Metastatic progression of pheochromocytoma and paraganglioma occurs via parallel evolution

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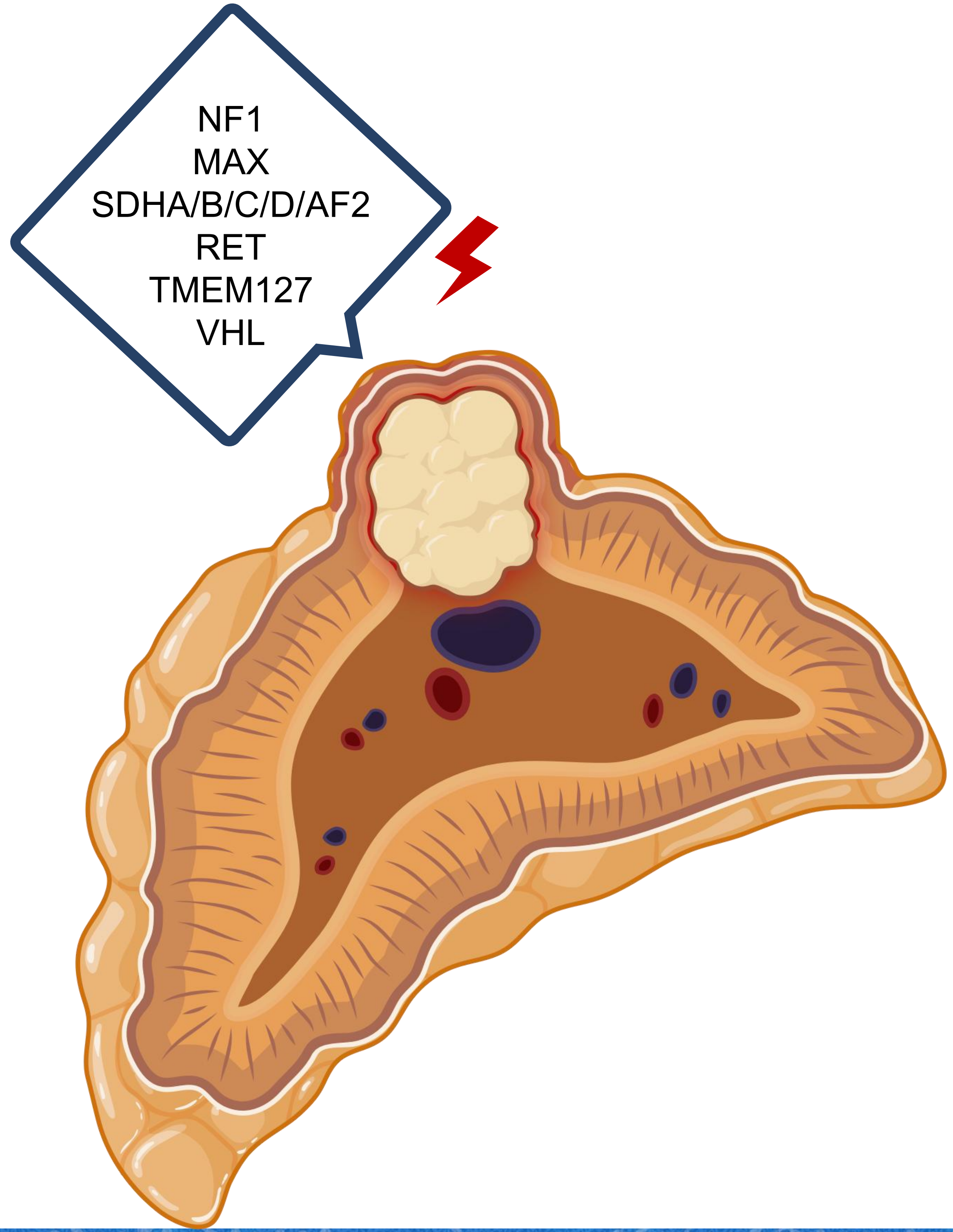
Disclosure

No disclosures

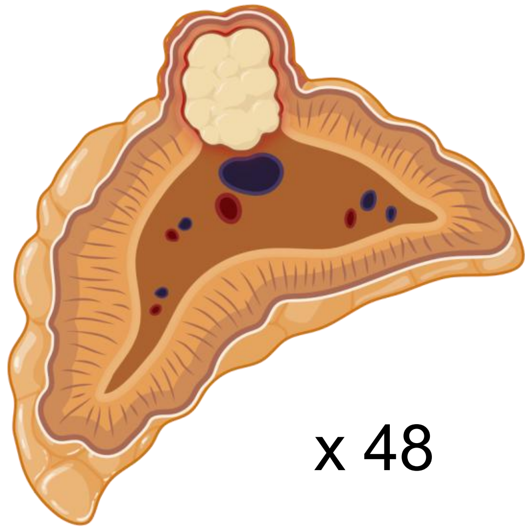
Pheochromocytoma and paraganglioma are the most heritable human tumors

- Pheochromocytoma and paraganglioma are neuroendocrine tumors that may secrete catecholamines
- Pheochromocytomas and paragangliomas have the highest association with germline susceptibility mutations of all human tumors
- There is no unifying hypothesis for tumorigenesis and progression



Methods

① Whole exome sequencing



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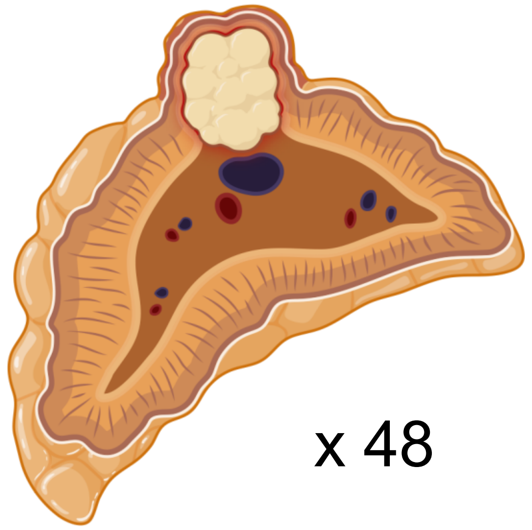
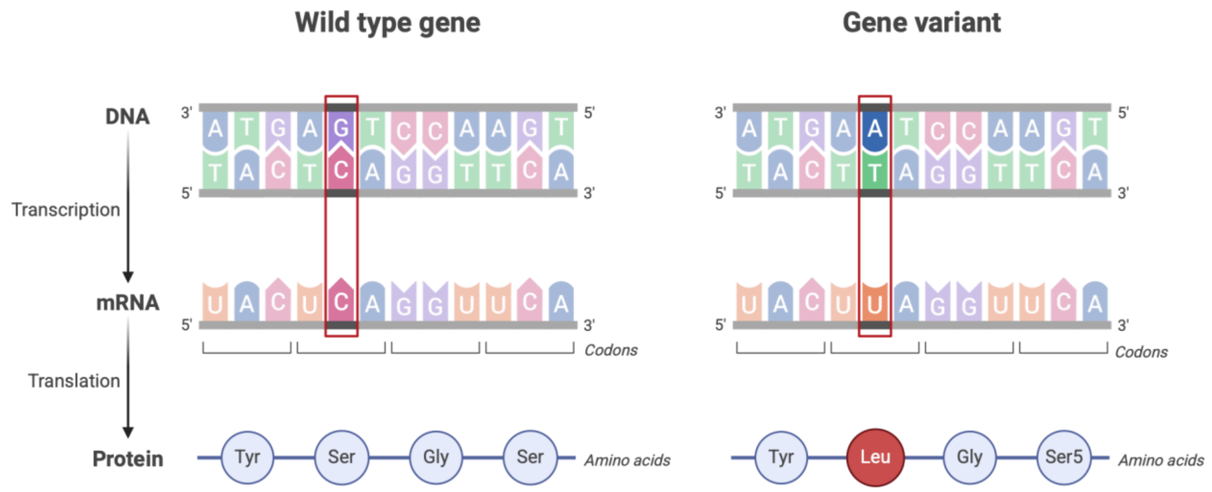


② Somatic and copy number variant analysis

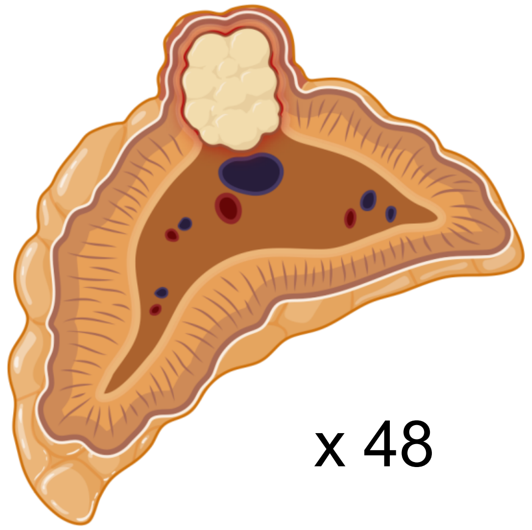


Methods

① Whole exome sequencing

② Somatic and copy number variant analysis

③ Molecular clock analysis



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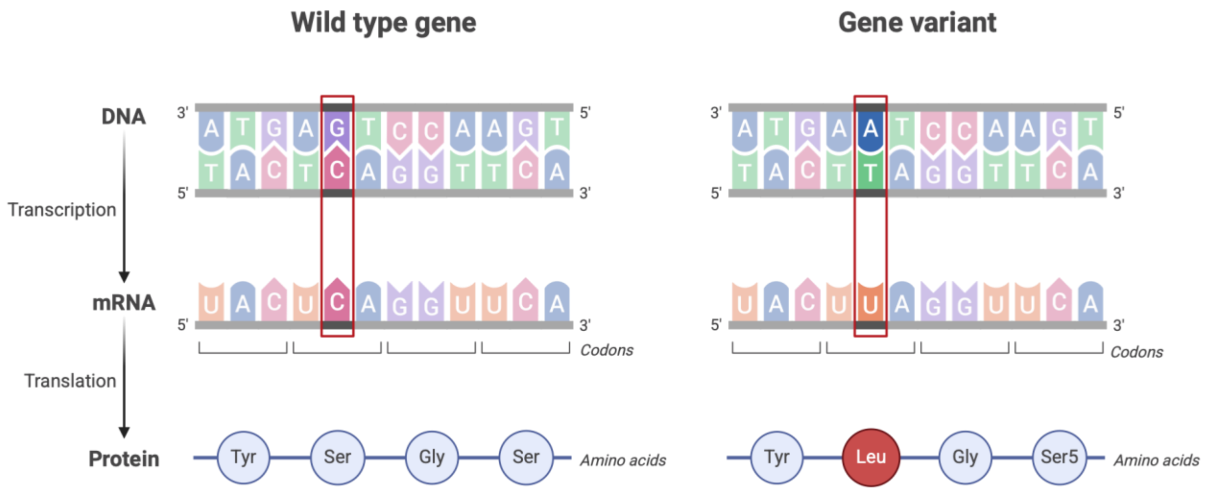
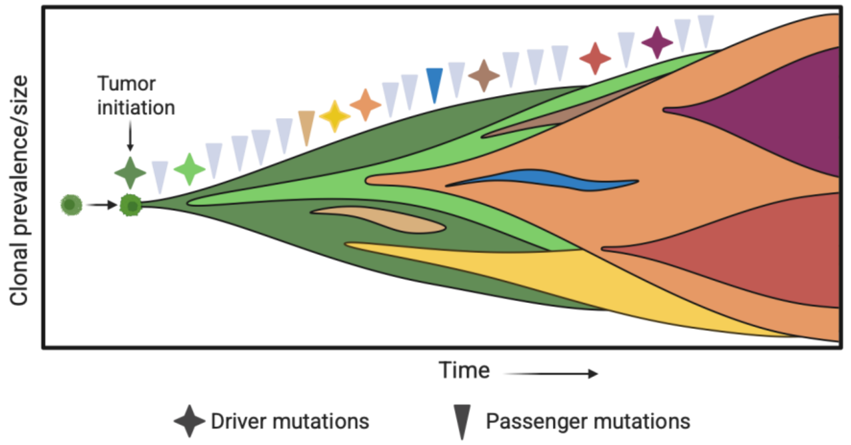
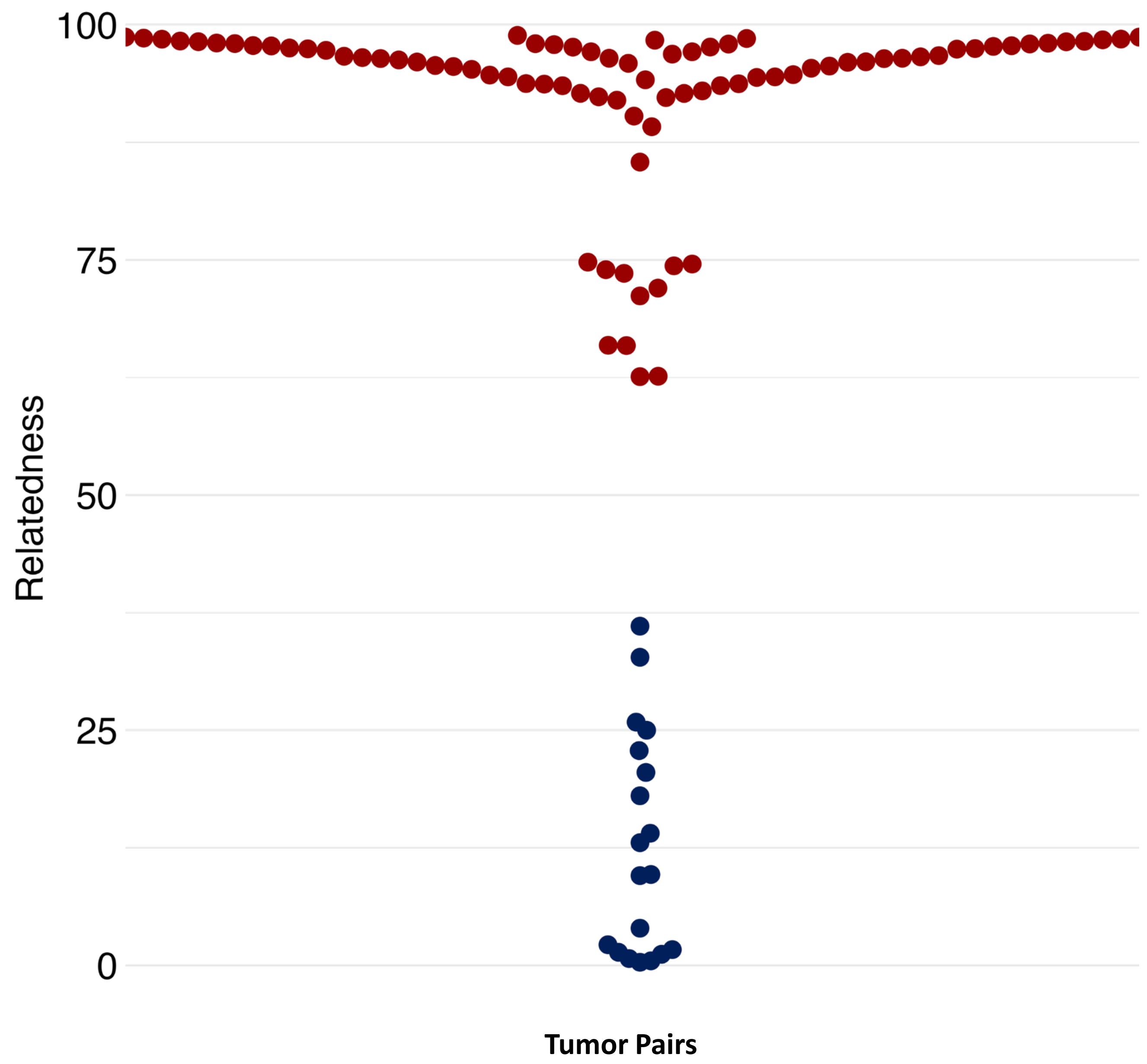




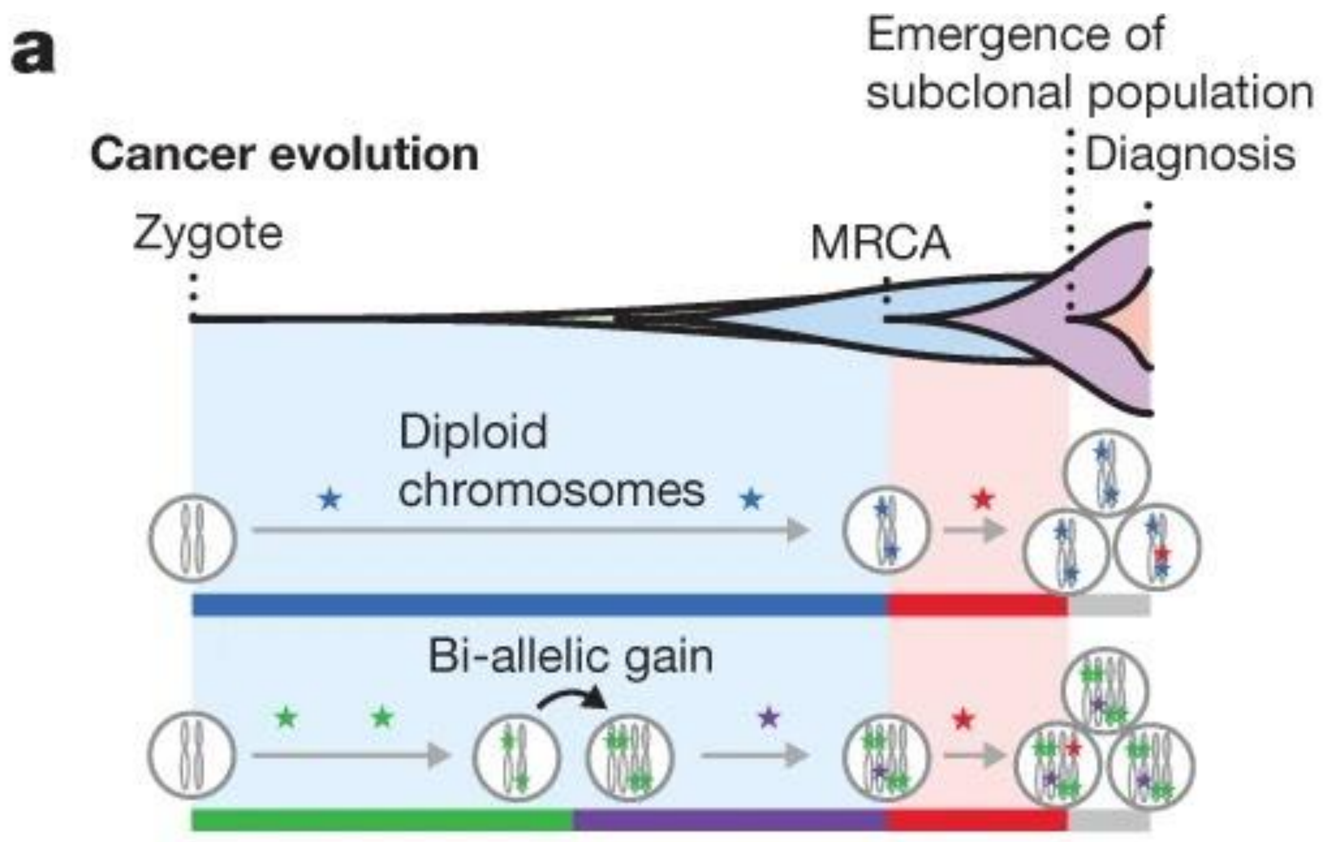
Primary-metastasis tumor pairs have a low shared fraction of somatic variants



Percentage of shared common single nucleotide polymorphisms

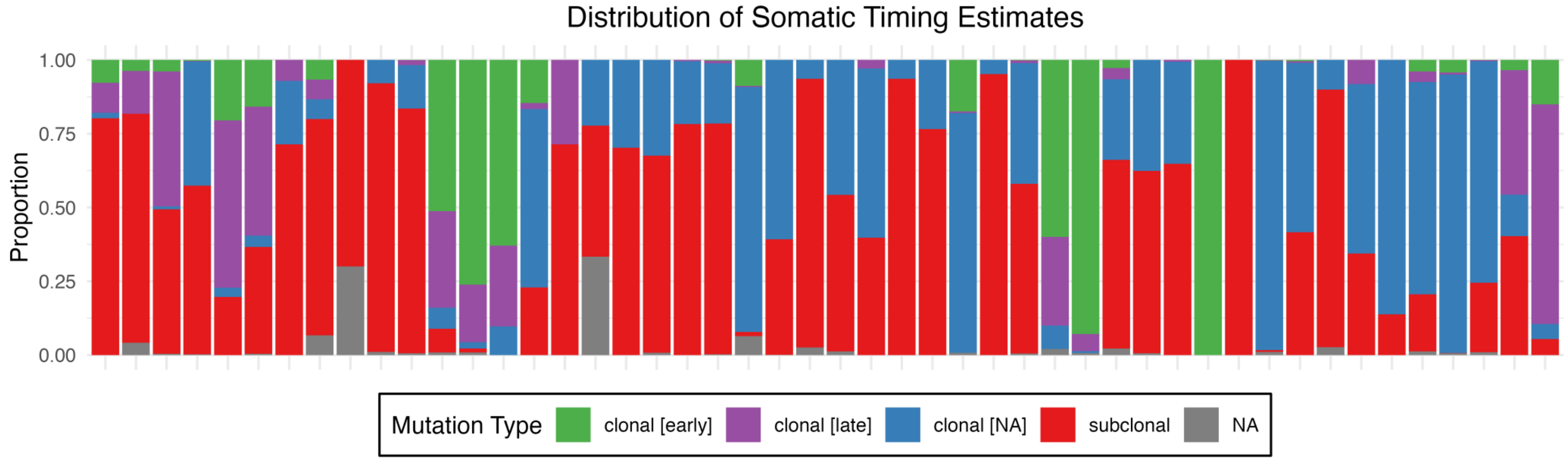
Percentage of shared somatic variants

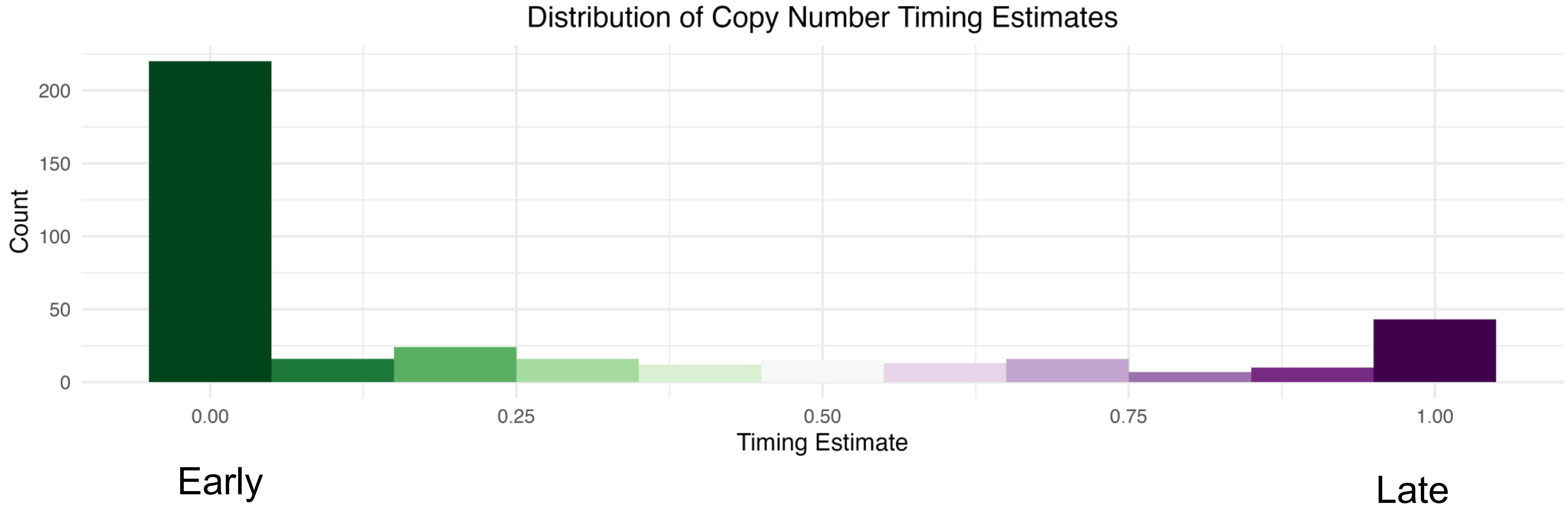
Molecular clock analysis reveals a pattern of early copy number gains and late somatic mutations



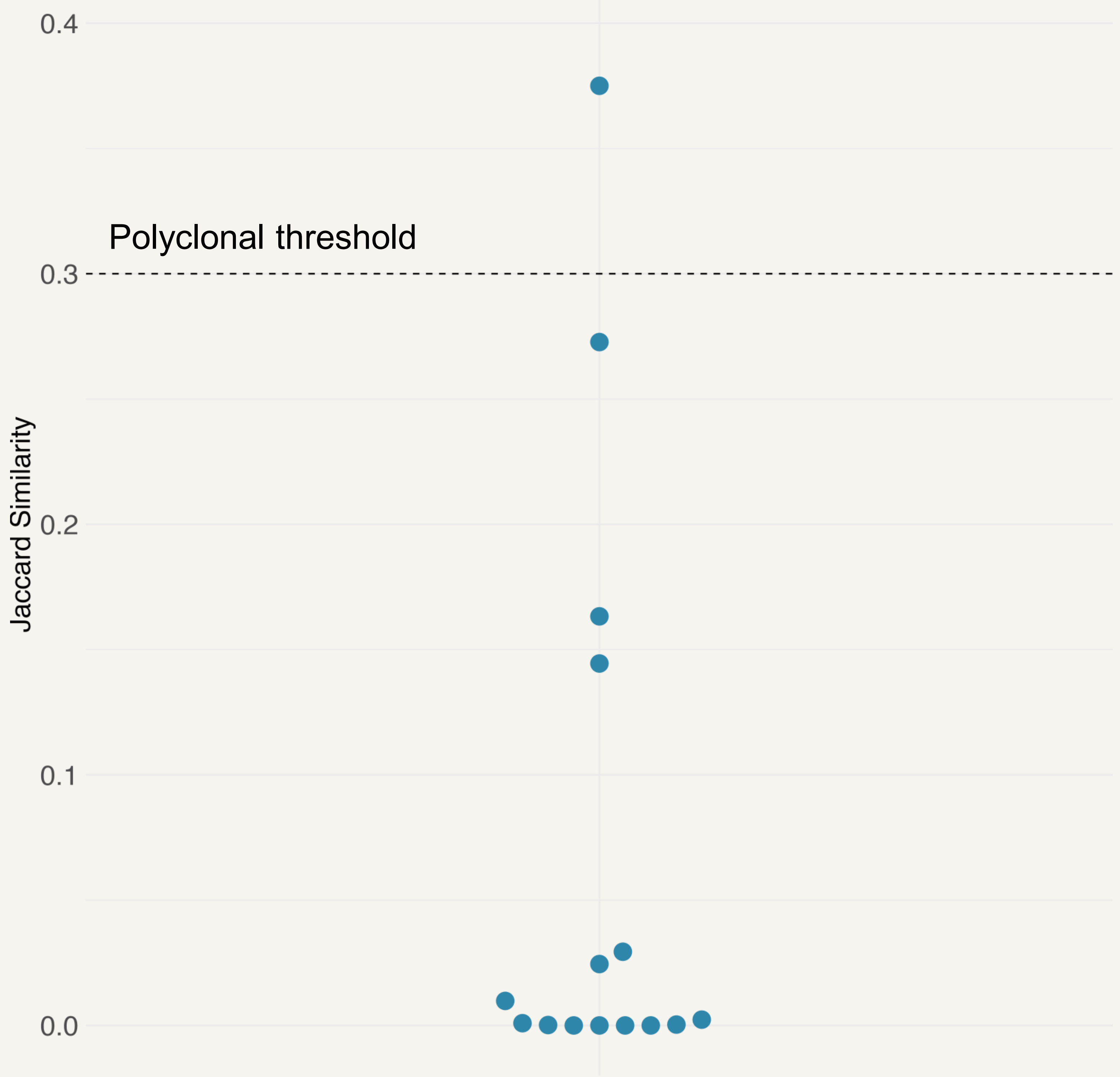
Clonal allelic status of point mutations

Early clonal	Mutation on ≥2 copies per cell
Late clonal	Mutation on 1 copy per cell, no retained allele
Clonal	Mutation on 1 copy per cell, either on amplified or retained allele
Subclonal	Mutation on <1 copy per cell





Modeling demonstrates metastatic tumors arise from monoclonal seeding patterns



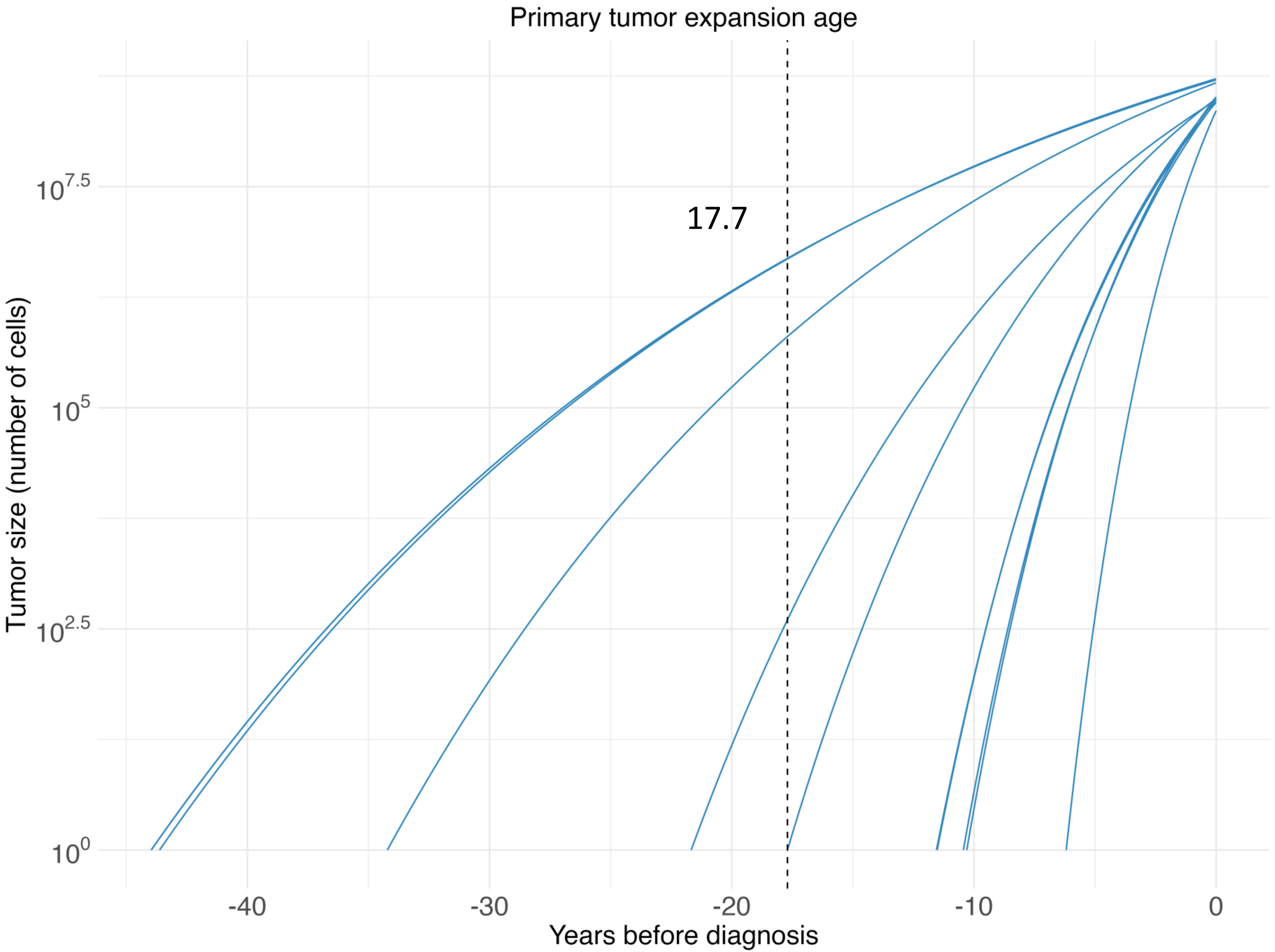
$$JSI = \frac{W_S}{L_M + L_p + W_S}$$

W_S: Primary-metastasis shared subclonal mutations

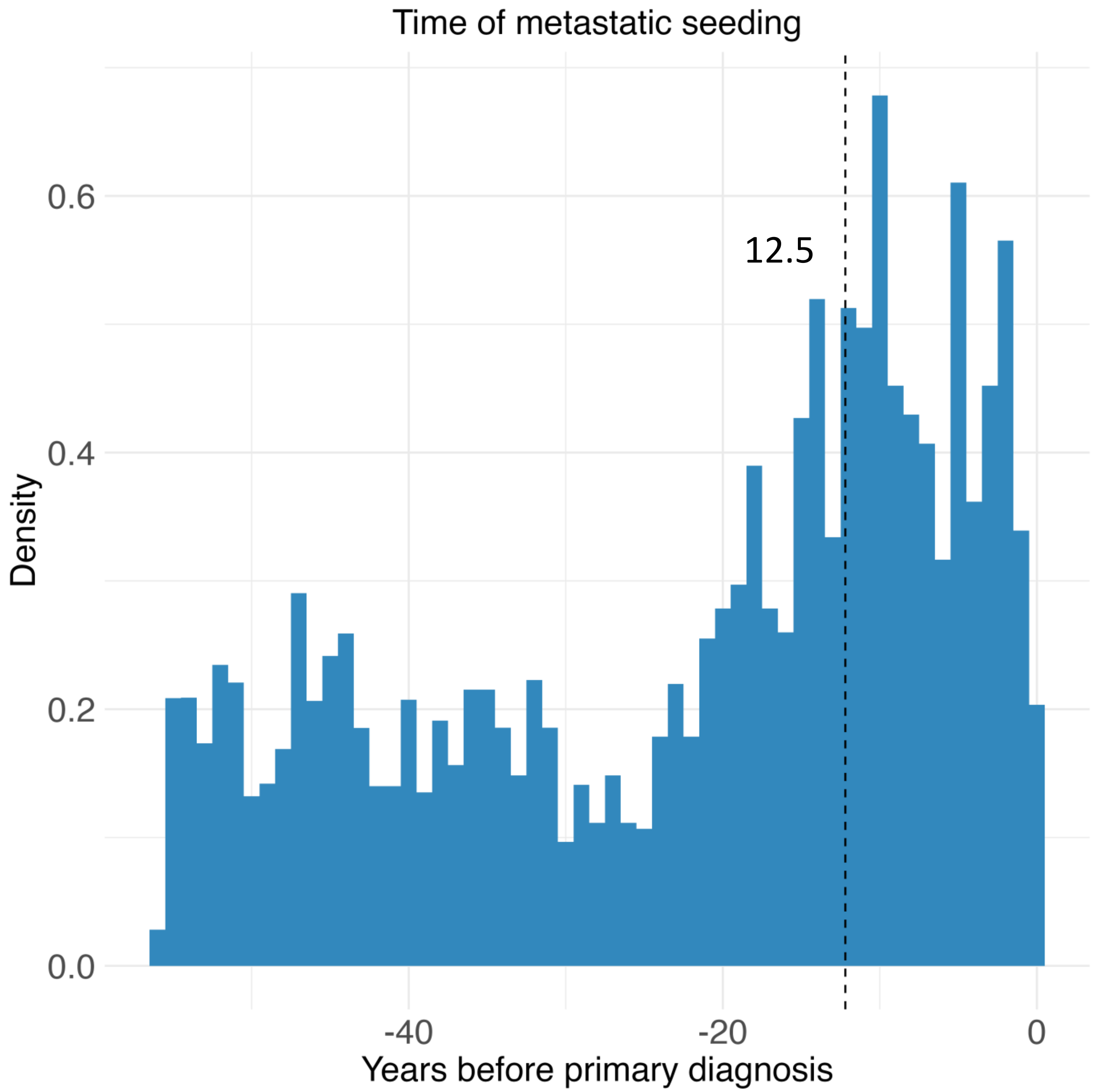
L_M: Metastasis-private clonal mutations

L_p: Primary-private clonal mutations

Metastases seed years before diagnosis of the primary tumor

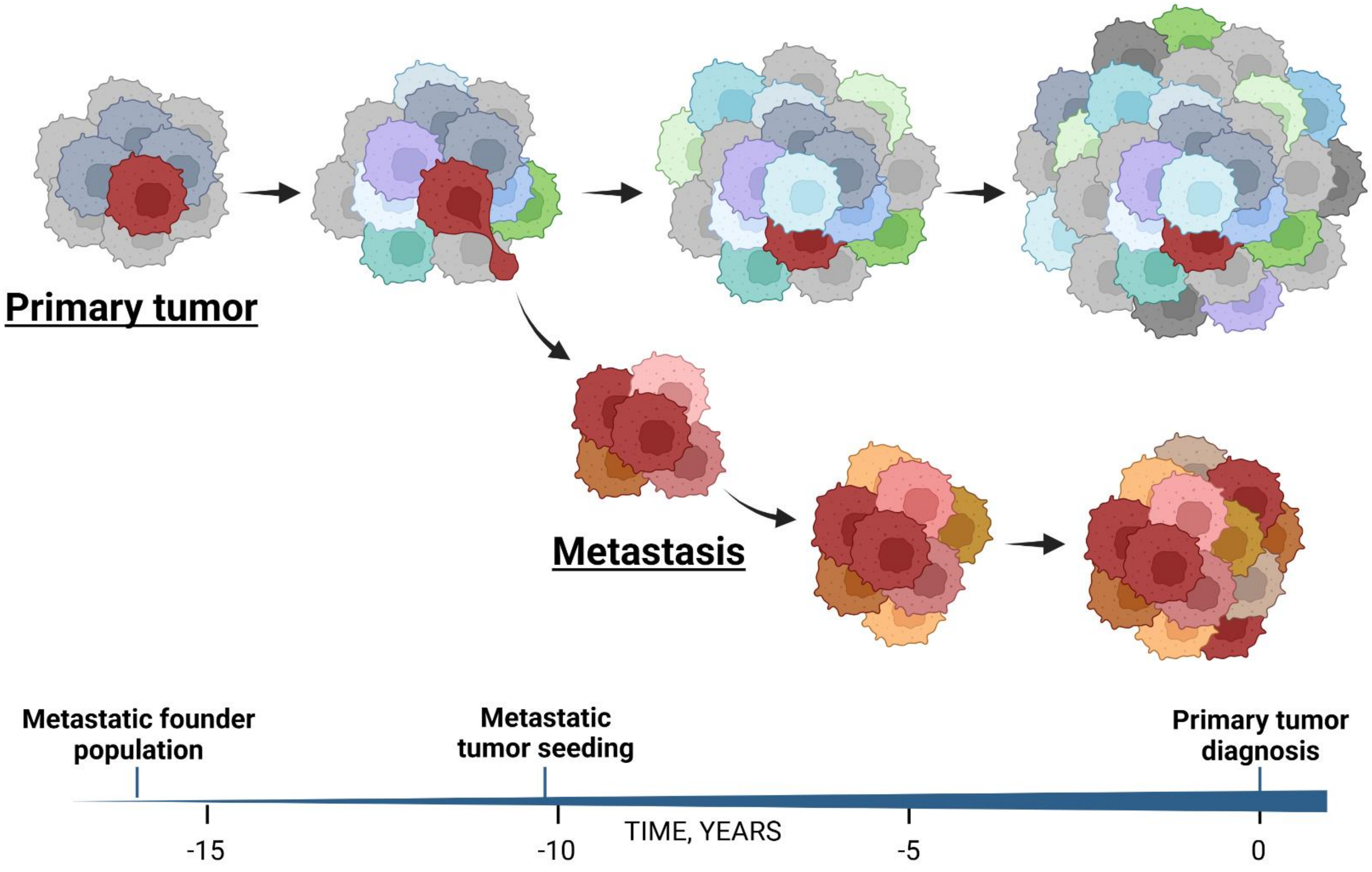


Primary tumor expansion age



Time of metastatic seeding

Summary



Primary tumor

Metastasis

Metastatic founder population

Metastatic tumor seeding

Primary tumor diagnosis

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