Supplemental methods

To determine the source of the observed bias in the TDT, we explored the role of missing genotype calls on the TDT design. Specifically, the expected number of informative families (i.e. those with at least one heterozygous parent) removed from the TDT can be examined through the proportions found in Supplementary Table 1

Parent 1	Parent 2	Offspring	Frequency	Major/Minor	M_{11}	M_{12}	M_{22}
11	12	11	$2p^3q$	Major	2	1	0
11	12	12	$2p^3q$	Minor	1	2	0
12	12	11	p^2q^2	2*Major	1	2	0
12	12	22	p^2q^2	2*Minor	0	2	1
12	22	12	$2pq^3$	Major	0	2	1
12	22	22	$2pq^3$	Minor	0	1	2

Where Parent 1, Parent 2, and Offspring refer the genotype at the locus (with 1 as the major allele and 2 as the minor), frequency is probability of observing that familial configuration, under Hardy-Weinberg Equilibrium, Major/Minor reflects the number of transmission of the major or minor allele, and M_{11}, M_{12}, and M_{22} are the counts of the probabilities of missing for the 11, 12, and 22 genotypes.

The frequency of missing for overtransmission of the major allele can be written as

$$2p^3q\,(2M_{11} + M_{12}) + p^2q^2(M_{11} + 2M_{12}) + 2pq^3(2M_{12} + M_{22})$$

and for the minor allele as

$$2p^3q\,(M_{11} + 2M_{12}) + p^2q^2(2M_{12} + M_{22}) + 2pq^3(M_{12} + 2M_{22})$$

Thus, if $M_{22} > (M_{11} = M_{12})$, then overtransmission of the minor allele will be preferentially lost, as $2p^3q\ (2M_{11} + M_{12}) = 2p^3q\ (M_{11} + 2M_{12})$ and $p^2q^2(M_{11} + 2M_{12}) + 2pq^3(2M_{12} + M_{22}) < p^2q^2(2M_{12} + M_{22}) + 2pq^3(M_{12} + 2M_{22})$.

Additionally, if $M_{12} > (M_{11} = M_{22})$ overtransmission of the major allele results, as $p^2q^2(M_{11} + 2M_{12}) = p^2q^2(2M_{12} + M_{22})$ and $2p^3q\ (2M_{11} + M_{12}) + 2pq^3(2M_{12} + M_{22}) < 2p^3q\ (M_{11} + 2M_{12}) + 2pq^3(M_{12} + 2M_{22})$, as $2p^3q > 2pq^3$ if $p > q$.

Therefore, we can conclude that preferential rare homozygote dropout coupled with heterozygote dropout yield a greater rate of overtransmission of the major allele. Furthermore, conditioning on strictly complete data (no missingness), there is no difference in the overtransmission of the major or minor allele.