Bioinformatic Study on Disease-causing Mutations of ATP1A3

ATP1A3致病突变的生物信息学研究

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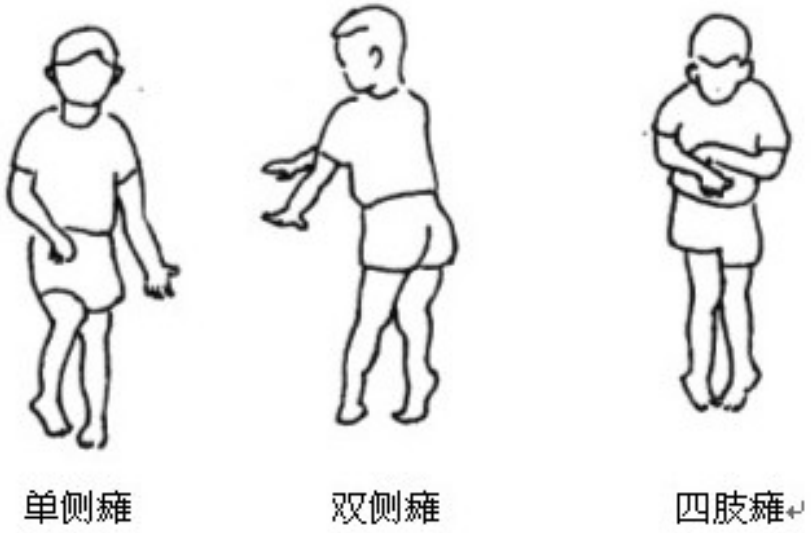
2015-01-25

Outline

- ATP1A3 and Diseases Associated with It
- Same Gene, Different Variants, Different Phenotypes
- Bioinformatic Anslysis on D801 Mutations
- Summary and Discussion

Alternating Hemiplegia of Childhood (AHC)
儿童交替性偏瘫

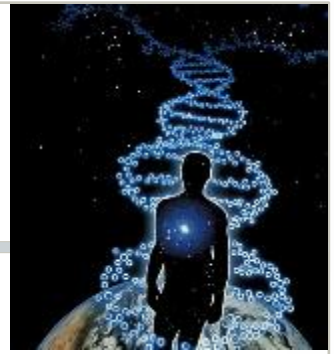


- An orphan disease
- Severe neurological disorder
- Age of onset: before 18 months
- Clinical features
  - Episodic hemiplegia or quadriplegia attacks
  - Paroxysmal symptoms, including oculomotor abnormalities, dystonia, seizures, and autonomic disturbances
  - Developmental delay and progressive cognitive impairment

Picture adopted from: http://baike.sogou.com/v49483093.htm

Yang, X., et al.,. PLoS One, 2014. **9**(5): p. e97274.

ATP1A3—the Causative Gene of AHC



Nat Genet. 2012 Sep;44(9):1030-4. doi: 10.1038/ng.2358. Epub 2012 Jul 29.

De novo mutations in ATP1A3 cause alternating hemiplegia of childhood.

Heinzen EL[1], Swoboda KJ, Hitomi Y, Gurrieri F, Nicole S, de Vries B, Tiziano FD, Fontaine B, Walley NM, Heavin S, Panagiotakaki E; European **Alternating Hemiplegia of Childhood** (AHC) Genetics Consortium; Biobanca e Registro Clinico per l'Emiplegia Alternante (I.B.AHC) Consortium; European Network for Research on Alternating Hemiplegia (ENRAH) for Small and Medium-sized Enterpriese (SMEs) Consortium, Fiori S, Abiusi E, Di Pietro L, Sweney MT, Newcomb TM, Viollet L, Huff C, Jorde LB, Reyna SP, Murphy KJ, Shianna KV, Gumbs CE, Little L, Silver K, Ptáček LJ, Haan J, Ferrari MD, Bye AM, Herkes GK, Whitelaw CM, Webb D, Lynch BJ, Uldall P, King MD, Scheffer IE, Neri G, Arzimanoglou A, van den Maagdenberg AM, Sisodiya SM, Mikati MA, Goldstein DB.

Lancet Neurol. 2012 Sep;11(9):764-73. doi: 10.1016/S1474-4422(12)70182-5. Epub 2012 Jul 30.

Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study.

Rosewich H[1], Thiele H, Ohlenbusch A, Maschke U, Altmüller J, Frommolt P, Zirn B, Ebinger F, Siemes H, Nürnberg P, Brockmann K, Gärtner J.

Picture adopted from: http://tech.enorth.com.cn/system/2013/08/29/011265775.shtml

ATP1A3—the Causative Gene of AHC

OPEN ACCESS Freely available online

PLOS ONE

ATP1A3 Mutations and Genotype-Phenotype Correlation of Alternating Hemiplegia of Childhood in Chinese Patients

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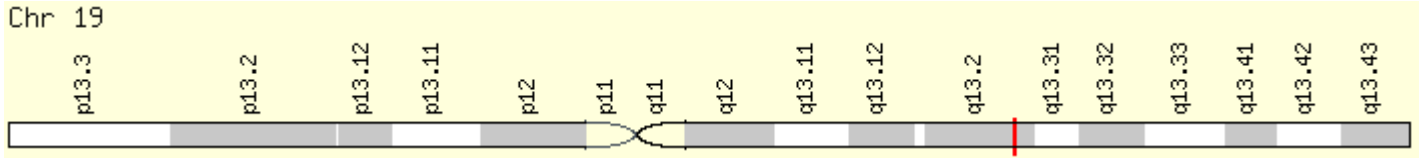
A Glimpse into ATP1A3

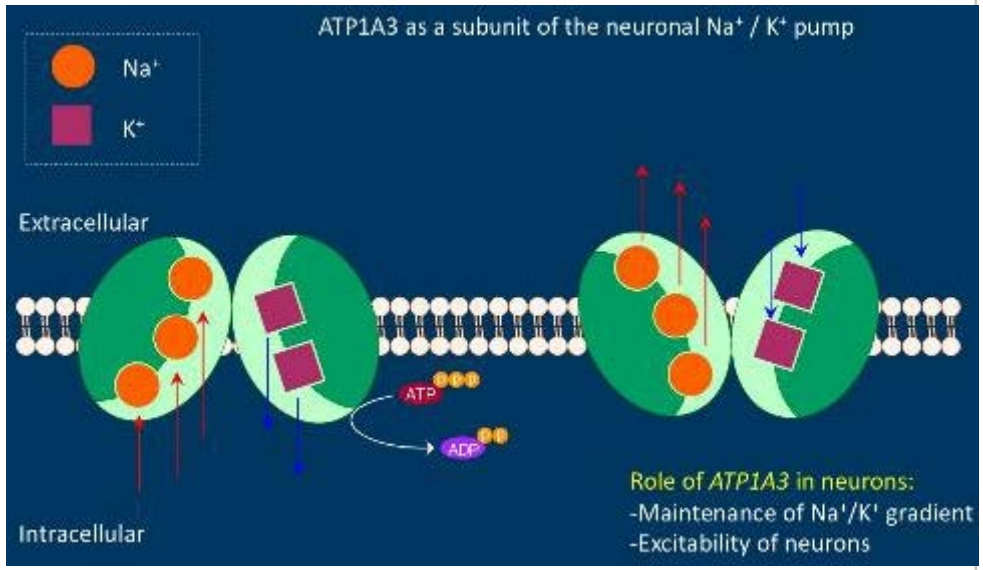
- The official name
  - Sodium/potassium-transporting ATPase subunit alpha-3



- Subcellular Location: Cell membrane
- Sequence Length: 1013
- Family: Cation transport ATPase (P-type) family

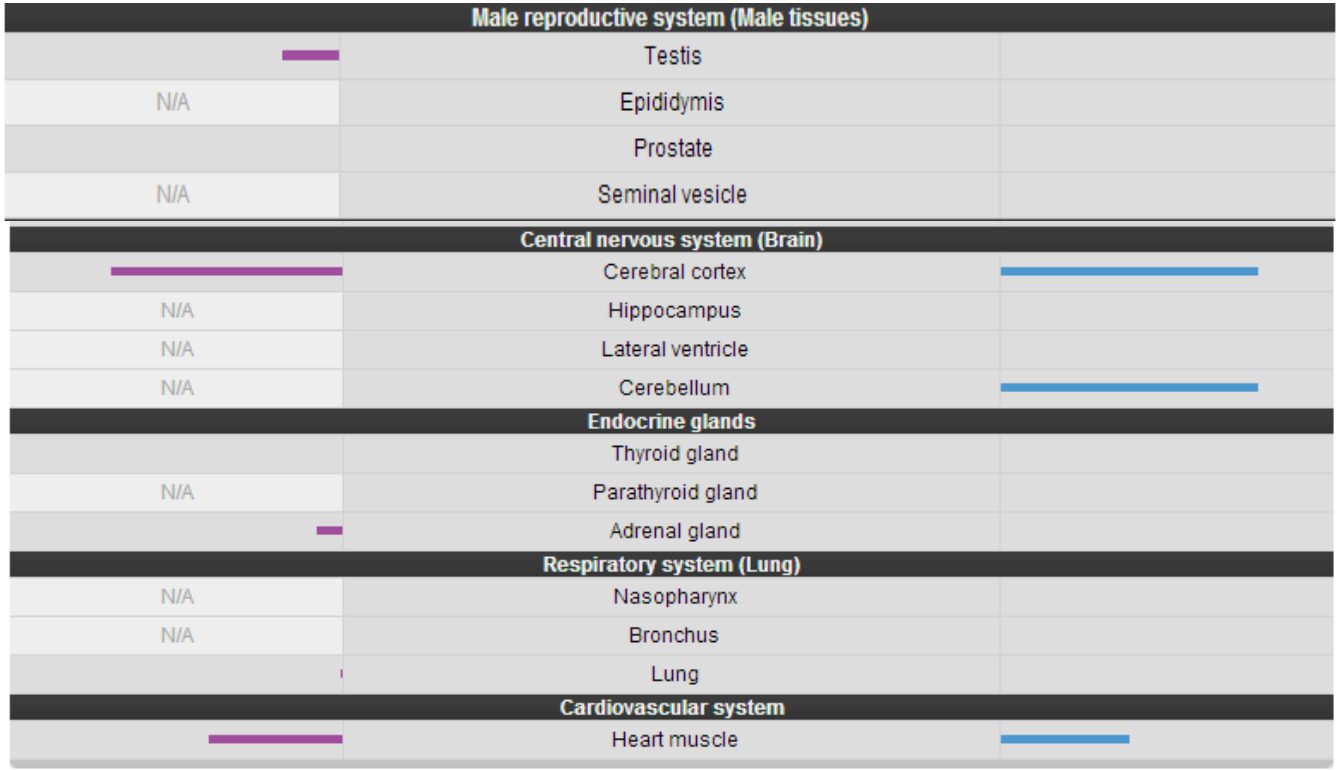
Biological Function of ATP1A3

- Biological function
  - A subunit of ATPase.
  - ATPase is a membrane-bound enzyme complex/ion transporter, which can hydrolyze ATP to supply energy.
  - It is responsible for maintaining the electrochemical gradients of Na^+ and K^+.
- Catalytic activity
  - $ATP + H_2O + Na^+(In) + K^+(Out) =$ $ADP + phosphate + Na^+(Out) + K^+(In)$.



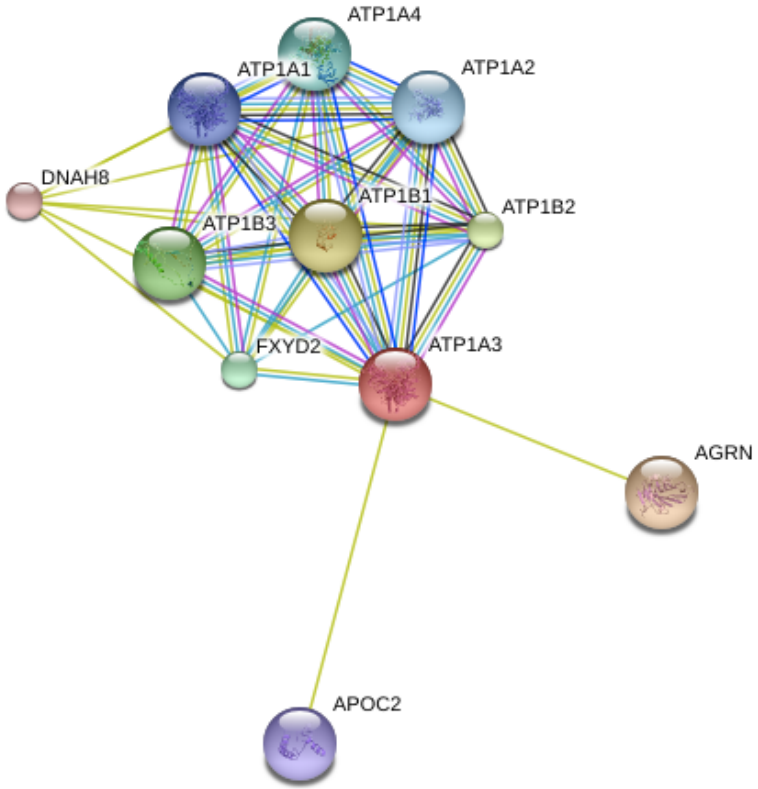
Picture adopted from: https://euroepinomics.wordpress.com/2012/07/31/atp1a3-links-alternating-hemiplegia-of-childhood-with-genetic-dystonia-and-parkinsonism/

Expression Profile



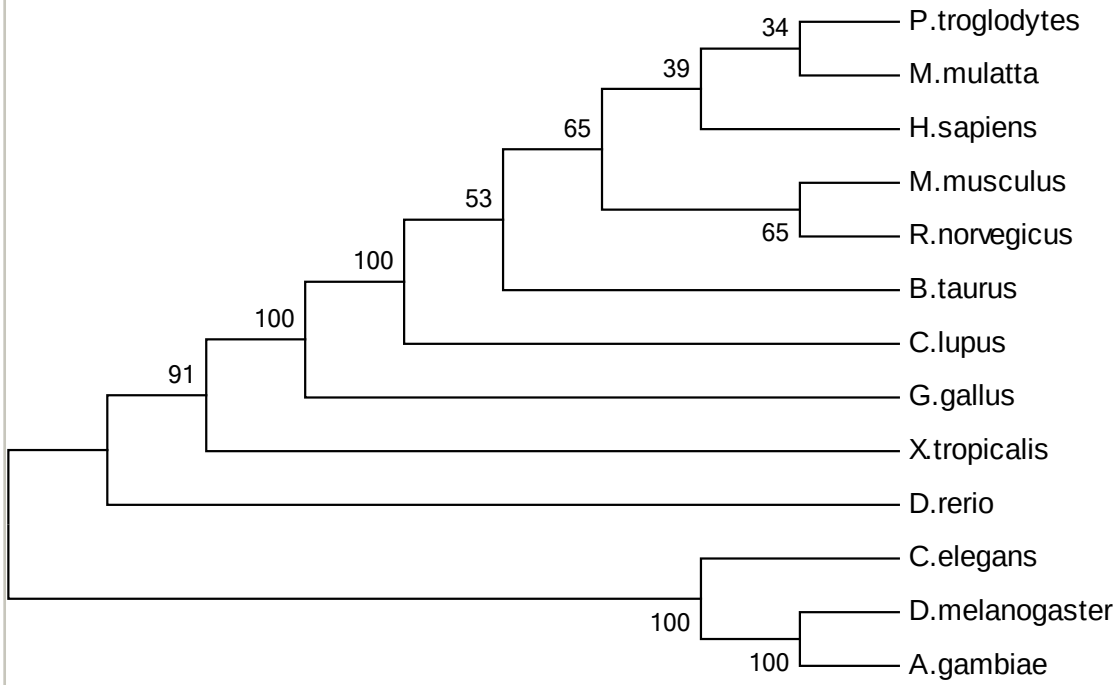
The Human Protein Atlas: CAB001988

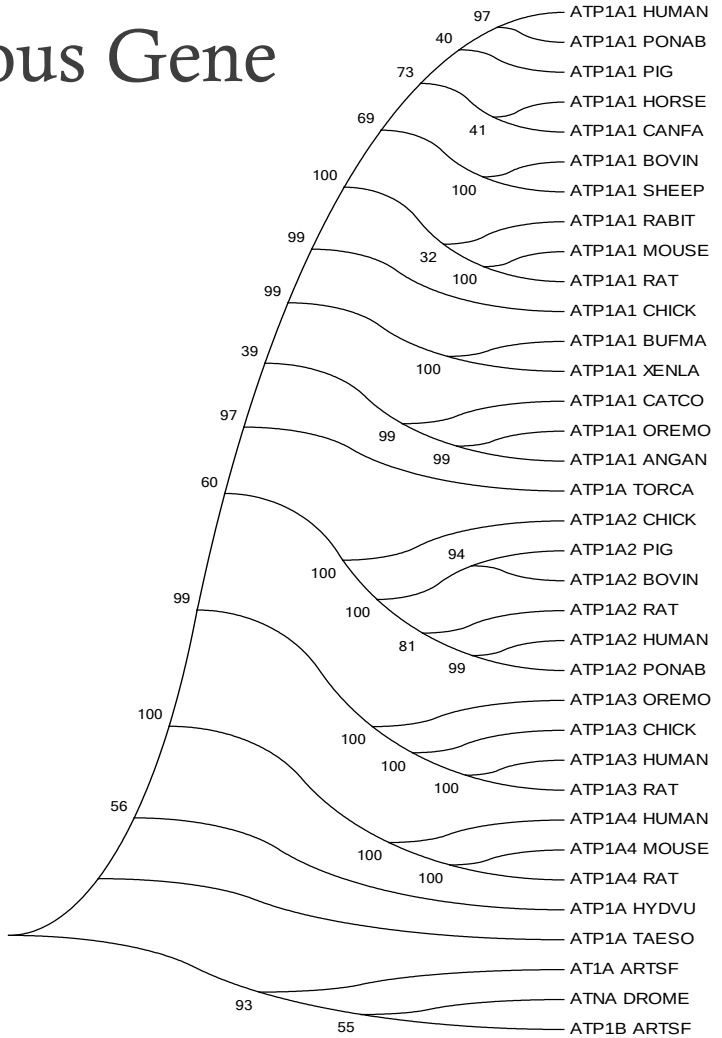
Protein-protein Interaction



STRING: 9606.ENSP00000302397

Phylogenetic Tree of the Homologous Gene





Tree produced by MEGA

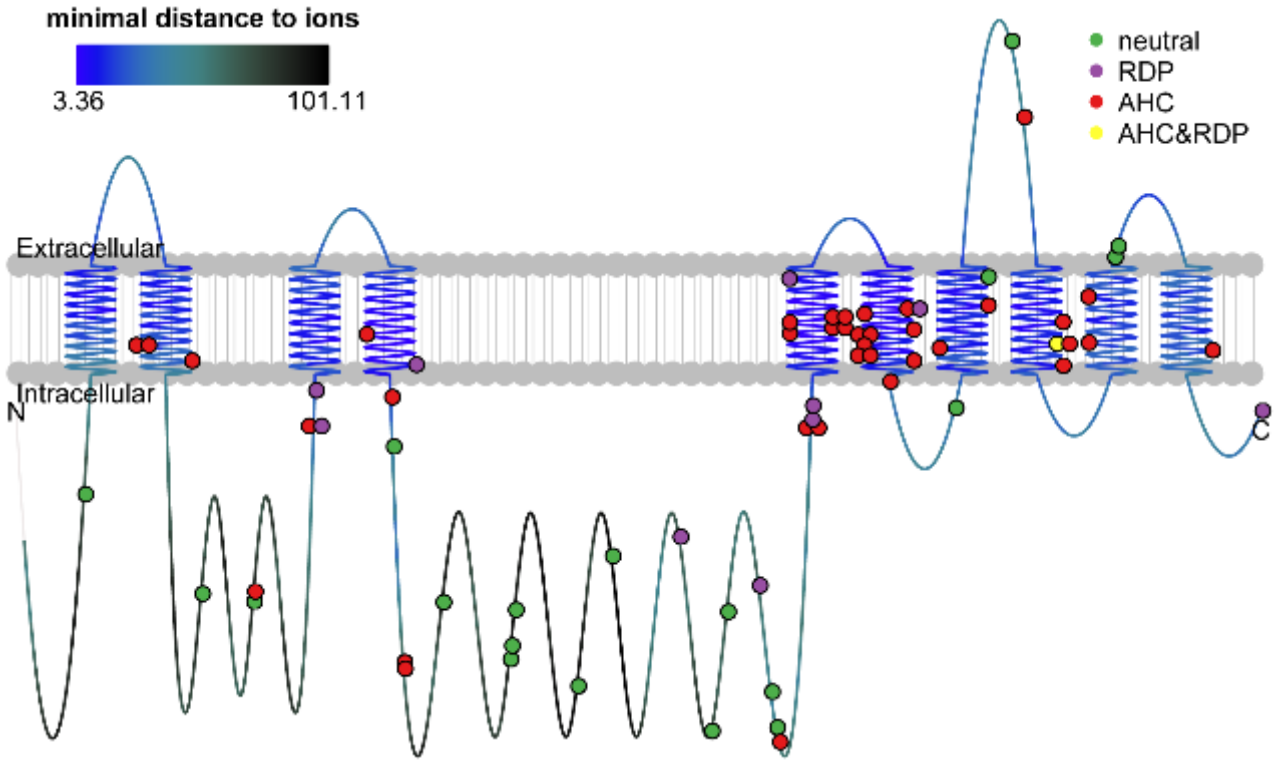
Rapid-onset Dystonia-Parkinsonism (RDP)

快速起病的肌张力障碍和帕金森症

- Another disease associated with ATP1A3
- An autosomal-dominant movement disorder
- Abrupt onset of dystonia within hours to weeks that can present with parkinsonism
- Age of onset: 4–55 years
- AHC and RDP may make up a continuum of a dystonic movement disorder

Ozelius, L.J., Lancet Neurol, 2012. **11**(9): p. 741-3
Rosewich, H., et al., Lancet Neurol, 2012. **11**(9): p. 764-73.

Same Gene, Different Variants, Different Phenotypes



Yang, X., et al.,. PLoS One, 2014. **9**(5): p. e97274.

- The D801 mutation is the only one that is detected in two different disorders.
- But they are different missense mutations.

Mutation Type	Disorder
D801N	AHC
D801Y	RDP

D801— Conserved Site

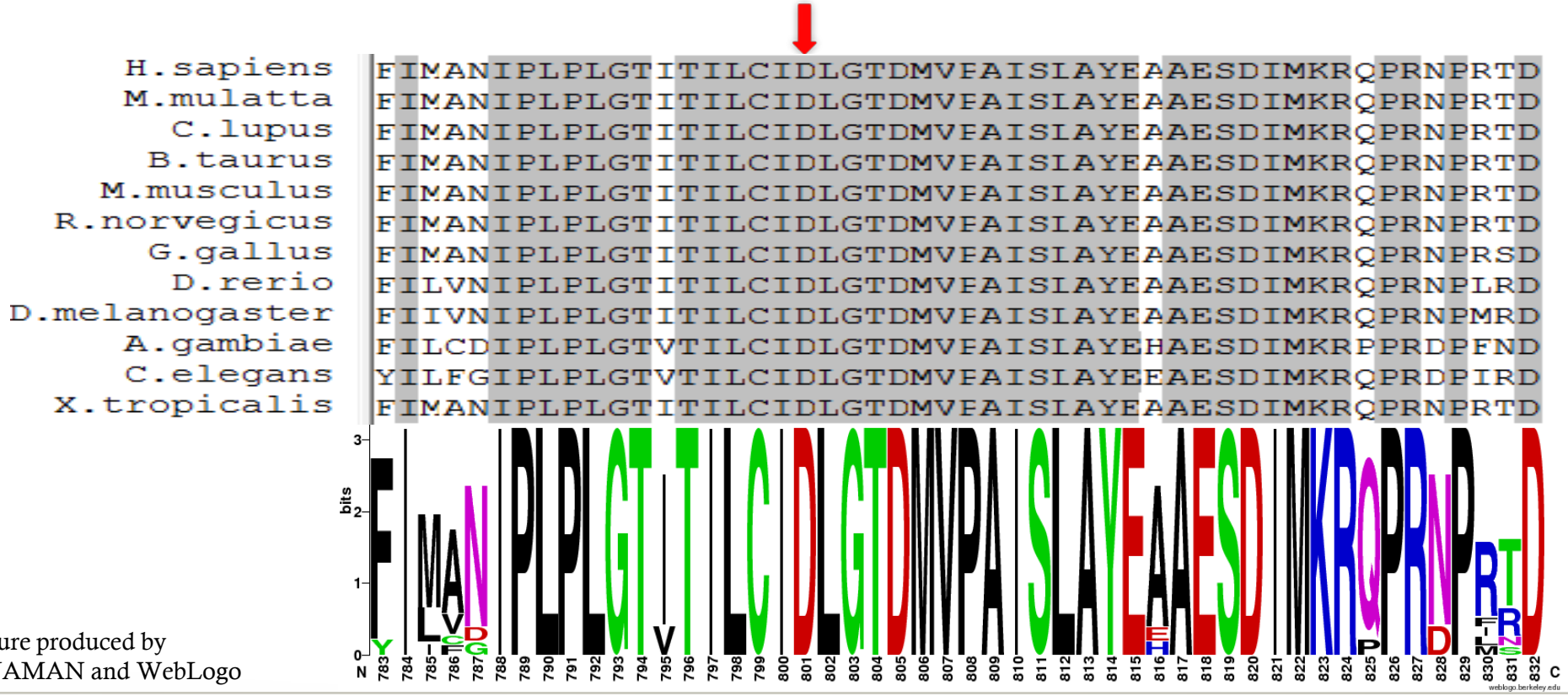
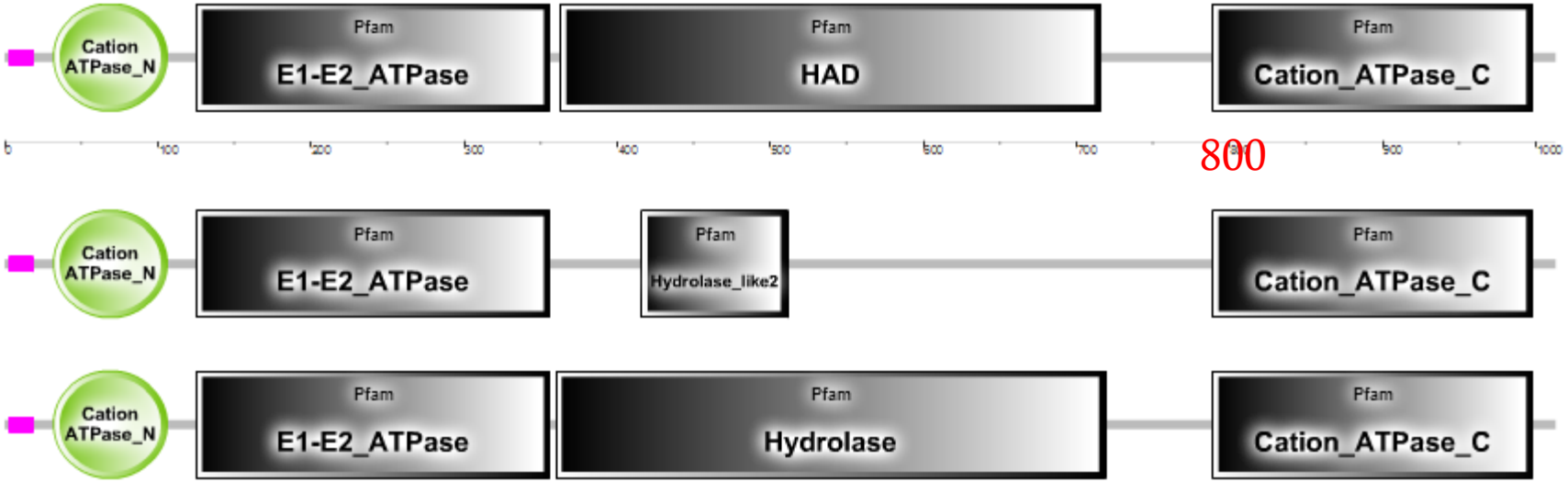


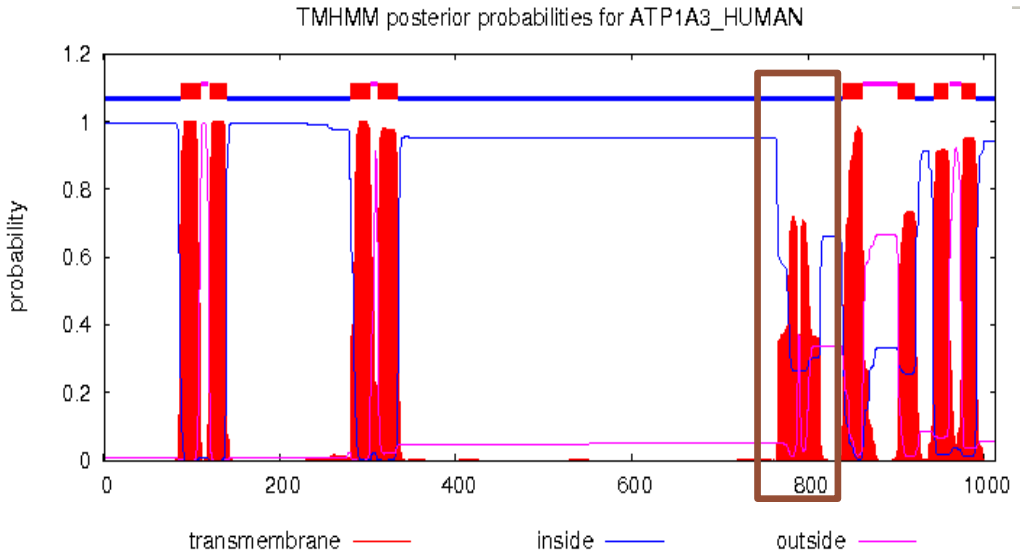
Figure produced by
DNAMAN and WebLogo

Motif Detected by SMART

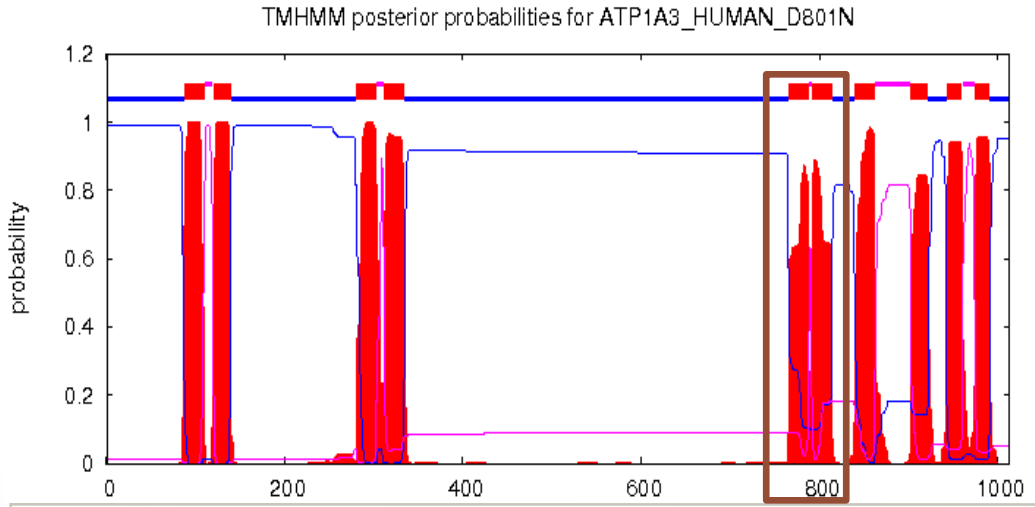


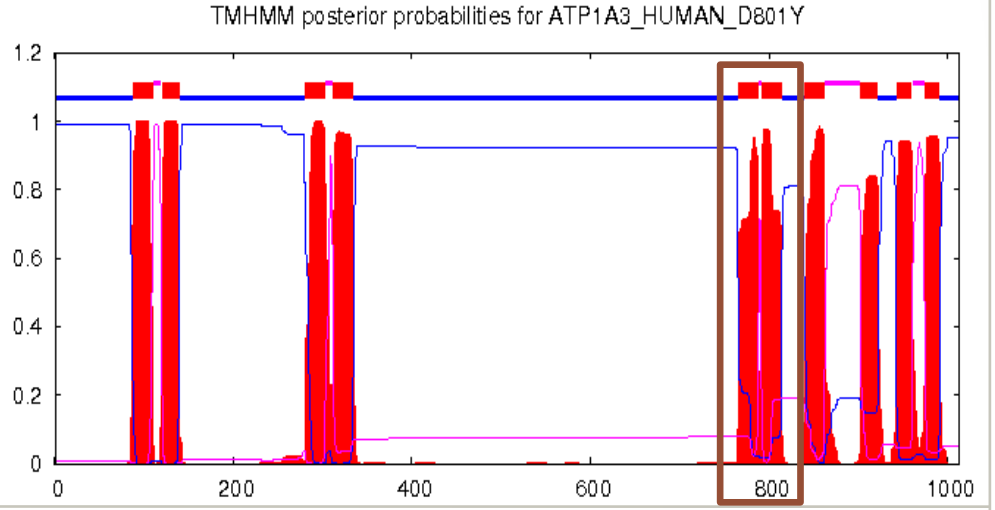
D801 is located in the Cation_ATPase_C motif, that is required for the cation binding.

Prediction of trans-membrane helices in proteins (TMHMM)



Seems interesting.
Is this prediction result right?





Structure of the Homologous Protein

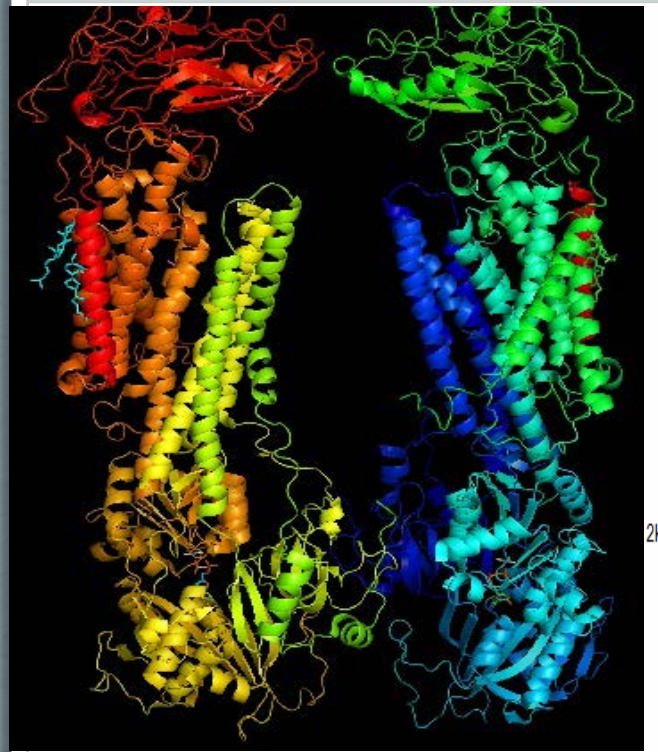
- UniProt: P05024
- Name: ATP1A1_PIG

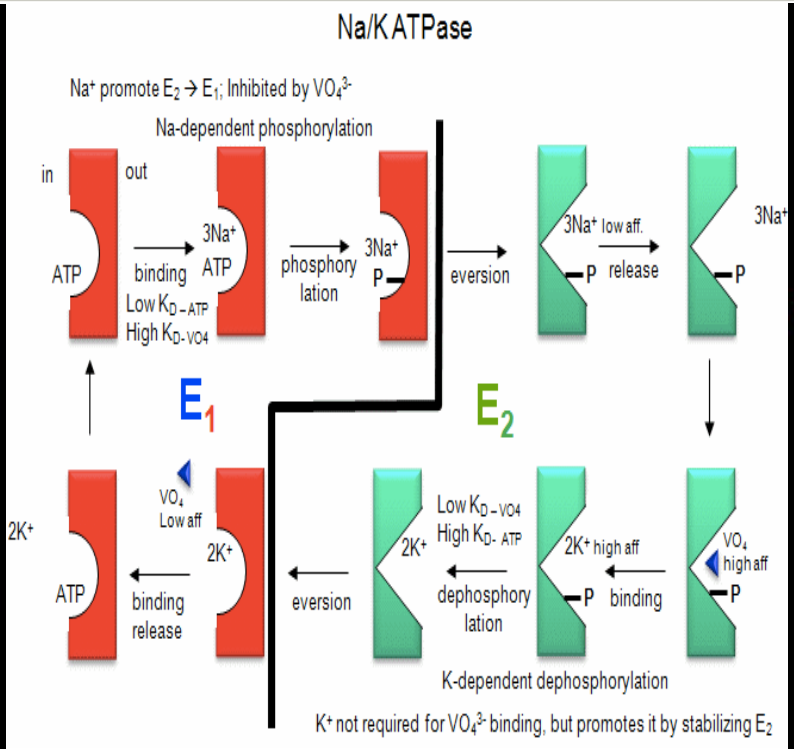
Local Alignment of ATP1A3_HUMAN and ATP1A1_PIG Chain A

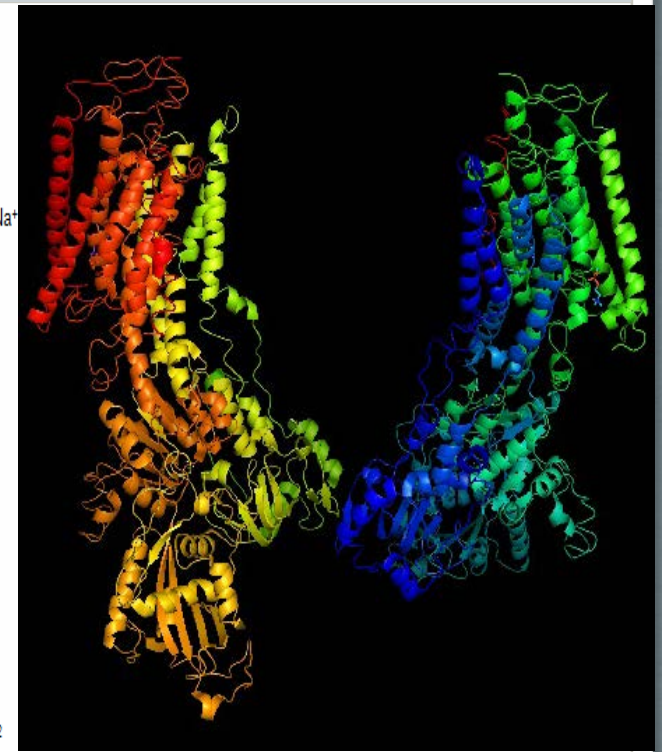
LENGTH	SCORE	IDENTITY	SIMILARITY	GAPS
997	4596.0	874/997 (87.7%)	943/997 (94.6%)	0/997 (0.0%)

Figure produced by water(v6.0.1) in WebLab

Two Protein Conformations of Two Stages





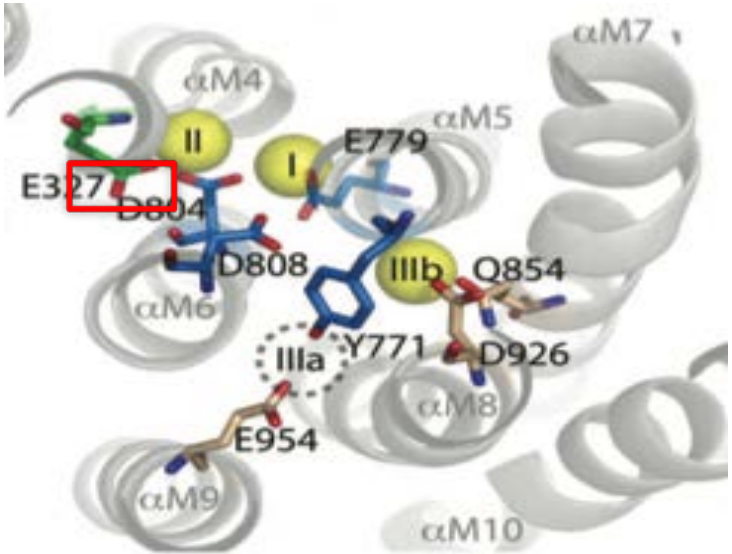


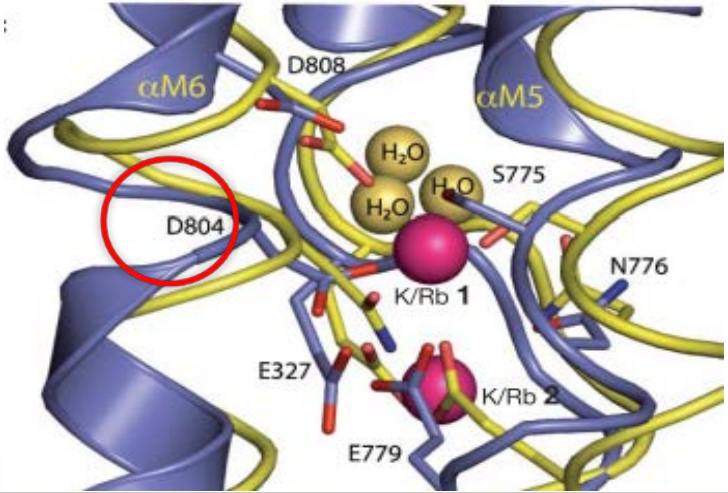
PDB: 4HQJ

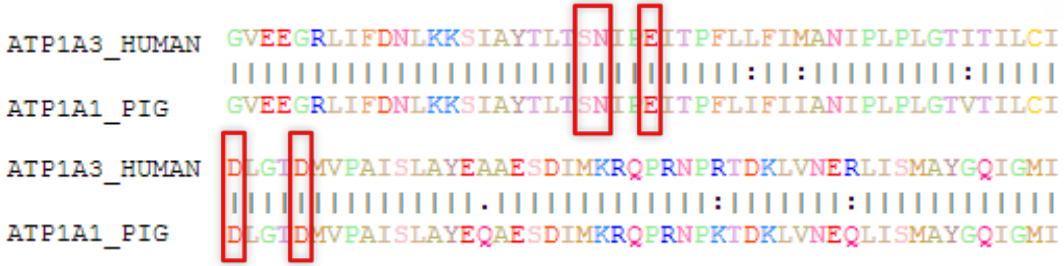
Picture adopted from Stryer, Biochemistry, 4th ed.

PDB: 3B8E

D801 is a Functional Site







- The 804th Asp of ATP1A1_PIG is corresponding to the 801st Asp of ATP1A3_HUMAN.
- D801 seems to donate side-chain oxygen ligands to ions.
- So it is necessary for the binding of Na and K.

Nyblom, M., et al. Science, 2013. **342**(6154): p. 123-7.
Morth, J.P., et al. Nature, 2007. **450**(7172): p. 1043-9.

D801 is Essential for Ion Binding

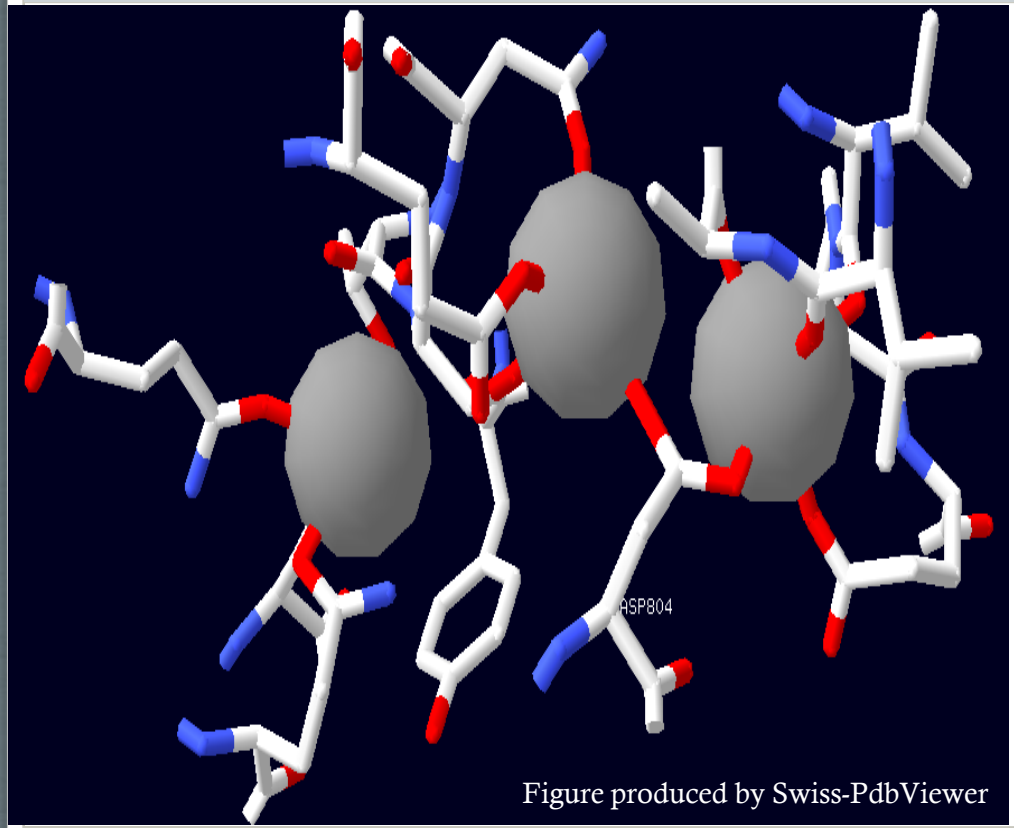
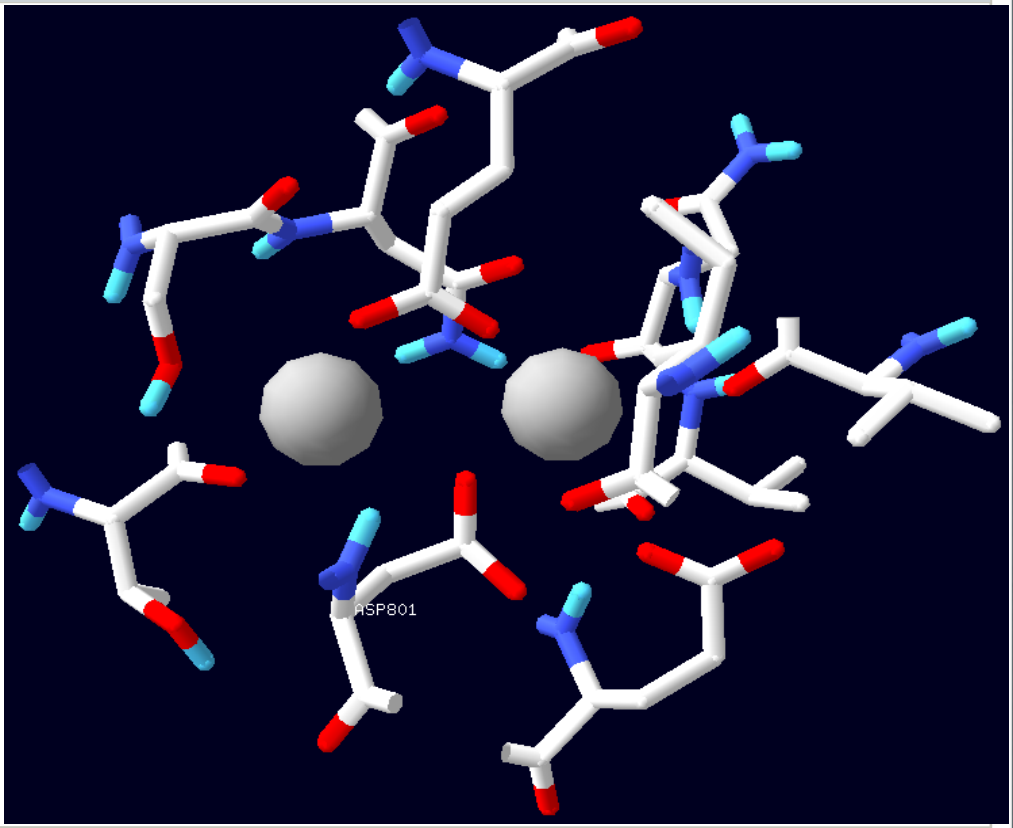


Figure produced by Swiss-PdbViewer



D801Y Can Block the Na^+ Binding Site

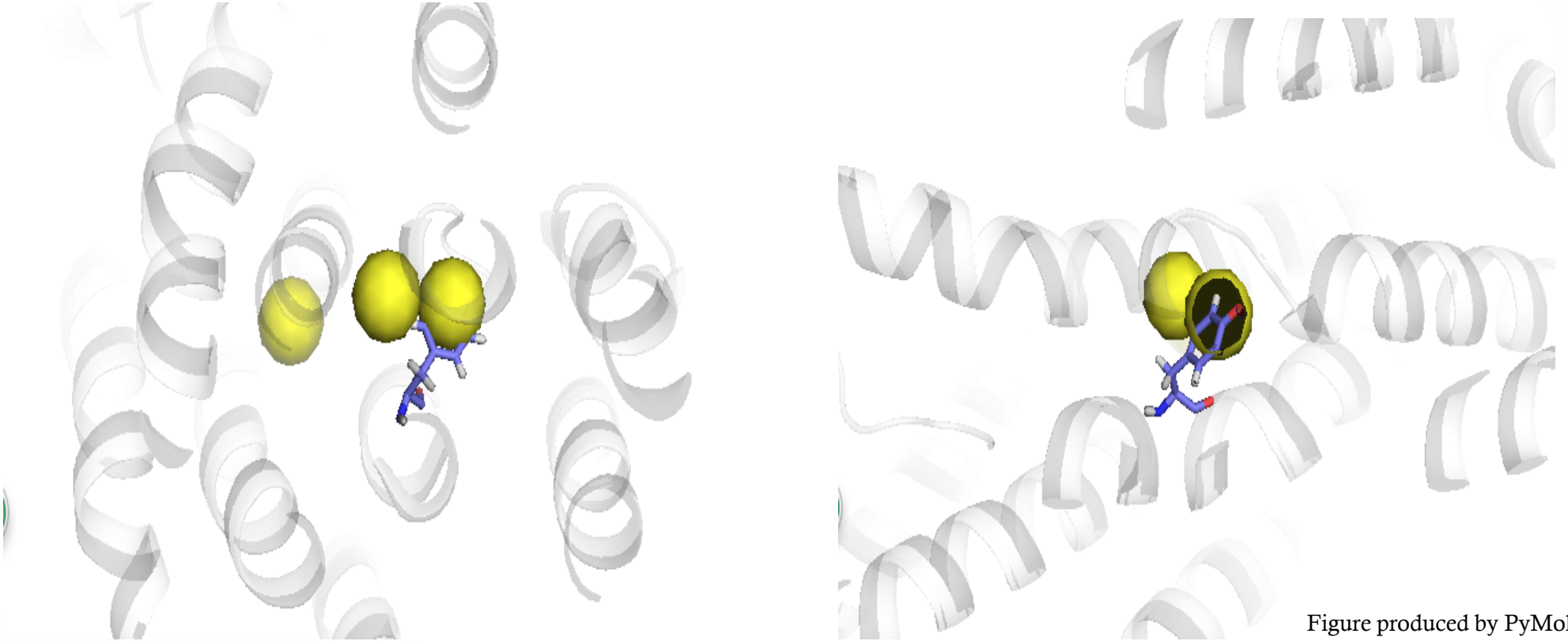
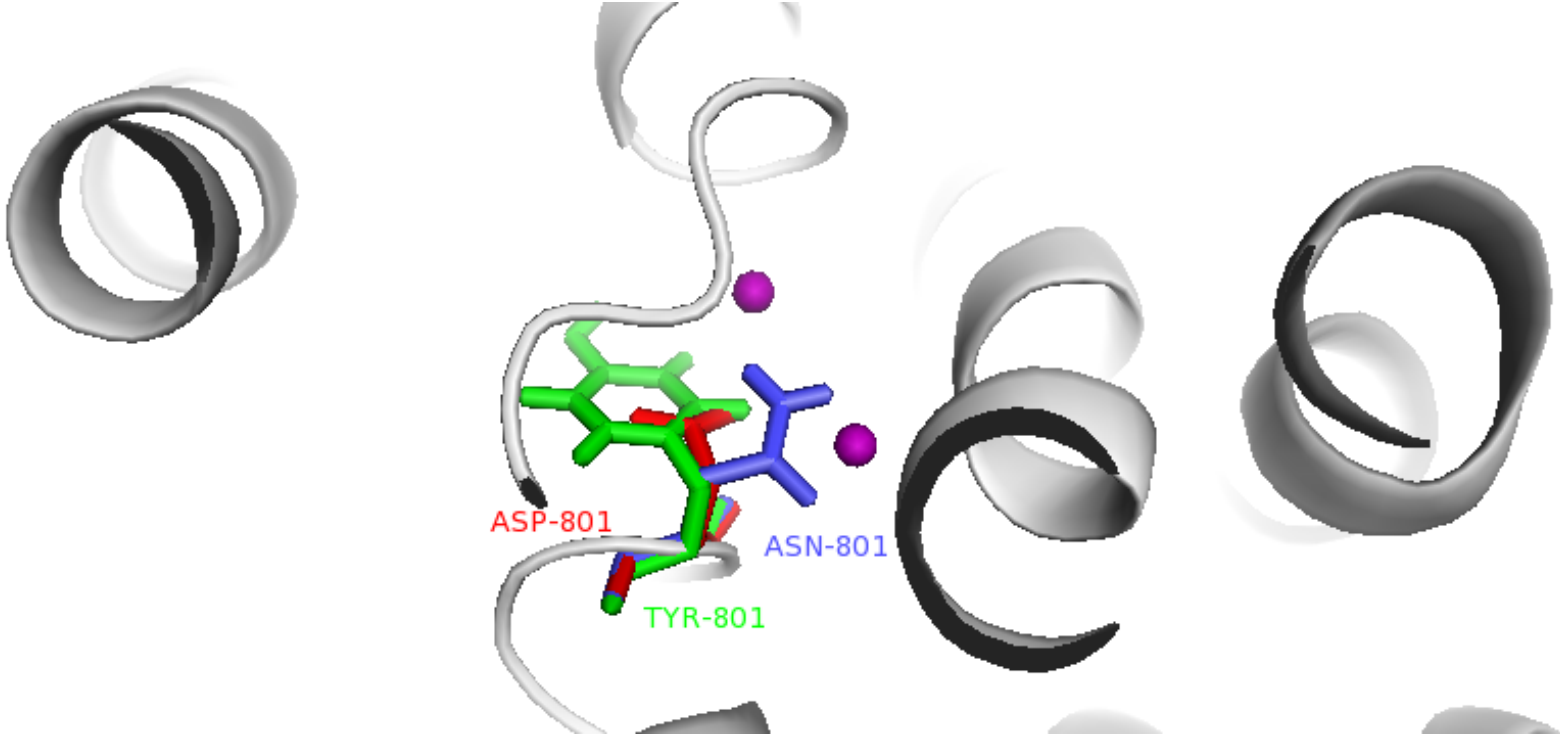


Figure produced by PyMol

D801N Can Block the K^+ Binding Site



Summary

- ATP1A3 is a causal gene of two disorders, AHC and RDP
- D801 mutations is one detected in two disorders
- D801Y blocks the Na^+ binding of ATPase and cause RDP
- D801N blocks the K^+ binding of ATPase and cause AHC

Discussion

- One mutation may cause different phenotypes by affecting the protein structure.
- D801 is No 1 potential drug target for two different diseases.
- Bioinformatic tools are useful for solving biological issues, but must be based on logical and rational interpretation.

Pictured adopted from: Wenner, M., *A new kind of drug target.* Sci Am, 2009. **301**(2): p. 70-4, 76.

Acknowledgment

- Prof. Luo Jingchu
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Thanks for Your Attention!