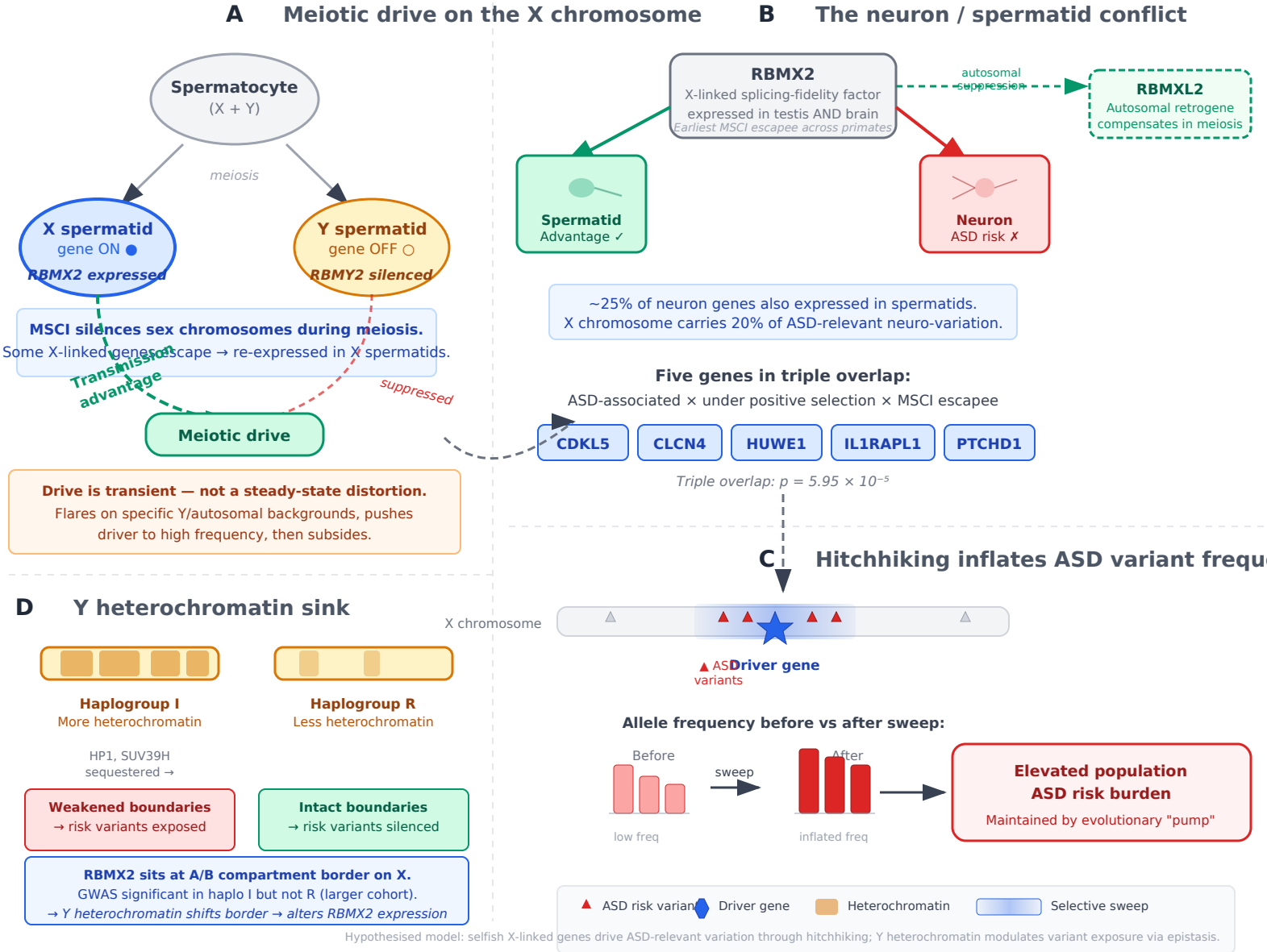
A Meiotic drive on the X chromosome
Spermatocyte
(X + Y)
meiosis
X spermatid
gene ON ●
RBMX2 expressed
Y spermatid
gene OFF ○
RBMY2 silenced
MSCI silences sex chromosomes during meiosis.
Some X-linked genes escape → re-expressed in X spermatids.
Transmission advantage
suppressed
Meiotic drive
Drive is transient — not a steady-state distortion.
Flares on specific Y/autosomal backgrounds, pushes driver to high frequency, then subsides.
B The neuron / spermatid conflict
RBMX2
X-linked splicing-fidelity factor expressed in testis AND brain
Earliest MSCI escapee across primates
autosomal suppression
RBMXL2
Autosomal retrogene compensates in meiosis
Spermatid
Advantage ✓
Neuron
ASD risk ✗
~25% of neuron genes also expressed in spermatids.
X chromosome carries 20% of ASD-relevant neuro-variation.
Five genes in triple overlap:
ASD-associated × under positive selection × MSCI escapee
CDKL5
CLCN4
HUWE1
IL1RAPL1
PTCHD1
Triple overlap: p = 5.95 × 10⁻⁵
C Hitchhiking inflates ASD variant frequencies
X chromosome
ASD variants
Driver gene
Allele frequency before vs after sweep:
Before
sweep
After
low freq
inflated freq
Elevated population ASD risk burden
Maintained by evolutionary "pump"
D Y heterochromatin sink
Haplogroup I
More heterochromatin
Haplogroup R
Less heterochromatin
HP1, SUV39H sequestered →
Weakened boundaries
→ risk variants exposed
Intact boundaries
→ risk variants silenced
RBMX2 sits at A/B compartment border on X.
GWAS significant in haplo I but not R (larger cohort).
→ Y heterochromatin shifts border → alters RBMX2 expression
ASD risk variant
Driver gene
Heterochromatin
Selective sweep
Hypothesised model: selfish X-linked genes drive ASD-relevant variation through hitchhiking; Y heterochromatin modulates variant exposure via epistasis.