Scientific Poster Session

n-lorem FOUNDATION

Nano-rare Patient Colloquium 2025

Monday, October 20 | 5:15 – 6:15 pm EST

The Importance of Understanding Mutation-specific Biology, Exemplified by JIP3

This study highlights the importance of understanding mutation-specific biology, exemplified by a toxic gain-of-function mutation in JIP3 (R578C) that disrupts axonal transport, signaling pathways, and overall neuronal function. By elucidating the molecular proximal pathological mechanisms associated with this mutation, we have successfully identified allele-selective ASOs as the optimal therapeutic strategy.

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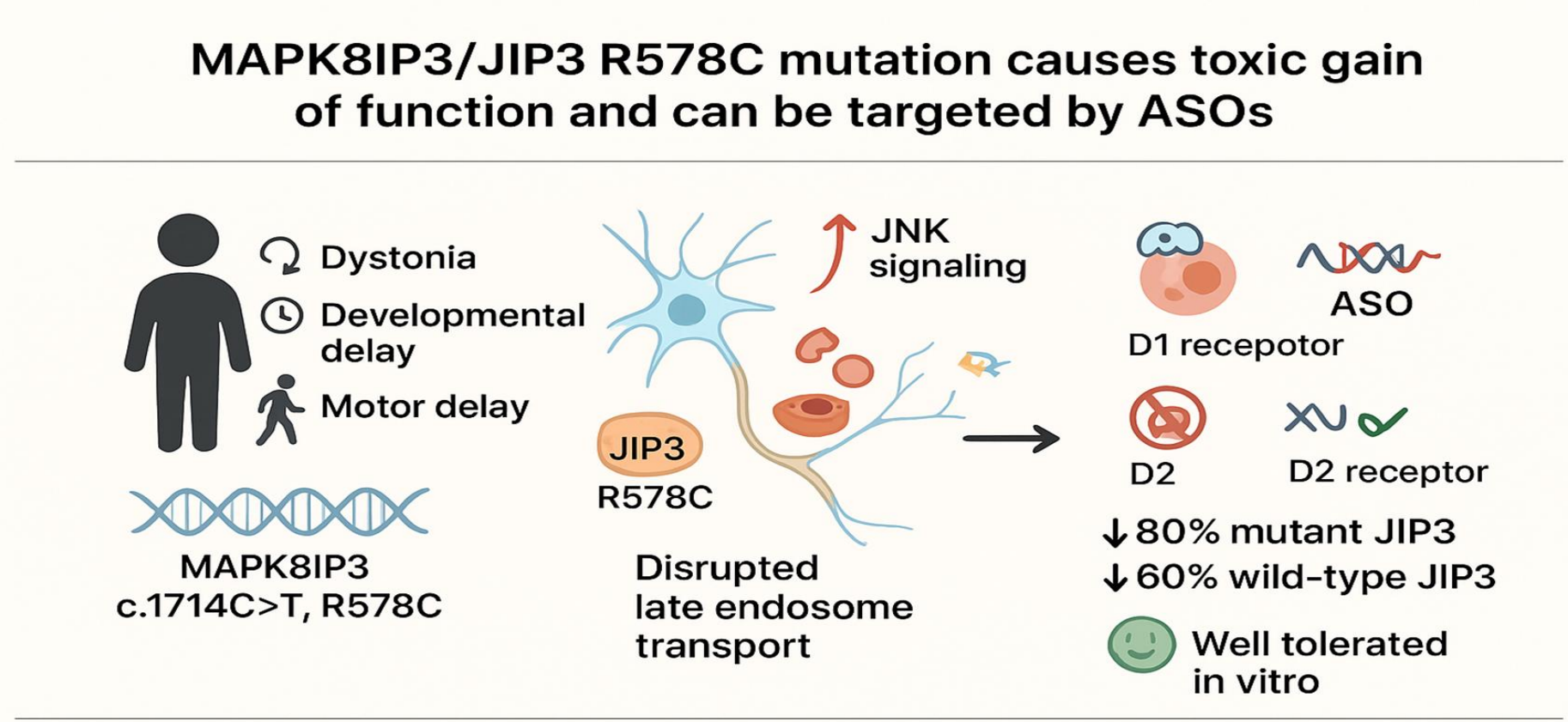
Associate Director, Core Research, n-Lorem

Hosted by:

Biogen

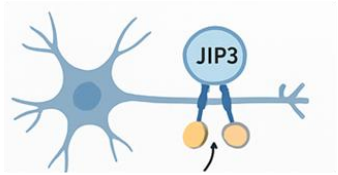
Abstract



Toxic gain-of-function JIP3 mutation alters interactome, disrupts axonal transport and dopamine signaling, activates apoptosis. ASO-mediated reduction of JIP3 offers a potential therapeutic strategy.

Introduction

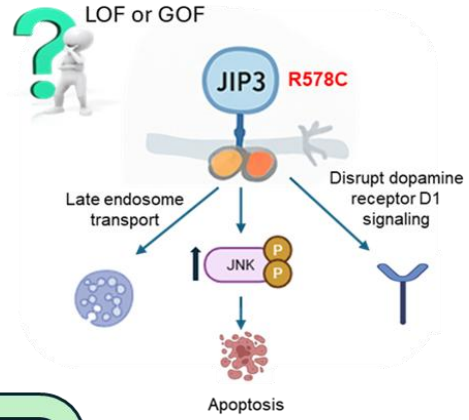
Normal



Normal Function of MAPK8IP3/JIP3

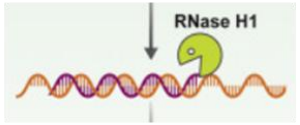
- JIP3 links kinesin/dynein to lysosomes
- Balanced MAPK/JNK signaling
- Cytoskeletal integrity maintained
- JIP4 = backup homolog

Pathogenic Variant R578C



- Toxic Gain-of-Function (R578C)
  - ↑ JNK signaling
  - Endosome transport blocked
  - D1 receptor signaling disrupted
  - Apoptosis

ASO Therapeutic Rescue

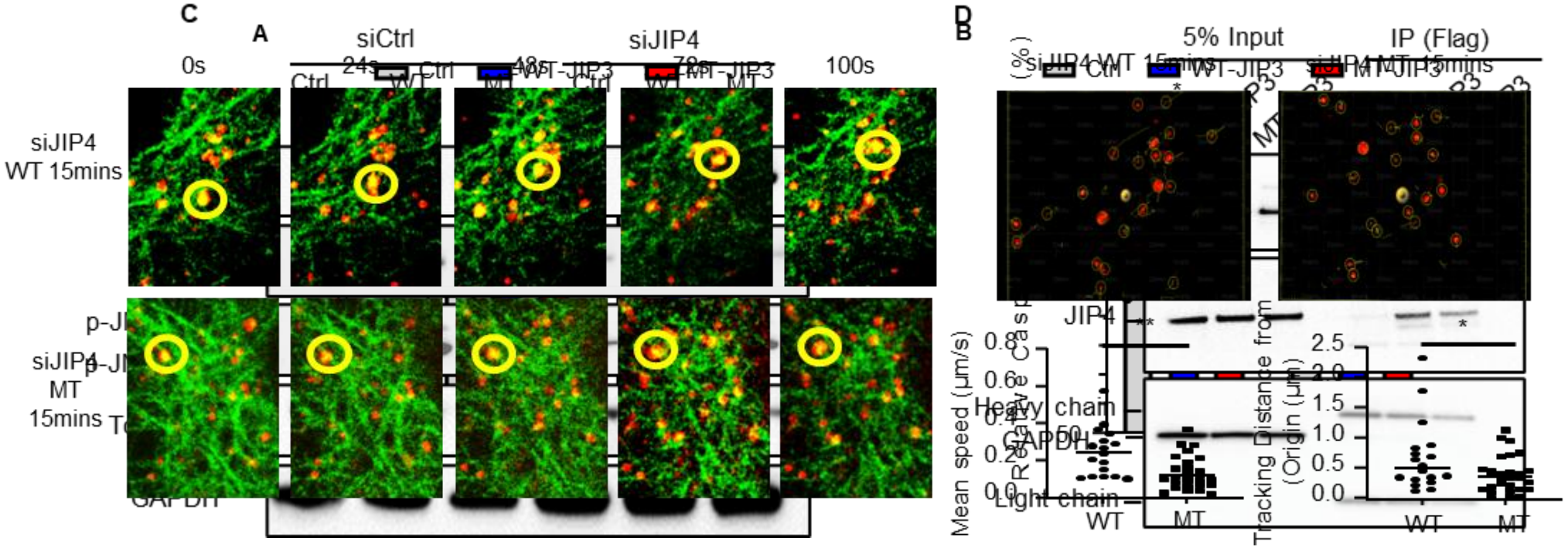


- Reduction JIP3:
  - ↓ 80% mutant JIP3
  - ↓ 60% wild-type JIP3
- Restored neuron with:
  - Normal cargo flow
  - Balanced JNK signaling
  - D1 receptor signaling recovered
  - No apoptosis

In this study, we establish R578C as a severe TGOF mutation and demonstrate that reducing total JIP3/JIP4 levels with a non-allele-selective phosphorothioate antisense oligonucleotide (PS-ASO) rescues all pathological phenotypes. These results not only define the molecular mechanisms underlying R578C toxicity but also highlight RNA-targeted strategies as potential therapies for MAPK8IP3-related TGOF neurodevelopmental disorders.

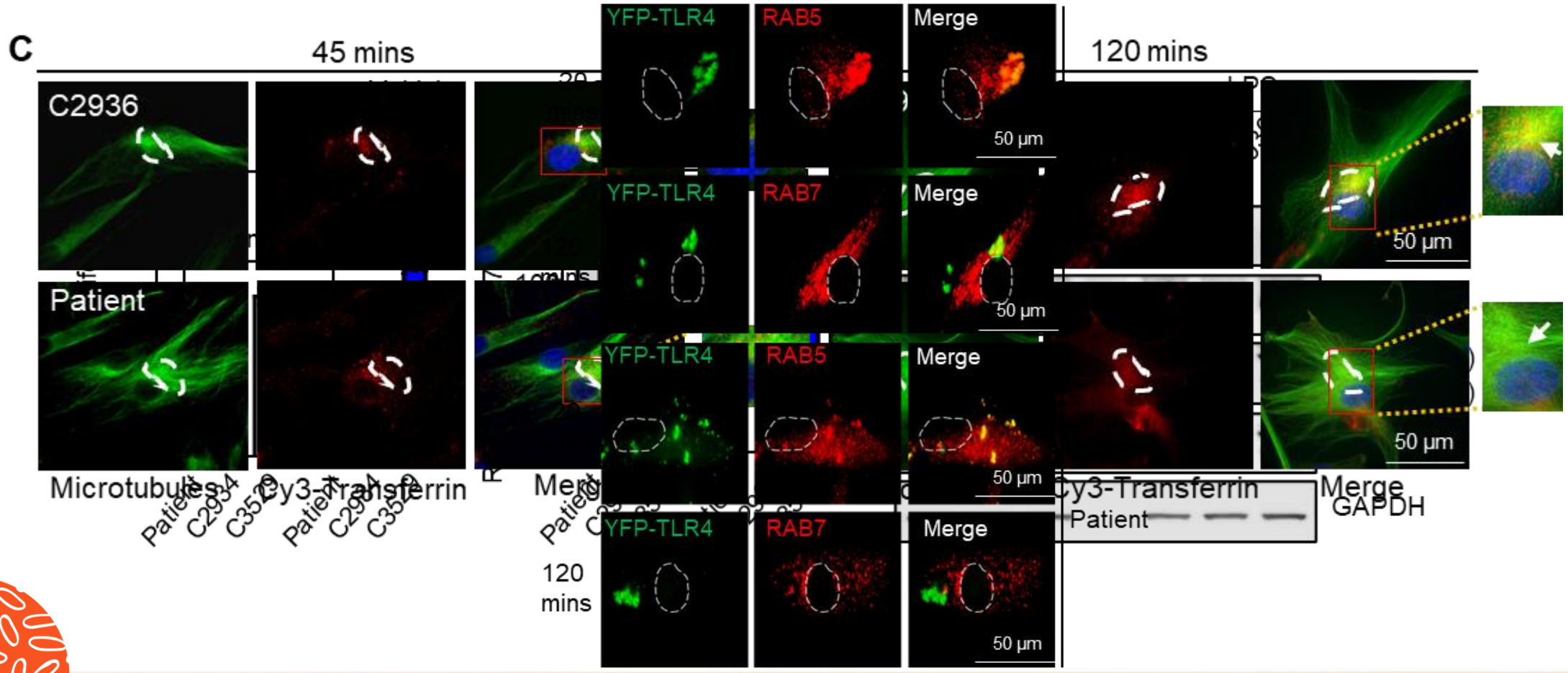
Results

MT-JIP3 induces JNK signaling-dependent apoptosis in Hela cells reducing cell growth and JIP4 interacts with JIP3, and altering the binding affinity with associated proteins



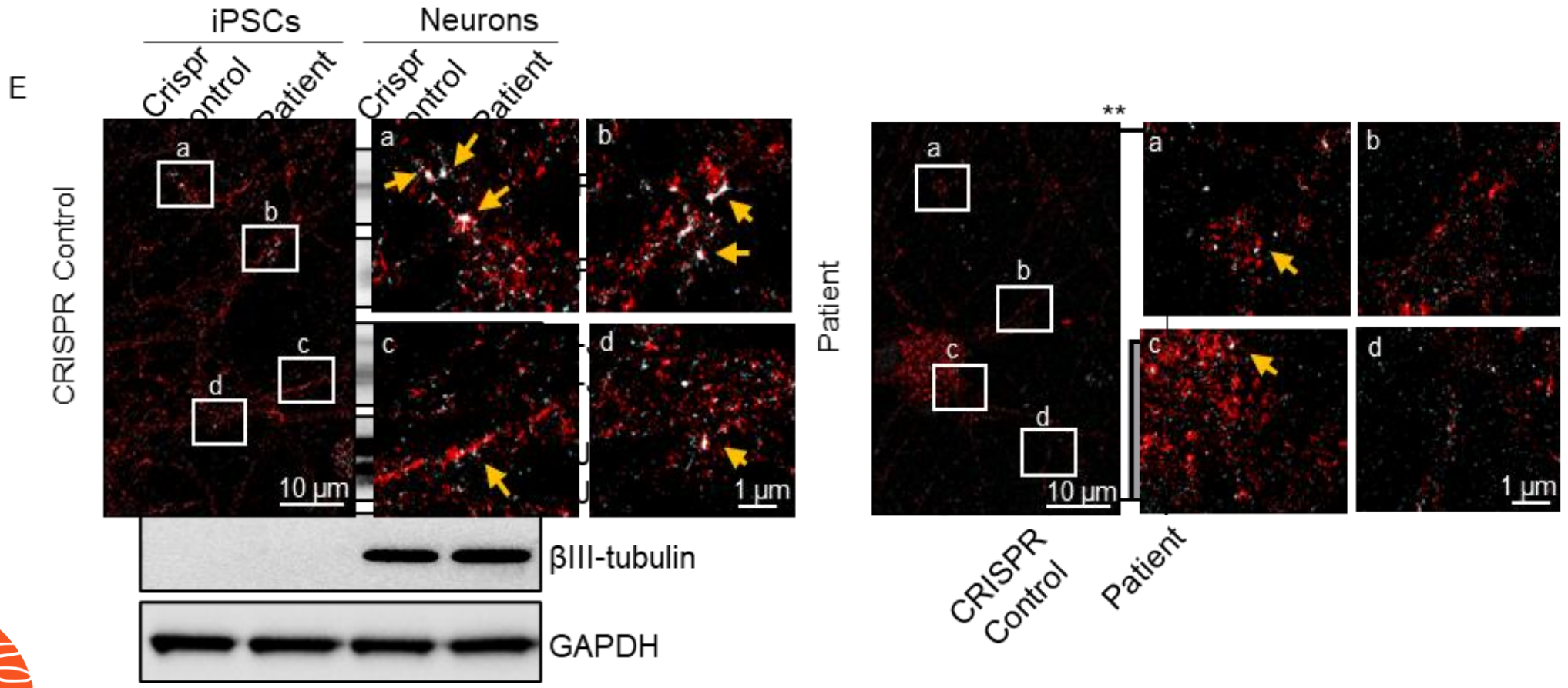
Results

MT-JIP3 reduces cell growth and disrupts endosomal mobility in patient derived fibroblasts



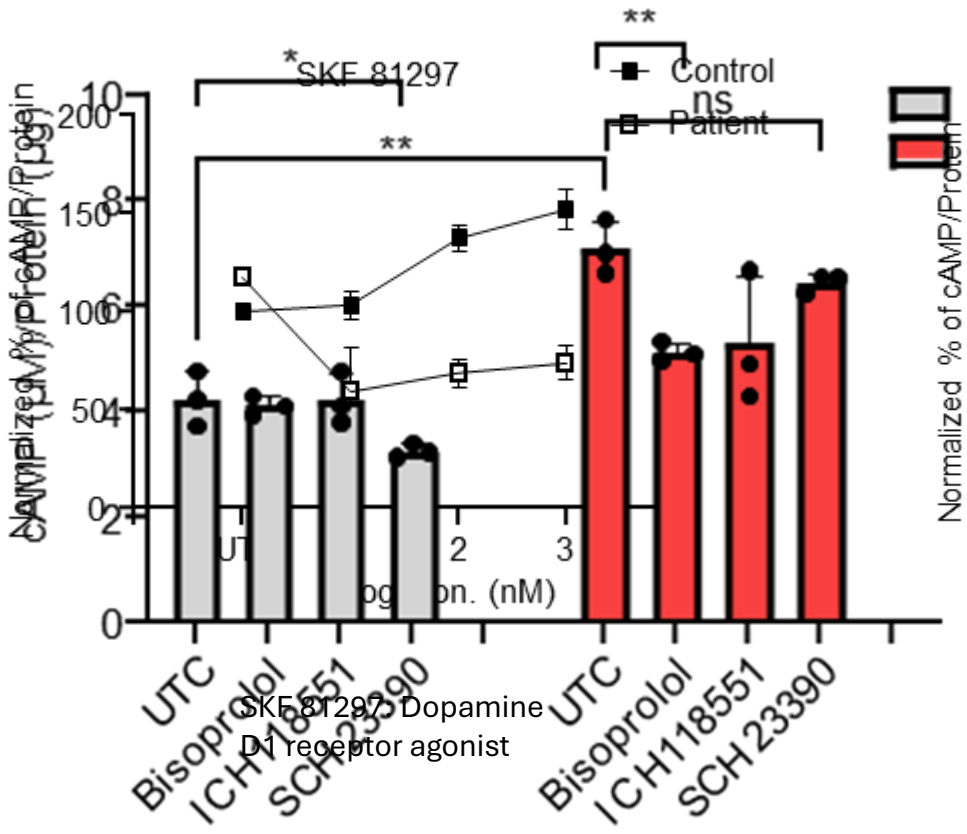
Results

MT-JIP3 induces JNK signaling, reducing cell viability and disrupts axonal trafficking in patient iPSC derived neurons

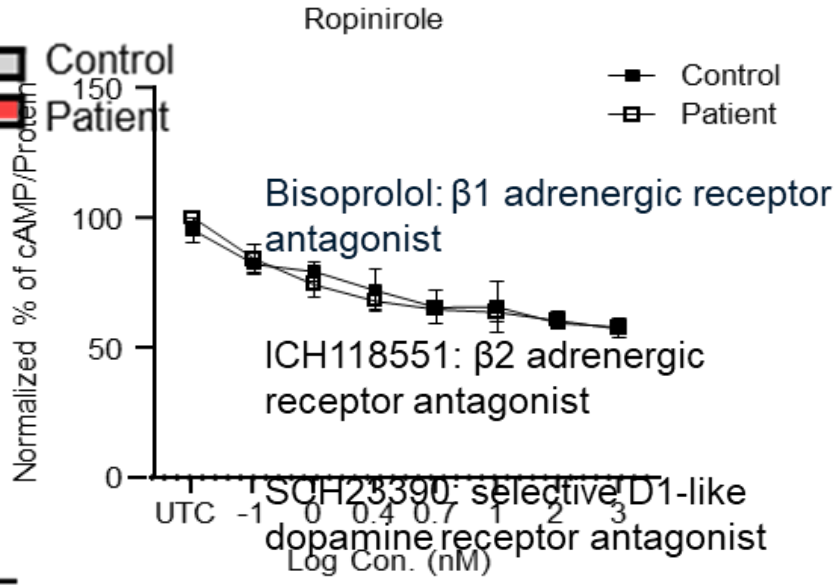


Results

Patient derived fibroblasts and iPSC derived neurons showed impaired dopamine receptor 1 signaling.



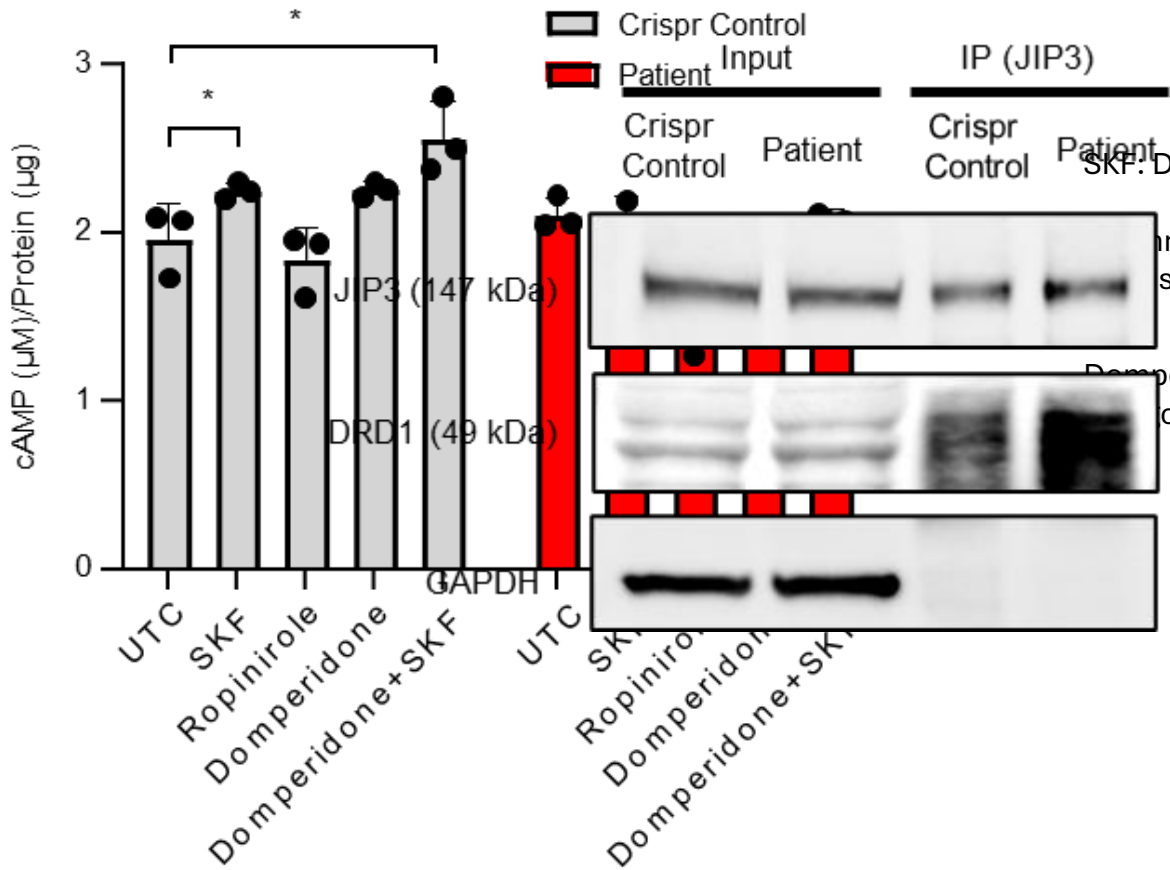
SKF 81297: Dopamine D1 receptor agonist



Ropinirole: Dopamine D2 receptor agonist

Results

Dopamine signaling was uncoupled in patient iPSC derived neurons



SKF: D1 dopamine receptor agonist

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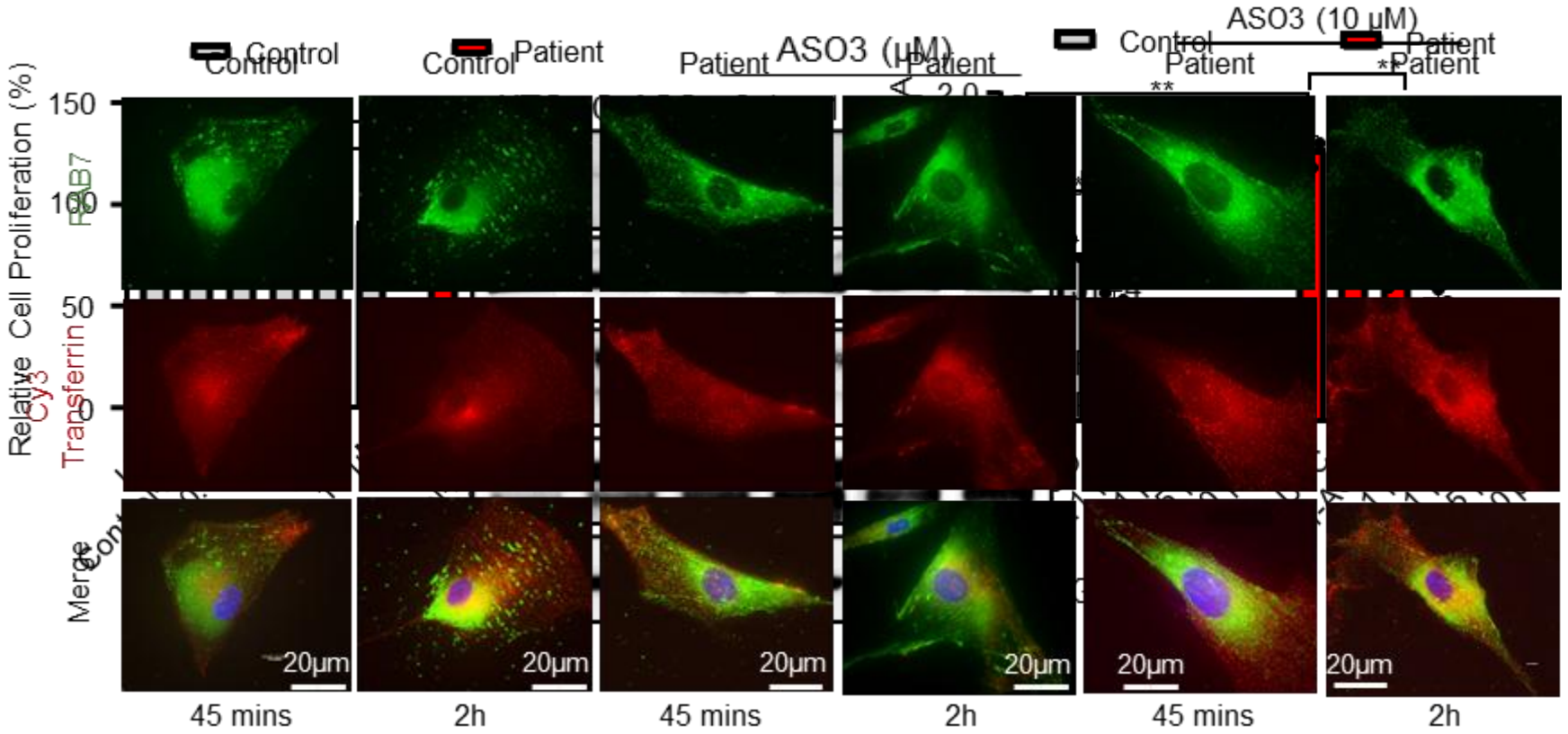
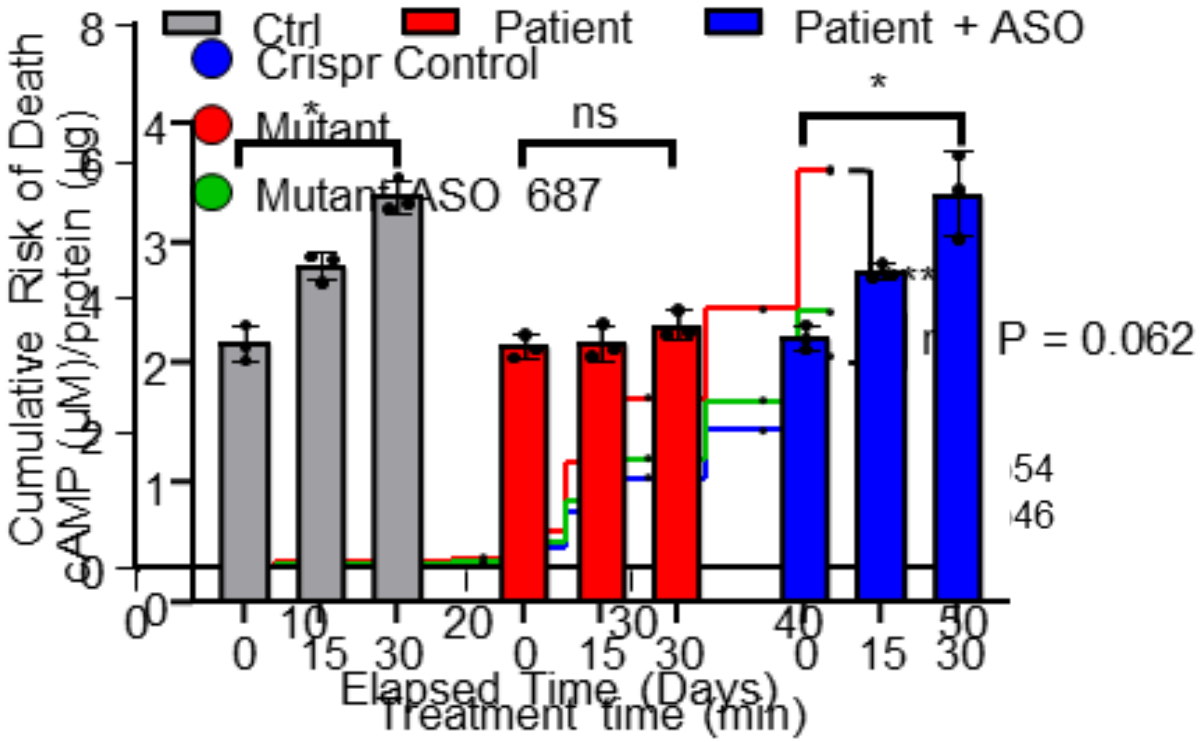
Results

Non-allele selective phosphorothioate 2 methoxyethyl gapmer antisense oligonucleotides (PS 2'MOE ASOs) to activate RNase H1 mediated reduction of both MT- and WT-JIP3 m-RNA and protein restore endosome mobility and rescue patient fibroblasts from mutation-induced cell death



Results

Suppression of MT-JIP3 by ASOs rescues patient iPSC derived neurons from mutation induced cytotoxicity



Conclusion

- MT-JIP3 R578C mutation causes:
  - Abnormal enhancement of the JNK signaling pathway
  - Deficient cargo endosome transport
  - Disrupted dopamine receptor responses

- These abnormalities ultimately result in cell death, showing that the mutation acquires a severely toxic gain of function

- Provides mechanistic insight into how this mutation leads to neurodegenerative diseases

- Demonstrates a reliable and effective ASO treatment method, offering a promising therapeutic avenue for clinical application

Acknowledgements

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Thank you

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