自闭症风险基因*FMR1*（*Fmr1*）的生物信息学分析

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自闭症简介

神经发育障碍

缺乏有效治疗手段

发病机制不明确

ASD

沟通障碍、重复行为

与*FMR1*突变相关

- 自闭症（Autism），又称孤独症，是一种广泛的神经起源的发育障碍。它的谱系很广，统称为自闭症谱系障碍（Autism Spectrum Disorder，ASD）。
- 自闭症的特点：①在多种背景下的社交沟通和社交互动持续存在缺陷；②有限的、重复的行为、兴趣或活动模式
- 自闭症障碍全世界人口患病率约为1~2%，大约每100个儿童中就有一人患自闭症

图片来源于网络

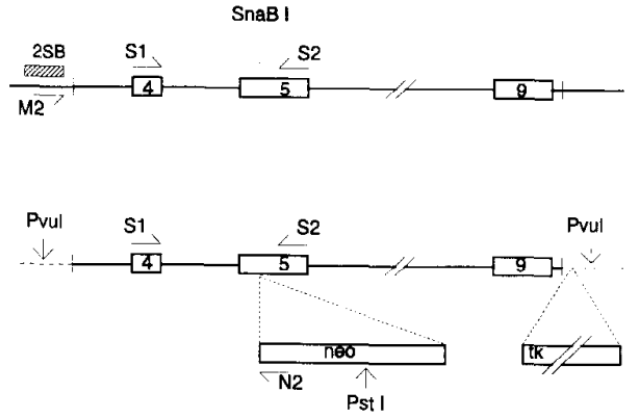
自闭症动物模型

动物模型

- 小鼠模型
- 果蝇模型
- 犬等其他模型

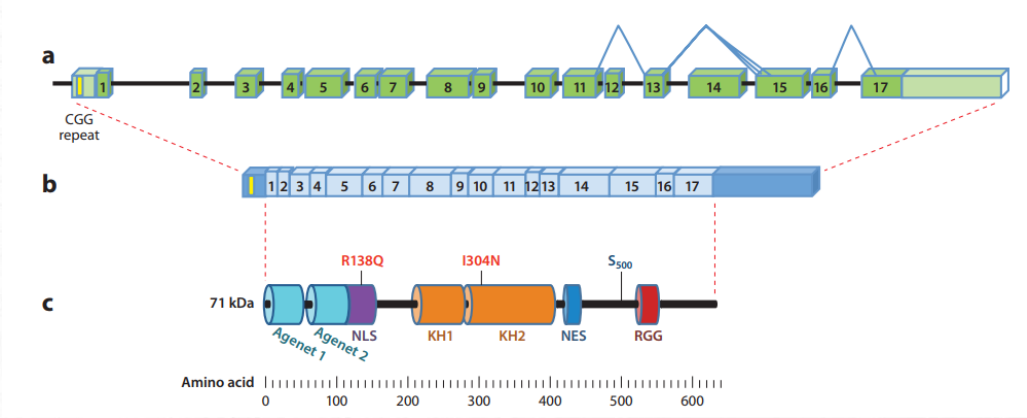
- 单基因模型
- 多基因模型

- *Fmr1*敲除模型



Cell 1994 Vol. 78 Issue 1 Pages 23-33

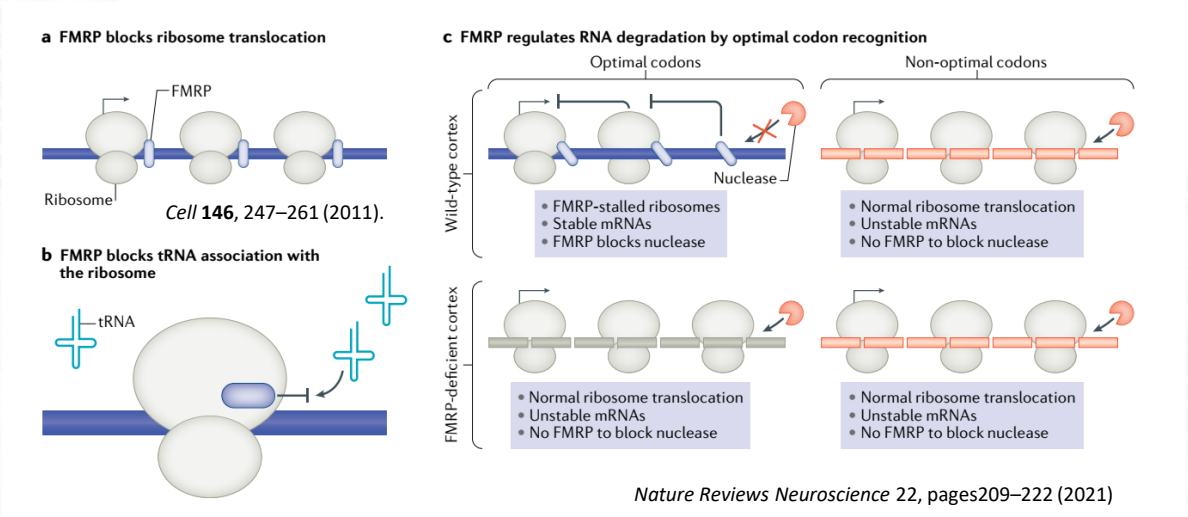
*Fmr1*及FMRP结构



Annu Rev Pathol. 2012:7:219-45.

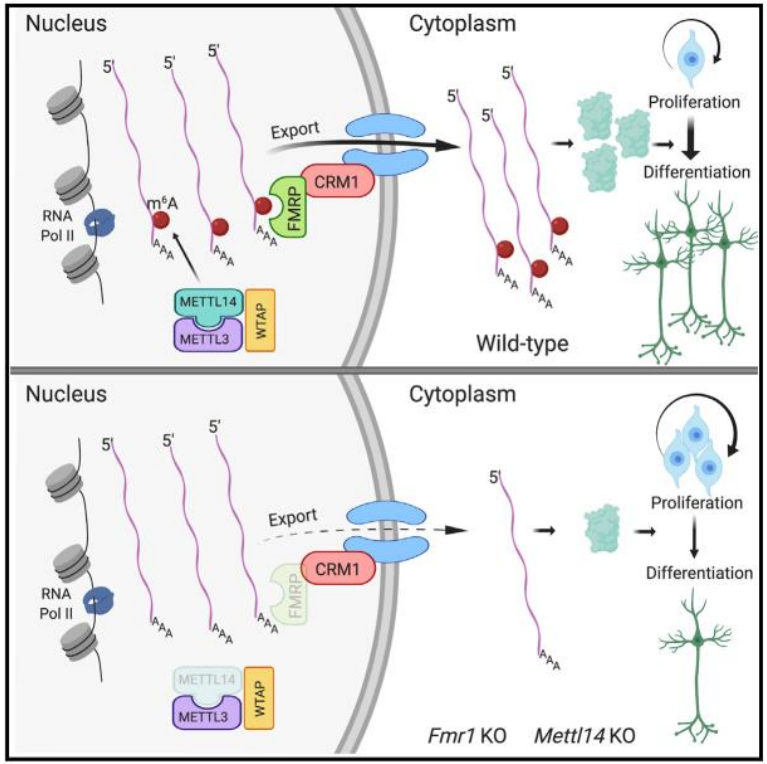
- Agenet 1 and Agenet 2, tandem Agenet domains, chromatin binding;
- NLS, nuclear localization signal; NES, nuclear export signal;
- RGG, arginine-glycine-glycine box, RNA-binding;
- KH1 and KH2, K homology domains 1 and 2, RNA-binding;

FMRP具有和mRNA结合



- FMRP与mRNA结合可能会阻碍核糖体易位，从而导致多肽延伸率降低。
- FMRP是一种抑制tRNA与核糖体结合的核糖体蛋白。
- FMRP直接或间接地与野生型小鼠皮质mRNA的翻译机制相关，这些mRNA含有最佳密码子并阻止这些RNA上的核糖体。

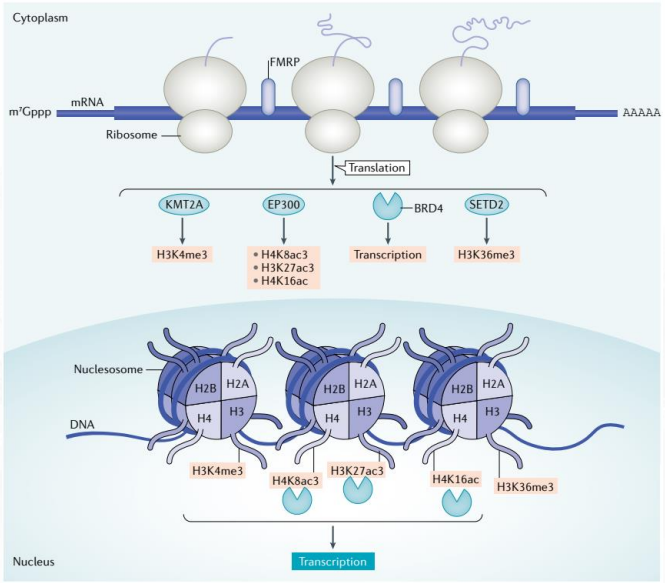
FMRP与核质转运

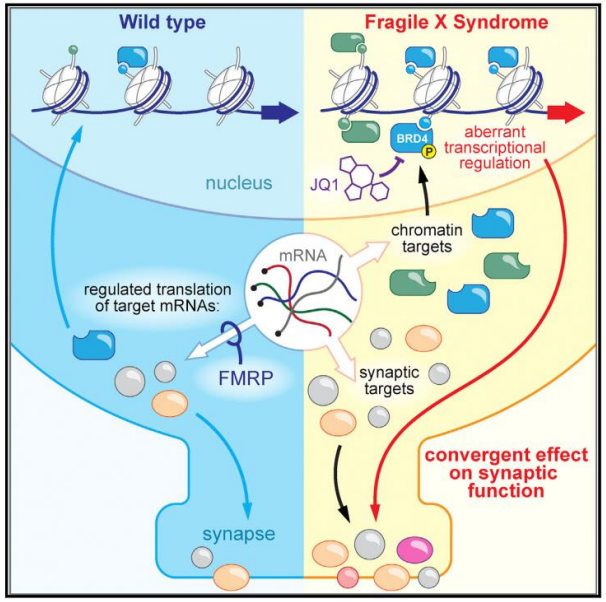


Cell Rep. **28**, 845–854 (2019).

- FMRP优先结合m6A甲基化mRNA并促进其核输出，这对于神经元分化至关重要。

FMRP与染色质调控





Cell **170**, 1209–1223 (2017)

- FMRP控制表观遗传修饰酶的合成，进而改变染色质景观，导致转录激活
- FMRP调控转录因子的翻译，进而调控基因表达

探究目的

- 是否鼠源*Fmr1* 转录的蛋白质功能研究能够对人源FMRP功能有参考意义？
- FMRP和哪些蛋白质可以发生相互作用？

*FMR1*基因序列的保守性

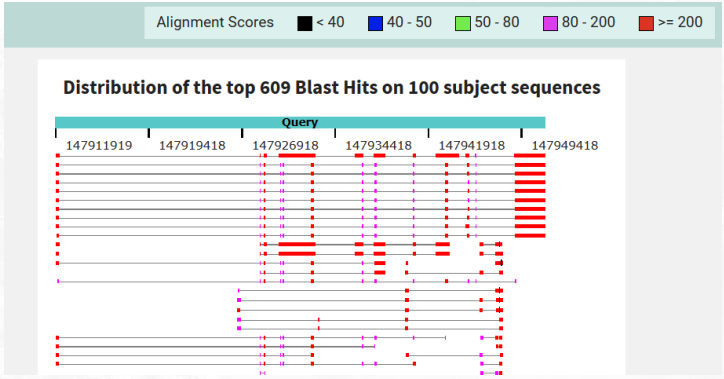
基因序列

Descriptions | Graphic Summary | Alignments | Taxonomy

Sequences producing significant alignments Download Select columns Show 100

select all *100 sequences selected* GenBank Graphics Distance tree of results MSA Viewer

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
Mus musculus X BAC RP23-149C7 (Roswell Park Cancer Institute Mouse BAC Library) complete seque...	Mus musculus	3048	9231	26%	0.0	88.46%	222658	AC055766.31
Mus musculus fragile X mental retardation syndrome 1 homolog, mRNA (cDNA clone MGC:90722 IMAG...	Mus musculus	2946	5555	10%	0.0	89.03%	4412	BC079671.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 3, mRNA	Mus musculus	2942	5546	10%	0.0	89.02%	4305	NM_001374719.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 6, mRNA	Mus musculus	2942	5347	10%	0.0	89.02%	4230	NM_001412091.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 4, mRNA	Mus musculus	2942	5485	10%	0.0	89.02%	4332	NM_001412089.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 2, mRNA	Mus musculus	2942	5353	10%	0.0	89.02%	4293	NM_001290424.2
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 5, mRNA	Mus musculus	2942	5479	10%	0.0	89.02%	4269	NM_001412090.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 1, mRNA	Mus musculus	2942	5551	10%	0.0	89.02%	4368	NM_008031.4
PREDICTED: Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant X4, misc...	Mus musculus	2942	5666	10%	0.0	89.02%	5147	XR_001782738.3
Mus musculus fragile X mental retardation syndrome protein (Fmr1) (homologue) mRNA, complete cds	Mus musculus	2726	5319	10%	0.0	87.57%	4240	L23971.1



*FMR1*转录本和蛋白序列的保守性

转录本序列

Descriptions | Graphic Summary | Alignments | Taxonomy

Sequences producing significant alignments Download Select columns Show 100

select all *7 sequences selected* GenBank Graphics Distance tree of results MSA Viewer

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 3, mRNA	Mus musculus	2942	5252	94%	0.0	89.02%	4305	NM_001374719.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 6, mRNA	Mus musculus	2942	5252	94%	0.0	89.02%	4230	NM_001412091.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 4, mRNA	Mus musculus	2942	5336	96%	0.0	89.02%	4332	NM_001412089.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 2, mRNA	Mus musculus	2942	5336	96%	0.0	89.02%	4293	NM_001290424.2
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 5, mRNA	Mus musculus	2942	5252	94%	0.0	89.02%	4269	NM_001412090.1
Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant 1, mRNA	Mus musculus	2942	5336	96%	0.0	89.02%	4368	NM_008031.4
PREDICTED: Mus musculus fragile X messenger ribonucleoprotein 1 (Fmr1), transcript variant X4, misc_RNA	Mus musculus	2942	5336	96%	0.0	89.02%	5147	XR_001782738.3

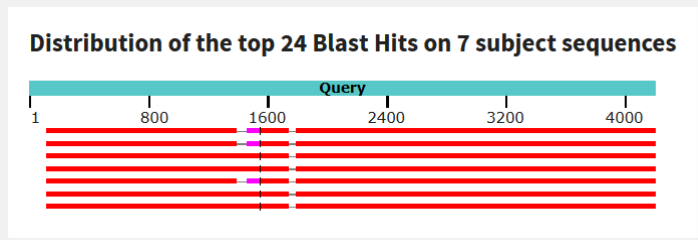
蛋白质序列

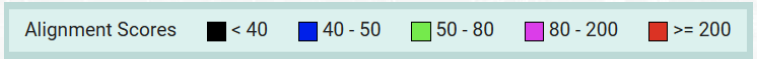
Descriptions | Graphic Summary | Alignments | Taxonomy

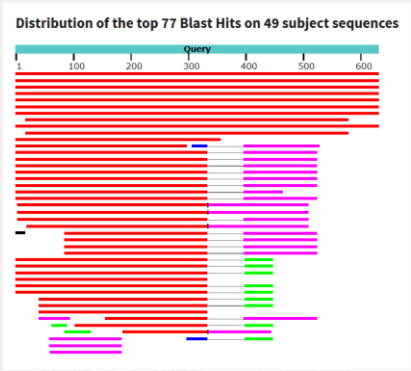
Sequences producing significant alignments Download Select columns Show 100

select all *49 sequences selected* GenPept Graphics Distance tree of results Multiple alignment MSA Viewer

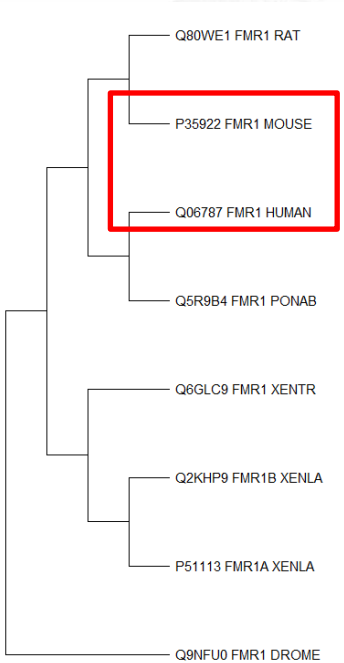
Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
fragile X messenger ribonucleoprotein 1 isoform 1 [Mus musculus]	Mus musculus	1221	1221	100%	0.0	94.15%	614	NP_032057.2
RecName: Full=Fragile X messenger ribonucleoprotein 1; AltName: Full=Fragile X messenger ribonucleoprot...	Mus musculus	1218	1218	100%	0.0	93.99%	614	P35922.1
fragile X messenger ribonucleoprotein 1 isoform 4 [Mus musculus]	Mus musculus	1190	1190	100%	0.0	92.25%	602	NP_001399018.1
fragile X messenger ribonucleoprotein 1 isoform 3 [Mus musculus]	Mus musculus	1179	1179	100%	0.0	91.61%	593	NP_001361648.1
fragile X messenger ribonucleoprotein 1 isoform 2 [Mus musculus]	Mus musculus	1157	1157	100%	0.0	90.19%	589	NP_001277353.1
fragile X mental retardation protein FMRP [Mus musculus]	Mus musculus	1153	1153	100%	0.0	90.03%	589	AAL66364.1
fragile X messenger ribonucleoprotein 1 isoform 5 [Mus musculus]	Mus musculus	1147	1147	100%	0.0	89.72%	581	NP_001399019.1
fragile X mental retardation syndrome 1 homolog, isoform CRA_a [Mus musculus]	Mus musculus	1132	1132	88%	0.0	96.98%	561	EDL01213.1
fragile X messenger ribonucleoprotein 1 isoform 6 [Mus musculus]	Mus musculus	1114	1114	100%	0.0	87.66%	568	NP_001399020.1

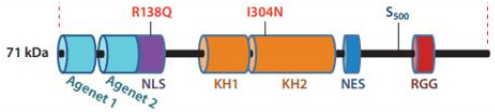


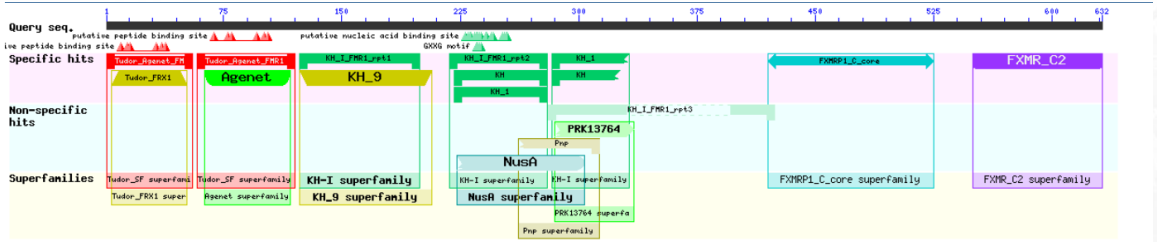


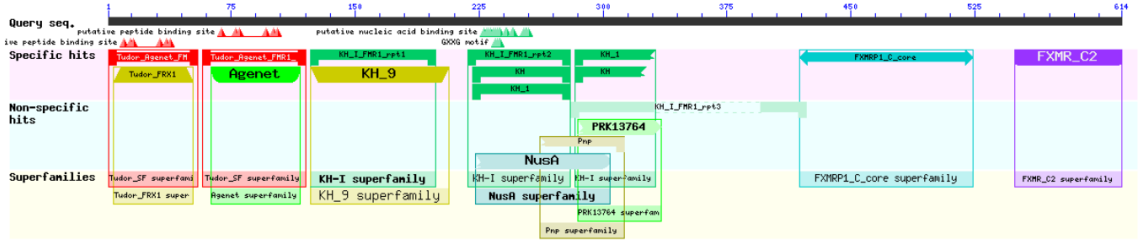


FMRP发育树和保守结构域分析

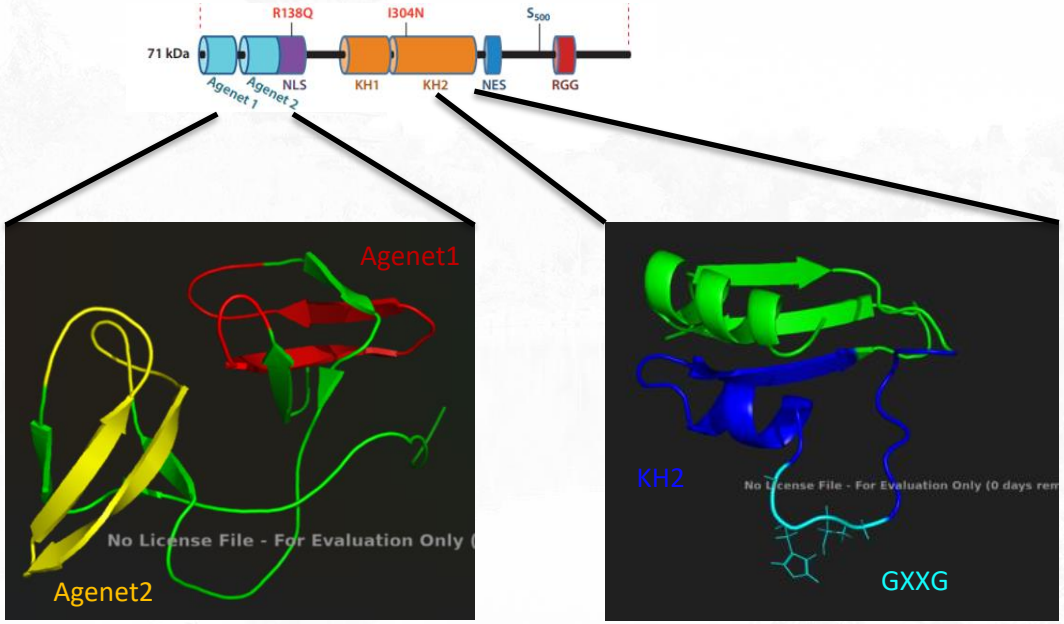




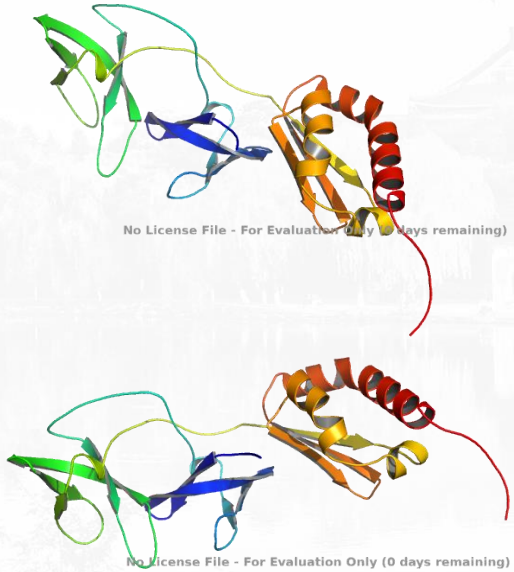




FMRP已表征结构域及全长结构预测



Mouse FMRP prediction



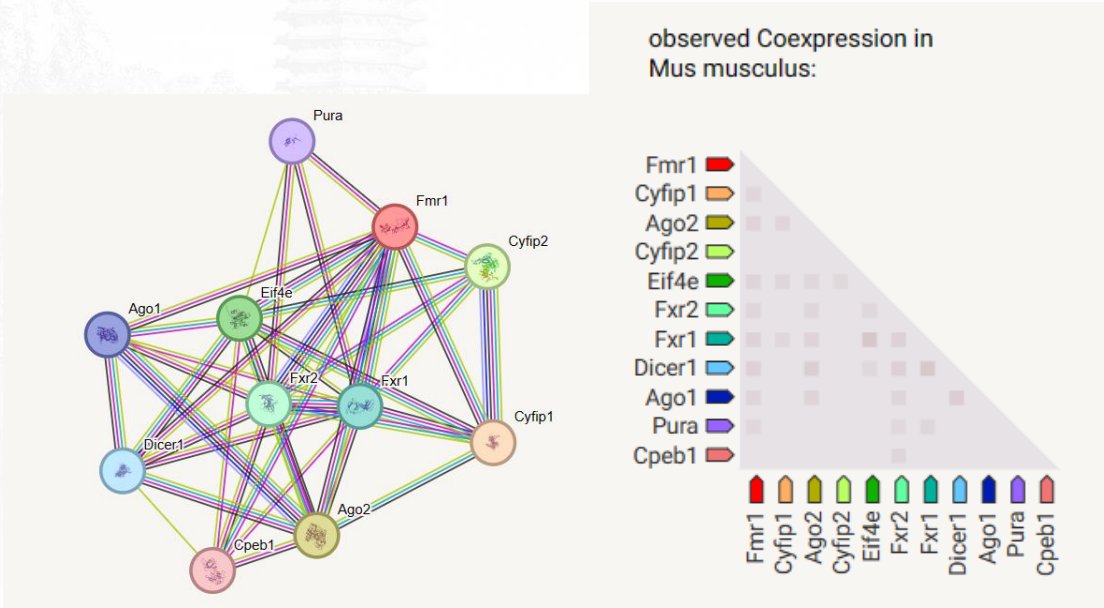
Human FMRP prediction

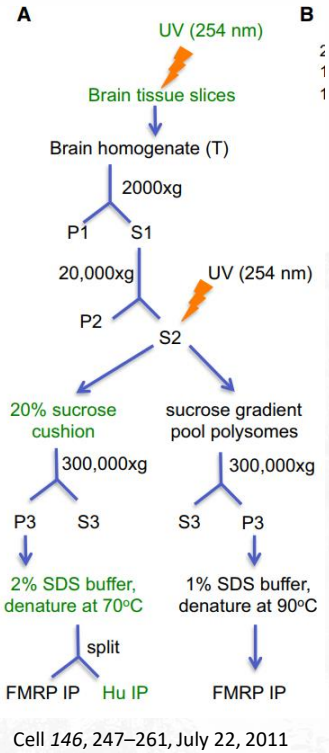
探究目的

- 是否鼠源*Fmr1* 转录的蛋白质功能研究能够对人源FMRP功能有参考意义？
- FMRP和哪些蛋白质可以发生相互作用？

鼠源FMRP蛋白相互作用分析及共表达情况

STRING数据库：





Cell *146*, 247–261, July 22, 2011

- 利用交联免疫沉淀分离RNA，之后进行高通量测序，
- 鉴定出842个FMRP靶标mRNA

- FMRP可以和多种基因、蛋白质相互作用，主要包括但不局限于蛋白稳态、信号转导、细胞骨架、囊泡运输、细胞周期、染色质调控等。

课程感悟

G4A毕金龙：

G4B李戈：

G4C程佳琪：

THANKS