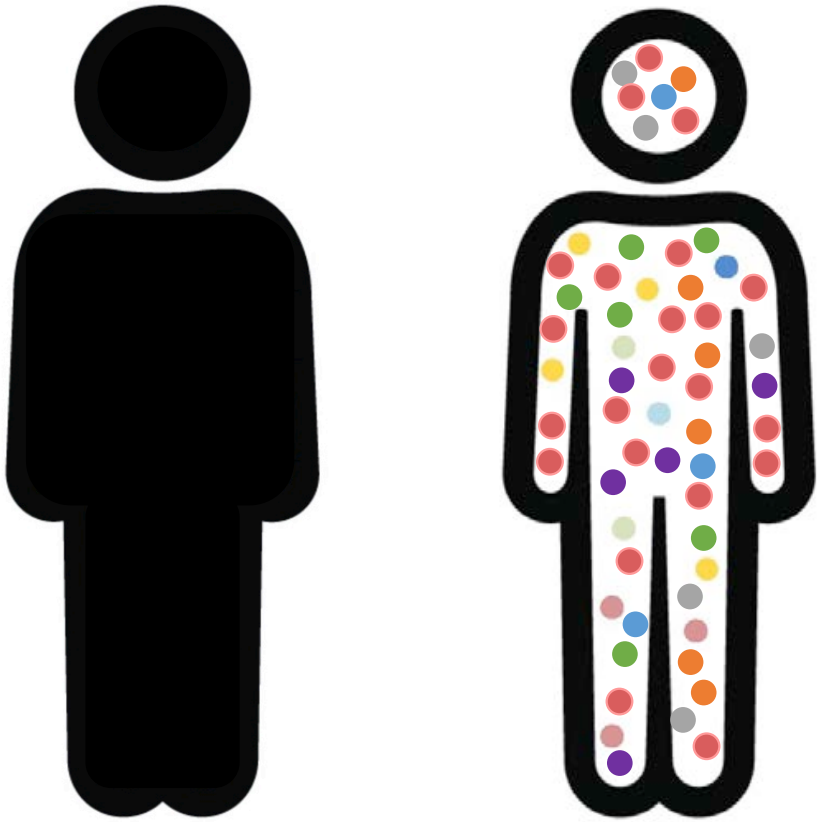
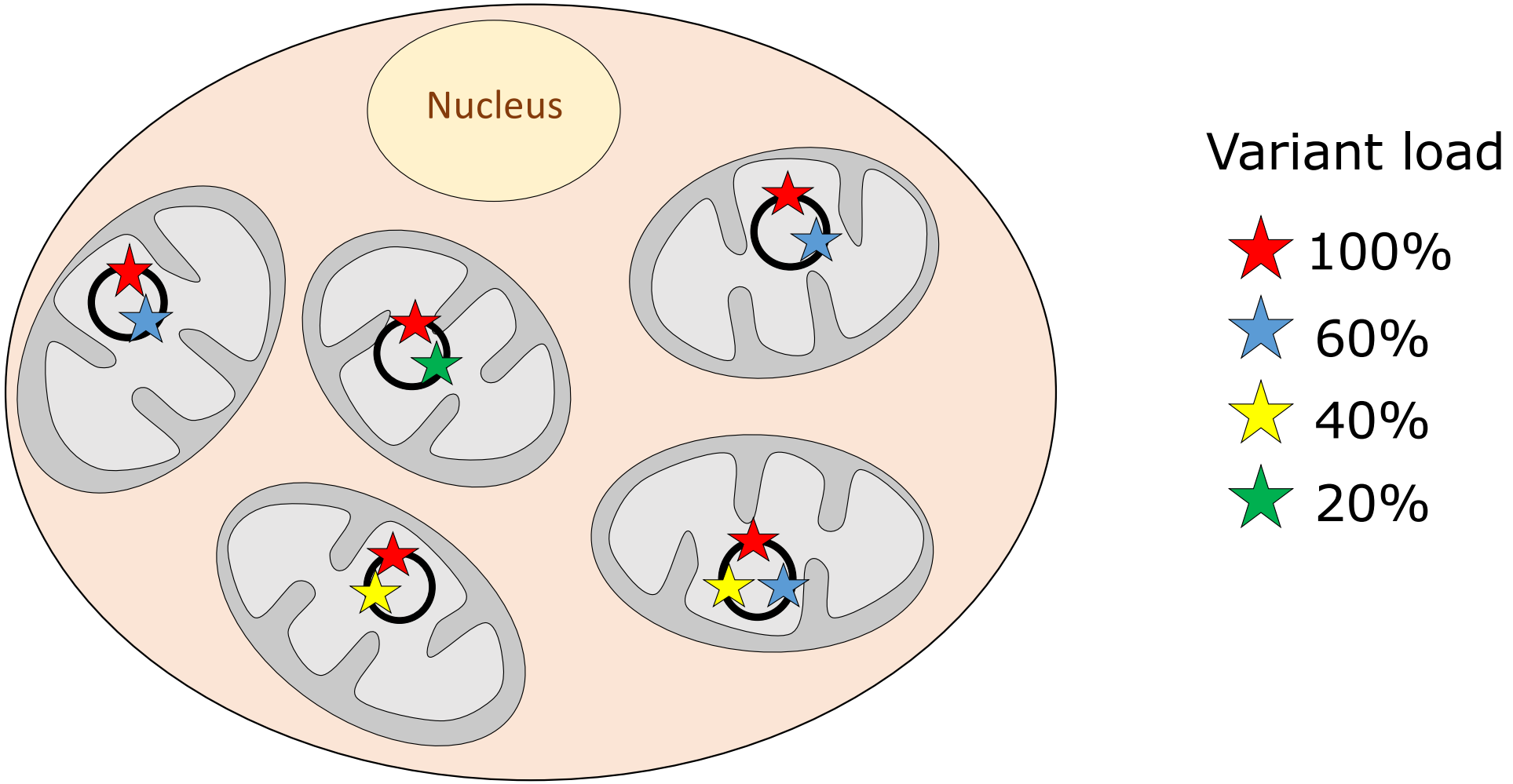
VUB REPRODUCTION & GENETICS RESEARCH GROUP

Mitochondrial DNA mosaicism in early human development

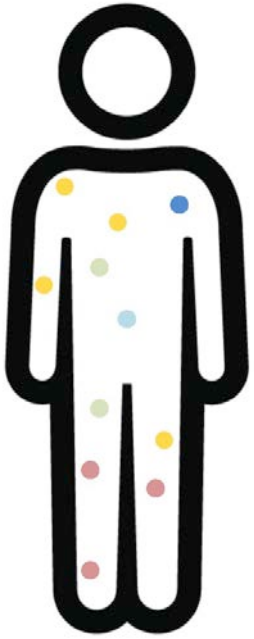
J. Mertens, M. Regin, N. De Munck, H. Van de Velde, K. Sermon, C, Blockeel, C. Spits




Nucleus
Variant load
100%
60%
40%
20%

Mitochondrial DNA sequencing of single cells of one individual shows significant somatic mosaicism

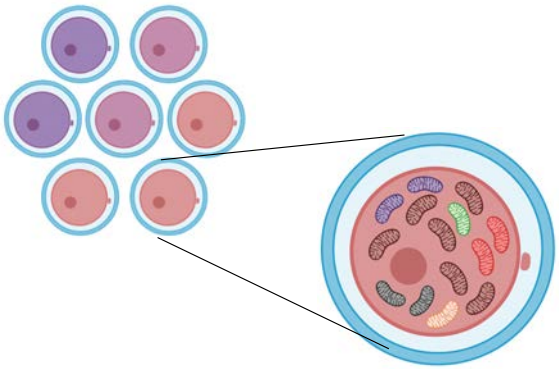
Variants	Cell 1	Cell 2	Cell 3	Cell 4
m.2760A>G	N/A	N/A	N/A	96
m.9276G>A	0	15	0	N/A
m.12071T>C	98	0	100	N/A
m.12850A>G	0	100	0	N/A
m.15617G>A	0	0	41	N/A



Zambelli et al., Stem Cell Reports 2018

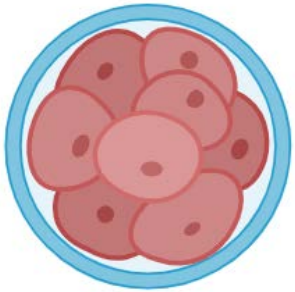
Do preimplantation human embryos show evidence of cell lineages with different mtDNA variants?

102 oocytes
20 donors



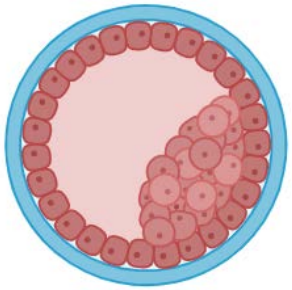
- Bottleneck
- Pool of >1 million mtDNA copies
- Germline mosaicism

158 blastomeres
25 embryos

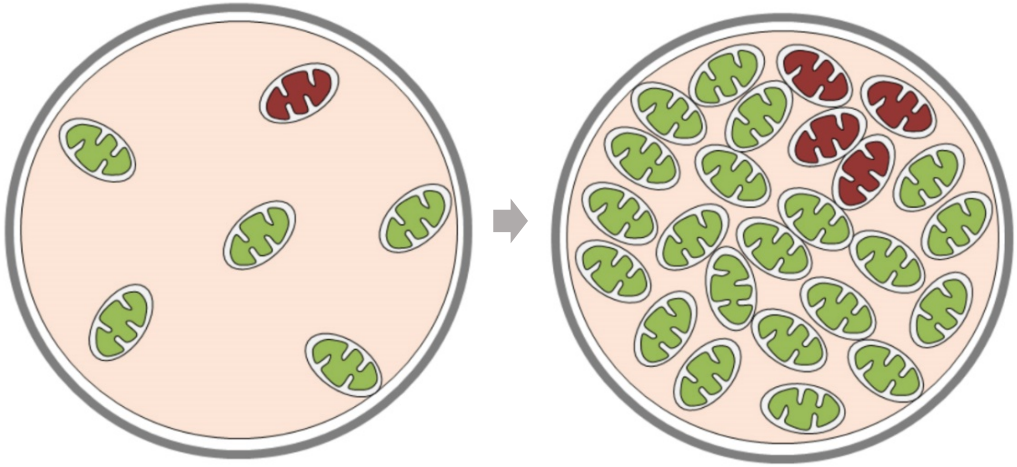


- Random segregation
- No mtDNA replication
- mtDNA copy number/cell ↓

17 samples
7 blastocysts

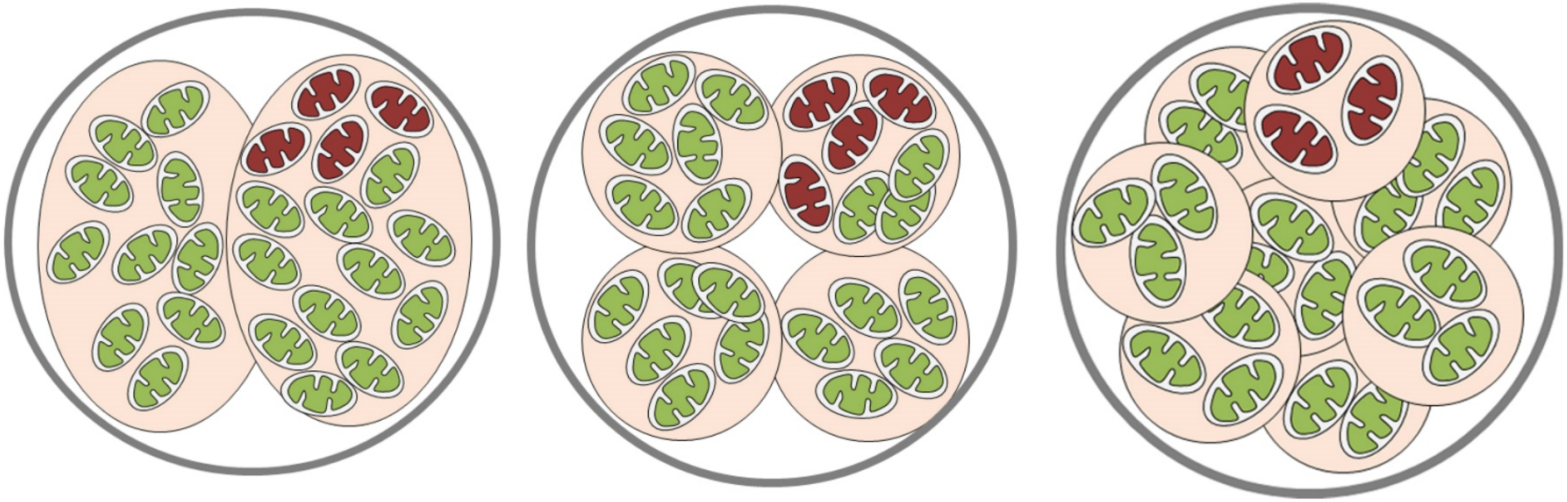


- Random segregation
- mtDNA copy number/cell ↓
- mtDNA replication starts in trophectoderm

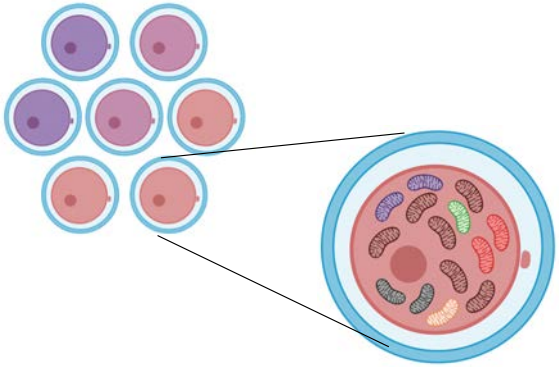


Primordial germ cell

Mature oocyte



102 oocytes
20 donors



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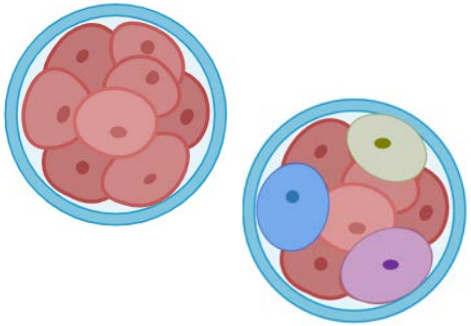

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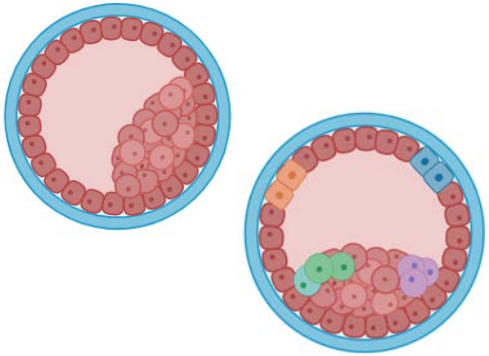
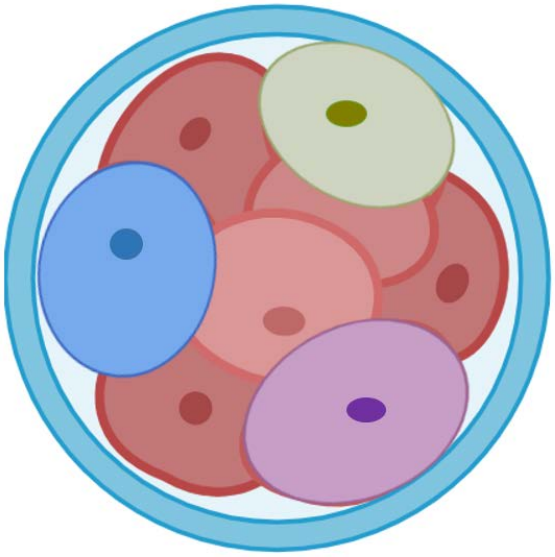
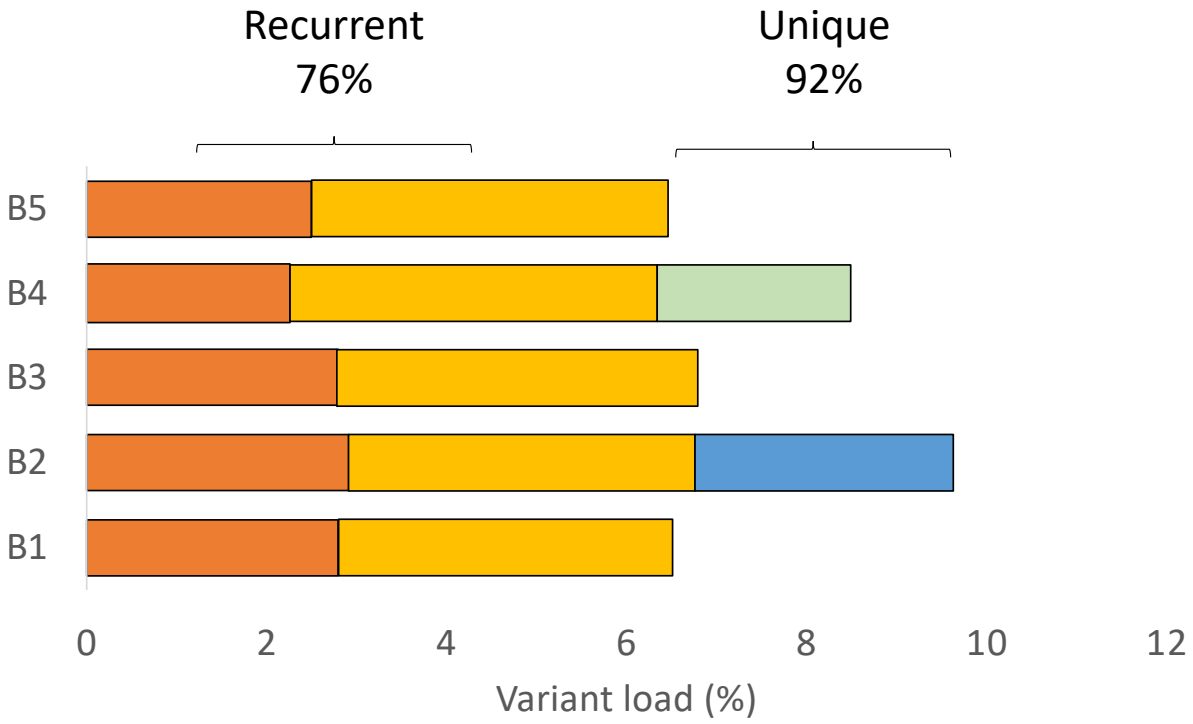


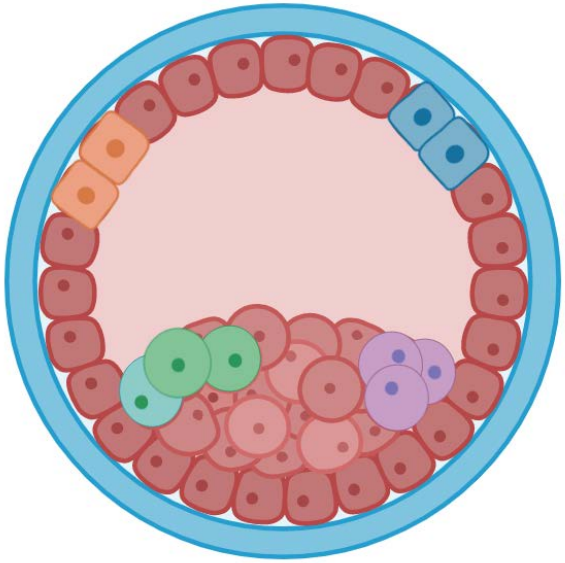
- mtDNA copy number/cell ↓
- mtDNA replication starts in trophectoderm
- Random segregation

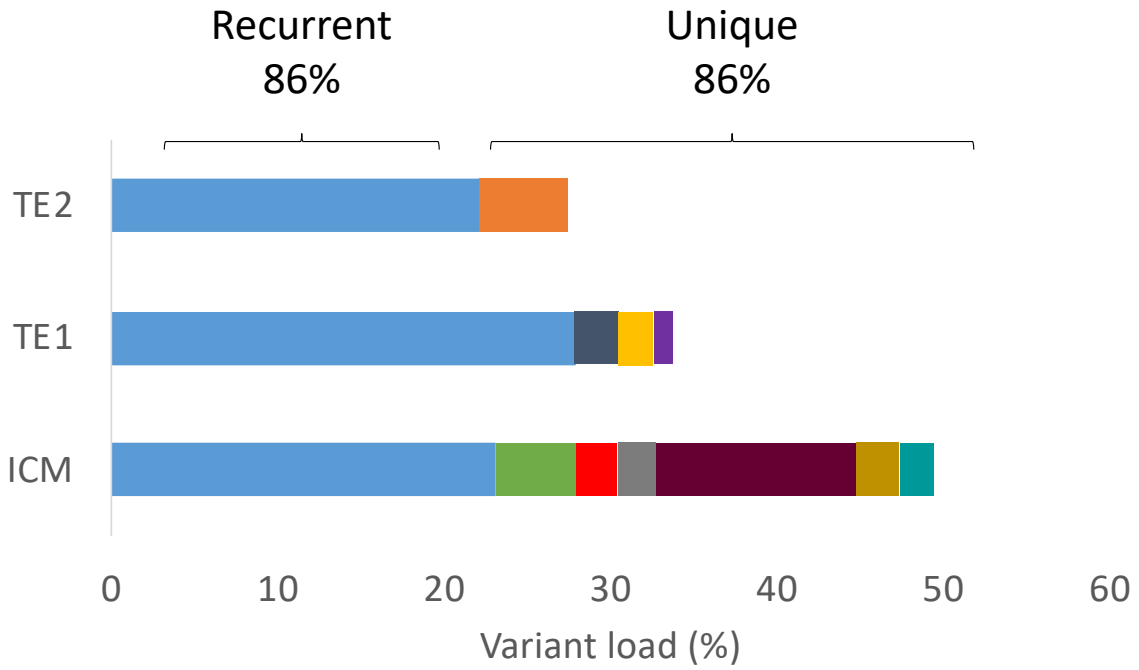
Day 3 embryos carry variants present in all cells at similar loads and unique variants in individual blastomeres

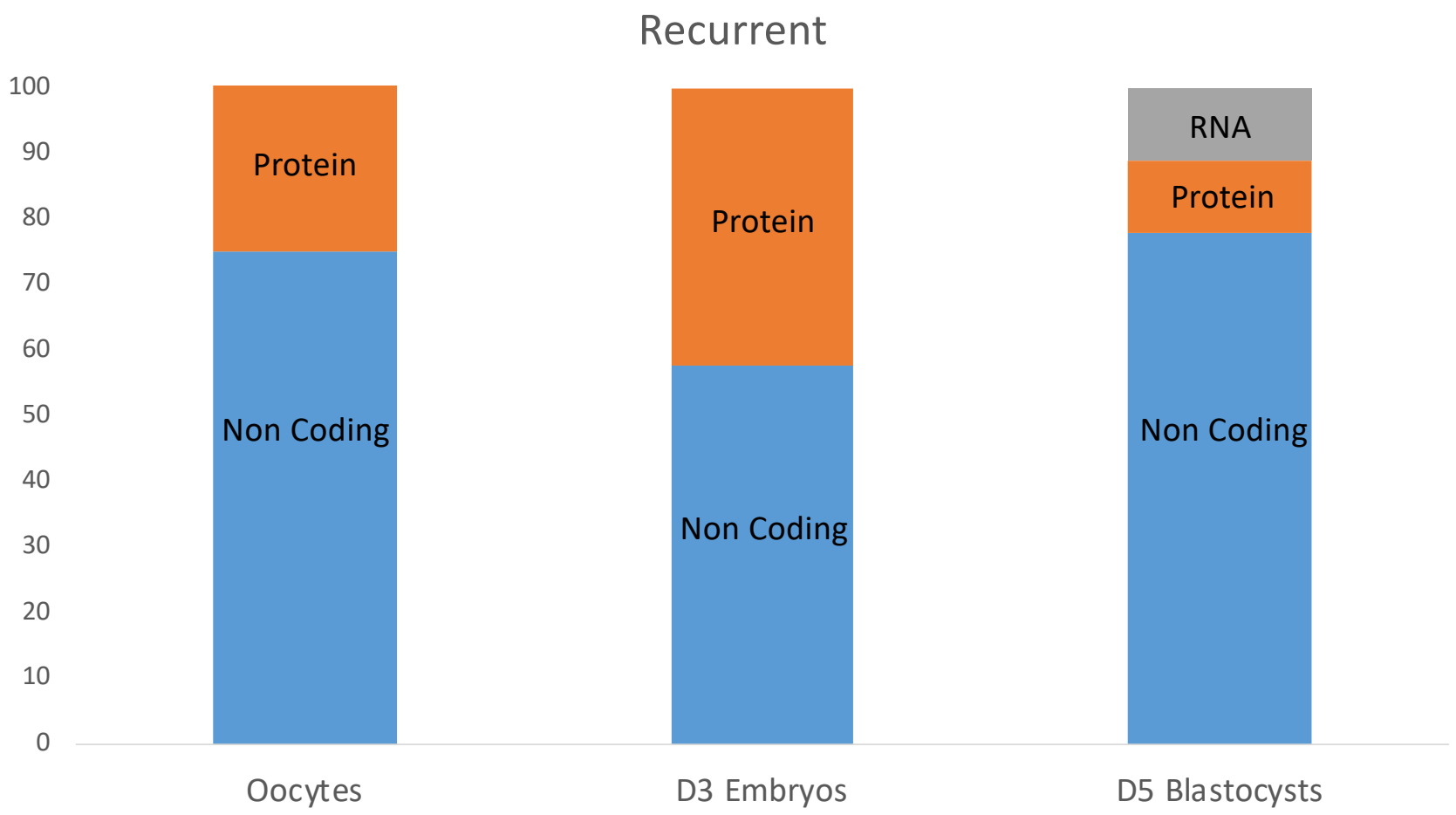


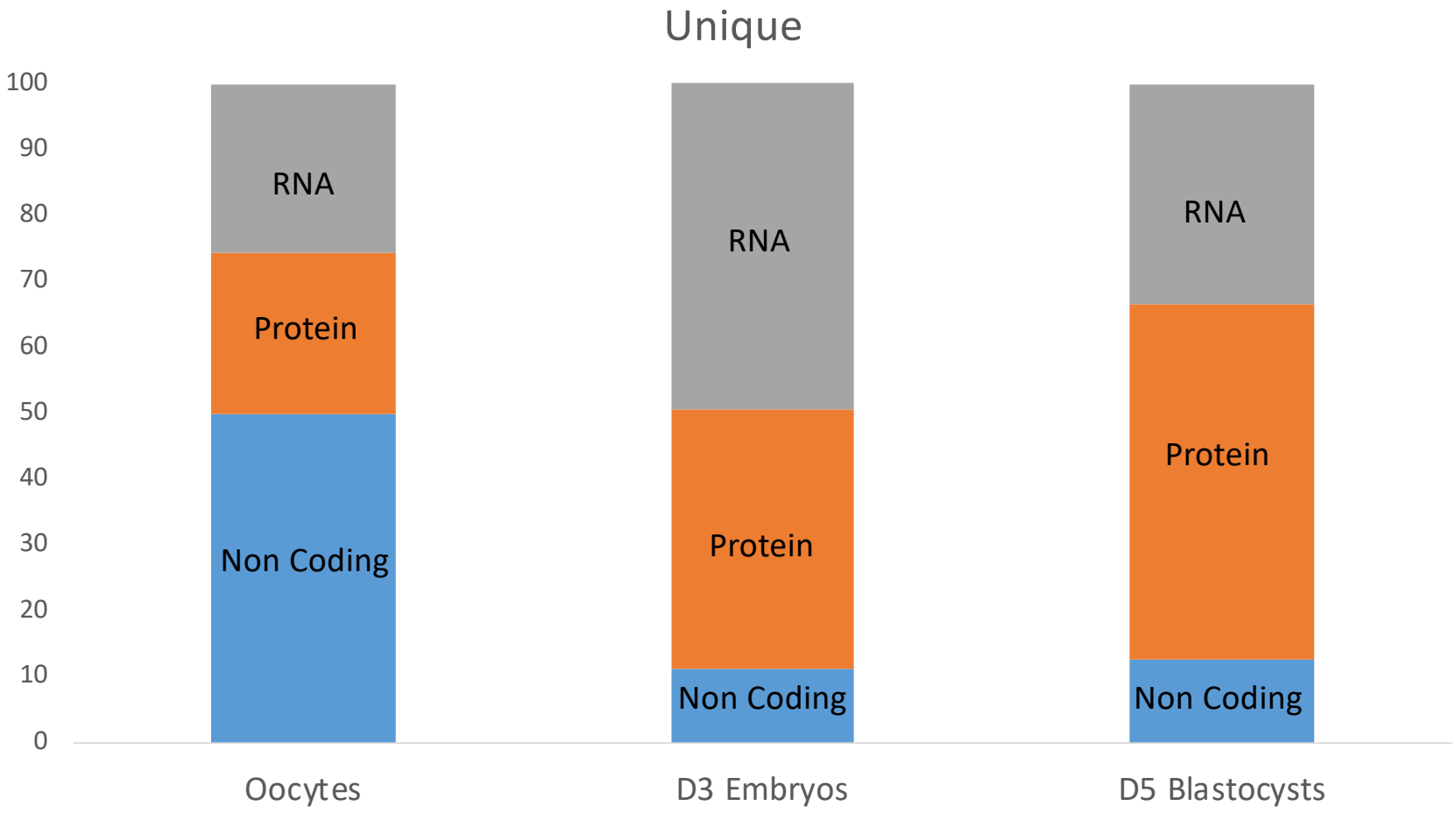


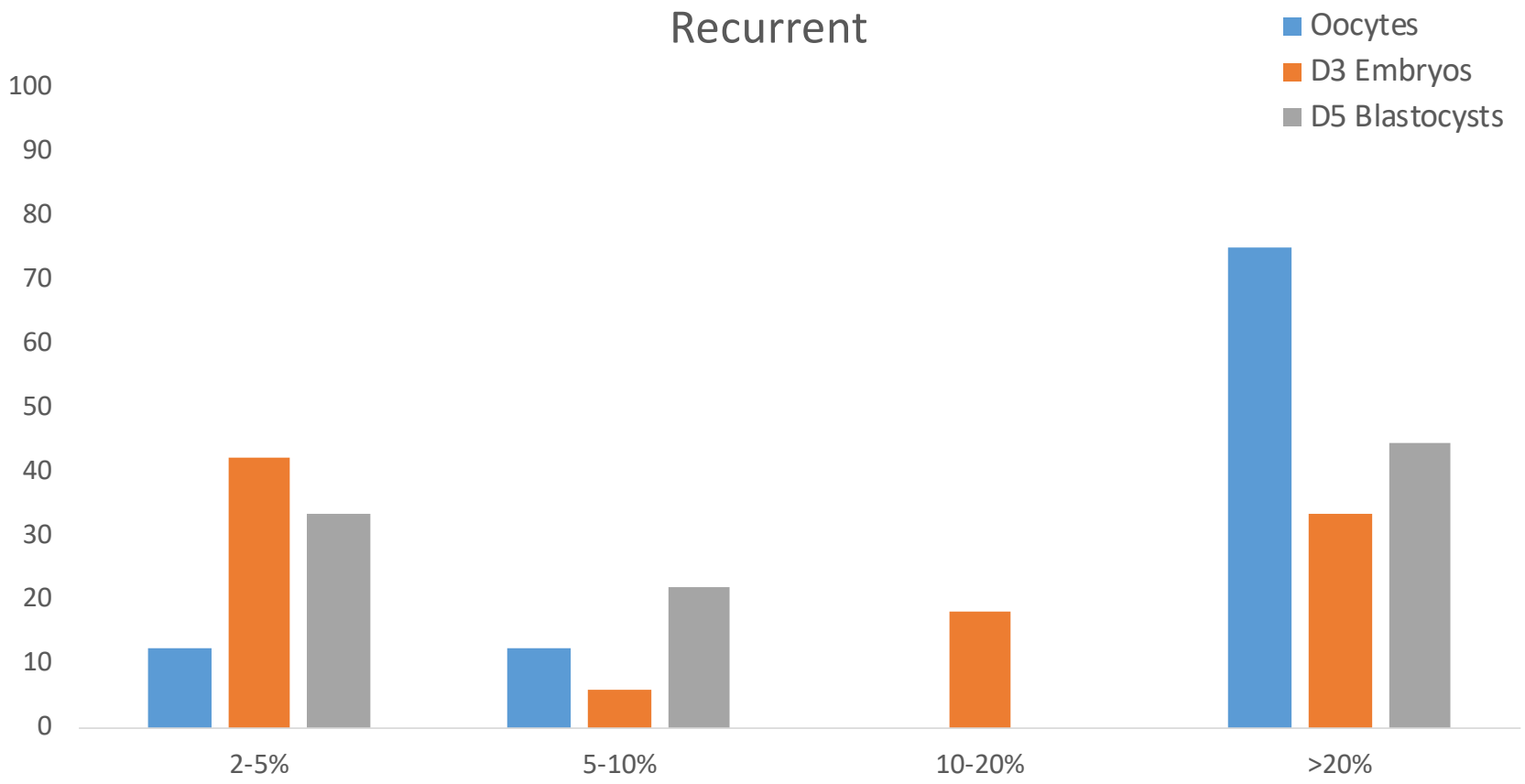
Day 5 blastocysts carry variants present in all cells at similar loads and unique variants in inner cell mass (ICM) and trophectoderm (TE)

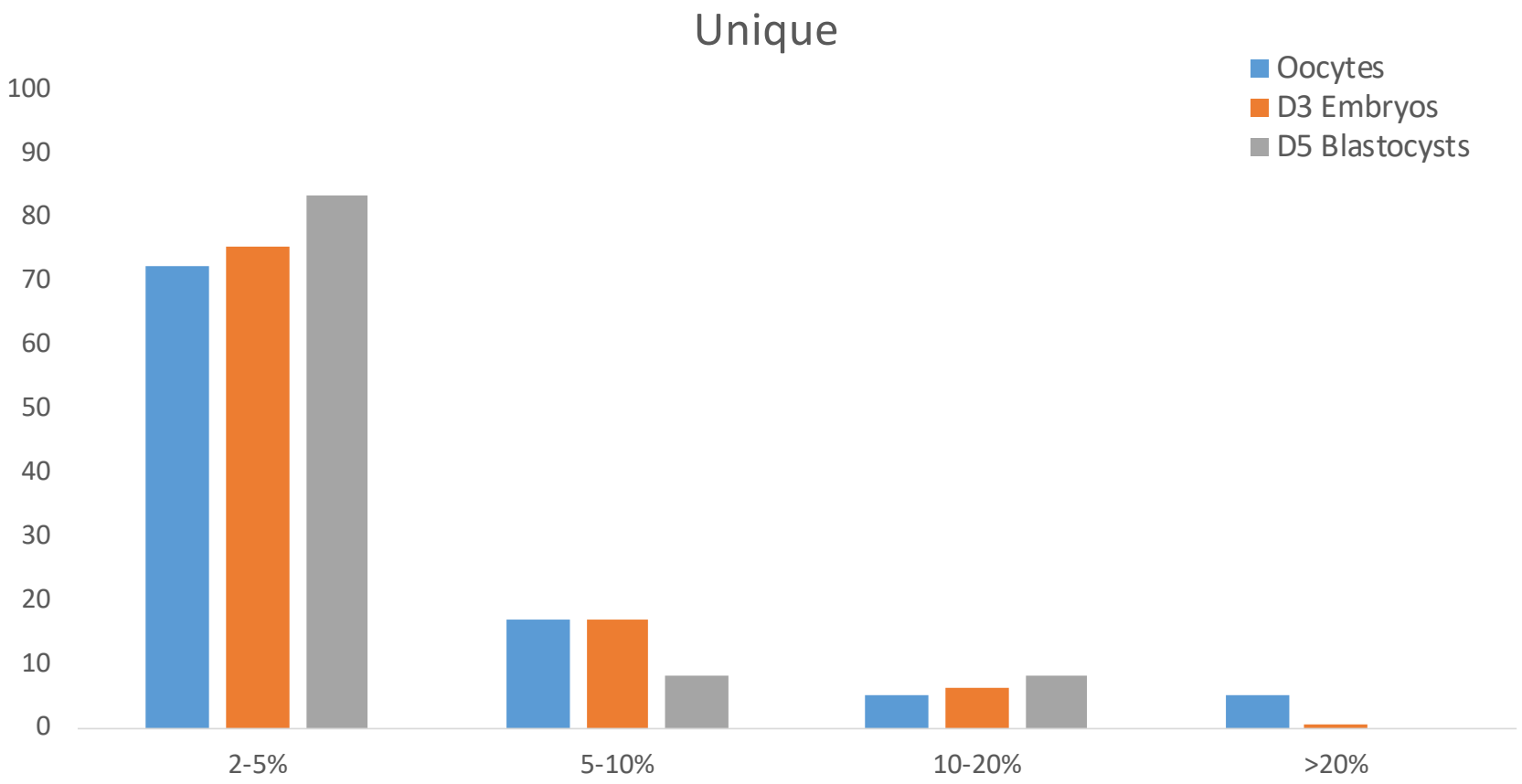





Recurrent
100
90
80
70
60
50
40
30
20
10
0
Protein
Non Coding
Protein
Non Coding
RNA
Protein
Non Coding
Oocytes
D3 Embryos
D5 Blastocysts


Unique
100
90
80
70
60
50
40
30
20
10
0
RNA
Protein
Non Coding
RNA
Protein
Non Coding
RNA
Protein
Non Coding
Oocytes
D3 Embryos
D5 Blastocysts


Recurrent
Oocytes
D3 Embryos
D5 Blastocysts
100
90
80
70
60
50
40
30
20
10
0
2-5%
5-10%
10-20%
>20%


Unique
Oocytes
D3 Embryos
D5 Blastocysts
100
90
80
70
60
50
40
30
20
10
0
2-5%
5-10%
10-20%
>20%

Take home message

- Preimplantation embryos show evidence of mtDNA lineage formation as early as day 3
- Unique variants are potentially more pathogenic and are present at a lower load
- Mosaicism seen in adults appears to originate during the first days of development

Acknowledgements

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https://rege.research.vub.be/

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