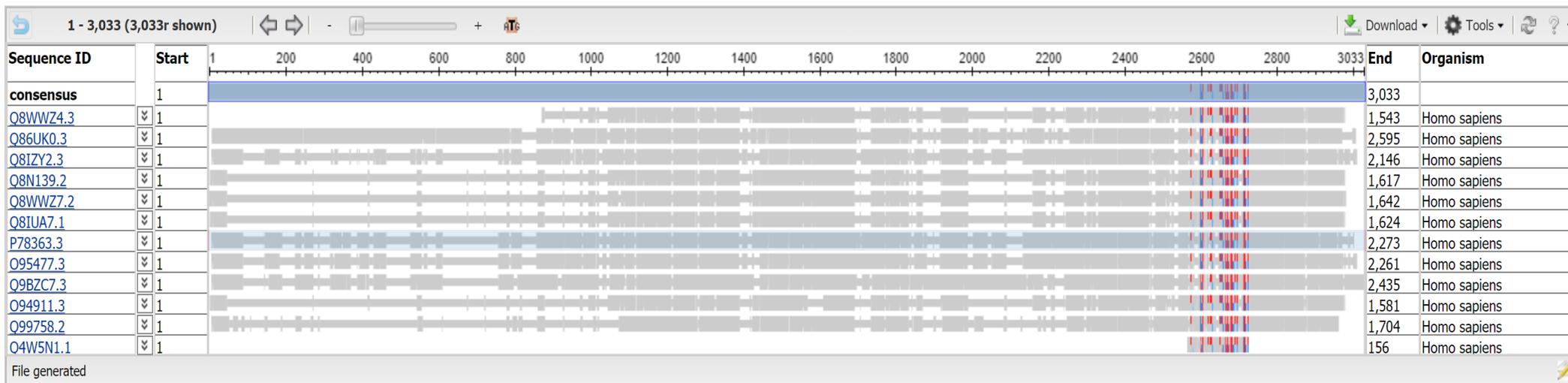
应答



Cysteine

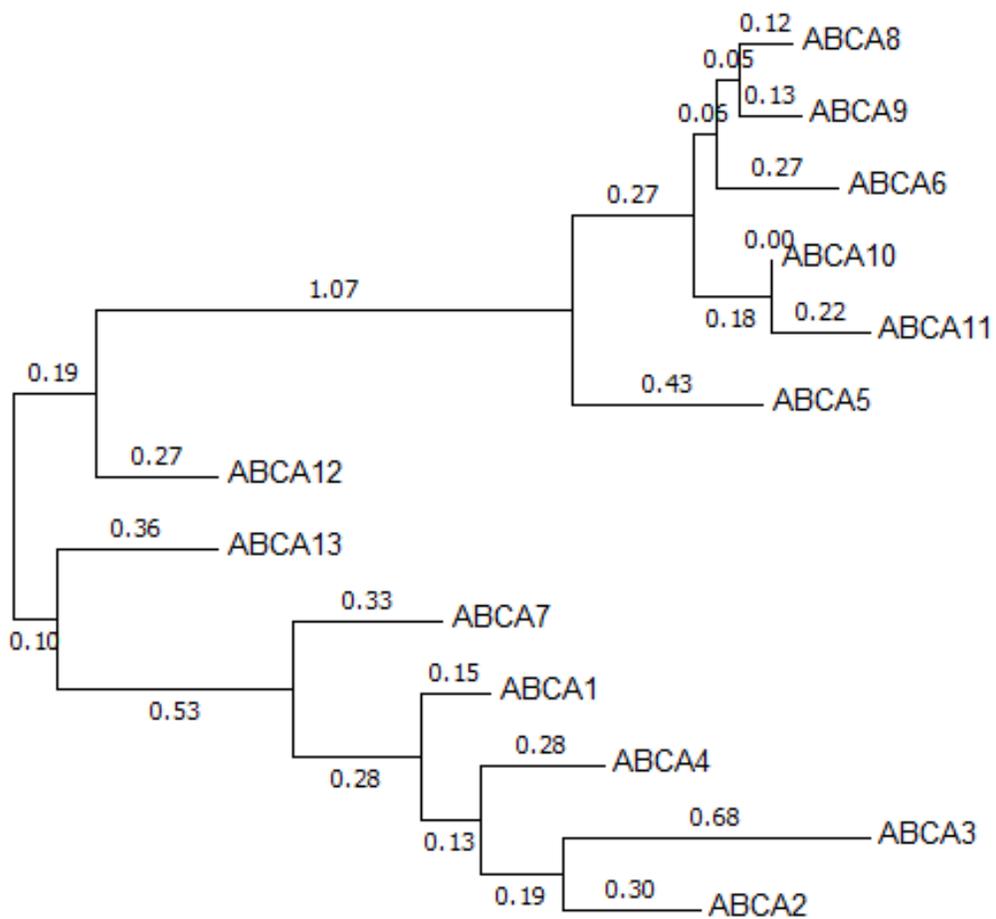


使用上图中的保守位点密集序列作为query进行blastP，使用swissprot数据库，替代矩阵选择BLOSUM62，结果只能找到此该家族13个序列，说明此保守性序列为该家族特有，暗示其与该家族蛋白特异性的功能相关。



可以看到ABCA11保守性最强，位点均位于序列较后段。

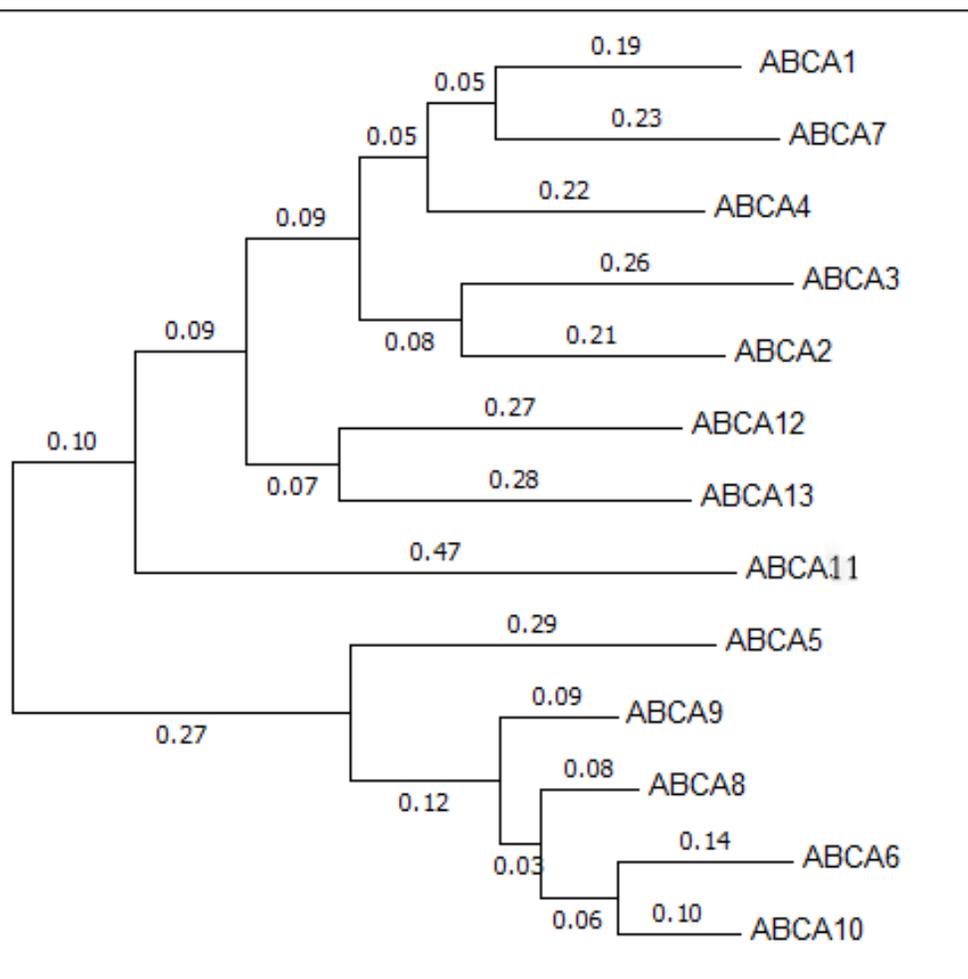
使用ABCA11的序列进行同样的blastP搜索，仍然只能找到该家族蛋白，说明了该段序列的功能性、特异性和保守性。



根据蛋白质序列构建的系统发生树可分为以下两组：

第一组：ABCA5      ABCA6      ABCA8  
ABCA9   ABCA10   ABCA12

第二组：ABCA1      ABCA2      ABCA3  
ABCA4   ABCA7   ABCA13



根据基因序列构建的系统发生树可以得出 ABCA 家族基因大致可以分为两组：

第一组：ABCA1      ABCA2      ABCA3  
ABCA4    ABCA7    ABCA11    ABCA 12  
ABCA13

第二组：ABCA5      ABCA6      ABCA8  
ABCA9    ABCA10

可能由于基因的表达问题以及在翻译过程中的简并问题出现了蛋白质与基因序列分别构建树的差异。



# 总结及展望



总结



治疗方法





- 鱼鳞病是一大类疾病，其有非常多的亚型，综合患病率约为5%（来自华大基因），多是单基因致病，但每种鱼鳞病可能由多个基因突变引起。
- ABCA12基因突变是其中的一种，它编码表达的蛋白质主要功能是负责脂质体的转运。
- ABCA是一个大家族，目前已发现共有13个，它们存在特定的保守序列，且集中于后续序列，即膜外部分。
- 我们这次发现了两个突变，C.2759A—>G,P.Y920C；C.7004A—>G,P.Y2335C。其中前者是首次发现。
- 从蛋白结构预测来看，两个突变一个发生在跨膜区域，该部分区域主要起通道作用，有特异识别作用；另外一个发生在膜外区域，该部分主要起应答作用，当外面有特定分子与之作用时，会把通道阀门打开，使通道内的脂质运出。但这两种突变具体如何影响还不清楚，需要进一步研究。



就目前来说，鱼鳞病属不死癌症，对生命没有威胁，但也无可救药！综合各亚型而言，该病发病率高达5%，所以研究此病的治疗具有重大意义。

### 四个层面

- 蛋白质层面
- RNA层面
- DNA层面
- 细胞层面



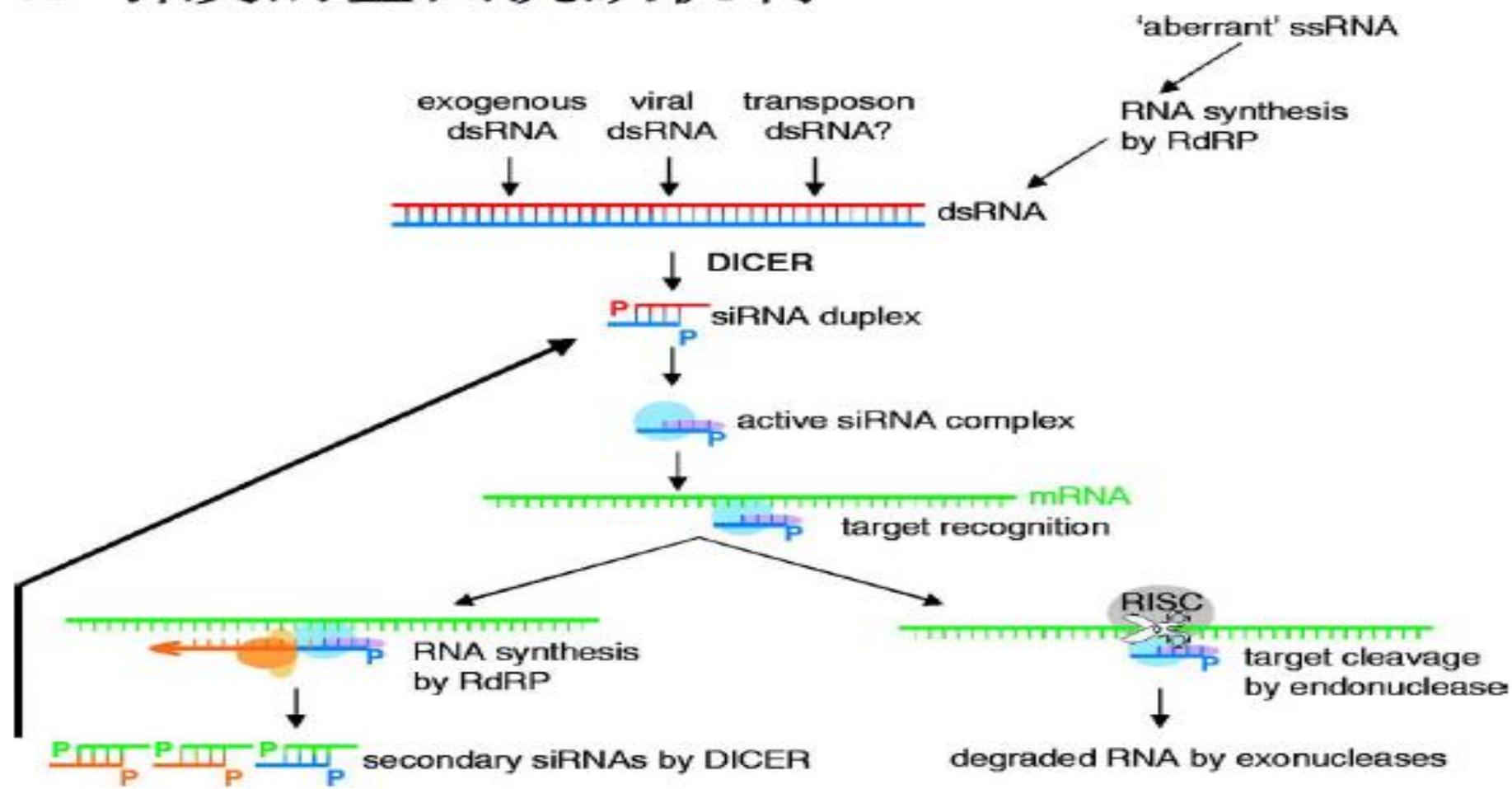
### 蛋白质层面（多肽药物）

- 热点：蛋白质蛋白质或蛋白质与其他物质相互作用时的关键位点。
- 为什么是多肽？
- 目标：找到ABCA12的热点，然后利用化学合成的方法设计相应的多肽，以此来模拟ABCA12的功能，从而达到治疗的效果。如果效果良好，还可以作为化妆品！！！！

一个把人变得更健康和美丽的事业！



# RNAi引发的基因沉默机制



Gisela Storz, *Science*, 296(5571):1263-1265, 2002.



## 总结及展望

### DNA层面

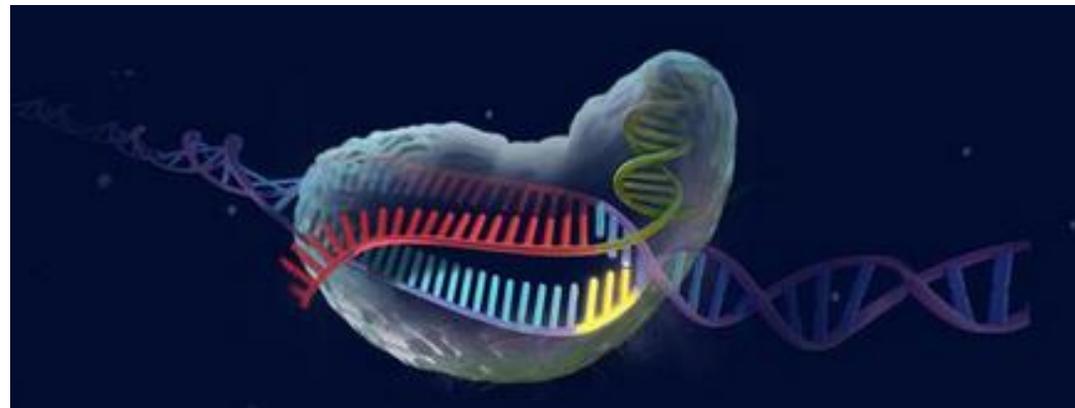
这方面或许是讨论最多，最直接有效，但又没太大进展的方法。

DNA是人体的遗传物质，对ABCA12定点改变可从根本上解决问题。

CRISPER等技术为该方法提供了方向，但遗憾的是，最近斯坦福一个实验室发现，约70%人体内有case9的同源蛋白抗体，所以……



## 治疗方法（希望）



### 细胞层面

- 首先得到人体干细胞，然后在体外对突变位点进行修正（crisper），并培养定向分化成人体皮肤。然后进行皮肤移植便可达到治疗的效果，但风险有点大，目前全球仅完成几例。



**GOOD JOB**

**THANKS VERY MUCH !**

