(1 5 Mb ecDNA al kn n a d ble min e) (Pa l en e al. 2018; Shiba a e al. 2012; T ne e al. 2017). Ci c la DNA can de i e f m i e i h li le n e ence h m l- g , h e e , highl e e i i e gen mic egi n , ch a he

ci c la DNA ecie d n f m a a high a e, n c n ain ac i e e lica i n igin and, he ef e, he c n mbe f he e ecie in m he cell ill emain a ic dec ea e i h age. A c i c me f he e di e ence in f ma- i n eed, e lica i n ca aci and a mme ic e en i n i ha he di e i f ci c la DNA ecie b e ed in ng cell i high, b he c n mbe f each indi id al ci cle and, he ef e, he hen ic im ac i l . A cell age, nl a b e f ci c la DNA can acc m la e b ha

megaba e f DNA, gene- ich ch m ! me c n ib e m e he al le el f ci c la DNA in heal h h man i e (M lle e al. 2018). F he m e, *TTN* (i in), he m ! an c ibed ein-c ding gene in m cle i e, i al he la ge d ce f ci c la DNA e gene (M lle e al. 2018). F mali ing hi idea, e gge ha gene hich ha e e l ed be ind ced in e n e a ic - la en i nmen al c ndi i n a e e cellen candida e f ada i e am li ca i n, and ha im l c nnec ing ci c - la DNA f ma i n an c i i nal ind c i n i a cle e mean b hich cell c ld gain he ma im m chance f acc m la ing ef l ci c la DNA, a he han nhel f l nega i e ecie .

B i elf, an ada i e hen e in an indi id al aged cell i f li le e if he ca al ci c la DNA i el hl e ained in he m he cell, a ! ld be he ca e if a m- me ic eg ega i n i main ained, and e m c n ide h ci c la DNA acc m la i n i an la ed in a he i - able ad an age. Fi , nce ci c la DNA ha acc m la ed, eg ega i n can be ela ed nde e all ing ci cle i h e lica i n igin aga e a high c n m- be in he la i n (Fig. 1, e 5a). Thi elea e f he a mme ic eg ega i n, em nde hea e ha been b e ed and e e en a gene al e n e ignalling f m he cell all in eg i a h a (Baldi e al. 2017). Sec ndl , acc m la i n f high le el f ci c la DNA inc ea e he chance f ch m ! me e-in eg a i n and, he ef e, e a i n f n mal he i abili f he am li- ed allele (Fig. 1, 5b). S ch ada i e ch m ! mal e- in eg a i n e en ha e been e ea edl b e ed, al h ! gh i i nclea he he he ha ened in aged cell (Be e le e al. 1984; B e e e al. 2015; Demeke e al. 2015; D kin e al. 2012; Gale e e al. 2011; K che e al. 2020; La e e al. 2018; V g e al. 2004).

The idea ha a b- la i n ade h - e m g h f ada i e ca aci i f mali ed in be -hedging (c nci el e ie ed in (Le e al. 2012)), and face f ageing ha i h a be -hedging m del ha e been dem n a ed e e i-

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