BIN1 accumulates in amyloid deposits in the 5XFAD mouse model but does not effect amyloid deposition or associated behavioural deficits

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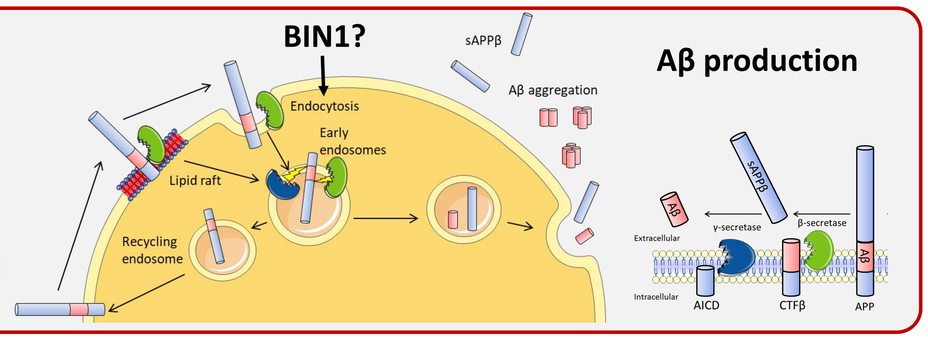
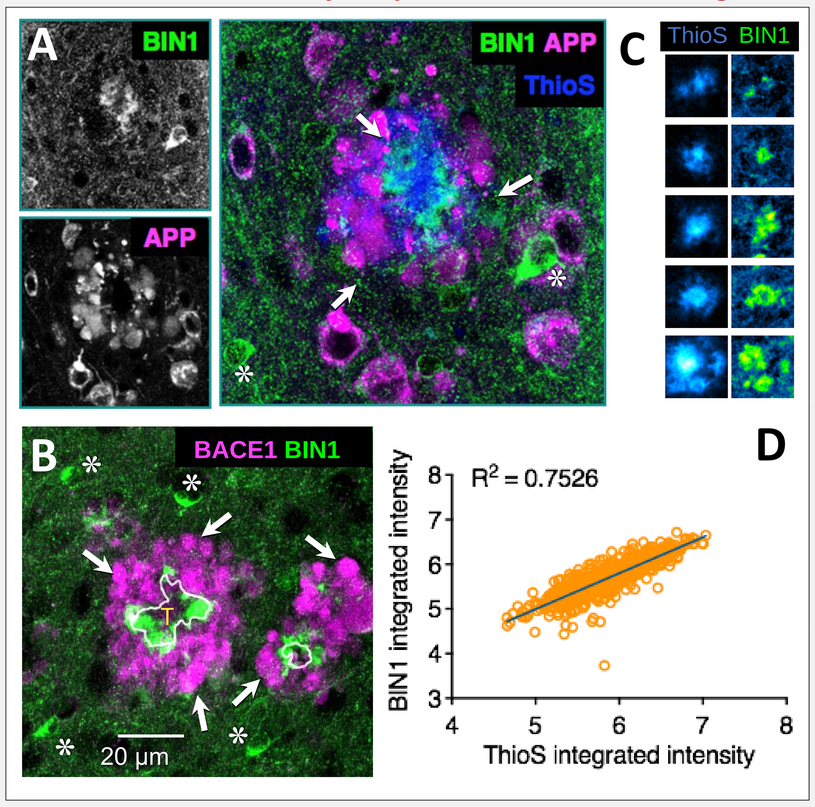
Introduction

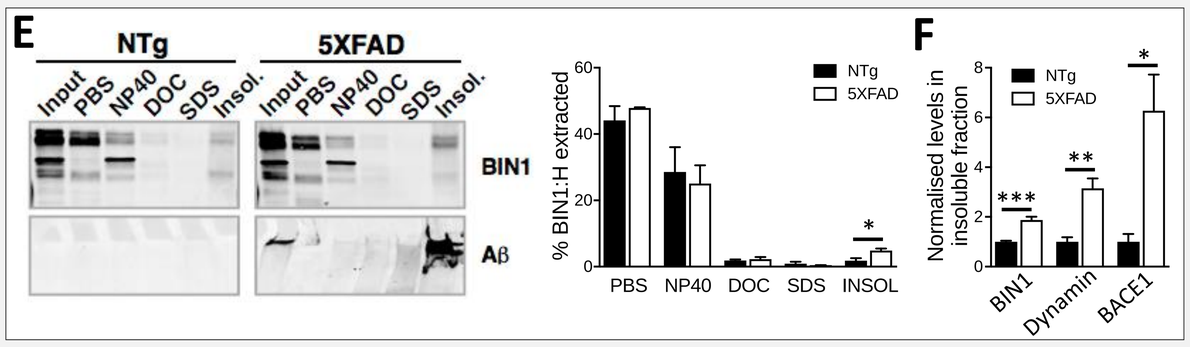
- *BIN1* was identified as the second most prevalent Alzheimer's disease risk-gene in genome wide association studies
- The role of BIN1 in the brain remains largely unknown, but it is proposed to play an important role in induction of membrane curvature and vesicle formation and in clathrin-mediated endocytosis (CME)
- CME is important for endosomal convergence of APP and BACE1 and subsequent APP proteolysis and Aβ production *in vitro*
- *In vitro,* reduction of BIN1 increases β-secretase levels through impaired endosomal trafficking and increases Aβ production
- To examine the importance of BIN1 in Aβ production and deposition *in vivo,* we generated conditional *Bin1* knockout mice and single germline *Bin1* allele deletion with a common amyloidosis mouse model



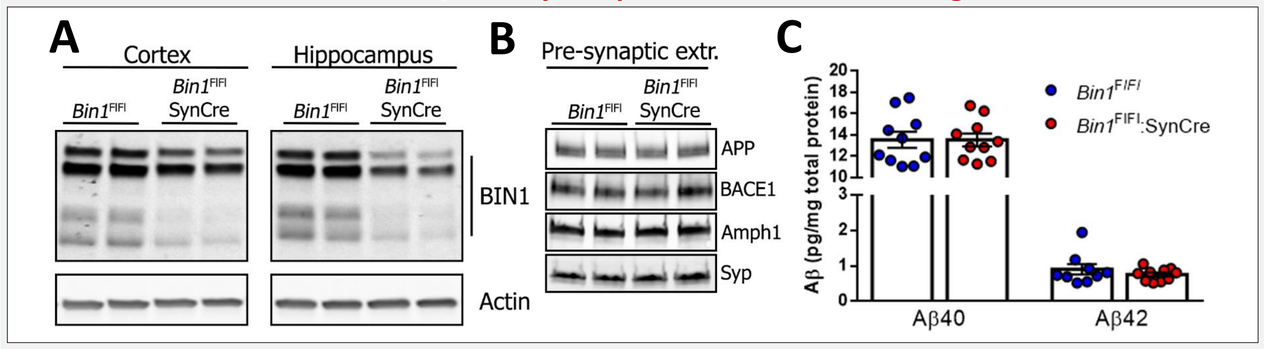
1. BIN1 loses solubility and accumulates in a distinct subcellular structure to dystrophic neurites containing BACE1 and APP

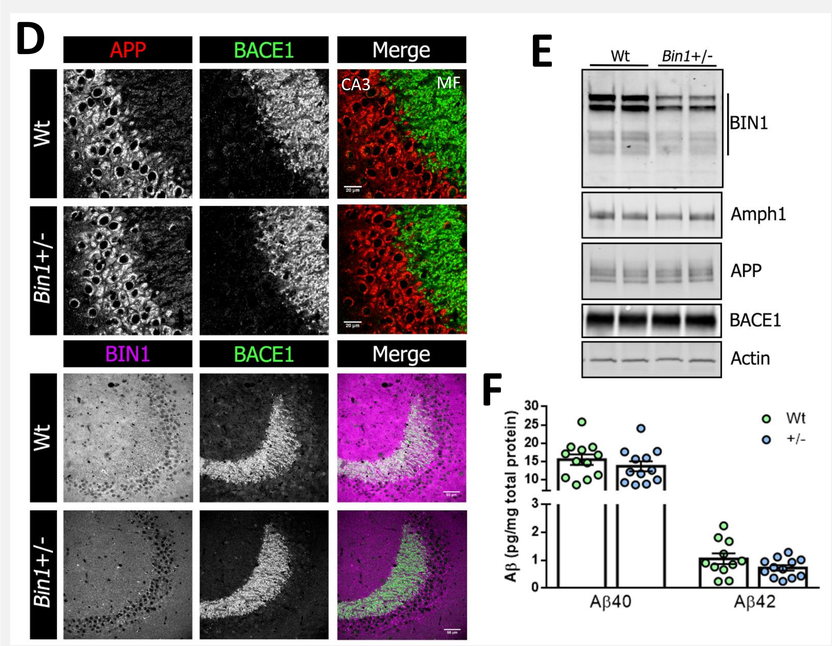


- **BIN1 accumulates in deposits in 5XFAD mouse model of amyloidosis but does not accumulate in dystrophic neurites** alongside APP **(A)** or BACE1 **(B)**
- **BIN1 deposition is also distinct from Thioflavin S staining (C)**, but correlates with deposit core size **(D)**
- Sequential detergent extractions on NTg and 5XFAD brains confirm **increased presence of BIN1 in the SDS-insoluble fraction of 5XFAD brains** where Aβ is found **(E)**
- BIN1 was found to accumulate alongside proteins that **were previously reported to lose solubility including BACE1 and Dynamin (F)**



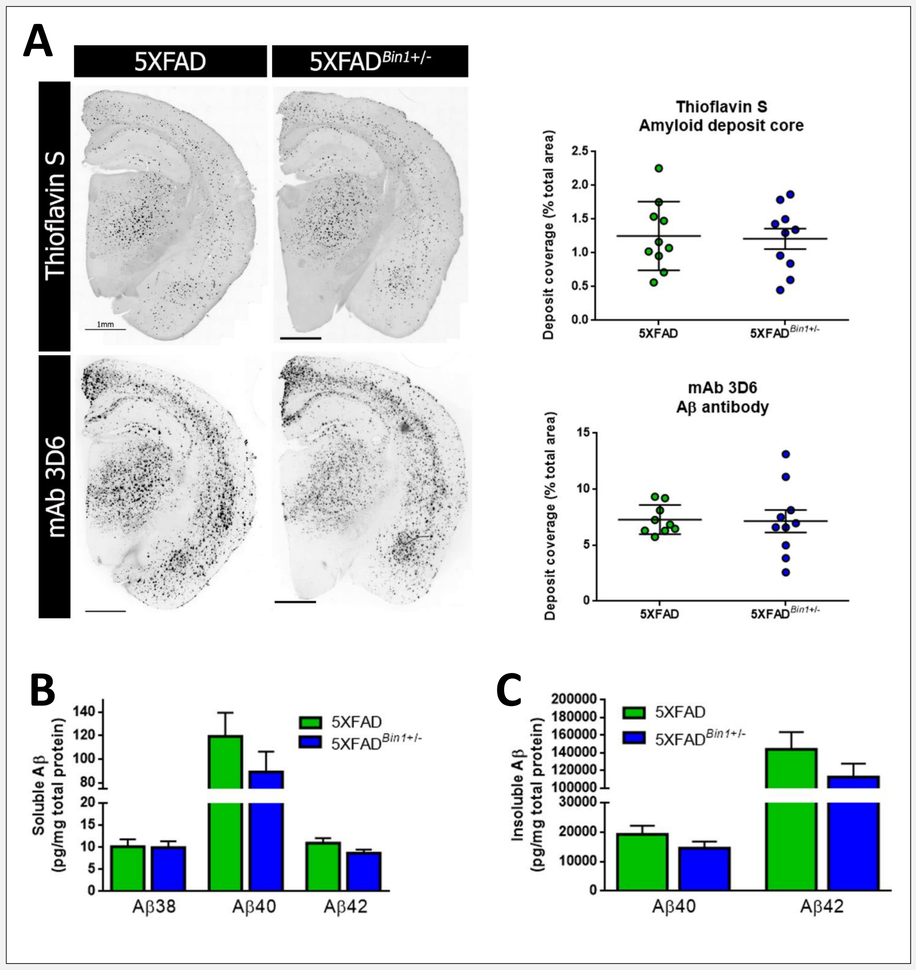
2. Conditional knockout or single allele deletion of BIN1 does not alter APP or BACE1 localization, or amyloid production in non-transgenic mice





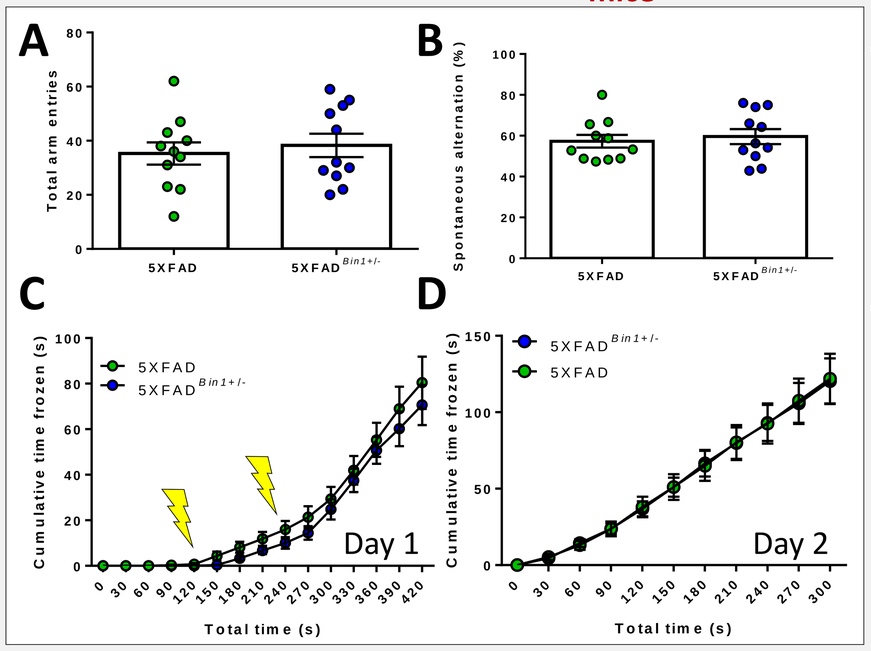
- **Synapsin-Cre driven conditional knockout of** *Bin1* reduced BIN1 levels in a region specific manner **(A)** but **did not alter presynaptic APP or BACE1 (B), or Aβ presynaptic production (C)**
- Germline deletion of a single *Bin1* allele results **in 50% reduction in BIN1 in mouse brain** homogenates with no change BACE1 or APP level **(E)**
- BACE1 and APP are observed in mossy fibres and CA3 neurons, respectively, **in both Wt and *Bin1*+/- mice as previously described (D)**
- **Global BIN1 reduction does not alter Aβ production**

3. Reduction of BIN1 does not alter amyloid-deposition in 5XFAD mice



- Female 5XFAD mice show significant deposition of amyloid by 4 months of age
- Reduction of BIN1 in 5XFAD mice by 50% **did not alter amyloid deposition** as analysed by Thioflavin-S staining (Aβ core) or monoclonal Aβ antibody staining **(A)**
- Analysis of TBS soluble **(B)** or formic acid extracted **(C)** Aβ showed **no reduction in Aβ peptide levels in the brain**
- Reduction of BIN1 expression didn't not reduce deposit burden in 5XFAD mice

4. Reduction of BIN1 does not alter amyloid-induced behavioural deficits in 5XFAD mice



- 5XFAD mice show cognitive **deficits in spatial and contextual learning tasks** which corelate with amyloid burden in these mice improves cognition in learning and memory tasks
- **No significant difference** in arm entries **(A)** or spontaneous alternation **(B)** in the Y-maze task or in freezing time during learning **(C)** or recall **(D)** in contextual fear conditioning in 5XFAD mice with 50% loss of BIN1

Conclusions

- BIN1 accumulates within deposits in the 5XFAD mouse model brain in an amorphous structure distinct from dystrophic neurites in which BACE1 and APP accumulate
- Conditional knockout or single allele deletion of *Bin1* does not alter APP or BACE1 localization or Aβ production in the brains of non-transgenic mice
- Furthermore, reduction of BIN1 in the 5XFAD model did not alter amyloid deposition or improve cognitive deficits associated with amyloid deposition
- BIN1 may not be a key player in the deposition of amyloid in animal models or in AD cases
- BIN1 is highly expressed in oligodendrocytes – for a possible role myelin breakdown in BIN1 accumulation in 5XFAD mice see Dr. Pierre De Rossi's poster.

References

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